NAMI Ask the Expert: New Horizons in Schizophrenia Research
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Presented by
Holly Lisanby, MD, Director, Translational Research Division, NIMH

Dan Gillison (00:00:00):

Thank you very much Teri and yes, we are now living in this new virtual reality if you will, and just wanted to say on today, we're incredibly excited to have you with us. On behalf of our board president, Shirley Holloway, and the entire staff of NAMI, we appreciate you being here with us. We're very excited. Things happen in threes, interest, development, and commitment and the interest in regard to this body of work started some years ago. As the development and the discovery took place, we're now at the point of commitment and execution. With that said, looking at AMP schizophrenia and science is so critically important to us making a difference in the lives of people that are living with mental illness and with schizophrenia.

We're incredibly excited to have a seat at the table in this body of work and with that said, what I'd like to do is to hand it over to NAMI's chief medical officer, Dr. Ken Duckworth. Ken.

Ken Duckworth (00:01:21):

If you are muted, the most common statement of this entire pandemic, it has been for me. We're very fortunate to have Dr. Holly Lisanby today. He's going to help us talk about one of the great unsolved mysteries in our field, which is how to provide progress towards understanding schizophrenia, so that we might develop better drug targets. You should know that NAMI has been intimately involved in this project for many years that has now come to the step of execution as Dan said. The accelerated medication partnership is one of the topics that Dr. Lisanby will be talking about. Let me tell you a little bit about her. She has been to many of our now 5-year meetings as we've begun the process of planning for this AMP.

She's a psychiatrist and the director of translational research at the National Institute of Mental Health. She went to Duke Undergrad Medical School, trained in New York afterwards and is a national expert on brain stimulation. While her talk is not on brain stimulation, in the conversation Q and A, I will be sure to answer questions relate to brain stimulation, which is another creative approach to helping people who live with serious mental illness. Dr. Lisanby, thank you for joining us today and for giving us this talk.

Holly Lisanby (00:02:48):

Well, thank you for having me.

Thank you so much for the opportunity to talk with you about some exciting new developments in schizophrenia research. I'm really grateful for the important work that NAMI does to get the word out there and to communicate this. I really am so excited to be here and joining you today. The title of my talk is New Horizons and Schizophrenia Research and let me see if I can get this slide to advance. These are my disclosures. As Dr. Duckworth said, I do work in the area of brain stimulation and I'm a co-inventor on a patent on a type of brain stimulation device, but my talk is not about that. Also, you should know that I work for the federal government obviously as an employee at the National Institute of Mental Health.

Here's the outline of what I'd like to present, and we're going to start by discussing some of the challenges. Why is it so hard to develop effective and safe drug treatments for schizophrenia? Then I'm going to talk about some of the strategies that the National Institute of Mental Health has taken to address some of these challenges. Then we're going to focus on an exciting new initiative that is actually a partnership with NAMI and other partners, which is called the accelerating medicines partnership for schizophrenia or AMP schizophrenia. We're going to leave a lot of time for discussion and questions and answers at the end, so let's get started.

What are some of the challenges in drug development for schizophrenia? One that I would like to start with is something that we call the uninformative failure. By that, I mean you do a drug trial and the trial fails to show a difference between the drug and the placebo, but we don't know why. Maybe we didn't use enough large enough sample size, maybe we weren't using the right inclusion criteria, we were targeting the wrong people for whom this was not going to work, or maybe the drug just doesn't work, but with certain drug trial designs, we're often left with scratching our head wondering why it didn't work and not being able to have a way to move forward.

A second challenge is heterogeneity, both in terms of the expression of illness. You take a group of people that have a diagnosis of schizophrenia, but there are many differences among them. There are also comorbidities. You may meet criteria for more than one diagnosis, and what do you do when those are overlapping. This challenge of heterogeneity has been really important in terms of drug development for schizophrenia. The third challenge I'm going to touch on is the fact that research suggests that the illness actually starts earlier in life than we first thought. In fact, things may be going on before the symptoms come to clinical attention.

When we have this early onset, but later detection it makes it very challenging to be able to develop preventions because we don't know what's going on. Given that in the case of schizophrenia specifically, research suggests that the process probably starts even years before the symptoms of psychosis are demonstrated. This is a big challenge when we talk about how to design trials to discover new treatments and then lastly, this prodrome, so this early onset, this has been called the clinical high-risk state or CHR. Even when we can identify people who have this clinical high-risk state, even within those individuals, again there's heterogeneity. If not, everyone with this clinical high-risk state goes on to develop psychosis.

Some do, others don't and there's significant heterogeneity in what people with the CHR experience, what types of symptoms they have, and their course can be variable across time. We're now going to talk about these four challenges, the uninformative failure, heterogeneity, early onset, and heterogeneity in the prodrome. Let's talk about some of the strategies that NIMH is taking to address each of these four challenges. Let's start with the uninformative failure. The strategy that NIMH has been taking in recent years to address this is something that we call the experimental therapeutics approach.

The idea of the experimental therapeutics approach is to design a study, such that whether the drug works or not, we get a win in terms of science because we have information about why the drug didn't work, which guides us to what next steps should occur. We want to be able to learn from our failures. A strategy that NIMH is taking to address heterogeneity is to develop reliable and objective methods to measure this heterogeneity, that's where biomarkers come in, things that we can measure, things that we can do reliably that help give us more information than just knowing what the symptoms are, more objective measures of the health of the brain and physiological processes.

Now because heterogeneity means that the people who make the same diagnosis are quite different, in order to accomplish this goal of discovering biomarkers, we need really big sample sizes, really large sample sizes in order to account for this heterogeneity because the more things you measure, the higher sample size you need for the study to be adequately powered from a statistical perspective. Now with this third challenge of early onset late detection, a strategy that NIMH has been investing in, and I'll show you some of our studies, takes a longitudinal approach.

It means these studies take years that we follow the same individuals over time to learn from them what happens over time, so that we can begin to develop ways of detecting risk at the earliest possible state, so that then we can design targeted treatments to intervene, and ultimately to prevent longer-term adverse outcomes. Now this issue of heterogeneity within this clinical high-risk state, the strategy we're taking to address this is to develop reliable methods to predict that variability in long-term course of people who have been identified as early risk. That's the area where the AMP schizophrenia project comes in, and we're going to be reviewing more of the details of that later in the talk.

That's our outline, the challenges, and the strategies. Let's start with that first challenge, the uninformative failure. Well, NIMH invests in clinical trials across this pipeline from first in human to exploratory experimental therapeutics to confirmatory efficacy to effectiveness trials. We have funding mechanisms that address each of these stages in the pipeline of intervention development, starting with first in human early stage clinical trials of novel drugs and devices. We also have these experimental therapeutics phase, and I'll be explaining more about what that means for early stage testing of drugs and devices, as well as psychosocial interventions.

Then once we have a signal that a therapeutic might be promising, we can move on to this confirmatory efficacy phase where we ask whether this is really effective in treating the clinical syndrome. Then we have closer down to the services and implementation in funding mechanisms to support a pilot effectiveness of treatments, preventions, and services interventions. We fund clinical trials, testing the effectiveness of treatments,

preventions, and services intervention, so that's the pipeline. Now, one of the issues is sometimes the pipeline leaks, and what can we do to prevent that leaky pipeline, to increase the chances that when we start with a novel early stage drug, that we're going to get all the way through that pipeline with a success that will be meaningful at the clinical level?

Well, that's a major challenge. In fact, this is a photograph of the valley of death, the gap between an early stage drug and getting it into the clinic is vast, and that's a problem that not just the NIMH has experienced, but this is in part led to why pharmaceutical industry has stepped back in prior years from their investment in developing drugs for psychiatric disorders because this gap was so vast. Our approach to be able to learn from these failures is the experimental therapeutics paradigm to basically bridge the valley of death. Well, how do we do that? The experimental therapeutics paradigm is built upon three pillars. The first pillar is target engagement.

That means if we're developing a drug, we want to know what is the drug binding to in the brain and in the body, and does it really enter the brain, does it really reach that molecular target, and can we measure that so that we know the drug got to where it was supposed to go? Now, when the drug gets to where it's supposed to go, does it have the action that it's supposed to have on the mechanism? That's mechanism of action to be able to actually demonstrate in these studies that the drug did it what it was supposed to do in terms of brain circuitry or changes in physiology. Then the third pillar is proof of concept.

That means when the drug reaches its target and it engages the mechanism of action, that this actually improves something that's clinically meaningful to people living with mental illness. Each of these three pillars are critical such that when a study that goes through this platform fails to find a difference between the drug and the placebo, we will be able to rule out that's the wrong target, or that's the wrong mechanism, or that failed the proof of concept. Rolling out these failures is very important because with limited funds, we have to be strategic about where we invest. We don't want to invest in dead ends. Let's talk some about the rationale for the experimental therapeutics' paradigm, and how we are going about learning from failure.

The rationale is the data show that over 90% of new drugs fail at these early stages. They're all into that valley of death. Given that is the case and given limited funding, our strategy has been to fail them fast and fail them often, so that we can pivot away from dead ends and increase our chances to test more and more novel targets to increase the likelihood of finding something that will be clinically meaningful. The goal of the experimental therapeutics program is to develop a reliable set of early phase methods to evaluate new drugs designed to act on prioritized neurobiological targets. We look at the literature and look at what are the most substantial targets and leads and select those for further development.

Then we fail them fast, so we test the feasibility. Does it enter the brain? Does it engage to the target? Does it engage the mechanism? Because if it fails those, there's not a reason to further invest. Rather, we would want to pivot to more promising targets. We want to fail fast and also fail in a smart way, such that the results of the trial whether the drug works or not advance the science and helps us learn more about the science behind the pathophysiology of the disorder. Some of the necessary elements of clinical

trials that we invest in, that take this approach are that we have a molecular target that is implicated in the disease, or the research domain, criteria domain of function.

We'll be talking more about RDoC later in the talk, that we have a drug that is selective for that target and that that drug can enter the brain, and that drug is approvable by the FDA for an investigational new drug approval. All those three things have to be in place because we're doing clinical trials in human subjects. If those three things are not in place, we can't do a successful clinical trial. Then after we have those three things, we need to know that we've got a measure of that mechanism. Basically, what is the drug doing to brain function that we think is going to be therapeutic? We have to have that measure. That measure might be an imaging measure or a physiology measure as just a few examples.

Then we want to understand what's the effective dose. Some studies fail because they're underdosed. That means that at the early stages in order to learn from our failures, we have to do dose-finding studies to figure out what is the effective dose to get into the brain, to engage the target, to change the mechanism of action, and to have a clinically meaningful effect. Then that proof of concept, we might change the target, but if it doesn't change things that make people feel better to improve their symptoms, then that would not be a win. This is really about therapy, it's about treatment. It's about funding clinical trials that are going to be clinically meaningful for people living with mental illness.

This approach started before I came to the NIMH. I came in 2015, and this approach was already underway. They started with funding the first contracts with this, what they called the FAST contracts that started in 2012. Three FAST contracts were funded. One of them was on psychosis the and basically, what they looked at is identify targets of interest, and then look for available drugs that met those criteria on the prior slide. They really focused on studies that could inform dosing. It means studying the quantitative pharmacodynamics and having measures of that readout. In addition to the three FAST contracts, there are other funding mechanisms which I showed you on that pipeline slide. They're called the R61/33.

The numbers don't matter, but that was started in 2014, and these are investigator initiated clinical trials to test new drugs, early stage drugs. We do it in a phased approach, where there's milestones and if the drug fails to reach the milestone of engaging the target, then the grant is stopped because that is an informative failure. We can rule out that target and move on to other more productive targets, and the study designs include this pharmacodynamics aspect, so we can look at dosing. This is a list of some of the drugs that we have tested in clinical trials in these experimental therapeutics program. Many of these were drugs that were repurposed from one indication to see if they could work in another indication.

Now let's talk about what we've learned so far from using these experimental therapeutics approach. I told you that we funded three FAST contracts. One was in autism spectrum disorders, and that helped to identify a biomarker using electroencephalography, EEG and a proof of mechanism study on this novel target, which is the GABA a2/a3 selective positive modulator for which there's a drug that engages that target, and that was studied in adults with autism spectrum disorders. The second contract was called the FAST-MAS study that was on mood and anxiety

spectrum disorders, and that was a clinical trial that studied a new drug, the Kappa Opioid Receptor antagonist.

It was a phase II study that was looking at brain circuitry involved in the ability to respond to rewarding stimuli and anhedonia. By the way, that study met its milestone, and then the third contract was on the psychosis spectrum. That was the FAST-PS study, and that contract developed novel imaging biomarkers to assess a novel target, the mGLuR2/3, the glutamate receptor target engagement in the brain using a drug that was shown to be able to engage that target. In addition to those contracts, we also fund cooperative agreements which are called the view mechanisms. We're currently funding this new study. It's a multi-center clinical trial on a novel drug target in schizophrenia.

It's called a translational and neurocomputational evaluation of a D1R partial agonist for schizophrenia, or it's also called the transcend study. The rationale for this study was that prior work had shown that the dopamine D1/D5R agonist agents were able to improve cognition and also showed antipsychotic-like effects, but prior studies wound up in that valley of death that I showed you in the prior slide. They weren't able to show a dose response effect, and some of them were not positive. We were concerned that these failures, which were not informative failures, we didn't know why those studies were failing. We thought it might be because of the failure to use the appropriate biomarkers, or failure to account for heterogeneity.

This cooperative agreement that we're currently funding addresses those to see if maybe the parasites had thrown out the baby with the bathwater. Maybe this new drug could potentially be helpful in a meaningful way in schizophrenia if we did a smarter trial that used biomarkers and accounted for heterogeneity. We're currently funding the study which is a multi-center study to characterize dose-related effects of the D1/D5R receptor agonist. You see the name of the experimental drug there, and we're using functional magnetic resonance imaging biomarkers that are listed by certain neurocognitive tasks like spatial working memory.

In order to reduce heterogeneity, we're targeting a subpopulation of early course schizophrenia, people who are earlier in their phases of illness who are experiencing difficulties with cognition because we think that the mechanism of this drug is likely to improve the things that they're experiencing cognitively. This study is using the experimental therapeutics approach. It's got a milestone, a go no-go criterion, such that if it doesn't reach the target, we will have advanced the science because we'll be able to rule out that target definitively, and then we can pivot to more fruitful avenues. That's what we've done so far at a very high level with experimental therapeutics approach, but is it working?

We asked ourselves that. How successful has this approach been, and just like your workshop here, ask the expert, well we went to RS experts to ask them how are we doing? Is this the right approach? Our panel of experts are the National Advisory Mental Health Council that advises our institute director, and they formed a working group on drug development. This was convened last year, and we asked these experts to provide us guidance on how best to define and evaluate target engagement, how to address special populations to help us evaluate the value of those FAST fail contracts that I showed you, to ask whether we should be supporting more confirmatory efficacy trials

of new drugs, and how we can better develop the next generation of the neuroscience workforce.

They met most recently last month, and they are developing a written report which will be delivered to our full council soon, and will help to advise our institute director, Josh Gordon, about the success of this strategy. That's some about the strategy NIMH has been taking to make sure that our new drug development pipeline isn't leaking and to make sure that we can learn from failures. Now let's move on to heterogeneity. What is our strategy there? When we think about how we would get a handle on heterogeneity, well what do I mean by heterogeneity? In this cartoon, think about people who are meeting the same diagnostic DSM criteria, like a bunch of people with depression, a bunch of people with anxiety, or a bunch of people who meet criteria for schizophrenia.

There's a lot of heterogeneity within these groups that are defined by the DSM, and that's a major challenge to find a drug that would work for all of those people that meet that diagnosis, or even most of them. Our strategy has been to not just look at the symptoms but use data that can inform us about brain health and disease process. This data may be genetic data, physiology, behavior, imaging, electroencephalography, all of these different things that we can measure about brain function and cognitive function to give us more information about what might be similar, or help us parse this heterogeneity.

Then we could ask the data to resort the individuals into these data driven clusters, so that now the groupings where we might test new drugs are less heterogeneous, have more homogeny and might be more alike on the brain basis, which is where the drugs were acting in the first place. Then we could use those data-driven clusters to help inform treatment selection and also to stratify clinical trials in the development of new treatments. That first stage of the integrated data, that's where the research domain criteria or RDoC comes in. Well, what do I mean by RDoC? This is a trans-diagnostic research platform, where we take domains of function, things that we can objectively measure in the brain, like negative valence or positive valence or cognitive functions.

These are things that we can objectively measure across levels of analysis, from genes to molecules to circuits to behavior. We can study these in the context of environment, the environmental influences which is that green marble surrounding it. then we can study that as it changes across neurodevelopment. Think of this gray arrow as coming at you, right through the screen and that green marble is rolling down that arrow because as infants grow into children and adolescents and adults and older adults, we know that our brains are changing and that our experiences is changing. We want to do this in a way that's sensitive to different phases of development. That's the RDoC approach.

It's basically a way of collecting data on these trans-diagnostic features that can help us resort the patients, and this is objectively quantifiable domains of function that are measured across levels of analysis. Then from that, we can ask the data to resort into these clusters and do something that's called bio typing. It means basically, it's not a diagnosis, but it's a description at a brain basis of what we can measure what the brain is telling us about these individuals. When we think about this process, we have a lot of sources of data that can help us achieve that goal. Originally, it was just paper records and charts and symptom-based rating scales, but now, the electronic health record we

can access not just information about mental health, but about physical health that may be irrelevant.

We also have omics, genomics, metabolomics, proteomics. We have a full palette of imaging approaches, structural, functional imaging. We have neural oscillations. we have receptor imaging to look at neurochemistry in the living human brain. We have all these digital trackers, where I'm wearing one right now. You probably have one in your pocket and these digital trackers can give us information about activity, about movement, about social interaction. It can ask us how we're feeling at different times in the day, and we have advanced computational approaches where we can learn from speech patterns, from language using lateral language processing. We can measure and quantify facial expression the content of a voice.

All of these things can be subjected to artificial intelligence analysis. This is a big universe of data and finding this biotype signatures, it might be across multiple modalities. We are investing in each of these areas across the portfolio research that we support. Let's give some examples of this RDoC informed approach to getting a handle on heterogeneity. This study looked at heterogeneity in psychosis trans-diagnostically. This is called the bipolar schizophrenia network for intermediate phenotypes or the BSNIP study. It took people who had psychosis. It didn't matter whether you had schizophrenia diagnosis, or schizoaffective disorder diagnosis, or a psychotic bipolar disorder.

Regardless, everyone who had either of these conditions were invited to participate, and then data was collected on them. Not just symptom rating scales, but physiology, neurocognition, and then the patients were resorted through the prism of basically their brain health. This was a trans-diagnostic approach using statistical techniques to look for patterns, and the patterns that emerged were a natural grouping of the patients based on their biology, rather than their symptoms alone. They called them biotypes one, two, and three and they had specific differences in terms of their EEG, as well as neurocognitive measures. Now these biotypes could then be used to stratify samples for new drug development, to address novel targets for psychosis.

It could also be used to try to do precision psychiatry, figuring out which of these biotypes might be selectively responsive to drugs we already have. This BSNIP multi-center collaboration has had a series of high-impact publications, and I'm just showing you a few of these here. It's an example of how we might go about getting a handle on that heterogeneity in psychosis. Now let's go back to our third challenge, early onset. We want to be able to detect what's going on before psychosis starts. Now the strategy for early detection, in order to do that, you need really big sample science, and you need to follow people for a really long time.

You need to enroll them during this prodromal period before psychosis develops, and our strategy has been to invest in several very large longitudinal studies that seek to do this in the service of our search for biomarkers that would be prognostic and clinically useful, develop risk calculators so that we could give some information about what is the likelihood of developing psychosis and over what period of time at the very earliest stages possible. One of those longitudinal studies was called the NAPLS study which is the North American Prodrome Longitudinal Study. This was a multi-site consortium of prodromal research across North America, and the goal of this project was to develop

methods to better predict transition to full psychosis in order to optimize treatment delivery.

These are the aims of the project. We wanted to better understand the predictors and mechanisms for the development of psychosis. We wanted to identify youth at risk at the earliest possible stages and better understand why some young people at risk develop psychosis and others don't. We wanted to have a deliverable that would be clinically useful. That's the individualized risk calculator. Basically, you go to the cardiologist and he or she plugs in your cholesterol and your lipids and your blood pressure and your age and your sex, and you get a calculation of your risk for getting heart disease. We wanted something like that for brain health too. An individualized risk calculator for psychosis that would be able to use clinical and demographic and neurocognitive data.

Then we wanted to understand will biomarkers help improve the precision of risk calculation, so biomarkers like hormonal levels, electrophysiological measures, anatomical abnormalities, and to understand when these develop during the course of illness, do they remain stable over time, do they improve with the treatment to really get deeper into what's going on at a mechanistic level. These were the sites across North America, and I'm showing you the names of the principal investigators and the universities that they represented, but it's really a cast of stars, just fantastic experts in the field of the program for schizophrenia and schizophrenia research.

This group has been highly productive, and we've funded them since 2006 in three different stages. The first stage NAPLS1 had almost 300 people with the clinical high-risk syndrome enrolled and followed up for two and a half years. NAPLS2, which was the next period of funding had almost 600 people with clinical high-risk participate, also followed up for two years. We added in these biomarkers, neurocognitive measures, hormonal levels, the omics, genomics, proteomics, physiology, and imaging. Then the third phase got even a larger sample size, over 750 individuals with clinical high risk enrolled in this and we were able to bring in new samples to validate and new populations, the risk prediction models and to determine these pre-onset trajectories.

One of the biomarkers that emerged was in the brain, the gray matter volume declined over time, and this in addition to other functional measures like functional brain connectivity which changed in people with high risk who later developed psychosis, these were real important leads about what might be going on in the brain that is associated with this transition to psychosis. It also identified some novel inflammatory measures and plasticity measures associated with the transition. Now the NAPLS group has been very productive in terms of contributing to the literature. These are just some of the really high impact papers, including the individualized risk calculator that have come out from this group.

Now that's North America. Wouldn't it be great if we could go global? That's what HARMONY was about. This was about harmonization of at-risk multi-site observational networks for youth. This first stage of HARMONY was a US European collaboration, and it took NAPLS, but then joined it with other initiatives like the PRONIA initiative and the PSYSCAN initiative. I'm showing you the principal investigators here, as well as the Philadelphia neurodevelopmental cohort or the PNC, and basically brought these

groups together to ask can we collaborate? Can we coordinate what we're measuring so that we achieve those sample sizes that we need to get a handle on heterogeneity?

This group was highly productive in harmonizing their protocols where their clinical measures, their cognitive measures, physiology, and all their other biomarkers. They paid attention to how to calibrate, how to do quality assurance across these measures, across countries, and across languages even. They did rigorous testing to look at replicability of their measures and your algorithms, and this provided a platform for pooling data across these sites. This table shows the number of individuals that participated in each of these different cohorts that were confined into the HARMONY study. Here, you need to see the number of sites where people were recruited from.

It was really an all hands-on deck effort, and some of the deliverables from this were the individualized risk calculator being validated in independent samples. The risk calculator is shown on the right part of your slide here, and you put in the age. You put in measures on some clinical evaluations and your cognitive tests, and then it gives you a risk measure. A measure of sensitivity and reliability of this is called the area under the curve or the AUC, and the overall AUC was significant at 0.72. This was replicated and validated in independent samples shown here, and you can see now it's just not just European collaboration with North America, but also China. There's ongoing validation underway.

Now one of the exciting things, new developments in this risk calculator is there's something called the biomarker qualification program at the FDA, and the way that program works is if you have a biomarker or a risk calculator like this one, that has some validity, you can submit that to the FDA to qualify it as a biomarker. Well, why would that be important? Of course, the FDA is critical for approving new drugs and if you want to use this risk calculator to identify individuals in whom that drug might work, or identify individuals that would be enrolled in studies to test the drug, the FDA qualification means that they are in agreement that this risk calculator meets their criteria for something they might accept as evidence.

We're really excited to say that the FDA accepted the letter of intent from the NAPLS group for the risk calculator. They were one of the first biomarker qualification letters of intent accepted in all of psychiatry, and it was about predicting schizophrenia. We're really excited about that development. Now the risk calculator to date primarily uses clinical measures and neurocognitive measures, but we're now looking at whether biological essays, whether it's genetics or other forms of imaging could help refine the risk calculator, and this is work underway.

Some of the advantages of bringing in biological measures is it could help to standardize how we collect these measures, help to point towards novel treatment targets, and some of these biological markers might be useful as endpoints, novel endpoints for clinical trials on testing new drugs and devices. Now let's bring it all together, let's talk about addressing heterogeneity in the clinical high-risk state, and talk about some really exciting new collaborations in this area. The accelerating medicine partnership for schizophrenia or AMP schizophrenia is a brand-new public-private partnership managed by the foundation for NIMH. It was just announced a few weeks ago, so this is hot off the presses.

This partnership addresses the urgent need for early therapeutic intervention for a person's at risk for schizophrenia, and the partners have a shared mission of discovering these promising biomarkers to identify individuals who are at risk for schizophrenia at the earliest possible stage, and biomarkers that help us track progression and identify novel targets for intervention. FDA is involved in this consortium from the beginning and they are providing really important regulatory guidance on the biomarkers of disease progression, outcome measures and endpoints because ultimately, this partnership is going to move towards supporting drug trials of new drugs to be used early before schizophrenia develops during this clinical high-risk state.

We wanted FDA involvement right at the earliest stages because we want to be sure that the types of biomarkers that we're collecting and the types of trial designs that we're conceptualizing will provide the level of evidence that FDA needs, such that that drug will get all the way to the end of the pipeline towards an FDA approval and be available to people who desperately need it now. Now, the AMP partnership has been around for quite some time accelerating medicine partnerships in other areas of medicine, but this one on schizophrenia is the first in the field of psychiatry. We are so excited that schizophrenia was chosen to be the first for this type of partnership. Well, who are the partners? Spoiler alert, NAMI is one of the partners, but here you see the other partners.

The American Psychiatric Association Foundation. There are a number of pharmaceutical industry partners, Boehringer Ingelheim, Janssen, Otsuka. We also have the Wellcome Trust and other advocacy groups like One Mind. Each of the partners has a vote on the steering committee, and we're really delighted that NAMI has a vote on the steering committee for the overall project. We're especially excited to learn that the NAMI representative is a person with lived experience because we really want to know that we're on track, that this investment is going to make a difference and address things that people care about most. Let's talk about funding.

The AMP schizophrenia program budget is $99 million over a 5-year period, and we believe it is going to cost that much. This is a major investment that number reflects our appreciation that we need a large sample, we need longitudinal sample, it needs to be a global sample, it needs to have all the biomarkers, it needs to be rigorous, and that will take a substantial investment. Well, how does that investment break down? The partners are investing 16 and a half million, and this is being managed through the foundation for NIMH, which is a non-profit organization that manages the project.

The NIMH is we expect to contribute 82 and a half million dollars over the five years, pending availability of funding and having a budget, but this number reflects our investment in being sure that we are doing the steps we need to be able to develop new drugs for the treatment of people at risk for schizophrenia. We're really excited to have announced this recently. Well, what are we going to use the money for? These funds will support an international research network focused on clinical high-risk populations to ensure that the research results are applicable to global clinical trials, and to extend the reach and impact of the project. I'm going to give you more detail about exactly what is the network.

The AMP Schizophrenia International Research Network aims to generate these tools, and I've been hinting about them all throughout the talk, the biomarkers to aid the development of early stage interventions for individuals at clinical high risk for developing schizophrenia. The research network will be focused on individuals with CHR to identify biomarkers, clinical endpoints, and other measures that can predict disease trajectory and outcomes. The hub of the network will be a data processing analysis and coordination center that will allow the researchers to pool their data, integrate the data. You can see, this is sounding really standing on the shoulders of the NAPLS project and the HARMONY project.

Now we're going global with this massive effort to pull the data, so that we can get those sample sizes to find the signals. The exciting thing is ultimately all the data and the analyses will be made available to the public through the NIMH data archive. We plan to recruit more than a thousand persons with clinical high risk and to follow the longitudinally over years. Let's talk some about the network. The clinical high risk for psychosis research network and the hub, that's the data processing center. This was designed basically we announced two funding opportunities, which are shown down here. These are RFAs, or a research funding announcement that we put out to solicit applications to create networks and to create this data center.

The rationale was really to be able to address this challenge of heterogeneity that I already introduced you to and to be able to define a core set of measures and functional outcomes in psychosis. We're interested not just in psychosis, but of other outcomes that people with clinical high risk for psychosis experience, like mood disorders, cognitive effects, negative symptoms, and functional outcomes. All of this is on the table and is being examined. We want to use these biomarkers to be able to prospectively stratify people with clinical high risk into more homogeneous groups, that's back to that bio typing from the brain level so that we can predict their likelihood of clinical outcomes.

That's important to be able to launch informative drug trials, the treatment trials that will be layered onto this network. Well, we thought this was feasible because already, there are over 30 clinics in the United States that study or treat people with the clinical high risk. We're so fortunate that so many of them applied for this funding opportunity. We were able to select some high-quality researchers to engage in this effort that is basically, this is the NIMH part of the AMP schizophrenia program.

The goals of the parts that the NIMH is funding is to establish this multi-site network that will recruit large numbers of people with CHR, that everyone that will receive this common set of biomarkers and clinical outcome assessments, and our deliverable, the take home is going to be a validated set of tools including the biomarkers, algorithms, and outcome measures that will help us to select help seeking individuals for enrollment in the future clinical trials, to address a variety of outcomes. Also, these biomarkers may serve as potential readouts for early treatment effect, and they may be useful in monitoring disease progression and functional outcomes.

We went back to our panel of experts, the National Advisory Mental Health Council, and we convened a subgroup of them to advise us about this clinical high risk for psychosis initiative. They brought in additional stakeholders, key public and private stakeholders with interest and expertise in early intervention schizophrenia, to advise us about how to

go about quantifying these biomarkers, how to do this trial, how to mitigate risk because we knew this would be a big investment. We charged them with helping us review the grants that were submitted to these two funding announcements. They helped us the results of the peer review, which is the summary statements and they gave us guidance on the funding decision.

They gave us that guidance in August, and here are the results. These are the grants that we've funded. These awards have been made. The first two bullet points are of the two networks that will recruit patients. The first one is, and I'm showing you the names of the principal investigators and the universities that they represent. The Nelson application from the University of Melbourne, the Woods application, Bearden and Kane from Yale, and the Shenton and Khan application from Brigham and Women's. This is an outstanding team and we're so excited that they are already working together to bring this dream alive. Now I want to talk about the important role that NAMI played in bringing and schizophrenia alive.

Years ago, NAMI convened a series of forums along with Broad Institute and brought in other thought leaders dating back to 2016. Through the actions of NAMI, this helped to stimulate interest. They've convened the scientists, the NIMH representatives, the stakeholders from the pharmaceutical industry to see if we could re-ignite and reenergize drug development for schizophrenia, and to do it in a smart way that would be productive and clinically meaningful. NAMI really provided ongoing leadership throughout this process by convening several meetings, keeping that momentum going, and it was at one of those NAMI convened meetings that the AMP schizophrenia concept was presented, and we got further input.

Of course, now you know what the rest of the story was with that $99 million investment. This is not surprising given NAMI's long history of research advocacy and as I said earlier, we're really proud that NAMI has a voting member on the steering committee and will be an active partner every step of the way through this process.

To conclude, I've talked about some of the strategies that NIMH has taken to address the challenges in treatment development for schizophrenia, including the experimental therapeutic approach so that we can learn from our failures, the use of biomarkers so that we can parse heterogeneity, the development of risk calculators to detect and predict risk for psychosis before it starts, the role of large-scale consortia to enable adequate sample sizes, the density of measurement, and long-term follow-up so that's the AMP schizophrenia program. I'd like to conclude by saying partnerships with key stakeholders, especially NAMI are really key to success.

I want to thank you again for the opportunity to join you for this Ask the Expert session. This is the mission and vision of the NIMH, and I hope I've left enough time for the Q and A. Let me hand it back over to Dr. Duckworth.

Ken Duckworth (00:49:31):

Thank you Dr. Lisanby. We have some great questions, and one of the things we are interested in is giving people as much science as possible and that was a lot of science. There are many good questions. I'm going to organize some of the questions about categories. We have these genome-wide analytics studies and of course, the paper out of the Broad Institute indicated a little over 100 possible gene equivalent sites that could

be markers for schizophrenia. Several questions relate to are you thinking about genomics as you advance the accelerated medication partnership?

Holly Lisanby (00:50:18):

Thank you for that question, and you're absolutely right. There's been some exciting progress in identifying signatures that might be telling us something about the genetic basis of schizophrenia and absolutely, genomics will be a key part of the AMP schizophrenia program. All those omics that we were talking about, we certainly will want to follow up on those leads and see if we can validate it in larger sample sizes and see if it's meaningful at that clinical high-risk stage. Absolutely, that is part of it. We think that that's not the full story though because it's not just the genes. It's well, what does it mean? If I've got this gene, does that mean I'm necessarily going to have some effect?

There are other things that modulate the effect of genomics. We want to look at the genomics in the context of the whole person, in the context of... Yeah, go ahead.

Ken Duckworth (00:51:12):

There is no gene for schizophrenia, but I think you're describing a pattern recognition process which could inform risk. Do I have that correctly?

Holly Lisanby (00:51:23):

Absolutely, yes.

Ken Duckworth (00:51:24):

Good. Three questions that relate to becoming a research subject for this. How do I volunteer? How do I engage? What is the process for participation in a metric this important?

Holly Lisanby (00:51:38):

Well, that is such a great question, and we are just at the early stages. We will be building out a public-facing website for this program, for the AMP schizophrenia program. Once we have the protocol finalized and are ready to be accepting participants, there will be all the information about the study, not only on the public facing website, but also on clinicaltrials.gov. Clinicaltrials.gov is a great place to go to search for all of the available research studies. You can search on keyword like schizophrenia. You could search by the funding agency like NIMH. When the AMP schizophrenia program is ready to start accepting volunteers, we will be live on clinicaltrials.gov. Those would be two great resources.

Ken Duckworth (00:52:27):

Thank you. Several questions about diagnosis. Now, we currently live with the APA's DSM-5. The RDoC is an effort to go the root of science, and to see if there's different patterns that emerge. Do I have it right?

Holly Lisanby (00:52:45):

Well, the RDoC approach is meant to serve science and basically be a research platform. It's not a diagnostic category- but rather, it's to help us get a handle on the heterogeneity within the diagnoses and to do that through the scientific method.

Ken Duckworth (00:53:07):

Thank you. The questions relate to the DSM-5 framework and the question is, in these projects, are you going to be including people with schizoaffective disorder, bipolar disorder? Is that part of psychosis spectrum? How do you think about the diagnostic framework as it relates to this clinical high-risk population?

Holly Lisanby (00:53:34):

Yeah. Well, thank you for that question. We have a number of studies that are already underway that use RDoC approaches to select participants. I showed you one example which was the BSNIP study. The BSNIP study took people with psychosis. Didn't matter if you had schizophrenia diagnosis, schizoaffective disorder diagnosis or bipolar disorder, didn't matter. If you had psychosis based on those measures, you were eligible for the trial, and that was an example of that RDoC informed recruitment. Now in the case of the AMP schizophrenia program, we're looking earlier in the stage before psychosis has developed. You might ask, "Well, what's your crystal ball? How are you going to know that someone is at risk for psychosis?"

There are some measures. Actually, there's a part of the DSM-5 that has research basically putative disorders where more research is needed, and you'll find there this thing called attenuated psychosis syndrome, and that has some terminology that's similar to the clinical high risk. For the AMP schizophrenia trial, we're going to be using assessments that look at before you have psychosis, but look at some of these clinical indicators, identifying a group of people who may be at risk for psychosis. It's not a DSM diagnosis. We're really trying to go before it gets to that stage.

Ken Duckworth (00:55:13):

Here's a question that's more symptomatic and is one or two steps removed from this important research. This is a question about progress on cognition and negative symptoms, and I'll just say these have been some of the big challenges that we faced in the field. The medications seemed to be reasonably good for positive symptoms, but both negative symptoms and cognition do represent new challenges that we haven't yet gotten to. How do you think about those important areas as it relates to drug discovery and this work?

Holly Lisanby (00:55:51):

Yeah, thank you for that, and focusing on the negative symptoms and the cognitive function is so important in terms of functional outcomes. Some research suggests that they might actually be the leading drivers of what influences how well a person functions in life. It may not just be all about the positive symptoms, but rather the negative symptoms, the ability to have initiative, to have motivation, to be able to organize and

work towards goals. These are things that really matter to people to be able to navigate life and family and work and education and so on. The RDoC approach really helps us here. If you remember one of those domains of function in RDoC was cognition, and we can break cognition down into it core elements that we can measure.

We have a number of studies that are targeting cognition. In fact, I showed you one of them that's targeting cognition in schizophrenia, and that's the transcend study, that's looking at this a novel drug, this D1/D5 agent that preliminary research suggests might have pro-cognitive effects in people with schizophrenia. That's one example and with...

Ken Duckworth (00:57:04):

When you say D, you mean dopamine, right?

Holly Lisanby (00:57:07):

Thank you, dopamine receptor and then the numbers are the subtypes of the dopamine receptor, yes. Dopamine receptors, we've known a lot about dopamine receptors of course, but this novel drug approach, it looks at this combination of two specific types of receptors which in combination seem to have this pro-cognitive effect. I think that Clozaril or clozapine is one of the few drugs that we currently have that has shown some signal in helping with negative symptoms and cognition, but we need more. We need more effective drugs. We need drugs that are safer, that are really able to help with these cognitive symptoms.

Ken Duckworth (00:57:49):

Yeah, thank you, and I've been impressed that cognition is really one of the keys to recovery-

Holly Lisanby (00:57:54):

Absolutely.

Ken Duckworth (00:57:55):

... in terms of both work life, school life, and social life. I'm delighted to hear that that's part of the thinking here. A couple questions about you mentioned a few terms biomarkers, biotypes. How are you thinking about that different than the diagnostic framework? They clearly can't be used interchangeably, but how do you think about them?

Holly Lisanby (00:58:20):

Okay.

Ken Duckworth (00:58:20):

Several questions on this.

Holly Lisanby (00:58:22):

Okay, so let me use an analogy in medicine. Let's say you have diabetes. Diabetes is a diagnosis and you go to your doctor, and he or she draws a blood test to test your blood glucose. Blood glucose is a biomarker. Blood glucose can identify people who are having trouble regulating their glucose, who may have diabetes. It's also a marker of how effective the treatment for diabetes is. If your glucose is too high or too low, then that can adjust your treatment. Think of a biomarker like blood glucose, but in this case, we're trying to find biomarkers not for diabetes or hypertension, but for psychiatric conditions like schizophrenia. What might that biomarker be? Well, some of the biomarkers I showed you use brain measures.

It's not a blood test per se, but a measure of brain function. One I showed you was electroencephalography or EEG so brain waves. There were particular brain wave signatures that were part of that biomarker that identified people with psychosis that were more like each other, and this biomarker for psychosis didn't care what your DSM diagnosis was. It was detecting something about brain function. That's what I mean by biomarkers, something that you would walk into your doctor's office, and he or she could measure, maybe multiple things that he or she could measure. Then they could tell you, "Well, look we think you might have this condition, and this is going to advise us what treatment to give you."

We are so far away from achieving that goal compared to let's say where diabetes treatment is or hypertension. Biomarker and hypertension, you go in and you get your blood pressure taken.

Ken Duckworth (01:00:19):

Right. It's right there.

Holly Lisanby (01:00:21):

Right. You take your blood pressure, I've got hypertension, so that's a biomarker. You know when you've got hypertension, you're at risk for heart disease and stroke. We want something analogous to that. We want like a blood pressure, but for the clinical high-risk syndrome, so that someone could come in and we get assessment, something that we measure. Might be a blood test, might be a brain measurement, might be a neurocognitive task, and we measure.

We plug it into a risk calculator, and then your doctor is able to tell you well, or tell your family member that you've got X percentage risk of developing psychosis and based on that knowledge, here's what we're going to do, this is how we're going to treat you, this is what we're going to look out for, and basically be able to prevent those long-term adverse outcomes, as well as to improve your functioning where you are at the day you walk in. Biomarker think of it as like a lab test. We're used to that in the rest of medicine, but in psychiatry and for schizophrenia, we need these lab tests, so that they can really give precise treatment.

Ken Duckworth (01:01:22):

It's a great analogy too because type one or juvenile onset diabetes completely different underlying pathology than adult onset or type two diabetes, but yet both would show an increase in sugar. The biomarker as you said is agnostic as to the underlying cause, but you need to know that there is a problem.

Holly Lisanby (01:01:44):

Right, that's right and that's a good analogy like type one or type two diabetes. I was showing you biotype one, biotype two, biotype three for psychosis. That's an analogous thing. We're just not yet less used to thinking about this bio typing process for psychiatric disorders.

Ken Duckworth (01:02:04):

A couple questions about the clinical high-risk studies. What's the age range and what kind of symptoms would you be displaying if you were a candidate for participation?

Holly Lisanby (01:02:17):

The finalized protocol is not yet finalized because we are going to be bringing the partners together to make those key decisions. I can't tell you the exact age range yet, but I can tell you that it will likely include adolescents because we know that the early warning signs start early in life. Also, the NAPLS study, the HARMONY study, other studies I showed you, they did take people even as young as 13 and older. It's a young adult phase. The early phases of when people begin to start to manifest these signs. I expect it will include adolescents and young adults, but the actual age range is not yet finalized. Now in terms of the clinical high risk, what people experience or also in the attenuated psychosis syndrome.

It's not frank psychosis, but there are a number of scales that have been developed, that have been used and developed through these prior studies that help to identify some of the things that lead people to seek treatment before they get to the psychotic symptoms. You may be experiencing things that make you anxious. You may be experiencing having unusual sensations. You may be feeling uncomfortable in certain situations, and their rating scales that have been validated to detect some of these signs. Now not everyone that's showing signs of clinical high risk is going to develop psychosis. Sometimes, these are the beginning stages of someone who's going to have depression, or someone who might have bipolar disorder and are just beginning to manifest some of these things.

Ken Duckworth (01:04:11):

Now at NAMI, we know that medications are only one tool in promoting recovery. This question relates to what about non-drug treatments, and what are we going to learn from AMP as it relates to non-medication?

Holly Lisanby (01:04:25):

Yeah, that's a very great question. The AMP schizophrenia program like the other AMP programs is targeted towards developing tools that will facilitate drug development. Now that being said, the data that's being generated in these large samples over time with all these biomarkers that will be publicly available, that data to my mind will be useful in informing the development of other treatments. Now how might that work? Let's take for example, if playing to my strong suit here brain stimulation, so let's say we have brain imaging data, and we will have brain imaging data from this study. The brain imaging data may give us targets for neurocircuitry that might respond to drug or might respond to a brain stimulation device.

We're looking for treatment targets, whether they might be engaged with a drug or a device or a psychosocial intervention. I think that the discovery phase of therapeutic targets will be useful down the road, not just for drug development, but also for the development of other modalities. Yes, I agree with you, the portfolio of research that NIMH supports, we invest heavily in psychosocial interventions, in developing comprehensive care models, and providing stage, treatments, basically wrap around services. I mean we know that it's not just all about medications, but it's also about these other approaches that are so vitally important.

Ken Duckworth (01:06:06):

We've had Ask the Experts on DBT for self-regulation and cognitive enhancement therapy in terms of the non-medication effects. I do also want to mention just in terms of the non-medication concepts for early psychosis, NAMI was very engaged with the promotion and the federal block grant for close to 300 early psychosis programs across America. They actually don't lean on medication. They involve the family, teach individual self-management, a lot of psychosocial support, a lot of recovery-oriented support, and that's available on our website or on the Stanford PEPNEP site where these programs are, which I think is just a really important thing.

While we're talking about stages of illness Dr. Lisanby, and you're doing great in terms of fielding questions from that cover the entire spectrum of this fascinating area, let's talk a little bit about people who are older, or have been ill for a longer period of time. How do you think the AMP project will teach us about the biology that might inform the care of people who've been living with these symptoms for decades?

Holly Lisanby (01:07:17):

Well, thank you for asking that. As you could see like with the NAPLS study, where we funded multiple waves and we kept following people longer and longer over time, it's my hope that AMP schizophrenia is just to start, that we may be able to extend the follow-up so that we could learn more to address that question about what happens over time, but we're just at the beginning, right? The funding that we have is just for the first five years.

That's what we're going to be able to do right now, but ultimately, if we were able to extend and to understand I think that how this would be helpful if looking at the early stages, if we could understand at a scientific level what's happening in the brain and

how it changes over time, and what are the trajectories and then project that out, it could help us better interpret the information we have about people that have lived with the illness for longer periods of time. It might provide insights into what might be better treatment targets for people with established schizophrenia, who've gone through unsuccessful treatments and are looking for a new hope, but I think that's a really important point, that the data which will be publicly available, that can be mined for all sorts of purposes.

Ken Duckworth (01:08:46):

Promoting scientific inquiry because it's all going to be publicly available. One of the remarkable things about the AMP project is this is all pre-competitive science. No one can take what's learned and run off and develop a product. Is that correct?

Holly Lisanby (01:09:02):

That's correct, and that's really what makes this a remarkable collaboration because typically, if you're a drug company and you need to have the competitive aspect basically, you want to get to the market before your competitors which means not sharing the data, and what would motivate a group of pharmaceutical companies to say, "Well, actually we want to share the data." What would motivate them would be if they couldn't succeed on their own, and that's what also motivates us to have these partnerships. We are more likely to succeed together, and the pre-competitive phase is to find these biomarkers. Then once we have established that reliable set and are able to predict risk, then we can start looking at well, what drugs do the companies want to be contesting, and that would be the next phase.

This is in an enabling study, and it is truly groundbreaking. As I said, it's the first AMP program in the field of psychiatry as a whole. It's the first time this has been done.

Ken Duckworth (01:10:16):

This is a total collaboration by multiple parties and if you go back to that slide, it is involving multiple parties. The whole idea is that the goal is advancing science, not the development of competitive product, right?

Holly Lisanby (01:10:33):

That's right. I don't know if you were thinking about the slide that showed the part...

Ken Duckworth (01:10:37):

Yeah, I was thinking about this slide. Obviously, I saw NAMI first and foremost, but obviously, there are companies, right? I mean you think about is there are multiple people approaching this from multiple perspectives including companies that know how to translate medications, ideas into products, but also this is going to be involving scientists and researchers, neuro imaging people, geneticists, of course NAMI and One Mind and the Wellcome Trust, and the American Psychiatric Association. We're covering a lot of territory here.

Holly Lisanby (01:11:16):

Yeah, that's right and I have to say that this is so helpful to us at NIMH because in order to achieve one of our strategic goals of delivering on the promise of treatments, preventions, and cures, we can't do that without the companies that will produce those products, that will be clinically available after FDA approval. Having FDA be a part of this, the pharmaceutical companies, we could not succeed in our mission if we did not have these partnerships because we really want to deliver on the availability of new treatments that go through that pipeline, don't fall into the valley of the death, actually get FDA approved, and you can go to your doctor, get a measure, your bio typing, a biomarker, and get the prescription of the treatment that is actually going to help you in a meaningful way.

Ken Duckworth (01:12:08):

Mm-hmm (affirmative). Yeah, people are asking about the website that I mentioned. Those are specifically the 300, first episode of psychosis programs which have a coordinated, non-medication, driven framework, right? Those programs are available on the NAMI website and Stanford's PEPNEP, P-E-P-N-EP. I know these slides are going to be available afterwards. I wonder if we can include those links to those resources because these programs are approaching early psychosis differently, very family oriented, very strength space, very recovery oriented. There's evidence that it's very effective for people in the early stages. The AMP project actually works a little more upstream than coordinated specialty care for FEP. Is that correct?

Holly Lisanby (01:13:09):

That's right. Yes, we're looking at before psychosis has developed at these early stages, but longer term, we do want to see this as part of something that would be nested into programs that would provide the spectrum of care. To be able to have coordinated specialty care services for individuals at whatever part of their illness course they are encounter for treatment.

Ken Duckworth (01:13:38):

Coordinated specialty care is available in 49 of 50 states. If you know somebody with early psychosis, coordinated specialty care is the type of comprehensive approach for FEP, so-called first episode psychosis. Again, it's early in the course of illness through a public health lens, but it is not clinical high risk. It's when a person has actually developed the symptoms. Dr. Lisanby, you've just been an incredible resource. It's humbling to hang around with somebody who can answer every question under the sun. I'm not going to transition just for a few more questions on your absolute wheelhouse to talk about brain stimulation.

This is a commercial break for you because you're the national expert on brain stimulation. Let's talk a little bit about where NIMH is going as it relates to repetitive transcranial magnetic stimulation, both for depression and for other conditions.

Holly Lisanby (01:14:40):

Great, thank you. Transcription magnetic stimulation or TMS is now FDO cleared for the treatment of depression for obsessive-compulsive disorder for smoking cessation, and it's being studied in a range of other conditions. Now what is NIMH doing? The approval of TMS for depression actually followed... First, there was an industry sponsored trial which did not meet its primary endpoint, and then an NIMH sponsored a trial on TMS for depression. Actually, it was before I came to NIMH, I was one of the principal investigators on that. It was called the OPT-TMS study, and that trial was successful.

When the data were pooled between the industry trial and the NIMH sponsored trial, it was adequate evidence to get the FDA approval and label expansion for treatment and depression. Now when I got to NIMH, one of the things that I did is I looked at our research portfolio and thought there's a potential to expand here. I created a program on neuromodulation and neurostimulation. I recruited David McMullen to run that program, and he has rapidly grown that into a large funding portfolio, not just with TMS, but also a variety of novel brain stimulation approaches for different therapeutic indications.

Now one thing about depression and this comes back to bio typing, so even though TMS is FDA approved for depression, it doesn't work for everybody. There's heterogeneity within depression. NIMH funded research was able to identify some biotypes. Brain circuitry that identified one biotype that was more likely to respond to TMS than the others. We're currently funding a trial to ask, would it work if you go to your doctor and get this brain scan, and then based on the brain scan, they put you into one group or another in terms of the type of TMS you get, whether it would be a way of personalizing your care based on your biotype. That study is currently underway, and we're also looking at ways to make brain stimulation more precise and more personalized.

We have supported a significant amount of research on electroconvulsive therapy or ECT in a variety of conditions, including schizophrenia when medications are not effective and illness is severe, also depression and specifically geriatric depression. On the topic of brain stimulation and just cut me off when I've gone too far, but we are-

Ken Duckworth (01:17:17):

You're doing great, you're doing great.

Holly Lisanby (01:17:18):

... one of the exciting developments is the BRAIN Initiative. You may have heard about the White House BRAIN initiative. NIMH is part of the BRAIN Initiative. The BRAIN Initiative is a huge assessment of funding to basically develop the next generation of the way we do neuroscience research, next generation tools. Basically, it's like a moon shot. It's saying need to do better, let's get the best science, let's do nano science, let's do implanted devices that can do things that could never be done before. Scanning's not good enough, let's make it better, let's have mobile scanners, let's do things that people might think of as science fiction, but the science is advancing so much.

Brain stimulation is benefiting from this. The BRAIN initiative is funding a series of studies that are working on next generation brain stimulation for psychiatric conditions.

The ones that we're funding so far, there's one on depression. We have one on OCD, obsessive compulsive disorder, we have one on post-traumatic stress disorder, and we have one on out-of-control eating. That's just the start. We hope to see more in terms of ways that we can translate our knowledge of circuitry into the next generation of brain stimulation treatments, where you can actually record from one part of the brain and have it trigger stimulation of another part of the brain, and really get sophisticated about the way we use this scientific knowledge to be able to restore healthy brain function for individuals.

Ken Duckworth (01:18:51):

Well, Dr. Lisanby it's always humbling to talk to the National Institute of Mental Health and to have our public and membership directly be able to ask you questions. You fielded dozens of difficult and interesting scientific questions. It's just such a privilege to be here at NAMI and be connected to the National Institute of Mental Health. I just want to thank you for your extraordinary dedication to our shared mission and for donating your time to us today. We'd love to have you back in the future as these research projects develop. We're going to want to know how they're going and what you're learning. Thank you and I'm going to turn it over to our CEO, Dan Gillison.

Dan Gillison (01:19:37):

Thank you, Dr., Duckworth, and thank you again Dr. Lisanby as you've walked us through quite a bit here. As you mentioned, the stimulating, the interest, and then keeping the momentum going, we're very excited for that and then to get to this point. As you looked at the partnership and you talked about the collaboration and the speed of the development, it's very critical that we have this threaded together. We're very excited about it and thank you for investing your time and sharing your time with us on today. These ask the experts are for you our audience, and we hope that you really did get good information in this session.

Please share with others about ask the experts as we bring them to you, to share important information and trends, best practices and models that are being used to make a difference in the lives of individuals living with serious mental illness and their families. This session is for you. I want to thank the production team Dr. Teri Brister, our national director of research and quality assurance, Elizabeth Stafford, and Elyse Hunt and last, but not least want to welcome two new members of the NAMI team, [Christina Bott and Jessica Waffle 01:20:48]. We all are looking to make a difference in the lives of individuals living with illness and their families.

A lot of time the work by staff is behind the scenes, but the critical part is that we're all in it together and no one is alone, and we want to make sure that everyone understands that. This is mental illness awareness week, and there's quite a bit that NAMI is doing during this time. We would love for you to go to our website and look at our body of work, and what we're doing, and also look at our partners at the National Institute of Mental Health. With that said, thank you again. We hope you have a great close to your week and an outstanding weekend, and again share, ask the experts with your peers and colleagues. We look forward to seeing you and hearing you in our next Ask the Expert.

Ken Duckworth (01:21:45):

Dan, may I add one more thing? I'm sorry to interrupt you. In November, our expert is Dr. Eden Evans. November is smoking quit month, and the problem of smoking contributes greatly to people's morbidity and mortality and premature illness and death for people with serious mental illness. We have Dr. Eden Evans from Harvard who will be discussing the latest research and practical strategies for quitting smoking. Back to you Dan, sorry.

Dan Gillison (01:22:17):

No, that's quite all right, and we look forward to seeing as many of you as can participate in that, and we'll have a couple of other very interesting sessions coming to you on after November 5th. Thank you to all of you all.