

NAMI Ask the Expert:
Precision Medicine Research: Hope for the Future
Featuring Dr. Jordan Smoller
June 15, 2023

Katie Harris ([00:00:00](#)):

With that, thank you again for joining and I'll hand it over to NAMI's Chief Medical Officer, Dr. Ken Duckworth.

Dr. Ken Duckworth ([00:00:08](#)):

Hello everybody and thanks for joining. My name's Ken Duckworth. It's my good fortune to be NAMI's Chief Medical Officer. The Ask the Expert sessions are designed to create as much information and access to some of the best thinkers in America and around the world, actually, to you. Today, we're very fortunate to have Dr. Jordan Smoller. But before I tell you about Dr. Smoller, I just want to remind you NAMI has a helpline. If you're having any distress, it's not a suicide lifeline. That of course is 988, but we do have 150 volunteers that take over 75,000 calls, chats, and texts every year, and they're available to you to help you problem solve for you or your family. The helpline is one of the gems of the National Alliance on Mental Illness and can be reached Mondays through Fridays 10:00 AM to 10:00 PM. We're working on growing the hours.

([00:01:12](#)):

All right, so let's go to the next slide please. Dr. Jordan Smoller is the Director of the Center for Precision Psychiatry at Mass General Hospital and a Professor of Psychiatry at Harvard Medical School. He's crafted a very unusual and creative career integrating genetics, neuroscience, and the quest for precision psychiatry, meaning taking the guesswork out of our treatment choices and integrating more science into what kinds of treatments will help different people. Dr. Smoller, I want to thank you for joining us today and you'll hear from me at the end, but I'll be asking Dr. Smoller your questions when he finishes his presentation. Thanks everybody, and thanks, Dr. Smoller.

Dr. Jordan Smoller ([00:01:55](#)):

Thank you so much, Ken. Thanks for the introduction. Thanks so much for having me today and letting me talk with you all. I'm, first of all, such a huge admirer and I guess you could say fan of NAMI and the work that you do and the support and information and all of the representation that NAMI has offered. So I'm especially honored to be here today. And this is the title of my talk, Precision Medicine Research: Hope for the Future. And before I get into it, I'll just mention disclosures in case that is relevant to anybody's questions.

([00:02:39](#)):

And now, let's go for the substance here. So I want to set the stage in terms of a number of things that I suspect many people here already know, and that is the magnitude of the challenges that we face in the area of mental health. We know that mental health conditions, psychiatric disorders are very common. Most people in this country at some point will meet criteria for a psychiatric disorder. They tend to have an onset early in life, which means that those who live with mental health conditions often live a substantial part of their lives with them.

Dr. Jordan Smoller ([00:03:18](#)):

And we know that they are responsible for a tremendous degree of what we would call morbidity or sometimes disability and mortality even. So enormous costs, as you can see there on the right, nearly \$1 trillion annually associated with untreated mental health conditions and substance use disorders. And studies have suggested that those living with serious mental illness actually have a substantially shortened lifespan, largely we think due to, well actually a number of factors including some of the metabolic complications, sometimes of treatments, associated risk factors and so on. And of course, there's the problem of suicide, which is it's actually not currently the 10th leading cause of death because of COVID, but it is still the second leading cause of death among young people in this country.

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We also know that there is a tremendous need for new treatments, and just in the realm of medication treatments, which is not of course the entirety of our treatment options, it's clear that these are medicines that can be very helpful for many people, lifesaving for some people, but almost all of them are based on mechanisms or biology that were suggested 50 or 60 years ago. And what we have, as I said, can be very helpful, but for many people, they are not the answer sufficiently in terms of quality of life, in terms of the likelihood that people can remain on the medication or that they will have really substantial benefit. And the bubbles that you see here actually give headlines from some of the largest clinical studies of these various conditions. So the chance that somebody beginning an antidepressant trial will have a remission of their depression with, say, the first SSRI that they try is less than 30%. We know it's very difficult often for people to stay on medicines partly because they have side effects and so on.

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And that's what leads us to the topic of today. So we have a number of big challenges, and this comes at a time when we're seeing an emergence of a new paradigm in many areas of medicine, and that is this idea of precision medicine. So precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in lifestyle, socioeconomics, environment, biology, and the emphasis there is on individual variability. Many of the things that we do, the treatments that we have are based on what works for the average person, but none of us is the average person. We are all unique, and if we can leverage that uniqueness, we might be able to do better. So this is in many ways a radical shift in how we think about getting to the best options for treatment, for diagnosis, for prevention and so on.

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And if you think about just familiar examples, it's not such a foreign concept. I use some very familiar examples here. Eyeglasses, for example. So if you have trouble reading, you could go down to your local pharmacy and pick up a pair of reading glasses off-the-shelf and they would probably be okay, but they would never be as good as a prescription that was tailored to your vision. Blood types, we wouldn't think of routinely giving people a transfusion with a blood type that's incompatible with their own personal blood type. And antibiotics, of course, we don't just pick something at random off the shelf. We try to tailor the antibiotics if you have an infection to what the bug is that's giving you the infection.

Dr. Jordan Smoller ([00:07:44](#)):

Well, now zoom out or zoom forward to precision medicine that we're starting to see today in many areas of medicine. I'll mention this again, but cancer is one area where this has really been dramatically helpful. We have new treatments for cancer that are targeting not just the broad concept of cancer and all of the toxic effects of just trying to kill a lot of cells in the body and hope that you're killing more cancer cells than normal cells, but actually targeting the genetic causes that are driving those cancers. And there are others. There are gene tests for dangerous drug side effects. There are now new ways we can use genetics and other things to identify people who might become ill before they do.

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And this is an example from the cancer field. You can see that in the last decade, what you're looking at here is a timeline of the approval or development of drugs for all kinds of different cancers that are targeting the specific genetic effects that are driving cancers. So that means that they're going to not necessarily be effective for everybody, but for those people whose cancer is driven by that mutation, let's say, in a gene like BRCA1 or 2 or something like that, they could be very effective, much more so at least than what we had to offer before.

([00:09:09](#)):

Cystic fibrosis is another example. People may have heard of this condition or know of it. It is a recessive mutation in a gene that was identified about 35 years ago. Recessive, meaning that you would have to inherit two copies of the mutation to actually develop the disease. And it's not that uncommon and it has very widespread effects on, won't go to the details, but on many organs in the body. And in the 1980s and certainly before that, life expectancy for people with this disease was less than 25 years and there really were no treatments that targeted the causes of the disease. And now, through the efforts of genetics and precision medicine, there are medicines available that could be useful for up to 90% of patients. And we expect that life expectancy for those with this condition will continue to increase. It's already doubled. So you can see that by targeting the individual things that are going on, there's the potential at least to really make some major advances.

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Now, if we think about precision medicine brought to psychiatry, we can probably all come up with a whole list of things, questions that we'd like the answers to, but here are a few of them. In the realm of diagnosis, how do we improve how we think about the classification and diagnosis of psychiatric disorders? As you know, we largely go by symptoms and the DSM, which people are familiar with, which lays out the criteria, but we also know that that's not really set in stone and that we could do better. How do we identify people at risk of outcomes before they occur and perhaps prevent some of the outcomes that are feared or that we worry about? Certainly self-harm is one of them. How do we identify the right treatment for the right person at the right time? That's what I have here under treatment stratification or matching. And how can we develop new treatments that actually target what's going on? Very much the along the lines of what I just showed you in other areas of medicine.

Dr. Jordan Smoller ([00:11:35](#)):

So I want to give you just quickly a couple of snapshot examples, largely this is from work that we've done here in our group and with colleagues around the country and around the world, frankly in some cases, in some of these different areas. What are we learning? So one of them I said is at the top, diagnosis. And one thing that we have begun to use to get a picture about these diagnostic ambiguities is genetics itself. And as you may know, genes play a role in many conditions, many mental health conditions and other conditions. And I'm going to ask you to take a look at this list, and this is in alphabetical order, but think about which of these conditions do you think is the most heritable. Heritable means that genetic variations in our genome account for the most proportion of who ends up becoming affected with the condition, how much do genetic variations contribute to the risk of the condition and the population? So you've looked at this, I'm going to now show you what twin studies have told us about this.

([00:13:02](#)):

I don't know if that fits with what you predicted, but there are a couple things to notice here. It's clear that genetic variation accounts for a big chunk of the differences in risk in the population for things like autism, bipolar disorder, schizophrenia, ADHD, et cetera. I included Parkinson's disease and breast cancer in this list, in part to give you a sense that many of the conditions that we think of as very related, for example, to genes like breast cancer, the heritability are actually less. And that's for a number of reasons, which I won't go into, but that doesn't mean for example, that there are... We know for example, that in breast cancer there are a couple of genes that those who have a mutation in the gene may have a very strong risk, but across the population they don't account for most cases. And in fact, most of the genetic risk for psychiatric disorders seems to be due to very common variations that are widespread across the population. We all carry some of them and each of them contributes a small amount on their own, but they can add up to a fair bit.

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Well, it was really just in the last decade or so that we started to see a tremendous acceleration in progress in genetics of psychiatric conditions. And what you're looking at here is a timeline at the bottom of years and the number of genetic variations that have been really pretty strongly established now for different conditions. And you can see that prior to about 2008, '09, there really wasn't much of anything that people could point to and feel very confident about. And now, you can see it's just taken off and there's more than 1,000. That's in part because our technology has advanced, also because the research has become much larger scale. It's related to something that we'll talk about. It's because many people participated in this research that the studies became large enough that we could actually begin to unravel this genetic puzzle.

([00:15:28](#)):

And what does this have to do with diagnosis? Well, not necessarily that much yet, but I want to make one point. So as you probably know right now, our diagnoses are based on the DSM largely, this Diagnostic and Statistical Manual book that gives us all the criteria. This is the additions of the DSM from the first one in 1952 to 2013, the fifth one. And what you see is a steady growth in diagnostic labels, numbers of conditions in the book.

Dr. Jordan Smoller ([00:16:01](#)):

And even if you just look at three groups of disorders, and again, you're going to see a timeline at the bottom as the DSM progresses, and you see that in these pervasive developmental disorders which are autism related, let's say, mood disorders, anxiety disorders, as it goes on, new conditions come in, others drop out. When we get to actually DSM five, a rare event happens, which is a lot of conditions suddenly merged into autism spectrum disorder. Mostly we have splitting of categories when we make these revisions of the book. But you also see new categories developing. Some of the anxiety disorders now moved into new categories of diagnosis.

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The basic bottom line here is we are not totally sure where the boundaries in these conditions are or how best to define them. And one of the most intriguing, and I think surprising things that we're beginning to learn from the genetic analysis is that many of the things that we thought of as being organized into groups or that were very different from each other are actually at a genetic level look much different and often are much more closely related.

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So this is a slide that just summarizes a whole bunch of data. And what you're looking at in that grid there is what we would call a matrix of genetic correlation. So what does that mean? That means that the darker blue, the square there, the more two conditions are related genetically at a fundamental genetic level. So one thing you see here is this is schizophrenia and bipolar disorder. They are very strongly correlated at a genetic level, even though actually in our diagnostic system they are two totally different categories and they're mutually exclusive. Depression is related to all kinds. You see some blue across the spectrum here. You have to imagine that all of these are also lined up on the columns here. Not important to know the details here, but what you see is there's a lot of blue. What that's telling you is a lot of these conditions are genetically and that is biologically related to other conditions.

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And in fact, you can do analysis and pull out the common factors that link these conditions. And that's what we and many others have begun to do. And we find that there are some basic common factors that seem to crosscut our diagnostic boundaries and may help us rethink or reshape how we classify conditions in ways that are closer to actually what's going on at a more fundamental level. So some of them have to do with thought disorder or internalizing. Those are things like stress, anxiety, depression, compulsive behaviors, and so on.

([00:19:08](#)):

Okay, another area where precision would help is in this area of risk prediction. We're not very good at knowing ahead of time whether somebody is going to develop a worsening of a condition or develop the condition to begin with or have a certain outcome. And I want to give you the example that we've been very deeply involved in trying to help with, and that is this question of suicide. And I just have some numbers up here which are pretty staggering and may be familiar to some of you that a million and a half people every year in our country attempt suicide. We've seen 35% increase in deaths by suicide over the last couple of decades, especially increasing among young people, nearly 60% in the last, say, 15 years or so.

Dr. Jordan Smoller ([00:20:06](#)):

And it turns out that most people who attempt or die by suicide are seen by healthcare providers in the months or even weeks leading up to the event. And what that means is, for example, nearly three quarters of people who go on to attempt or die by suicide see a healthcare provider in the 90 days prior. That gives us in healthcare settings a very important opportunity to identify folks who need help and perhaps intervene in ways that might be lifesaving. However, decades of research have shown that we clinicians don't do much better than chance at really knowing who's at risk, and that makes it very hard to provide the needed interventions to those who need the most.

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One of the things that has developed in this new era of precision medicine and a lot of other advances that have gone on in medicine and in computer science is the ability to use lots of data to get answers that are more precise than the ones that we currently go on. And in that realm, artificial intelligence, which people have probably heard of maybe more than you want to lately, but until six months ago, I think was not all that widely followed.

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As you know, companies like Amazon or Google or Facebook or whatever use artificial intelligence to identify things like what do you want to see in your feed, or if it's your Spotify, what do you want to listen to next. And the way they do this is by gathering lots of information about people's behavior and developing models or algorithms that can predict future behavior, and it's remarkably effective. But the good news is, well, whether that's good news in itself or not, I'll leave to you, but the better news from my point of view is we can now apply those same kinds of tools for purposes that improve people's health and perhaps prevent outcomes that are really devastating. And suicide is the one I'm talking about here.

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So for just as an example of some work we've done, we had several years ago had developed a suicide risk prediction model using data from electronic health records, which as you know are anytime you see the doctor go to a hospital, there are electronic health records that are documenting what condition did you have, what procedures did you have, et cetera. And it turns out that that information can be very useful if models are developed to again predict future health outcomes. So we developed this model in a very large sample, 1.7 million patients. It was able to detect 45% of all attempts or deaths by suicide on average two to three years in advance. We then did a study validating that approach in five other healthcare systems and found that it performed just as well. We also asked the question, how accurate would a precision algorithm like this have to be to be cost-effective in reducing suicide risk and primary care? And found that our model and similar models are in fact cost-effective when, or would be, when paired with evidence-based prevention strategies.

Dr. Jordan Smoller ([00:24:02](#)):

And we did a prospective study and we showed that yes, indeed, our model can outperform clinician assessment. And in fact, for example, this was a large study in our psychiatric emergency services and for those individuals who the model predicted to be at very high risk, 40% went on to make a suicide attempt in the next month and nearly 60% in the next six months, so really actionable numbers. And we have now developed a clinical decision support tool, meaning a tool that can be in the electronic health record and help clinicians and patients develop a care plan, a safety plan, identify really who is more likely to be at risk and hopefully intervene earlier. This is not yet in clinical practice, but we are really trying to move the ball forward to do this.

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We've done this in other areas as well with colleagues across multiple healthcare systems. We've used these same kinds of methods to identify whether somebody might be at risk for developing bipolar disorder. As you probably know, the average duration in terms of when people have symptoms start to when they actually get an accurate diagnosis, on average that's 6 to 10 years. If we can shorten that odyssey, that journey, we think it could be very helpful. And of course, the longer conditions like this are untreated, evidence suggests the worst the outcome. So that's another area, for example, where having data, having a precision medicine approach might be helpful.

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Another one is this idea of precision treatment matching, getting the right treatment to the right person at the right time. And people know this, that our current approach to treatment is largely a one size fits all trial and error approach. And so, we may try something, for example, a medication, see if it works, it might take weeks to really know if it's working, and if it's not, then we have to either try something else or add something else. Meanwhile, folks are struggling often with the symptoms of depression or not able to work or all of the potential consequences. Same thing for schizophrenia, for mania and bipolar disorder, et cetera.

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One area that has actually been a research for a while is something we call pharmacogenetics. And what that means is can we use genetic information to help match people to the right treatment, because we know that genes influence response to medication. And so, there's been actually now few decades of work in this area. And the two kinds of genes that we look at when we do gene analysis to predict treatment response fall into two categories. One is what we call pharmacokinetic genes, which is a fancy way of saying genes involved in how drugs get metabolized in your body, how does the liver break down your antidepressant or antipsychotic medication. Because some people metabolize medicines really quickly, and so maybe they're not even getting the dose they think they're getting and others metabolize it very slowly. Maybe they're getting too much and maybe that's contributing to side effects.

Dr. Jordan Smoller ([00:27:42](#)):

The other category is what people call pharmacodynamic. That's about how do the drugs actually work in the body. If it's an SSRI antidepressant, we think that it's probably at least in part working by blocking the serotonin reuptake transporter. So you can look at variations in these genes, and this has now been done many times. And in fact, the FDA and organizations have identified a variety of medicines where variations in certain genes, and almost always, I'll just say, these genes are of that drug metabolizing category. So when you see CYP or CYP219, that's one of the enzymes that breaks down or metabolizes things like citalopram or Celexa or sertraline.

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So we know about some of these associations and sometimes they're actually in the drug labeling, although we don't routinely test for them, however you can now, there are commercial tests available that have looked at is it helpful to test for these things. The commercial tests are, it's a little bit hard to know sometimes exactly what those tests are doing because they are often proprietary. But here's a couple of large scale clinical trials that tested the benefit of getting this pharmacogenetic testing. And my guess is that there may be some people listening who've had this. And so, this is what they found. The first one looked at this commercial test. For half the people, their clinician got the results of this test and used it to guide their treatment. And the other half were treatment as usual, meaning they didn't use the test.

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The answer was after eight weeks of treatment, there wasn't a significant difference on the primary endpoint of the study, which was how much did your symptoms improve? Although there was a difference on other ways of looking at the data, how many people got a, what we would call a good response, or how many people had a remission. The second study, which was in a VA population, veterans population, slightly larger even and longer, also had mixed but somewhat significant results, where those who had the test guiding their treatment were less likely to be prescribed drugs that might have interactions or where the gene involved might be affecting how the drug gets metabolized. And they were slightly more likely to reach remission, although it wasn't still significant after 18 weeks.

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And so, people have done lots of meta-analyses, putting studies together, and the results seems to be that they show some benefit for these tests. You might be up to one and a half times more likely to get a remission of depression if your treatment was guided by the test than treatment as usual according to these meta-analyses. But some of these studies have been criticized due to potential for bias. There's often missing data, often for these commercial tests, the company's involved and so on. And actually, these have been somewhat controversial.

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So the American Psychiatric Association issued a statement in 2018 that said, "There really isn't enough data to say that these tests should be widely used." The International Society of Psychiatric Genetics said, "In a few cases like testing for genes that might produce a really severe immune response for carbamazepine, that makes a lot of sense. Beyond that, it's still not clear how useful they are." And the American Academy of Child and Adolescent Psychiatry also was not strongly in favor, but the evidence is still growing and we will see where it lands, I think.

Dr. Jordan Smoller ([00:32:08](#)):

There are other ways that people have tried to predict treatment response. And a way that we start to see more of now because there have been some studies supporting it has been to actually use brain signatures. In this case, it's based on an EEG, which is the test that you wear the cap, and it's a test that can hopefully predict or detect seizures, for example. But some studies have now suggested that there may be signatures of EEG that are associated with the likelihood that you would respond in this case to sertraline or Zoloft as opposed to placebo, and maybe also the drug as opposed to transcranial magnetic stimulation, which is another treatment for depression. So stay tuned for more on that in the future, I think.

[\(00:32:58\)](#):

So what are clinicians facing now? Well, what we face now is if somebody comes to see me for depression, I might choose one of four different categories first line for an antidepressant. An SSRI, an SNRI like venlafaxine, let's say, bupropion also known as Wellbutrin, or mirtazapine also known as Remeron. What's the chance that this person in front of me is likely to respond? It's about the same as far as I know for any of this. I don't know ahead of time.

[\(00:33:32\)](#):

So one thing that we've begun to do is to again, try to use big data and artificial intelligence to see could we do better. So in this study, we had data from more than 17,500 patients who had depression and were started on one of these categories of drugs. We had lots of data from the electronic health record and we tried to build models that could predict treatment response after a month up to three months of treatment, that is 4 to 12 weeks. And so, let's imagine you've got these two folks, Tom and Megan coming to see somebody for treatment. And again, right off the bat, we don't exactly know what's going to work best.

[\(00:34:19\)](#):

When we build and apply this model, which actually correctly predicted response for about 74% of patients, you see that Tom's probability of responding to an SSRI was actually 94%, whereas Megan's was only 28%. So that's a big difference. Immediately tells you people don't respond the same, but also that the SSRI would be a good choice for Tom, maybe not so much for Megan. But the other thing you can do with these models is actually compare the likelihood that you're going to respond across these different categories of medicine. So in this case, it turned out that Tom was likely to have a pretty good response to all of these categories. It turned out that SSRI was the best choice, but none of them were terrible. For Megan, the SSRI wasn't the most likely to produce a response in this case, it was the mirtazapine. So you could see how knowing this kind of information could again give us some tools to be more precise and reduce this kind of trial and error prescribing. Again, this is not in clinical practice, but we are working on this kind of research.

[\(00:35:29\)](#):

And then, finally, another example is developing new precision treatments, like I said before, we've seen in other areas of medicine. And one of the striking things about the genetics of psychiatric disorders is we're not just getting a list of gene variants that seem to be associated, but just as we hoped, they're pointing us to biology, to the genes that are associated with, let's say, schizophrenia. Those genes are doing something. And if you have enough of clues of different genes that are involved, they start to tell a story, they start to actually point to pathways and they start to make sense of the biology.

Dr. Jordan Smoller ([00:36:08](#)):

And what's striking is many of the things that we're learning from those genetic clues are things we didn't know about before, we didn't think of. And that's the hope actually, is that you can learn something fundamentally new from these genetic studies that points you to what's actually causing or going on in the condition, and that perhaps we can then develop treatments that target that. I'll give you one example again, pretty preliminary of an area that we've been pursuing here. And this is many of these genetic studies, large scale genetic studies of schizophrenia have identified lots of different variations that might be involved.

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One of them is in a gene, which the name you don't need to remember, but it's called SLC39A8. And this variant actually changes the amino acid function or the protein function in the gene, in the protein that it makes. And it turns out that that variant reduces levels of manganese in the blood, we've found. And that's because the gene itself is responsible for bringing manganese. Manganese is just a mineral, essentially. It's in the foods we eat. And this gene is responsible for conserving it, bringing it back into nerve cells and processing it. And the reason that that's important biologically is that manganese is important for driving a process that we call glycosylation. And I realize we're getting a little bit in the weeds here, but here's the bottom line of that.

([00:37:58](#)):

A very important process in the brain and the development of the brain and how the connections in the brain develop is that we put little tags on different proteins or other molecules on the surface, let's say, of the brain cells, and that helps guide them in certain directions. That putting these little tags, these are tags of sugar, adding molecules of sugar, that's what's happening at a biochemical level. That's what we're calling glycosylation. And manganese is important for that process. And it turns out that through work led by Robbie Mueller in our lab, if you take that variant that's associated with schizophrenia and you put it into the mouse, it changes this brain glycosylation and a variety of work, what I haven't gone into the details of, now suggests that this kind of glycosylation pathway could be an important biological component of schizophrenia. Again, we didn't think about this before. We didn't know about it before. It's through the genetic research.

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And interestingly, if you give manganese to people who lack this gene, which that rarely occurs, but can have devastating effects to not have a functioning gene, you can partly reverse those biochemical changes and it leads you to wonder, could we be approaching the idea of a new treatment based on this biology that might approach the problem in a different way? So clearly, there's a lot of complicated stuff there, but I think the takeaway there is by learning about the genes, we learn about the biology. By learning about the biology, we learn about how to design better treatments, we hope.

([00:39:50](#)):

Okay, so I think we all know, and we've talked about already that what we're facing are many challenges. Recently, the White House issued a report, a first of its kind call to action for mental health research. Mental health research is so important, and that's really a big theme of what I'm talking about today because it's the way we change the game. It's the way we have hope for the future. So the White House, for example, commented that we are facing a mental health crisis and research and innovation are key to this challenge.

Dr. Jordan Smoller ([00:40:32](#)):

We know that some tools work in some settings, but we need to figure out how to make them work for everyone everywhere. And we need to improve how we prevent, diagnose, treat, and de-stigmatize mental health conditions, and research is key to doing so. And these were the eight priorities that they really focused on, some of which we've already talked about. So that brings me to what I think is a really important thing for people here to know about, and some of you may already, and that is a once in a century research program, the All of Us Research Program,

All of Us Research Program Video ([00:41:20](#)):

We are one nation, one people. When called upon to give from within, we come together and find that our capacity to help others is limitless. Here, we are fearless. What lies inside all of us is more than data, it's life. It's more than insight, medical research, it's vision and honor, passion. What's flowing through America's veins is its diversity. The next great breakthrough will be found in each and every one of us, and what we find there will unlock mysteries, heal the sick, and eradicate disease. We ask for 1 million individuals to come forward and stand on this landmark in history. We ask America to do once again what she has always done, lead the way forward. We're one nation, one people, but all of us are different. And it's those very differences that will lead to answers for generations to come.

Dr. Jordan Smoller ([00:42:43](#)):

So as you might have gathered from that, All of Us is a monumental effort to really advance precision medicine, to really make these changes and to leverage what we are learning and what we have yet to learn to make things better. So this is a nationwide study that was launched in 2018. So we're now just past our fifth year anniversary, and it is the largest, most ambitious research effort I think around, certainly in this country. Its mission is to gather health data from a million or more people living in the United States to accelerate health research in the hopes of improving health for everyone. And so, it is trying to really nurture relationships, partnerships with at least a million folks who want to be part of this effort and who reflect the diversity of our country, deliver one of the largest, richest biomedical data sets to drive research for the future, and foster an environment of collaborative communities and researchers and funders who are going to make this the bedrock of a lot of discovery that happens in the next decades, frankly.

([00:44:03](#)):

The program, which I'll tell you a little bit more about in detail momentarily, has some core values. This is one of the things, and I'll say that I'm part of the program, but this is one of the things that inspires me the most about it in addition to just the opportunity to make advances, is that it really is core value driven. So here are some of the values. Participation's open to everyone. It reflects the rich diversity of the United States. That is so important because as many of you may know, many communities in our country and in the world have been either neglected by research, left out, not at the table, or worse, have been mistreated in the context of research. This is an effort to really address that in a different way, to really make sure representation in all these various facets is a core part of this.

Dr. Jordan Smoller ([00:45:09](#)):

Our participants are partners, not simply subjects. Trust will be earned through transparency. Participants have access to their information. This is not a one-way thing. Please, I'm a participant in the study in addition to being one of the principal investigators, usually when you participate in a study, you provide information and maybe you learn about how that worked out somewhere down the road. This is more of an active partnership, and the data and information that you provide is available to you or as we'll see other information that may derive from the study. Data will be accessed broadly for research purposes. It's not somebody hoarding the information and not making it available so that the greatest use can be made of it. Security and privacy will be of the highest importance. We're all concerned about this, and the program will be a catalyst for positive change in research.

([00:46:12](#)):

So participant voices are a central part of this effort, which is I think a really wonderful thing about it, and it's been true from the very beginning. Why does it matter? Well, I've tried to make this case particularly with respect to psychiatry, but enabling research discoveries that drive more precise approaches to care. Make sure that people are not left out of medical research, make sure that we have a whole holistic sort of view of what's going on, biological factors, social determinants, and make sure that it's large enough of a study that we can actually get answers, that it's easily accessible to researchers so that all ideas and good ideas that might make a difference can be investigated. And it's following participants as they move, as they age, as they grow. It's a longitudinal study, which is again, relatively uncommon, certainly at this scale. I won't go into detail about all the possible kinds of research it will enable, and we'll say a little bit more about this, but I think you've got a flavor already of the kinds of things we might learn and need to learn.

([00:47:29](#)):

It is a big effort involving many people. It is really a remarkable coming together of researchers, participants, advocates, community partners to get this done. And there are health centers across the country, including our own here at Mass General Brigham and Boston Medical Center, their participant centers and communication and engagement centers and data centers, and also crucially provider and provider partner networks. Organizations including NAMI has been a part of our discussions to try to make sure this is answering the questions that matter to people, that it's representing the communities that need to be represented.

([00:48:19](#)):

In 2019, I particularly have been committed to making sure that advances in mental health research can come from this study and that we are represented in this study. And so, in 2019, the program invited representatives from more than 21 organizations, including NAMI. You see this little word cloud over here, and NAMI is one of the biggest contributors there, to talk about how can we build awareness, how can we design questionnaires or other materials for the study, communications materials, that are sensitive to the communities involved that asked the right kinds of questions. There were interactive webinars, feedback surveys, brainstorming sessions, and they really made a difference. They really helped us design the mental health components that we are building into the study and have already to some extent.

Dr. Jordan Smoller ([00:49:18](#)):

So already, more than 630,000 people have signed up. About 413,000 participants have data available for research. And true to the mission, 75% are from communities that have been underrepresented in biomedical research, including 45% from racial and ethnic minority, communities who have really not have this opportunity often to participate in an equitable way.

([00:49:52](#)):

What types of the data do they get collected? The basics are folks enroll, they consent. There's a informed consent process as there is for all research where you learn about what's involved in the study, you make a decision about whether you want to participate, which of course, you could always withdraw from the study at any time. And then, there are surveys asking about health and health history. There's a brief in-person visit to just measure things like blood pressure and height and weight. People provide a blood sample or, in some cases, it can be a saliva sample or urine sample. And that's stored for research. And there's also the ability to contribute wearables or digital apps. And in fact, the program has made available things like Fitbit devices, I did this as part of the study. You're tracking your steps or turns out that information is a really important health marker as you might guess, and now we have the ability to incorporate that into the research.

([00:51:02](#)):

This is a number of the surveys that are involved in the program. I'll just mention that there is a dedication to social determinants of health. Things like what's the lifestyle, the environment that people are living in, how does that affect their health? There was a survey which I'll say a bit more about in a moment on people's experience during COVID. And this is really important and I'm super excited about. And that there is now the opportunity to include a lot of information about mental health.

([00:51:38](#)):

So we have designed self-report surveys, questionnaires that you fill out electronically, digitally, on your smartphone or however you do those things that include mental health information in terms of family history. This COPE survey, which was a survey that we made available over successive months early in the pandemic and asked about people's experience with the pandemic. How was it affecting their mental health? Were they experienced loneliness? What was their access to care, social determinants of health? And two new mental health surveys that are coming soon, and we expect that to be really soon. So this is going to be a tremendous opportunity to gather information that we think will create the basis for a lot of discovery.

([00:52:31](#)):

Electronic health records, of course, also provide information about medications, labs, diagnoses and so on. And there's another new component of the study which is going to be really, I think, actually fun in addition to creating a lot of really interesting information. And that's something called exploring the mind, which allows participants to essentially like playing cognitive games, asking things about memory and attention. And here's a screenshot of, or just a cartoon version of guess the emotion. You're shown faces, what's the emotion out of a bunch of choices that you see there? People differ in those things and that turns out to be related to mental health as well.

Dr. Jordan Smoller ([00:53:21](#)):

The COPE survey I mentioned, I had the privilege with Holly Garriock, who is our chief cohort development officer of helping to design, and this was a survey that again asked about people's experience during the COVID pandemic, the early part of the pandemic. And tens of thousands of folks completed this survey, which created an enormous resource for research. If you just look at, and I think in the slides, and we can certainly distribute this, there's a website where you can go and look at the basic characteristics of how many folks in the study have various conditions, how does it break out by sex or by age. So it turns out that for mental health conditions, the top 10 conditions, mood disorder, more than 70,000, nearly 75,000 people already in the study. Depressive disorders, other variations of mood disorders are common as we would think they were. Already 120 research projects are under underway to study depression and 85 to study anxiety. That's remarkable because the data are made available and people are beginning to do the research. We hope they would.

([00:54:47](#)):

I'll just give you a couple of examples from things that we've done using these data to try to answer certain questions. So this was a study we published using data from that COPE survey that I mentioned which asked about people's experience during the pandemic. And we were particularly interested in is there a link between everyday discrimination, the ways that people feel stigmatized or ignored or worse mistreated and their risk of depression. And particularly during the pandemic when we were starting to see a lot of these things come to the fore and certainly come to public attention, what we found was by looking at these repeated measures over time, those who experienced discrimination more than once a week had a, this is unbelievable, a 17.7-fold increased odds of having or developing moderate to severe depression, and a 10.8-fold increased odds of suicidality.

([00:55:52](#)):

This was especially true when the reason for discrimination was related to race or ancestry or national origin. And that risk factor of experiencing everyday discrimination was as strongly associated with developing moderate to severe depressive symptoms as was a history of having a mood disorder in the past. So this was really, we thought a really important message and discovery for people to be aware of.

([00:56:22](#)):

We just last week, I guess it is, or maybe now it's almost two weeks, we're able to publish a second study using data from the COPE survey again. And this was looking at a positive exposure of let's say, or a positive experience, and that is social support. And again, we don't have time to go into the details, but basically we were asking how important is social support in preventing depressive symptoms during this pandemic, and does it matter what kind of support you get? For example, you might be getting tangible support, people giving you resources that can help you not have to worry about food or that kind of thing, or you could be getting emotional support, or having positive social experiences. Overall, social support was associated with a 55% lower odds of developing depressive symptoms. That's a really potent protective factor and we've seen that in other studies as a matter of fact, especially emotional informational support and positive social interactions. So again, having this magnitude of data allows us to ask and answer questions much more precisely than we've been able to in the past.

Dr. Jordan Smoller ([00:57:39](#)):

I mentioned that we are really excited that a new survey, two new surveys actually, focused on mental and behavioral health are about to be released. And that will mean that more than 500,000 participants and more, we hope, as more people join the study, will be able to contribute information about things we care about, depression, and mood, anxiety, suicide, the effects of adversity and trauma, ADHD, psychosis and so on. We're also including a brief personality measure which actually, the results of which will be returned to participants with a customized real-time brief personality report which people might find interesting. So this is really when I said this is kind of a once in a century perhaps opportunity to generate information that can be then used to generate discoveries and research advances for the care of mental health, this is an important one.

([00:58:52](#)):

Just briefly, what happens to the data and how does it get done? Well, the program has gone to enormous and very innovative lengths to create a secure but accessible environment for having the data. There's a thing called the data browser, which you can log onto right now at researchallofus.org. And you can look at some of those summary tables, like how many people have a certain condition, et cetera. You don't need to register yourself in any way or anything like that. But that doesn't have any individual level data. The individual level data are accessed through something called the workbench. They never leave the secure enclave where the data sit, so people can't download the data or anything like that. And even to access it at that level of individual data, you need to go through a number of things.

([00:59:48](#)):

So anybody can access what we call the public tier, again, through researchallofus.org and welcome you to do that. If we have time, we could even demo that for a second. And you can look at snapshots of the data and explore the surveys that we use and so on. And then this is the more detailed researcher workbench, which has different tiers of access depending on how detailed or sensitive the data might be. And they have been, this is where the individual level data are. And to access, again, the overall researchallofus.org data, you can get these things. It tells you how many people are in the study today, how many samples have been received, all the different variables and measures.

([01:00:42](#)):

But there is an enormous backend to ensure that we have rigorous security and data privacy behind all this. So the partner organizations have to meet strict data security standards before we can even collect or transfer the data. All of the data is encrypted, all of the identifiers that obviously identify somebody, your name or your social security number or something, is removed. The researchers have to register with the program, complete an ethics training, and agree to a code of conduct. There are independent reviewers who are checking and testing the system on an ongoing basis. And so, there's really a lot of attention to that, which makes me feel happy about that, that we are doing that, because that's a concern for everybody.

Dr. Jordan Smoller ([01:01:38](#)):

So there are many ways you could get involved if you would like to. The two big categories are you can either get involved through a local health provider organization like Mass General where I am, and you can go to the website at joinallofus.org and you can search for what's nearest your area. You can even do it if you're not just online, sign up on your own. Again, it's available to anyone in the United States. So you're welcome to do that as well. And again, this is the journey that we talked about. What happens, you create your account, you do go through the informed consent and make your decision, you answer health surveys, have the measurements, donate bio samples, you receive \$25 for your efforts and you decide if you want to receive your DNA results, your genetic results, which you can. And I'll mention that again, and then you have joined this remarkable effort here.

([01:02:48](#)):

What's the value to participants? Well, one is you get in information, so genetic information, for example. This has already become the largest diverse genetic study available. And so, if you choose to participate in the genetic component, your DNA will be analyzed and you will get results that may tell you about things like hereditary disease risk or medicines, remember that pharmacogenetics thing for certain medicines. And if you have questions about it, you also have free access to genetic counselors that are provided through the program to answer any questions even if you don't decide to get your results back.

([01:03:34](#)):

Survey data, I showed you that example of the personality thing. Other information that you contribute is available to you as a participant. You get ongoing study updates, scientific findings, opportunities to participate or find out about other studies and plain language summaries of some of the science that emerges. What are we learning? What are the studies doing? We want to continually be partnering with people to keep them engaged with the whole point of this, which is to advance things and explain how the research is done, what the findings were, why is it important and so on.

([01:04:18](#)):

So you can join, you explore the website at joinallofus.org here. You can sign up either online or in person. As I said, you'll get these slides if you'd like, and any information I'm happy to provide after as well. We have a support center that answers questions for you. And I'm really excited about this and I hope folks will be inspired just to look into this. You can also, if you're interested, register to be a researcher, and there are steps to do that as well. Here's, what do you call that? QR code that would link you to information about how to go through those steps. Part of the idea here is we don't think that the only good ideas are the people who are sitting in research institutes at certain universities. There are many good ideas. We want to have the opportunity to make the most of this. And you can also sign up for our bimonthly newsletter to get information in an ongoing way about what's going on with this study.

Dr. Jordan Smoller ([01:05:34](#)):

So we're starting to see these new tools and resources emerge to enable the application of precision medicine to psychiatry by this attention to our unique individual differences. But we got a lot to do, a long way to go. We have some major gaps in how we diagnose and treat and prevent illness. And so, I think it's really important, and this is the call to action, that we ensure that individuals and families who have been touched by mental health conditions and those who care about them are represented so that everybody gets to benefit in the future and we don't look back and feel like we didn't learn enough.

([01:06:17](#)):

And I always love this phrase that research is hope because I think that's really true. That's why I'm in research and I think when we have opportunities and we can be forward-looking, it's really exciting for me, it has been at least, to be a part of it. So I think that is where I was going to land with this last slide and I think I'll unshare, but I want to thank all of you for your attention. That was a lot to get through. Ken, I think, can tell you that we might have what set a record maybe for more information in one little-

Dr. Ken Duckworth ([01:06:58](#)):

All-time record for slides and information, but this is quite complex. When you submit your feedback, you'll get the slides, and the entire talk will be available the nami.org/asktheexpert in a week or so. So Dr. Smoller, we had over 600 people on the call.

Dr. Jordan Smoller ([01:07:19](#)):

Wow.

Dr. Ken Duckworth ([01:07:19](#)):

[inaudible 01:07:20] engagement, another 600 people will listen to it online and a lot of information. So let me start with one theme. This is fantastic, this is comprehensive, it's another level of research. I think people pick up on that. When might some people on this conversation see some practical benefit, either in diagnosis or in a treatment that doesn't have side effects, or in prediction of self-harm or suicide for someone they love? I know that's a hard question, but I wanted to start with it because I'm going to say 20 other questions relate to this in some way.

Dr. Jordan Smoller ([01:08:01](#)):

Yeah, that's the question I have.

Dr. Ken Duckworth ([01:08:04](#)):

Yes.

Dr. Jordan Smoller ([01:08:05](#)):

Yes. And I think it's slightly different answers to each of those sub parts of the question that you gave me, but I am impatient as I know everybody is, because all of us are affected, all of us are involved in this mission to make things better, and it's frustrating to see the possibility but not feel like it's out of reach. So I think a few things. One is there are advances already going on that have not necessarily leveraged this focus on precision psychiatry yet totally, but where we have some new treatments being developed and FDA approved and so on. When we talk about the kind of thing I talked about here, new diagnostics, so that new diagnostics thing is probably a long-term process, because as you might imagine, there are many considerations.

([01:09:13](#)):

I think what has already happened as a result, let's say, of the genetic research is that people have begun to think about conditions, first of all, as a spectrum in many cases, that there's no bright line between one condition in another or between, say, a disorder and what people call "normal." I think we've helped to break down some of those silos, but there are many considerations in how you diagnose and classify conditions. That one, I think, is a work in progress for sure.

([01:09:50](#)):

In terms of the treatment matching, I do think actually that that is something that we can make a lot of progress on in, exactly what the timeframe is, I don't know. As I said, there are pharmacogenetic tests out there. They're not home runs as far as I'm concerned. And so, that is still some years away, but it's exactly this kind of effort that's going to get us to, I think, those kinds of answers, because one of the limiting steps in a lot of research that's happened before is it gets done by either one scientific group and there is an adequate sharing of information, or by a pharmaceutical company. And again, that's not widely shared. The studies have often been too small to get clear answers, or they aren't including everybody. And so, that's where I think this has a lot of hope.

([01:10:58](#)):

The question of developing these new mechanistic treatments, I know that is going on now and there are a number of drug companies and startups and so on that are actively working on targets that have emerged from, for example, these genetic studies and other kinds of studies that are entering the early stages of development. And I see that as maybe being, believe it or not, the soonest possibility if some of the things that people are betting on actually do pan out, because there is such a recognized need for new approaches to treatment that I think there's a lot of appetite for moving those things along. So I can't give you the time exactly. I do think that those things are in the foreseeable horizon. I think research, again, is going to help drive that.

Dr. Ken Duckworth ([01:11:54](#)):

Fair enough. I just want you to know that was a common theme. Excitement but impatience both [inaudible 01:12:01].

Dr. Jordan Smoller ([01:12:01](#)):

Totally. That's exactly how I feel.

Dr. Ken Duckworth ([01:12:03](#)):

Precision treatment, yeah, you're there. Let's talk about All of Us studies particularly. You mentioned that you've been able to attract people who are underrepresented, both in terms of race, ethnicity, and presence of things like mental illness. How have you accomplished that? Because we have a history of discrimination and leaving people out. So how did you create the trust that certain subpopulations would participate in a project of this nature?

Dr. Jordan Smoller ([01:12:31](#)):

Yeah. Well, again, I think that's a never ending effort, meaning people are often mistrustful for reasons that are very good reasons. There have sometimes been history of everything from neglect to abuses that people have seen in research. And certainly, the stigma associated with mental illness has been a big force there. This program from day one has built, there is a chief engagement officer. There are community partners and organizations that have been elbow to elbow with the program at a national level who have reached out to their members to try to first of all get people's inputs and get their stakeholder representation so that the program is as thoughtful as it can be about the issues that people are concerned about with respect to trust.

([01:13:41](#)):

At a local level, for example, I'm one of the principal investigators here in New England, we have a whole team of unbelievably dedicated and, in many cases, visionary and passionate folks involved in building community trust and transparency and community engagement. We do events throughout the community. We are on the ground at events, whether they're recent pride events, for example, or in communities that have been hard hit by socioeconomic disadvantage, racial and ethnic minority communities. We make sure that the staff and the folks in the program itself and representing the program are themselves a diverse representation of the communities. And frankly for what we're talking about today, this is part of it. This ability to share the importance of this and talk with you all, I can't think of another organization and venue and group of folks who are on the ground. Just parenthetical, it made me think of when I came to the NAMI meeting in New Orleans, you graciously invited me to give a talk. This was now what, four or five years ago.

Dr. Ken Duckworth ([01:15:07](#)):

Yes.

Dr. Jordan Smoller ([01:15:09](#)):

I was just blown away by, it was not like any other meeting or conference I'd ever been to.

Dr. Ken Duckworth ([01:15:15](#)):

It was better!

Dr. Jordan Smoller ([01:15:16](#)):

It was better. Exactly. It was the passion, the fact that the commitment. So NAMI itself I think is in this domain I think a crucial partner for us to build trust and to hear from people what they're worried about. I think that's the only way we do it and it's not a how did you do it and isn't that great. It's a how do we continue to do it in a way that makes it worthy of people's trust.

Dr. Ken Duckworth ([01:15:49](#)):

That gets to these kind of privacy IRB questions. Before you participate in this, what are the protections for privacy? You mentioned that was a high priority. What is the IRB protection for? Institutional Research Board, protecting people's information, knowledge, that sort of thing. So let's just review the privacy and protections angle.

Dr. Jordan Smoller ([01:16:13](#)):

Great. Okay. So as you might guess, there has been a lot of attention to this. The All of Us program has a central IRB, which knows the program has been to which all of the research procedures and communications and everything has to go through IRB review as it does. There's an engagement with ethics experts, ethics and legal experts. But in terms of the privacy and security of the data, which is I think what we think about frequently, and it's a question that comes up all the time, so just to review, the data, and I'll actually go back to that slide just to keep it in people's minds, which I think is here. There's a lot of detail behind this slide, which is not represented, but which we can get into. So for our organization, for example, at Mass General Brigham, we had to go through an enormous degree of review and meeting strict data standards to collect the data, to transfer it.

([01:17:35](#)):

The data are kept in a data enclave, which means it's a cloud-based environment which reaches a certain level of security that is got a lot of, those involved in info security will know this level of security, but it's a very, very high level of security that is maintained. The identifiers are stripped, the data are encrypted. And one of the things that this study did, which in retrospect, in some ways obvious and yet nobody had really done it, and now others are doing it. Well, not nobody had done it, but it had never been done on this scale is usually what happens is you have a data set and if you're sharing data, the data are going to the investigator who's going to do the research. You download the data and you analyze it. This flipped that.

([01:18:35](#)):

So instead of the data coming to the researcher, the researcher has to go to the data. And what that means is you can't just have this data outside of that secure environment and everything that you, if you're analyzing the data, it's all audited and logged and there is what people call penetration testing. So there are independent reviewers and folks testing the security repeatedly in an ongoing basis. Those who use the individual level data have to register with the program, everybody has to go through an ethics training, and adhere to a conduct code that prohibits misuse of the data or stigmatizing use of the data. There is a committee or a board that is involved in, if questions like this come up or there's a questionable research project. Another thing that's really remarkable is the transparency.

([01:19:45](#)):

So if I want to use the data, because I want to answer a question about depression, let's say, I have to submit that to the program and it is publicly displayed. So if you go to that research allofus.org, you can see all of the projects, the hundreds and hundreds of projects that have been proposed and many of them ongoing. It tells you who's doing the research, where are they from, what level of training do they have, what's the question they have? It's a level of transparency that I've never seen before, but there's no sort of minimizing the importance of this. And if people are really concerned about it, they should think about it and nobody's under any obligation to participate, of course.

Dr. Ken Duckworth ([01:20:36](#)):

There's no place that you go. There's a couple questions. Where do I go in New York City? This is all online at that website, correct?

Dr. Jordan Smoller ([01:20:43](#)):

Correct. And at that website, you can plug in, here I am or I'm in New York, where's the nearest place to go, and it'll tell you.

Dr. Ken Duckworth ([01:20:54](#)):

Got it, got it. All right. Well, Dr. Smoller, I know you're an incredibly busy person running run of the biggest genetic meta-studies in American history, probably the biggest. Would you be willing to give out your emails for the questions we didn't get to today?

Dr. Jordan Smoller ([01:21:12](#)):

Sure. My email is jsmoller@mgh.harvard.edu.

Dr. Ken Duckworth ([01:21:24](#)):

And as a man who receives many emails, mine is ken@nami.org. I'd ask you to ask one or two questions and be patient with time for a response. Dr. Smoller is a busy lad. Let's go to the next slide. I want to thank you, Dr. Smoller, for this comprehensive work talk and for the work you're accomplishing and what you're trying to take on. I want to let you know next month, we're going to do a one-year retrospective on the anniversary of 988, which is essentially a NAMI work project in collaboration with many other people. The fact that there's a 988 three-digit suicide prevention lifeline is a success of our policy team, all of you as advocates in the world and many other people that we worked with. But I believe strongly NAMI conducted this orchestra. The one-year anniversary is July 16th.

([01:22:21](#)):

We'll be doing a ask the expert with Hannah Wesolowski who runs our policy team and David Covington on how to reimagine mental health crisis care, and that'll be on the 20th. You Are Not Alone is NAMI's first book. The author is speaking at this point. All royalties go to NAMI. We're pushing 40,000 books. We're a USA Today bestseller and the book just keeps on humming. So if you're interested, buy the book. If you like the book, write a nice review. If you don't like the book, take a vacation instead. If you like the book and you want to do a book club, I've done over 100 events, send me an email ken@nami.org, and with planning you can meet people in the book, 130 real people shared what they learned and they used their names. The idea is information is to be shared, not hide in shame.

([01:23:18](#)):

Some of these themes are very similar in Dr. Smoller's work at All of Us. The information is available to a larger group of people instead of just a narrow select few. So let's go to the last slide. You are not alone. We like donations. If you're interested in donating to NAMI, individual donations are our major source of income and revenue. We're proud of that. We like that, and if you want to keep it going. Dr. Smoller, I want to thank you for everything you're doing. Thank you for spending your time with us today. I hope to have you back in a year or two so that you can update us on the progress and how we've done together pulling this off.

Dr. Ken Duckworth ([01:24:03](#)):

I want to thank the team behind the stage, Katie Harris, Juliana Hicks, Hagen Stauffer, Genevieve Ellsworth. Nothing is possible without the collaboration of many people, and our team continues to produce these Ask the Expert webinars for free and get the best people in the country to teach us. So I want to thank you all for joining. Hope you have a wonderful day. Take care.

Dr. Jordan Smoller ([01:24:28](#)):

Thanks.