EXPANDING THE TOOLBOX FOR BRAIN DISORDERS

Naveen Rao 00:10

All right. Can you hear us okay? Well, thanks for choosing our breakout. My name's Naveen Rao. I'm going to be moderating the session today. And just quick, let's give a round of applause to the Milken Institute for putting on just a heck of a show. *[Applause]* There's so many events, and just this one feels very different to me anyway, so it's wonderful. So, today, we're here to talk about brain disorders, and a new class of tools, technologies, that's really expanding what's possible in medicine and beyond, as my panelists here have been talking about. So, I won't read through the whole thing. I want to get right into it. Before we kick off our discussion, you should be able to scan a QR code, which I think is either on the back of the program or maybe it's up here. And that'll let you upload your questions into an iPad that I'll use to select and get the Q&A off the ground at the end. Our goal is to leave plenty of time for that, so it's a good time to start thinking about your questions now. Kicking off here, well, why don't we just quickly—do you want to go down and everybody give a quick intro of who you are, tell us a little bit about your company? I'm Naveen Rao. I'm a writer. I have a contributor role at Forbes, and I publish a Substack called "Neurotech Futures," where I analyze the market and try to figure out where things are going.

Christian Howell 01:36

Hi, I'm Christian Howell. I'm the CEO of Cognito. We are a breakthrough neurotechnology company that's using sensory stimulation to drive activity in the brain that orchestrates biology that's incredibly important for the preservation of brain structure and function. We have recently completed what is the largest nonpharmacologic study in the history of neurodegenerative disease. We studied 673 participants for 12 months, measuring the preservation of cognition and function in mild and moderate Alzheimer's disease. My team has a shock collar on me right now because we are announcing the data on Monday evening. I have the single worst poker face in the history of man, so please do not ask questions about what we expect, but I will say that we are incredibly excited. That's the right language, I think, about what we will see on Monday afternoon.

Najat Khan 02:38

Hi, everyone. Najat Khan, I'm the CEO of Recursion. Recursion is an AI-native company that makes medicines. It's a public company. And we have therapies in neuroscience, oncology, immunology, and rare diseases. We just had positive clinical data, so I'm hoping some for you, too. Just a few weeks ago, in

diseases where there's nothing approved. One thing I just want to say from a neuroscience perspective, people talk a lot about maybe we understand at best 10 percent of biology. When it comes to neuroscience, it's probably more like five. And what Recursion does is—the goal is to actually decode biology at scale. So, we've built the largest proprietary maps of biology in the world. One of them is based on a trillion iPSC-derived neuronal cells that we built from scratch in our automated labs. And we knock out the entire genome, all 20,000 genes. And then you can actually study biology at a systems level, which is important because we are complex systems to begin with. So, I'll share a little bit more about what we're doing there, but very excited to be here.

Amy Kruse 03:49

Great. My name is Amy Kruse. I'm currently general partner and chief investment officer at Satori Neuro, which is a venture fund focused on mental health, brain health, and neurotechnology. I've been in the neuroscience space for several decades now. I started my career as a DARPA program manager, leveraging and using neuroscience and neuroscience technologies to improve human performance. But right now, very much more focused on clinical outcomes in this space, particularly as it relates to noninvasive neuromodulation, which we'll talk a little bit about today, but also different therapies and therapeutics in the neurotechnology space. For me, since I've been on this journey for quite some time, one of the most exciting things and one of the most challenging things is that neurotechnology itself is a platform technology. And so, a lot of times as a venture investor, companies get very railroaded into picking particular indications and picking particular clinical outcomes. And one of the most exciting things about neurotech is that it can actually go after a lot of different indications. And so, I think that'll be part of the conversation today is not just what are the most immediate indications that companies are going after, but what are some of the long-term things that are very exciting. So, thank you.

Ali Rezai 05:08

Good afternoon. Ali Rezai. I'm a neurosurgeon and neuroscientist, and I'm the executive chair of the Rockefeller Neuroscience Institute at West Virginia University. We created this institute about eight years ago, and with a goal to help rural America and come up with new solutions for large public health challenges, and we have about 350 full-time physicians and scientists. We take care of about 450,000 patients a year across four states in rural America. And we strongly work with public-private industry partnerships to accelerate discoveries and innovation. So, thank you.

Karen Rommelfanger 05:42

Hi, I'm Karen Rommelfanger, and there's a huge bright light here, so if you see me doing something weird, that's why. I'm a neurotech ethicist and a strategist. And I am one of the cofounders of the Institute of Neuroethics, the first global think and do tank dedicated wholly to exploring the ethical issues inherent in neural innovations and their applications. I'm also a professor at Georgia Tech, in the new Institute for Neuroscience, Neurotechnology, and Society, where we'll be launching a neuroethics by design clinic, a pro bono clinic for neurotech startups. And we'll be talking a little bit more about that today.

Naveen Rao 06:17

Thank you. So, what we're trying to do in the time that we have is really understand what is innovation today, and how do we bridge that into the near future and bring it into society? And what is it going to take on the inside of that industry, as well as all around to get things ready? So, with that, the format is I'm

going to pick one person for one question, but that's just the first answer. So, I'll encourage all of you to weigh in and have a brief discussion, then we'll move on to the next one. We're going to start by taking a look at the current landscape. And Najat, my first question is for you. When most people think of brain disorders and mental health, they think of pharma, pharmaceutical products. My question is, what is pharma well-positioned for? And what is it not so good at and still learning? And what innovation is Recursion bringing into the mix here?

Najat Khan 07:08

Yeah, it's a great question. Look, in terms of neurological disorders, and neuropsych disorders as well, we have about 3 billion people that are suffering from it, and the number's just going up. I would argue it's probably higher than that. They just don't get diagnosed at the right time either. So, when I'll talk about therapeutics, we have folks that are doing therapeutics. We also have folks that are doing nontraditional therapeutics. So, I think there is a holistic way to approach these diseases. I think what pharma is really good at—look, if somebody has a loved one that has Alzheimer's, Parkinson's, ALS, or any other disease today, or major depressive disorder, you're really focusing on therapeutics first. Sadly, that's the case today, and most of them have been made by pharma. I think the evolution that we're seeing is long, and what Recursion's trying to do is, instead of just understanding one target at a time—that is a reductionist approach because most of these disorders—look at cancer. In cancer, it's not usually just one mutation that's driving the disease, it's multiple things. And being able to intercept at the right time is very important. What we're doing, as I was mentioning, at Recursion is if you look at the top of the funnel, you need to understand what's driving the disease. That's the basic core that we have to do. I said before, we understand about 10 percent of biology. In neuro, it's about 5 percent at most. If you look at the number of medicines that are approved for neuro, it's about half that of even normal other diseases. That's like a 10 percent success rate gone down to 5 percent. So, the numbers are really low, and I think that's because we don't understand the foundation of disease to begin with. So, what we've done is we said, instead of starting with mouse models, instead of studying just one gene, can we start with the neurons or the microglia that are actually driving the disease? Neurons, I told you we made a map with a trillion iPSC-derived neuronal cells. That is the largest anybody's made in the world. That is equivalent of 12 human brains' worth of neurons, just to put it in perspective. We have these large factories where we can actually knock out all 20,000 genes at once. From that, we actually have our own foundation models that learn which genes have biologically similar activities as another gene. So, you start to understand not just one gene, which is like understanding one street, but you actually understand multiple streets. You understand the highways. This is so important to understand systems-level biology.

Najat Khan 09:34

Okay, that sounds very theoretical. What happens next? The foundation models are great in terms of pinpointing biology that's already in the books. We see associations that you'll read in a paper that are showing up in our proprietary maps. But then the beauty of it is you learn things that are unseen today. So, I call it the lamppost. Anchor in genes that you know drive disease, but then we can see all of the other genes that are also associated with it. And the last part of it is you go back in the lab and you say, "If I hit these four genes, do I actually reverse disease?" We do this in partnership with Roche Genentech, which is a—we have a 10-year partnership in neuroscience with Roche Genentech. And just three weeks ago, they accepted the first unexplored target in Parkinson's using our proprietary map. That is the first example in the history where you go from novel data that's generated, models that are predicting what could be driving the disease, all the way to validating that back in the lab. That's super powerful, and we have more

of these targets coming up. Last thing I'll say is why is this so different? This is an unbiased, full study of the human genome way of understanding what's driving the disease. And the maps become useful for years. If you think about the frontier models like ChatGPT, Claude, they're trained on millions or maybe thousands of years of human text and knowledge. We don't have that in science. We just don't. LLMs and publications are not going to be enough because you're searching the same known. So, the fact that we have these—we have about 65 petabytes of proprietary data built over the last 10 years. That is going to be core to understanding biology better. So, very, very excited about that work. And not just in neurons, we actually built a hundred billion cell microglia map as well. Why is that important? Microglia are the immune cells that actually drive disease in the brain. Now we can layer neurons and the microglia. The neuroimmune axis, that's core to Alzheimer's, Parkinson's, and ALS. So, we're finding novel targets for all these diseases. Like you said, it's agnostic to a certain indication. It's more focused on how's the biology changing.

Naveen Rao 11:53

Thank you. Any other perspectives on iPSCs or iPSCs neurotech? Anybody want to weigh in? Okay, great. Dr. Rezai, I want to turn to you, and I think this is particularly resonant for this crowd. But let's talk about current standard of care in neurology and brain health. What does it look like at most places? And then at RNI, where you've led innovation really around the corner, what are you doing to sort of bring the whole system forward?

Ali Rezai 12:30

So, current standards, you have the traditional medications that you try and behavioral therapy. You can do other therapies, PT, OT, other things if you have stroke or brain injuries. But really, for me, it starts with the patient and what their need is first in terms of how they're living their lives and with the disability. And I think a lot of these neurological conditions and mental health, Parkinson's, different types of dementias, Alzheimer's, frontotemporal, others, they've been brewing inside your brain and nervous system for 10 to 20 years, and without even you being aware of it. So, it takes that decade or longer before it manifests itself. So, we need to really understand earlier on what's going on so we can detect it earlier, and we're not good at that. We're getting better and better, but imagine we can detect Alzheimer's a decade from now or 20 years from now, or Parkinson's. So, I think understanding that is really important. And also, there's a lot of patients that don't have a solution. People with drug addiction, a lot of failures with drug addiction. There's not many good solutions. We need to understand the neurobiology of things, the brain networks that underpin Parkinson's or Alzheimer's or ALS. So, we're understanding better than ever before what's going on in the brain in terms of these different networks that are malfunctioning, causing tremors, causing stiffness, rigidity, or cognitive problems. So, really, there's a lot of opportunities for us to detect the conditions earlier. So, prevention, earlier detection, and earlier interventions, and I think some of these new technologies that are coming—you discussed traditional medications and other therapies, but a new sector that's really growing very rapidly is called neuromodulation. And what you do is you use light energy, sound energy, magnetic energy, electrical energy with implants and nonimplantable devices that can be targeted specifically to the part of the brain that is malfunctioning, causing the tremor or anxieties, cravings for drugs, and change the function of that network. So, this is a new technology, highly precision-targeted technologies, and we're moving from invasive surgery, brain implants that we've been doing for 25 years, to less invasive or noninvasive magnetic waves, light waves, sound waves that are immediately changing cravings, anxiety, and depression. So, I think this neuromodulation sector is going to move more and more, and it's going to become less and less invasive, even at home—home-based neuromodulation

treatments that can be used for various neurological conditions. So, the combination of medications, talk therapy, and other therapies, plus neuromodulation, is going to transform the way we are dealing with neurological conditions. So, I'm really excited about neuromodulation specifically as far as they can go.

Christian Howell 15:23

Yeah, can I bolt onto that? There's something really interesting that's happening, which is the first question you asked is about what does the pharmaceutical industry do well, and I think one of the things that they've done really well is this idea of thinking about combination therapies, right? The idea that many of these diseases are polypathologic, so the idea that there's going to be a single mechanism to solve the problem is silly. But what we've seen in other disease states and conditions is this combination between pharmaceuticals and medical technologies. If you had a loved one with arrhythmia, you wouldn't say, "Oh, just give them drug therapy." You would say, "No, give them a pacemaker." My wife's a radiation oncologist. No one would say, "Oh, well, just give them chemotherapy. Don't give them radiation." And I think in neurology, what we're seeing broadly is things like deep brain stimulation and focused ultrasound and transmagnetic have been used much more broadly—but in Alzheimer's, we've not. Alzheimer's, there's been—I don't want to call it a rigidity—but there's been a real conviction to taking a chemical or biologic solution to addressing specifically the amyloid thesis. And I think that there's a real moment that you're going to see a breakthrough—maybe on Monday. *[Laughter]* But you're going to see a real breakthrough, which is, I think it just begins to open this door of Alzheimer's disease is a polypathologic disease. It is as important to restore network function as it is to reduce the amyloid load. And so, I think for the first time, the idea here is expanding the toolbox. What you're going to see is the expansion of that toolbox, and I think the ask is that community is as receptive to chemical, biologic, and physics-based interventions as their physician colleagues have been, because we've seen it absolutely transform cardiac and radiation and oncology. So, I think that's what's going to be really fascinating in this.

Amy Kruse 17:19

Yeah, I was just going to add that I think what you were talking about, Ali, was the context of thinking about the brain from a systems-level perspective. When I was in graduate school, it was just a soup of molecules and synapses and how these things interact. And I think now that we've had breakthroughs in imaging, we've had breakthroughs in how we're using fMRI and other structural tools that have given us those targets to start going after, I think it really does advance things very quickly because if you have tools that you can use, particularly in clinical laboratory settings, you can actually go, "How about this? How about this? How about this? How about this?" Right? And you can actually start testing different sites and seeing if someone gets relief from a substance abuse disorder with a particular brain region. And so, I think we've really advanced in neuroscience to more of this, I call it systems-level perspective, where we don't have to worry about pharmaceuticals bathing the entire brain, and off-target effects, and things like that. And so, I think that's one of the most important things, both having the tools to go after those very specific areas and having the systems-level understanding of how complex brain diseases are and the networks that are involved.

Ali Rezai 18:36

Amy, it's a great point in terms of now we can pinpoint, using brain imaging and other technologies, exactly where the problem area is causing your shaking, your stiffness for Parkinson's, your tremors, anxiety, cravings for drugs, mood. So, we know where the regions are in the brain exactly and why they're

malfunctioning electrically, chemically, so we can see them on imaging. Then you can direct light beams, sound beams, and modulate it. So, it's really a new era where you can detect a problem, see where it is, pinpoint it, and then deliver a very focused treatment versus medications. You need to do medication, no question. Medications, you take a pill, it goes into your stomach, gets into your bloodstream, bathes your body head to toe, then it has to go into your brain, cross your blood-brain barrier, get to the area in the brain, and then it exerts mode of action. That's why you have to take a lot of medications, frequent medications, side effects, and so on. So, it's targeted, but it's not super targeted. It's very diffused therapy, and it's necessary, of course. But the new way of doing things is pinpointing the problem, delivering drugs to the exact area by opening the blood-brain barrier or delivering sound, light, and other energies to the area to reset the brain, accelerate the clearance of plaques in the brain, and others. So, that's where the excitement is about this pinpointing the disease and modulating it versus systemic medication therapies.

Najat Khan 20:01

I just wanted to add another point I think that's important is—yeah, I think combinations are very important, but if you don't understand the root cause of the disease, it's a band-aid. You're actually not going to cure any of it or even treat it effectively. We talked about understanding biology better. We talked about these maps. You can understand the relationships. The other place that pharma companies, especially at Recursion, too, that we're starting to use a lot is AI to actually design those molecules, exactly to your point, because what you want is not just molecules that will have systemic exposure, but molecules where you can precisely target it to that protein and ensure that there's good crossing of the blood-brain barrier, which small molecule medicinal chemistry has been a challenge for decades. So, think about designing small molecules. There's 10 to the 60th combinations you can do to design a molecule. That is more than the number of grains of sand on Earth. And as an organic chemist and a computer scientist, I can tell you the best ideas are not located just in my brain. So, it's great to have help. And this is where machine learning models are being used a ton, where gone are the days where you would start with a structure and say, "Hey, let me try to modify it and see if it works." Now what you do is you don't even have to have a 3D structure of the protein that you're trying to target. Even if you don't have a crystal structure, you can simulate it. And what you do is you take the end in mind and say, "If it has to look like an L, give me all the combinations in the world that could give me an L that would cross the blood-brain barrier, that would not go to your liver, that would not do X, Y, and Z." And we can do that now.

Najat Khan 21:37

On average, it takes us about 16 months to make a small molecule that's ready for the clinic, which usually in industry today takes four to five years. And then another stat to note, we end up designing physically about 300 small molecules for the one that goes into the clinic. And in industry today, it's about 4,000 to 5,000. So, you're getting a 10x productivity, a third of the time. That's just the start. And I think that's really important if you think about not just understanding the root cause, but then saying, "How can I design that small molecule that would actually be what a patient would take in addition to all of the neuromodulation solution?" So, you're coming at it with many different solutions. The third piece I would say where we're also using AI is figure out which patients would respond. If you look at any clinical trial, in general, 20 percent to 30 percent respond. Why? Why are we exposing patients that would not respond to this? And how do you do that? It's exactly what you said. We're starting to use a lot of the brain MRI images, whether it's in oncology, solid tumor images, the biopsies and stuff, and ML models that are predicting that based on the biology that you're modulating, I think these patients would respond. I don't have a great neuroscience example for that, but we just had an oncology study that had positive data in

endometrial cancer patients late line. They're on the verge of palliative care. We predicted those patients would respond, and they did. So, I think this is how you go end to end from the biology to making the molecule and then figuring out which patients would respond, at least from a—which would benefit not just whether you're doing small molecules and therapeutics, but quite frankly, it would also benefit even if you're doing other approaches like neuromodulations.

Naveen Rao 23:16

This is great. I'm going to just jump on into the next question. You set me up perfectly. I wrote this article saying there's no moonshots with paper planes. And something that persists to this day is the gold standard for measuring what happens in a patient is asking them questions. And I'm going to ask Karen later about how to really keep people at the center of innovation, but huge bottleneck. Huge bottleneck from designing a study to seeing if these new treatments work, how they're working. It's incredibly subjective. And I think that is changing in real time. And Christian, this question's for you. You've been leading a lot of this work. We're seeing a big shift past these rater questions, in addition to them, towards biomarkers and multimodal measurements that are really changing the way we evaluate if a treatment is effective or not. So, why is that so critical with the brain, and how are you guys really proving out your science?

Christian Howell 24:13

Yeah, this is again—now I'll go back two questions. Another thing that I think pharma does really well, which is, I used to work for Scott Gottlieb, and Scott used to say the evidentiary burden for drug therapies is in the premarket, and the evidentiary burden for device therapies is in the postmarket. And the reason is because devices don't meet that premarket requirement, and that has to change. The idea of doing a six-week study on 40 bike-riding Norwegians and saying, "I've got really strong clinical outcomes," can't be the case. You have to do really robust clinical research because you have to build trust with the clinicians and with the patients and their families. And so, I think all of these advances are incredible, and I think there's a way to very safely get them to patients and their families, but I think it is critical that we have a much higher validation bar on the medtech side of the house. And part of that is not just saying that this is safe and is effective, but getting much more clarity to the mechanism of action. And boy, I will tell you, device companies, MOA is a four-letter word for device companies. They don't love the idea of a mechanism of action because oftentimes it's a tool, right? They're not thinking about what's happening biologically. We had to take a very different approach and say, "We understand what's happening at the proteomic level. We understand how those proteins are then manifesting into changes in brain structure through volumetric MRI, how they're changing into brain function through the measurement of EEG," and then we had to track that longitudinally with patients because I can't, in good faith, go to a neurologist and say, "Hey, you should give this to your patients. I don't know how it works, but the outcomes are really good." Right? And that comes through much more rigorous clinical research. And candidly, it's a bit of a call to action to the investors in the room. Stop with the, "We will invest a little bit up front, but then we want to put all the money in on the backside commercial," because the valley of death is real for medical technologies. Spend the time up front to build a comprehensive evidence package. That package will help you through regulators, it'll help you through CMS, it'll help you through insurance, it'll help you with patients and families. But we don't think that way. We think episodically. Get from one point to the other, and then you're in the valley of death, and man, it's a painful process. So, I think these technologies have an unbelievable opportunity to impact patients. We cannot underfund the validation of them, and we have

to be able to demonstrate not just the CDRH standard of safety and efficacy, but also the patients and the families and the clinical standard of, help me understand how this works.

Naveen Rao 27:13

I'm new to neurotech. I'm like four years in. I had never heard of this phrase, the valley of death. Who's heard of that phrase in the context of med—okay, there we go.

Christian Howell 27:23

Same hands, how many people have invested in a company that's in the valley of death? Okay, same hands go up. *[Laughter]*

Amy Kruse 27:27

How many people have been in the valley of death? *[Laughter]*

Naveen Rao 27:31

But I think, I'm just sort of going a little off script, but one of the most exciting things that I've written about is your collaboratory. And since I got the one-two punch here on stage—maybe just a couple of minutes, walk us through this model of really a tech company partnering with a health system to do things that are not possible individually.

Christian Howell 27:52

Yeah, this is the furthest I've been from Ali in a long time. We are connected at the hip in many ways. So, look, the discovery at MIT was remarkable, right? This idea that you could modulate the brain's activity to drive biology that was going to have such a profound impact on brain structure and function. And so, when I was fortunate enough to become the CEO of Cognito, what I realized was, holy sh—like, the opportunity here, how do I even think about delivering to 10 million people with mild to moderate Alzheimer's, or MCI to mild, while I explore all of these other indications like Parkinson's and MS and epilepsy and stroke and traumatic brain, while we think about all of this biomarker research? And I could raise billions of dollars and hire thousands of people, and I still couldn't create the ecosystem necessary to be able to do all of that, which is my responsibility as the steward of this technology, to make sure we answer these questions. So, the first thing I thought of was, we need to build collaboratories with leading neuroscience centers where we break down these traditional walls between life science companies and academic centers, and we say, "Look, for the greater good, we need to explore as many elements of this as possible, understand where it works and where it doesn't, how we get it to patients and where there are inefficiencies, where the cost makes sense and where it doesn't." But all these questions, and I needed an ecosystem to test that in, and I was stress-eating one night on a Sunday night, and I saw a *60 Minutes* piece with Dr. Rezai, and I said, "Okay, let me reach out," and we've been unbelievably connected through this whole process. And what started as a collaboratory with RNI grew to a collaboration with West Virginia University, which then grew to a collaboration with the state, which has now got this footprint and this model that we've taken to Louisiana and Rhode Island and other states. So, I just think that with these breakthrough platform technologies, we can't let hubris get in the way of their development, and we have to reach out to the great minds and say, "Help guide us on how we bring this to patients." And that's what our goal was with RNI.

Ali Rezai 30:09

I think you've got to look at real-world data. So, you have to go like—we're a rural footprint, four states. Pennsylvania, Maryland, West Virginia, and eastern Ohio. So, while longitudinally we follow hundreds of thousands of patients, so we have the data longitudinally. So, if you have new technologies, you got to understand if it's going to save money ultimately. You got to look at electronic medical records and follow the patients, not just if they meet the primary inclusion/exclusion criteria. So, I think this real-world data that people talk about is really an important element. And what we're trying to do is deploy these new technologies in the most rural parts of the country at home, minimal invasive technology. So, I think that's really important. And we have to go beyond just the basics of clinical trials and get quality of life and real-world data built into everything. That's how you can expand things versus just getting your primary and secondary outcomes.

Amy Kruse 30:58

Right, and I was just going to add, we were talking in the back as we were waiting to come on stage, and as an investor, one of the things that I've, from the get-go in terms of the work that we've done in neuromodulation, is think about things that can be deployed and can be used at home. One of my companies just got a plus-up from ARPA-H in the EVIDENT program, which is mental health-focused, to actually put their low-intensity focused ultrasound devices in vans and drive them out into the community and treat folks there. And so, I think it's really, really important, as we have these incredible centers of excellence and fantastic university hospitals, that we also think about how does this technology sort of get out into the world. And so, I have been biased as an investor to things that can travel. Maybe that was back to my DARPA days when I used to think about what technology was deployable to the field, right? And I think that's something that is really important as we think about health, because it's not enough to just have folks have to go somewhere to get excellent treatment, but to have those treatments go to them.

Christian Howell 32:07

Yeah. In more mature markets, you think about a competitive advantage. How am I better than this other solution? In markets, certainly in Alzheimer's, that are as nascent as they are, and the lack of infrastructure. I mean, look, the standard of care at RNI is incredible, but is not the standard broadly. What we need is a collaborative advantage, right? It's how do we work with the pharmaceutical companies? How do we work with the diagnostic companies? How do we work with the care delivery? Because that's how you get cancer centers that are doing tumor boards and cross-functional. We need the exact same thing in the neurosciences. And I think companies need to be less concerned about how does my preservation on the CDR-SB compare to their preservation on the CDR-SB and saying, "How do we create an ecosystem where we put the patient in the middle, and we allow that collaboration to form around them so there can actually be impact?"

Amy Kruse 32:59

I was just going to say one last thing. In interventional psychiatry, what's happening is clinics are standing up that are deploying multiple modes of intervention. So, there's TMS and there's Spravato, and maybe they're a clinical trial site for low-intensity focused ultrasound, and I think that's going to be a wave of the future. I agree that, of course, we want individuals to have all accessible care and have it be reimbursed and have it be covered by insurance, but as an investor, companies also need to get out there, right, and

start eventually generating some revenue. And so, I think some of these models that are popping up that are more intensive clinics or other things like that, obviously, probably in metropolitan centers to start, but I think that's very exciting in this space.

Naveen Rao 33:43

And there's a huge rural health opportunity that sells itself. So, we've spoken a lot about doing things for people, clinically doing things to people. I want to shift gears and talk about doing things with people. And Karen, this question is for you. It's, in terms of translating this into better futures collectively for everyone, how do we do it? No, just there are a lot of vulnerable populations when we talk about mental health, brain health, neurology, dementia. How do we avoid paternalism—and do things to people, even if we mean well—and really center human agency at the heart of this innovation?

Karen Rommelfanger 34:28

Yeah. That's easy.

Naveen Rao 34:32

No pressure.

Karen Rommelfanger 34:32

Yeah. That's easy. No, I think foundationally though, I think there's something that brings us, probably many of you to this room. There is something different to you about the brain versus another organ, right? If you had a kidney transplant, you're still you. You have a brain transplant, hmm. I've written about that. We can talk about it later. But there is something different because from the brain, science and philosophy for thousands of years has been building the case that from that arises our identity, our free will, our emotions, our cognitive experience. And so, when someone in your family has a stroke, or when someone has a catastrophic injury or dementia, the question isn't what are predictive biomarkers to that person? Although that's helpful. It's is that person still there? Hmm. Is my mom still going to be there tomorrow? Can you bring him back? So, this is foundationally, we are working on technologies that are self-narrative building and empowering. And because of that, necessarily, the people that you're trying to serve, the patients you're trying to treat, need to be involved in that process. And we need to trust that there is some lived expertise in that, even if they don't know what foundation models are, even if they think AI is conscious, even if they're X, Y, Z. So, one of the ways that we think about doing this in our think tank is often trying to bring in lived expertise into a lot of our—we do a lot of global governance in this space. So, how do we bring people who have expertise in science? How do we bring expertise in technology? How do we bring people with expertise in the lived technology to talk about not just how the science works, but how it's going to be implemented in society and what kind of safeguards need to be in place? And so, we work on those kinds of solutions.

Karen Rommelfanger 36:33

But then, secondarily, we've been developing a systematic method. So, this is—it's kind of in vogue to hear this type of language. You might have heard ethics by design, and so we've been working on neuroethics by design, and that means considering ethics as a core design criterion. So, from the minute you're thinking about what your scientific question is, even how you're going to represent a disease—and a lot of brain

disorders and diseases are highly stigmatized, right? And it varies across cultures. You can get communities involved to talk about how are ways that we can talk about modeling this in ways that aren't going to reinforce stigma, that are going to further lift people up. When we're designing technologies, can we design technologies that are recording our brains and let us know when that's happening? Can we just have a light? I've worked with some clients where I just say, "Can you have a light on when it's recording so people know?" Can you have human-readable consent policies? Even—I've advised for the National Institutes of Health, I've been on their neuroethics advisory group for the longest time. We still can't get everyone to write consent forms at the eighth-grade level that are human-readable. It was unbelievable. You can just run them through your Microsoft now and do a Flesch-Kincaid thing, which I often have to tell clients to do. So, there are ways to do that, and there are ways to involve participants in how you think that these technologies are going to be deployed. So, like Amy was saying, what would it be like to have these deployed in the field? What is it going to mean to have a technology that you can see that I'm wearing on the outside, and what is that going to make me feel like when people can see that? So, it's really important to think about how these technologies are changing people's fundamental—not just capacities for who they are, but even their conceptualizations for who they are. And these are partners, and they can also be powerful partners, even research partners at the earliest stages of research.

Naveen Rao 38:20

Thank you. I have this dad joke. I always say, health-care innovation, like, oh, things can't get worse. But I think here they really could. And I just want to underscore that your work is incredibly important, especially at this moment where we're really translating this into people's lives. So, thank you. Okay, Amy, you're going to bring us home. Last question before we turn it over to the audience. You are someone who, like me, you're at 30,000 feet just looking at trends, and you've been in this game for the whole time it's been a game. So, I'm just curious, as you think about neurotech's evolution, what have you seen evolve over the course of your career? And then the shadow question is what have you seen that has not yet evolved and really needs to?

Amy Kruse 39:05

Very provocative. So, I think at that 30,000-foot level, a lot of the things that we used to think were science fiction, thinking of implanted brain-computer interfaces and other things like that, we really are standing on the shoulders of 20 years of government investment and innovation and communities coming together to build those systems. And so, one thing I would encourage folks to think about is that this really is the culmination of a lot of research from a lot of different laboratories and clinical research centers and things like that. And so, that's the top level because, as an investor, I have to convince other investors to invest in my companies. And a lot of times people are like, "Oh, I don't know. The brain seems so complicated. We'll never figure it out." And we actually have a lot of data and a lot of clinical evidence to point us in that direction. And so, I think that's one thing. Where I think things have not developed is actually, for a long time, folks thought there was going to be a big consumer neurotech space. That measuring all these brain states in real time, we're all going to be walking around with brain headbands on and things like that. That's not happened, and as far as I know, most people don't want to wear a headband—nobody. People might wear earbuds or headphones, but I think we have, in that space, we have developed a really different relationship about data about ourselves. And so, as we measure our sleep, as we measure our stress, as we measure these things, we are getting into this interesting landscape of, we used to think, like, "Oh, you'll never be able to figure out who somebody is based on their EEG data." And now with AI, maybe you could figure out who somebody is based on their EEG data. And so, I think

neuroscience hasn't yet come to grips with the big data questions that are impacting other spaces. And I think as we race to create new solutions and new technologies, I'm very heavily influenced by Karen and her work on thinking about the ethical implications of this space. And so, for me, the patient is sort of front and center. The clinical outcomes are front and center, even though there's a lot of noise and excitement around the brain space.

Karen Rommelfanger 41:46

Can I add something to that?

Naveen Rao 41:47

Sure.

Karen Rommelfanger 41:48

It's just, I think there is a danger these days in becoming almost too, like bowing at the altar of data analytics. Bowing towards a digital simulacra and a significant devaluing of subjective experience. It's not to say there aren't shortcomings in relying solely on subjective experience, but just because we get to these great foundation models, just because we can use AI wherever we want, doesn't mean that it doesn't still need the input of the subjective experience to validate and make sure that we're getting something that is going to be useful. So, the more and more data that we collect, and by the way, I think the danger too, is that people aren't digital libraries. People provide data information. That's a distinction that we have to remember. People are more than that. And so, we have to remember to keep that human element in there and get that kind of human feedback even as we move towards these models. Because as we collect more and more data, and we only rely on the data, and we have massive amounts of data that we should use, it's true, we see the disappearance, the ghost of the data donor, the ghost of the research participant. And in their ghostliness, they become dehumanized, and we forget that if they were a participant, a human participant that you were pulling blood from, for example, you might give them a different kind of dignity, different type of regard, a different type of consideration for interest that become easy to forget, especially when we think we're pursuing such a noble cause. Like, I want Alzheimer's to disappear. I want cancer to disappear, but not at the cost of the people that we're trying to help.

Ali Rezai 43:34

I mean, these are human experiences you're saying. So, for example, and we don't understand, but the brain disorders, like people can have PTSD, depression, anxiety, addictions. It's a spectrum. You can have cognitive problems as a patient with Parkinson's disease. You can have behavioral problems, a patient with Alzheimer's, frontotemporal degeneration, others. So, there's a large spectrum, and that's why some of these medications and drugs don't work, because you asked me earlier—because we don't know. So, we label obsessive-compulsive disorder very heterogeneous. Depression, very heterogeneous. So, these are symptom-based conditions. So, I think the human component is really important, and we box people into different categories, but it's not. It's really a continuum of symptoms that we need to address.

Christian Howell 44:20

There's something really interesting we learned at Cognito, which was when you design a traditional medical device, you are designing it for a surgeon to use, right? So, you have this sort of singular endpoint

of design, and I think when you're designing a drug therapy, you're thinking about a target or a mechanism. In Alzheimer's specifically, it's a plus-one disease, right? So, when someone is diagnosed with Alzheimer's, it's not just their life that's impacted, it's their husband or wife's life. And so, in our UX research, we took those people into consideration. Things like when should the therapy be delivered? Are there signals that we can give to a caregiver to understand how somebody is progressing? Is there data we should be sharing with them? It's a very interesting dynamic with noninvasive, and specifically in neurodegenerative disease, because it is impacting the family. The health of the caregiver is dramatically impacted with a diagnosis of Alzheimer's disease for a loved one. And so, how do we design ecosystems where we're not just thinking about the impact of the therapeutic to the patient, but the ecosystem around the technology and the platform for that broader continuum?

Naveen Rao 45:36

Yeah. I wish we had another hour so we could answer all these questions, but they're coming in hot and heavy. So, this is wonderful. We're going to take some Q&A from the audience. This is a wonderful question, so I'm going to start here, and I'll ask for lightning round responses. Yeah. And we'll start with you, Christian, and just go down. If you could smash one piece of misinformation in each of your focus areas, what would it be?

Christian Howell 45:47

If I could smash one piece—

Naveen Rao 45:59

Hulk smash.

Christian Howell 46:00

—of information—

Amy Kruse 46:01

Misinformation. Misinformation.

Christian Howell 46:03

Oh, I mean, look, I adore my job. But trying to convince the world that sound and light is going to have an impact on Alzheimer's disease has been an incredible—there is a massive headwind to that. Now, thankfully, that forced us to do a great deal of clinical validity, and now that becomes a tailwind for us. But I think oftentimes just the initial disposition toward—if it's not pharmacologic, I enter with a state of distrust. It drives me nuts. Right? We have seen exercise be one of the most impactful things to cardiovascular health. Imagine if back in the day they said, "You're going to jump on a treadmill, and your heart's going to get better?" Like, come on, right? So, that would be one, which is this sort of over-indexing that it has to be a chemical or a biologic to change mind. I don't want anyone to just believe it right off the jump, but don't start in a hole.

Naveen Rao 47:05

Sure. Right, Najat?

Najat Khan 47:07

So, many to pick from. I think there's such a duality right now in the media, which is you hear some folks saying, "With AI, cancer, Parkinson's, Alzheimer's, cardiac diseases are going to be cured in sometimes three years, sometimes 10 years." We can't even run a trial in three years in Parkinson's, or seven years even. So, that's one piece. And then you have others that are huge naysayers, right? In terms of AI is never going to make a difference because it threatens our self of knowledge. And I wish we could have a more sensible conversation about the fact that there is so much to explore, so much to figure out, but you're not going to cure things in three to 10 years, and you're also, we can't keep doing things the way we have done it. And then the other thing I'll say, just tied to that, is often when I say that, people say, "Yeah, but people are going to be gone." Every single example that I have mentioned is a combination of AI being used by a person. So, what the future's going to look like is, take people who have the heart and ingenuity and supercharge them with a lot of these agents. And I feel like there's just this misconception that we're all going to be robots, and Terminators are going to jump out of somewhere, and it's just not how it works.

Amy Kruse 48:24

I'm going to tell you something absolutely crazy. So, I'm an investor, and I have to fundraise from other investors, right? They're called LPs, limited partners, and they invest money in us. And when you present them with a thesis around the brain, brain health, brain technology, people ask you, "Isn't that a niche area?" *[Laughter]* And then I just had to start saying, "Everyone has a brain." Like, that was my answer. Hopefully. That's all I got.

Ali Rezai 48:59

I echo that. People need to understand there's a new era for people having neurological conditions. We can better than ever detect it earlier and have better therapeutics. And Christian, I agree with you, neuromodulation, I think it should be a routine standard at home, outpatient clinics. And I think people say, "No, let's try medications first. Let's try to make patients refractory." When I was doing the surgeries, I remember 25 years ago at NYU for Parkinson's, they said the patient has to be completely disabled, in a wheelchair and end-stage, before you consider neuromodulation. So, I think you should explore minimally invasive neuromod technologies in the beginning, as well as medications. So, I think that's really important. And not give up. And I think also, don't wait to do 20, 30 years of animal research. Very important to understand mechanisms, but get into patients quickly. So, you don't want to wait 30, 40 years because Alzheimer's is not going away. You've got to tackle it or other things. So, you've got to jump on also exploring patients versus less than 30, 40 years of animal research before going to patients.

Karen Rommelfanger 50:04

Okay, let's see. Ethics is not compliance. Smash. *[Laughter]* Legal compliance, I often get this: "Oh, I'm legally compliant, so I'm ethical, okay?" And I'm like, "Remember slavery?" So, it's important to be, especially in this space, as I mentioned, this technology's amazing. It's going to transform who we are, who we can be. And that requires something a little bit faster than regulation, right? That requires regulatory readiness, adaptability, being nimble. And this is, again, where I say, if you design ethics into your product from the very beginning, then you're not having to wait later until the catastrophe happens, and it

undermines the whole already tenuous field. So, working towards being regulatory-ready is something that you can design into a process. It doesn't have to be after the fact. So, that's my smash.

Naveen Rao 51:03

Nice. Well done. What are some opportunities to combine neurotech with pharmaceuticals?

Amy Kruse 51:08

Hmm. I have a couple of examples. So, one of my companies that's working in transcranial magnetic stimulation has started to combine that therapy with what we call psychoplastogens or neuroplastogens, and have been able to accelerate a five-day treatment in depression down to one day in depression. And so, I think there are many opportunities for combining things that perhaps enhance plasticity in the brain with neuromodulation techniques to get faster responses. We've also seen—I think Ali referred to this earlier—we've also seen using low-intensity focused ultrasound or other modulation devices to uncage molecules at very specific parts in the brain. Folks are using bubbles or other things to cross the blood-brain barrier in very specific places. So, I think it's emerging, but I think it's very exciting.

Najat Khan 52:08

Can I just provide a counterperspective on that? I think one of the challenges on the therapeutics side is when you do a combination for therapeutics, let's say you take two drugs and you want to do it versus placebo or whatever, a lot of the time regulators will ask you, "I want to see what does A contribute, what does B contribute, and then A plus B." And then you still have to do the control. So, think about that study. That's a four-arm study. It's going to be expensive, it's going to take a long time, and there's a lot of placebo effects, too. Now you add on top of that a neuromodulation or some sort of medtech. And I was at J&J, so I did the pharma and the medtech side, so I believe in both. I think the challenge is, unless you actually understand the mechanism of action, which is a "yay" word on the therapeutics side, unless you understand that, you get a lot of pushback from regulators to be combining that with another investigative small-molecule agent, because you're like, "Well, tell me the contribution of each." And so, a lot of the research as to how medtech, neurotech is done has to evolve a little bit of what you're saying, where you actually understand what is driving the potential benefit. Because without that, we can have that conversation, but you go into that regulatory conversation, it's very different. You get a ton of pushback in terms of combining. So, I think we need to hold a high bar in understanding the science. Not taking 20, 30 years, couldn't agree more. But that's a reality of what we face.

Christian Howell 53:29

Yeah. I'll just say for Cognito, we're not a company that's going to die of starvation. We're a company that's going to die of indigestion, meaning—*[Laughter]* Right? So, obviously, combination with the monoclonals in Alzheimer's disease, combination with just DMTs in MS around myelin, combinations with the GLPs. We stand firmly in the known that we can stimulate the brain starting at 40 Hz, staring out into an abyss of the unknown, which is, what are all the biomarkers that we're seeing? So, if we're upregulating myelin proteins, what could be the impact to MS, and how could that be coupled? We're seeing expressions of things like vasoactive intestinal peptides, which the GLP manufacturers want to use in metabolic disease. So, I think we are just at the dawn of this, but I agree. I think we want to be super responsible about it, and we want to be early to the regulators to say, you have to be thinking about this from a risk-benefit analysis and not slowing the progress by overburdening the evidence requirement.

Ali Rezai 54:34

You got to break open the silos. The medtech and pharma, they don't talk to each other. They're like—no. And I think this window of plasticity that happens at a young age all the way to your 90s is really important. So, that's when you combine pharma and devices together, so that plasticity window is critical in all of our lives. So, we need to have better collaboration. I think they're too siloed.

Naveen Rao 54:56

Great. It wouldn't be a health-care conference if we didn't talk a little bit about reimbursement, which is shockingly like half the questions on here. So, I'll try to combine them and just ask, maybe Amy, we'll start with you: "What is reimbursable? What is reimbursed today? And with these emerging modalities like focused ultrasound, how far away are we from having an actual market to bring these companies in and have them run a sustainable business and help a lot of people?"

Amy Kruse 55:24

Yeah, I think all the companies in this space are interested in reimbursement because we know that, A, it unlocks a very large market, and B, more importantly, it gives it more access to individuals who need the treatments. I think we are—and I said this earlier—I think we are seeing innovation in ways to get first-to-market revenue into companies, so they make it long enough to go through the reimbursement pathway. Obviously, we have companies in our portfolio and other companies that have gone through the breakthrough designation process. We still lack clarity on how those breakthrough designations will result in faster reimbursement pathways. There's the new rapid program. Nobody knows how it's going to work. And so, there is some confusion there, but there's also, because there's so much unmet need in the market, there is this sort of frontline interest in cash pay that I think can help some companies get there.

Ali Rezai 56:32

I think as people know, FDA approval does not mean reimbursement, so that's a big window. So, when you design trials, you have to also bring in quality of life and other elements that CMS is interested in, into the trial. So, that's critical. Every trial should incorporate those elements at the beginning, versus waiting, getting the approval, and then looking at those.

Amy Kruse 56:51

Right, and then going like, "Oh, we missed it."

Christian Howell 56:53

Here's the headline that'll be picked up by my bad comment, which is, "Medtech CEO fiercely defends CMS," which is—look, I think CMS is oftentimes put in an incredibly difficult position, which is we're looking for reimbursement without the data necessary to support what the economic benefit is and what the clinical benefit is, which is why I'm such a fierce supporter of early-stage clinical evidence and developing, asking those questions early. The idea that medtech companies aren't thinking about a comprehensive evidence strategy and understanding all the questions that are going to be asked along the way is just amiss, right? And so, I think it's an unrealistic ask of CMS if we are bringing light evidence packages to the table—I think it's no better timing in the history of the world than Lee Fleisher walking in

as I'm defending CMS, by the way—is the idea that we should really be thinking about giving as robust an evidence portfolio to them as possible.

Naveen Rao 57:50

Thank you. One final question, probably. This is an awesome one, but we're talking about neurotechnologies and next-generation treatments. I think there's this—the misinformation I would smash is, oh, this is a silver bullet. It's going to fix everything. Boom! Dementia, done. Depression, gone. Actually, these are potential treatments, but then afterwards, people are left to rebuild their lives, physically with rehabilitation, whether it's a brain-computer interface or PTSD. How does the industry partner with communities and nonprofits and the sort of social determinants of health layer that make up so much of our lives following a successful treatment, that last mile? Any thoughts?

Ali Rezai 58:36

I think you need to have an ecosystem. So, you're right, you can't just say treatment and then one and done. So, you have to have a system and infrastructure to look at going back to work, going back to school, being able to have the mechanism to pay for your families. Because a lot of times when you have a disease, you cannot take care of your families, and the loved ones have to take care of you. So, that ecosystem after the treatment is critical, and that needs to be operationalized as part of a management approach after the treatment as well. It's really critical.

Amy Kruse 59:04

Right, I was going to add, specifically speaking about the implanted BCI community, we have the collaborative community that's been built that includes lived experience, caregivers, and other input, and I think it's been one community where we've really leaned into thinking about all those elements of how that works. I don't think it's that sophisticated yet in other places within the kind of neurotech toolbox that we've been talking about, but it's one place where we're definitely leaning in as a community.

Karen Rommelfanger 59:42

I've actually been surprised to see more companies take on trying to set up a patient advisory board. In earnest, not just for ethics washing. But just trying to set up a group who can co-create some of the solutions to understand the problem space and what that's going to look like long term, whether it even means backwards compatibility for products that are produced. Like, that's an implant. How can we make parts of it so we can get software updates on the outside? And how do we maintain those products, and how do you get reimbursed? So, I think there's hope that there is a little bit of a shifting culture in that space, and I hope that it gets adopted more widely.

Naveen Rao 1:00:27

I want to bring it back to the Milken Institute, which has really been at the forefront of so much of this innovation if you look at its website and its programs across the board. So, how about a round of applause for our hosts and for my panelists? *[Applause]* Thank you so much.

Announcer 1:00:49

We hope you enjoyed the discussion. Be sure to utilize the mobile app to stay up to date on the latest programming changes. As you exit the room, please remember to bring your belongings with you and make your way to the grand ballroom.

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