Interest Group 3: Leveraging Biomarker Enabled Deep and Frequent Phenotyping Studies in Neuropsychiatry and Neurodegeneration: Promises and Challenges

Husseini Manji: Thank you very much Victor. I think we'll get started with this interest group.

I'm Husseini Manji. On behalf of our committee, which includes Danny Pine, Frances Jensen, David Holtzman, Marina Picciotto, and Richard Mayeux, it's a real pleasure to welcome you to what I think is going to be an outstanding National Academy of Medicine session under the auspices of the neuroscience, behavior, brain function, and disorders group.

I think you know, everyone who's in this audience really well knows that the major neurodevelopmental, and neuropsychiatric, and neurodegenerative disease really exact a tremendous personal and societal toll worldwide. Unfortunately, a global burden and societal impact is just continuing to grow. So it's clear that we really need to come together as a society and tackle these diseases and disorders in a meaningful way to improve outcomes for millions around the world.

I think in this regard it's really noteworthy that we are making tremendous advances in the basic science arena, and just some of these advances would include the tremendous insight from genomics that are providing insight into both disease biology as well as the mechanisms by which gene and environment interact. Similarly just this past week or two, The BRAIN Initiative announced a comprehensive description of the cell types in the cortex or courtesies of mice, monkeys, and humans. I've no doubt that this landmark achievement will undoubtedly, dramatically, and broadly accelerate progress in neuroscience research.

I think it's also clear to most of us that in addition to this outstanding basic science research, there's also much that can be learned from longitudinal biomarker-enriched human studies. Such human studies, which can be built on a strong foundation of data science, can help drive success using multimodal human data to enable research. I think we're very fortunate that there are several important studies underway that are yielding novel insights. Indeed, this year's NAM meeting will bring together leading investigators to bring their expertise to bear on these critical issues.

As you can see, we have outstanding presentations planned today. We'll hear about the growing understanding of dementia including some very elegant studies on early onset dementia. Something that's obviously very timely, we'll hear about the neurologic and psychiatric impact of SARS=CoV-2 infection, which is really causing tremendous burden to society. Importantly, as you will hear, many of the mental illnesses strike individuals when they're relatively young, so we're delighted to have a presentation on innovative youth mental health studies from the UK. We'll also hear about early emotional development and a landmark study called the Adolescent Brain Cognitive Development Study. We'll end with a few comments about the critical importance of what we call "cognitive and mental capital."

Logistically, each speaker will speak for about 20 minutes and each talk will be followed by a 5-minute question-and-answer session. We would ask that you submit your questions through the question function in Zoom, and we will field them for the particular speaker.

Now it's a great pleasure to hand it over to my colleague, David Holtzman, to introduce the first session. David?

David Holtzman: Thanks very much, Husseini.

Our first speaker is Randy Bateman. Randy is the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University in St Louis. He's a member of the National Academy of Medicine.

Randy has developed pioneering approaches to measure the synthesis and clearance of central nervous system proteins in humans. These approaches have led to new discoveries of the mechanisms underlying the buildup of proteins in the brain, such as amyloid beta, and more recently to the development of the first clinically available blood test for brain amyloidosis. He also leads an innovative and game-changing program in which he and colleagues worldwide are performing primary and secondary prevention trials in individuals with autosomal-dominant Alzheimer's disease. This initiative promises to hopefully develop some of the first treatments that delay and prevent the development of cognitive decline due to Alzheimer's disease. Randy, we look forward to your presentation.

Randall Bateman: Thank you, David. Thank you, Husseini. I'm going to show an overview of Alzheimer’s disease and dementia and try to highlight a few parts of recent development in our field.

Shown here in this next slide are my disclosures. I'm going to particularly cover a lot of research that's been supported by the National Institutes of Health and supported by our pharmaceutical partners as well as philanthropic groups, and also talk about the recent development of blood tests that have now been commercialized by C2N Diagnostics, a company that I helped co-found.

To start with the basics about what is the difference between dementia in general and Alzheimer's disease, dementia is any impairment in cognitive thinking or performance that impairs function; Alzheimer’s disease is one kind of dementia, and it's defined by the presence of plaques and tangles in the brain.

Many people will develop amyloid plaques as they get to their later years in their 60s, 70s, and 80s, and when those plaques are associated with tau tangles, it's typically associated with the dementia of Alzheimer's disease. The dementia of Alzheimer's disease typically starts with a short-term memory impairment and then progresses to other cognitive decline, eventually affecting most central nervous system functions, including those needed for life. The challenge of Alzheimer's disease is enormous. There are millions of people affected by this disease. They and their family members suffer as the disease progresses over time, eventually leading to death.

Alzheimer's disease is defined by these pathological features of amyloid plaques and tangles and has a common pathophysiology amongst its different forms but may have different pathogenic causes. Some of these causes are known in rare cases, such as mutations in PSEN1 or PSEN1 or amyloid precursor protein. Also, there are risk factors including the genetic risk factor of ApoE4 alleles and environmental risk factors. And Alzheimer's disease is a relatively unique disease that exists in humans, unlike other diseases that are not animal models that recapitulate the entire Alzheimer's disease process.

Shown here is a photomicrograph of an amyloid plaque. You can see here where the dystrophic neurites within the plaque and a tau tangle within a neuron in the brain. This was the first biomarker per se of Alzheimer's disease and is what we use to define the disease today.

Now we can track these pathological changes with imaging studies in life. Shown here in the ticker is the number of years before first-symptom onset in individuals who will get the disease. You can see the amyloid plaques depositing throughout the cortex and subcortical regions in the brain, followed by hypermetabolism in the brain, shown here by an FDG pet scan, and cortical atrophy before symptom onset at zero.

These units are in years, and so you can see that the Alzheimer's disease process is quite long. It really begins about 15 to 20 years before first-symptom onset with the growth of amyloid plaques, followed by changes in metabolism, cortical atrophy, and other biochemical changes. By the time the first onset of symptoms occurs at zero, people have already had 20 years of progress in the disease process before the symptomatic phase continues in the next 10 years.

Shown in this graph is the measurement of these changes and how they occur. As I highlighted, the symptomatic phase of the disease really is about the last third of a disease process that starts 20 years before symptom onset. We tracked these changes, including now the changes in tau pathology by tau PET, and have noted that the tau pathology really increases in the symptomatic phase—and so we call this the tangle-predominant phase—while the amyloid plaques predominantly increase in the asymptomatic phase in the 15 to 20 years before first-symptom onset.

The period before this is prepathology, before there's pathological changes that can be detected in the brain, but there are biochemical changes that may be occurring even before then. When we think about clinical trials, we think about the clinical stage of disease in terms of the symptomatic or asymptomatic phases. In the asymptomatic phase, we break these down by secondary prevention, when pathologies are already present, and primary prevention, before pathology begins.

In terms of biomarkers and our ability to track the disease in life, why would we perform tests for Alzheimer's disease? Why develop more biomarkers on the pathology? There are two main reasons. One is research based and the other is clinically based.

In the clinic today, the cause of cognitive impairment in most older adults is often unclear or multifactorial, and diagnostic accuracy in the clinic is not so good. We estimate that about 50% of diagnoses, either incorrectly diagnosed as Alzheimer's disease when it's not or not being diagnosed with Alzheimer's disease when it is, is only about 50% accurate in primary care settings while in specialty centers it only gets upwards of 70% or so.

Currently, very few people who have symptoms of cognitive decline and dementia undergo specific tests for Alzheimer's disease pathology. Instead what we do is we screen for other causes of the disease, and we take a wait-and-see approach so that we monitor people until we're clinically more confident that they have Alzheimer's disease and then treat them with the drugs that are approved for use.

Patients and families oftentimes want to have high certainty of what the disease is and what's causing the cognitive decline in their family members. There are available the use of PET scans, both amyloid and now tau PET scans, and CSF biomarkers, which can detect the pathology in the clinic.

The history of diagnostic development in Alzheimer's disease is long and accelerating. As I mentioned, we have now identified the pathological proteins of amyloid, beta, and tau and the pathologies, and based on mutations that were discovered we further developed models that were used to develop other biomarkers, including the PET scans, amyloid and tau PET scans. Most recently over the past few years, blood-based biomarkers have been discovered and described that allow us to track the pathologies of Alzheimer's disease in the blood with a simple blood test.

This blood test, which was first described in 2017, being accurate and specific for amyloid plaques can detect amyloid plaques much in the same way that our cerebrospinal fluid biomarkers do. The amyloid beta 42-to-40 ratio decreases in individuals who have amyloid plaques in the brain as detected by PET scan or CSF and has a very high concordance with the blood test. This blood test is now offered in the clinic in the US, since October of 2020.

The performance of the test is good. Shown here is its relative accuracy across three different studies in Australia, Sweden, and the US in multicenter studies showing that the cutoff is similar across these studies When using this cutoff, we have area under the curve of the receiver operating characterization of 0.87 to 0.83 using just the ratio. Or, by adding genetic factors such as ApoE4 to the estimate, that that increases it a few points from point 0.87 to 0.93.

This is quite important, and so as we've gone on to study these amyloid beta 42-to-40 ratios in the blood, we've looked at people who've been followed longitudinally. In this study, Suzanne Schindler led the analysis to look at people who had amyloid PET scans at baseline and how they change over time. What you can see here is that in those who are amyloid PET–negative or amyloid PET–positive, the cutoff largely distinguishes these two groups. But what was interesting is there's a group of people who at baseline are abnormal on the blood tests but still negative by PET scan, and so we call these people amyloid PET converters if they become PET positive or amyloid PET nonconverters if they stay negative. What's fascinating is that the amyloid beta 42-to-40 ratio in blood is predictive of who will become PET positive later, on average by 5 years later. So it indicates that, similar to CSF, blood amyloid beta 40-to-40 levels may be predictive of who will get amyloid plaques.

These assays are challenging to do, and the field has been searching for them for several decades. It's only recently that high-precision, high-accuracy measures have come about. It's important to distinguish these assays from each other in terms of their ability to detect amyloid plaques. General recent studies have shown that the mass spectrometry–based essays have a level of performance typically above that of the immunoassays.

Alzheimer's disease, as I mentioned, is caused by two pathologies, amyloid plaques and tau tangles. Tau tangles have been a more recent development in biomarkers. Shown here in the study of people who carry mutations where we estimate their age of onset similar to the imaging that we reviewed before, we can track the relative years before symptom onset, the changes in these biomarkers. What we found was that some of the first changes that occur shortly after the amyloid plaque deposition seems to begin is that tau that becomes phosphorylated at specific sites, in this case to 217 and 181, increase almost 20 years before symptom onset. This is subsequently followed by increases in 205 and total tau, and finally at symptom onset the tau tangles begin to appear in the brain by PET scan.

This indicates several things. One is that there is a cascade of events that occur in tau that lead up to symptom onset and that we may be able to stage where someone is at and even predict when they may

have their symptom onset in Alzheimer's disease. This is critically important in the design of prevention trials.

Shown here are some data using some of these same isoforms in blood, compared to the prior slide where I was showing CSF data. What you can see is that in blood, p-tau217 and to a lesser extent 181 has a very good performance for detecting Alzheimer's disease pathology similar to cerebrospinal fluid. There are many groups in the field now analyzing the data for these, and these biomarkers are very promising.

A part of the protein that we hadn't previously studied is the C-terminal half, and that's the microtubule binding region shown here by these repeat domains. This is the part of the protein that deposits in tau tangles. When it was discovered in cerebrospinal fluid, we analyzed the different species here across this into MTBR region and found that some specific regions are highly correlated to the amount of tau PET pathology indifference to the amyloid plaque pathology that we could detect by the other biomarkers. Showing this allows us now, potentially, to be able to track tau tangle pathology in the brain using biochemical measures in fluid.

What is the utility of this in our development of clinical trials and our efforts to try to prevent and treat the disease? The utility of blood biomarkers is enormous. One of our greatest challenges in Alzheimer's disease is our ability to test different treatments quickly enough. The average clinical trial in Alzheimer's disease takes 3 to 5 years; A prevention trial takes 7 to 10 years. That time adds up to enormous expense in our tests of these drugs at their doses and therapeutics.

Shown here is a simulation of a prevention trial using the metrics of the current biomarkers that we have and estimating how much time and how much funds could be saved. And shown in this study, you can see that the amount of time, which is perhaps the single greatest factor in our ability to have more shots on goal, is decreased dramatically if we use blood tests for screening as opposed to CSF or amyloid PET. In addition to that, the funds taken for these trials is substantially lower but in reality it's this time that’s essential for clinical trial testing of new therapeutics in Alzheimer's disease.

In terms of Alzheimer's disease modifying trials and prevention, we're in a new era in Alzheimer's disease. Things have dramatically changed just in the past year or two in terms of our ability to treat and target the disease and what we understand about these treatments and how it impacts the ability to treat the disease.

Throughout history Alzheimer's disease and dementia have been known, even though it may not have been called Alzheimer's disease until after Dr Alzheimer described it initially in 1906. Some mutations led to the discovery that these mutations can cause early onset Alzheimer's disease in families, and that's inherited in an autosomal-dominant fashion. Those mutations were really the first pathogenic cause of Alzheimer's disease discovered. In 2000s, the development of drug, based on these mutations in animal models were developed, including active vaccinations and later passive immunizations, where targets to amyloid beta were made by these antibodies. Subsequent discoveries along the way led to the ability to launch prevention trials, and as these clinical trials developed the field became more knowledgeable about the stages of disease that could be treated by removing amyloid beta, as well as the kinds of treatments that are needed. As this has progressed, prevention trials have launched with the understanding that to have the largest impact we may need to go even earlier, before the first symptom onset.

These prevention trials were initially launched in the DIAN-TU trials in 2012 and sporadic trials shortly thereafter, and now many prevention trials are underway, including tau drug trials, combination, and primary prevention trials before the pathology is established.

There are challenges in disease modification. These challenges include our ability to find the right stage of disease. This is why we're moving into prevention trials. Are we too late for current clinical trials to have a large impact? Is the drug being given having too little effect? Recent developments have discovered that our dosing was insufficient in prior trials, and higher dosing was able to have a larger effect in completely removing amyloid plaques out of the brain.

There's always the question of, which is the best target to try to treat the disease? The DIAN-TU platform was built to treat a very rare form of the disease, autosomal dominant Alzheimer's disease. To account for the relatively uncertain nature of drug development, a platform was launched where we test a variety of targets and drugs over time and in parallel, increasing the amount of samples and data over time, which increases the platform's power to determine a drug effect. We launched these studies at the end of 2012 with two drugs, monoclonal antibodies targeting amyloid beta, and subsequently launched a beta secretase inhibitor. We are now in the cognitive run-in period and are preparing to launch the first tau drug arms, including with potential combination treatment with amyloid drugs. The primary prevention trial is also and in its run-in period, and it's preparing to launch soon.

In the first two drug arms, we randomize people with the mutations amongst the treatment arms as well as placebo. Noncarriers were also included in the study and assigned to placebo.

In this study, which concluded in 2019, what we found was that gantenerumab, a monoclonal antibody that targets amyloid plaques, removed large amounts of amyloid plaques during the trial. Partway through this trial, we discovered that we needed to increase the dose of this, and so approximately year 2 the dose was increased. What we found was that there were larger effects in amyloid removal as well as downstream biological effects in tau, phosphorylated tau, and even a slowing in a neurodegenerative biomarker, neurofilament light chain.

This indicated to us that the biological effects of these drugs are really quite profound and have the potential to have cognitive and clinical impact. Recent findings across the field in sporadic Alzheimer's disease studies have now shown, in phase 2 studies as well as one phase 3 study, a slowing of about 20% to 30% of clinical and cognitive decline in this class of drugs that removes amyloid plaques by monoclonal antibodies, which target those. There are side effects, including amyloid-related side effects of removing this, including edema and hemorrhage that is being tracked needs to be managed; but based on this information the FDA granted accelerated approval to one of these drugs, aducanumab, for the removal of amyloid plaques. Others are following in suit for their reviews.

With that, I'll end. I'd like to thank the many people that made all of this research possible, including the folks in my lab shown here, the Dominantly Inherited Alzheimer's Network shown here with its associated centers, and DIAN-TU with its many partners that make that global platform trial possible as well as the people who help run it Thank you.

Richard Mayeux: Thank you, David. My name is Richard Mayeux, and I'm going to help field the questions for David. We have a question already?

David Holtzman: For Randy, Richard, this is for Randy.

Richard Mayeux: I'm sorry for Randy. I think because David sort of answered the question, but I'll give it to you anyway, Randy.

Are amyloid beta and tau biomarkers just for diagnosis and prognosis? What do we know about causal pathways and targets?

Randall Bateman: In fact these biomarkers have been used mostly for understanding the disease process, the kinds of changes that occur, how they're associated with progression, and as well as mechanisms of disease. That's been the predominant use of amyloid and tau biomarkers over the past 20 years.

It's only recently that we've been talking about using these for diagnosis and potentially one day, prognosis, when there's something to treat with in terms of prevention. For example, the realization that amyloid plaques begin to accumulate 20 years before symptom onset, growth throughout that time period before they largely start stabilizing—the symptomatic phase—and that the tau tangles really take off in that period has led us to understand the disease process in a much greater detail than we could before only based on clinical pathologic studies.

Richard Mayeux: There's another question about whether the plasma-based biomarkers can be an addition to the prediction of subsequent disease in cohorts, you know, the epidemiological type cohorts.

Randall Bateman: Yes. There are actually a large number of studies now that are pulling out of their freezers, samples that have been taken over the past 10, 20,40 years, and taking a look at those blood samples, measuring them at different times when they were taken, in the nested design study, when those blood samples were taken relative to that person's monitoring over time, and using that to try to estimate what kind of risk factors is having an abnormal blood test for developing things like cognitive impairment and dementia.

A lot of these large longitudinal studies that have led samples can help answer some of these questions that would normally take us decades to collect over time to help address.

Richard Mayeux: Someone asked if you could comment on the potential use of focused ultrasound for clearance of amyloid alone or in combination with monoclonal antibodies.

Randall Bateman: There is research in this area; there are some groups that are looking at ways to go across the blood-brain barrier. One of the challenges in treating any brain disease and Alzheimer's, in particular, with its plaques and tangles being inside the central nervous system, is administering the

drugs that get into the central nervous system. Small molecules are designed to have permeability across the blood-brain barrier, but of the monoclonal antibodies only about point 1% gets into the space where the plaques present.

There are different techniques that are being tried, ultrasound is one of them, whether using ultrasound to try to temporarily break down the blood-brain barrier to get the antibodies across, others include transporter or shuttle mechanisms where they use a receptor at the blood-brain barrier to transport across things like antibodies or other drugs to get them into the central nervous system, where they need to hit their target.

But that is a challenge in this disease-development process.

Richard Mayeux: Thank you very much for your talk, Randy.

I'm pleased to introduce the next speaker, Serena Spudich, who is the Gilbert Glaser Professor of Neurology; Division Chief, Neurological Infections in Global Neurology and Co-Director of the Center for Neuroepidemiology and Clinical Neurological Research at Yale. She's one of a few neurologists with specialized training in infectious diseases of the nervous system and a clinical practice devoted to studying individuals with HIV.

She primarily cares for people with HIV, although she does other CNS infections as well, including Lyme disease and West Nile virus. She's a professor. She believes that patients can lead longer lives and healthier lives when HIV is diagnosed early and treat it.

So I'm pleased to introduce Dr Spudich for the next talk.

Serena Spudich: Thanks so much for the introduction, and it's a great honor to be here. Can I just ask if you're seeing the correct screen? You can? Thank you, thanks so much.

What my introduction didn't include is that over the last 18 months or so I've shifted some of my focus to trying to understand the neurological and psychiatric impact of SARS-CoV-2 infection, very different from HIV. I'll say, in contrast to the last topic of Alzheimer's disease where we've had about 118 years or 120 years or so of understanding, medical observation, and research, we've had about 18 months in this area. So I'm going to hopefully today provide you an update of some of what's understood about these complications of SARS-CoV-2 and how they may affect the nervous system.

I don't think anyone really needs a reminder of the scope of the problem, but I do think that, after all of the news about COVID in the lay press all the time, we have become almost numb to the number of cases worldwide that have been reported. And 240 million people have reported cases, which means they have a diagnosis, but probably the number of people who have had COVID-19 is at least 10 times this much, if not more, and about 5 million deaths so far have been attributed to COVID. Importantly, and we're going to talk about this later, there's a very, very large number of people who get this infection and fortunately survive, but this may be leaving them with consequences that we have to grapple with.

What do we know about how COVID affects the nervous system? The first things that we learned were totally based on clinical reports. There were early, early reports coming out of Wuhan suggesting that there may be an excess of neurologic complications in people hospitalized with acute COVID-19. At the time, it wasn't clear whether they were really specific to this infection or whether they were the types of syndromes that one sees in critically ill, ICU-hospitalized patients.

Because of those reports we quickly set up but a focused consult service here at Yale in March of 2020 to try to characterize, gather, and try to provide some expert consultation information for hospitalized patients who were developing neurological and psychiatric manifestations. I ran this with a terrific neurology resident who is now a junior investigator fellow.

This is a snapshot of the kinds of cases that we saw, and this was very consistent with some of the UK-wide surveillance studies that have actually reported on a much larger catchment of patients around the UK, where we saw that about a quarter of patients have stroke as a neurologic complication in the setting of acute COVID. Then there was a large group that also had encephalopathy and seizure. Seizure mostly occurred in people who had underlying seizure disorders already, so maybe just a nonspecific relation to acute infection and hospitalization. But we did see excess encephalopathy, and then some other neuromuscular disorders, and others which were mainly psychiatric presentations, including psychosis.

I think there's two main buckets in the types of conditions that we saw and that have been reported. These include what seemed to be immune-mediated conditions, and we'll talk about that in a minute, and the other large group are the cerebral vascular injury cases. And really, stroke is seen in the context of normal risk factors for stroke as well as things like aging, AFib, or known coronary artery disease, but we also see stroke occurring in the context of heightened endothelial activation. There are a number of different reports of generalized endothelitis in acute COVID-19, and this seems to probably be related to some of the stroke that’s seen in these cases.

How can we understand a little bit more about these cases? This is one of the UK-wide surveillance studies. They also saw a preponderance of cerebrovascular events reported, and then they also saw many people with altered mental status or encephalopathy.

I think what's a little bit interesting is looking at the distribution of age in the patients that they saw, which really shows that this—although stroke is very much clustered in the older age groups, and this is what we saw as well in our clinical experience in people who had otherwise cardiovascular risk factors—fortunately not lots of major strokes in young people, but there was a lot of the neuropsychiatric—delirium, encephalopathy, and psychosis—happening in the younger age groups. This may be a little bit of a hint of what are some of the pathophysiologies underlying these conditions.

Another really interesting thing to look at is the timing of onset of these different syndromes. although they're all categorized as being associated with acute COVID, a larger study in the UK undertook a pretty close look at when these presentations were occurring for these different types of syndromes. One thing that's interesting is in about 30% of people their neurologic or psychiatric symptoms actually predated the onset of symptoms, and this is something we've seen quite extensively as well.

The other thing that's interesting is that cerebrovascular were some of the things that were earliest. So possibly, the cerebrovascular complications are happening for some kind of a mechanism that’s related

to the onset of acute disease; however, some of these symptoms occurred after the respiratory conditions. Some of the most interesting findings were that there is a longer-term onset of about 14 days, or 2 weeks, in some of the, what we would consider central inflammatory, psychiatric, and peripheral nerve complications. As a neurologist, that makes one think because that's from a different mode of action, or mechanism of action, and is this really a postinfectious autoimmune inflammatory condition?

What do we know about the actual pathophysiology of COVID-19 in the nervous system? One of the really surprising things early on was that although there was a lot of speculation that SARS-CoV-2 may cross the cribriform plate and enter the brain or may be carried in through a Trojan horse mechanism in immune cells the way HIV is carried into the brain, there really has been very, very little reported detection of SARS-CoV-2 to in the brain.

This is the cerebrospinal fluid information. Its compiled of 449 cases that have been reported in the literature. Less than 3% actually had detectable SARS-CoV-2, and this includes using PCR testing, metagenomic sequencing, lots of different methods. There doesn't seem to be a really, really robust amount of viral replication in the nervous system, at least not when people have undergone lumbar punctures.

We have seen, however, that there are robust markers of inflammation and immune-mediated changes in the nervous system in patients who are having neurologic manifestations. Most of these studies are pretty small and limited by the fact that there are all these infection-control issues—lots of limited resources, concerns about PPE—that have limited the kind of translational studies that have happened in live humans, but this is one study by my colleague here at Yale, Shelli Farhadian, in infectious disease and neurology, who found a number of different patterns that suggest immune activation and autoimmunity. This includes a compartmentalized increase in certain CSF cytokines in the nervous system compared to plasma, increasing the frequency of B cells in the CSF based on single-cell RNA sequencing, and then detection of anti–SARS-CoV-2 antibodies. In fact, some anti–SARS-CoV-2 antibodies that seem to be reactive both to the spike protein and to antineural tissue. This may suggest that some of these syndromes, going along with the clinical presentation, seem as if they may be autoimmune.

Going along with this issue of what's actually causing the problem, I mentioned that there's not that much detection of the virus in the cerebrospinal fluid. The same thing has been looked at in the brains. Autopsy studies have lots of caveats; They're only looking at the most severely ill patients. These studies were not focused on people who have neurological diseases, but they were focused on anyone who died of acute COVID-19. This is one study, and actually a couple of studies here that are cited, that really looked very carefully with immunohistochemistry analysis and did not detect any virus in any of the brain cells, including endothelial cells. The quantitative PCR for parts of the protein were equivocal in some of the blocks, but overall there didn't seem to be significant viral infection, including in the olfactory bulb and tracks, which had been thought of as a potential portal of the virus into the brain.

Several other studies have substantiated the idea that there's not a lot of viral detection; there's widespread inflammation and immune activation in the brain. This is a very, very large swath of data collected from 43 patients, again they didn't have neurological symptoms necessarily, who died during the acute COVID-19. Anything that's not blue in this grid is indicating infiltration of cytotoxic T lymphocytes. In some cases high numbers and other cases low numbers, but basically widespread

inflammation in a variety of different brain areas. As you can see in the bottom section that's showing in the same brains' detection of SARS-CoV-2 proteins and virus, you can see that there's really limited detection of the virus or of the spike proteins. The same thing in the same sort of figure also holds for microglial activation. Basically, it looks as if, although there may not be a lot of viral antigen detected in the brain, there seems to be widespread immune responses in the brain during acute COVID-19, at least in these acutely ill, hospitalized patients.

Finally, there's been some really interesting evidence of microvascular injury in the brains of with people with COVID-19. I mentioned earlier that endothelial activation is a hallmark of severe acute COVID-19 and may also have some overlaps with the changes that are seen in children with the multisystem inflammatory syndrome.

In this case an 11.7 Tesla MRI of postmortem tissue revealed changes in microvascular injury including some microvascular hemorrhages and changes in just leakage and integrity of the cell walls.

Where does this leave us? Well, it tells us that there may be a combination of immune-mediated and vascular-mediated injury. Some of this vascular-mediated injury is also likely immune-mediated, and separately there are increased thrombosis and increased coagulopathy in people living with acute COVID-19.

What does this mean for those who survive? I think this is now one of the major questions. Again, as I noted, we've had about 44 million people in the US who have documented COVID-19. Unfortunately we lead the world, not only in the total number of cases which is shown here, but also in the cases per capita. We have a very, very major group of people who are at risk of long-term complications of COVID-19, if such exist, because so many people, thankfully, have survived.

I'm going to spend the rest of the talk really talking about these post-COVID neurologic issues. This has come up in a number of different ways. There have been lots of clinical reports and individual reports of patients reporting they feel like they have dementia, they have brain fog. This has been something that has been brought up in a widespread way, but really we have very little pathophysiological information about it.

This summer we ran a meeting funded by NIH that really focused on a variety of neurologic and psychiatric effects of SARS-CoV-2, and I think that there was a lot of interesting input, including from this group that has reported from a patient-led research standpoint. One of the things that's happened in COVID-19 is that because there's such a lack of understanding and it's an urgent problem, there will be many, many patient groups and people coming together to try to answer questions themselves.

This is an interesting study where this patient-led research group, which is actually led partly by a neuroscientist who also experienced COVID-19, conducted an online survey. On one hand, this has all of the problems of online surveys; it's not clear whether or not people actually had COVID-19; some of them only had suspected COVID-19; and it's a survey that tells people about just their symptoms. But the findings are somewhat interesting and I think can inform us, or at least start help us to start to ask some questions.

First of all, they looked at people who had had some symptoms after COVID-19 and look to see what the pattern was of their symptoms over time. As you can see, there are some people that as they were followed up over 7 months had recovery over time, but there was a group of people who did not seem

to have recovered over time. This suggests that although some of the symptoms are solving, and this is something we see in our clinics, there are some people who seem to be having long-term problems that they don't feel are resolving after 7 months. Although there are a number of different symptoms described by this group, and actually there's a very nice large grid describing shortness of breath and other things, the predominant symptoms that are described in the self-reported questionnaire relate to neuropsychiatric issues.

They break them into cognitive, sensory, motor, and other, but these include things like acute confusion, brain fog, memory issues, neuralgia, neurologic sensations, and some psychiatric conditions including hallucinations and headaches. I think this is actually consistent with what we've actually seen; we have now a clinical practice here at Yale looking at these patients. I think the question now is to try to understand what's the underlying pathophysiology of these disorders.

I'll say that this is an extremely difficult area to study. It's almost impossible to tease out the differences between what's due to COVID-19 and due to other aspects of experiences in the pandemic; what may be premorbid versus post-COVID; and what may be conditions that have primarily psychiatric manifestations. Some of these may actually be related to premorbid disease, and we have to figure out how to tease those things apart.

What is the biology that's known so far? There's some evidence that there are some cerebral functional structural changes in post-COVID neurologic syndromes. This is a PET study that used FDG PET to look at cerebral metabolism. This suggested that participants with persistent symptoms actually had regional hypermetabolism, and the hypometabolism was actually associated with their currents of symptoms.

Another study that was recently posted as a preprint, it's actually really interesting, where the UK Biobank, which conducts surveillance imaging at every-2-year intervals, found about 400 participants in their surveillance imaging who had documented COVID between the two scans, and they had a matched group of about the same size that did not have documented COVID. In this analysis, again a preprint, they suggest that there's actually focal loss of gray matter, and these are actually in regions that are actually computatively associated with some of the symptoms that people have with COVID-19.

What's underlying these changes that are structural, potentially, in the brain? One is the potential that there's still persistent nerual inflammation in the brain. I don't think we have any good data for this yet, although people throw this around all the time. But a couple of studies have suggested that either inflammation during post-COVID symptoms or inflammation during acute COVID may be predictors or associated with neurologic syndromes. These are two early studies, suggesting those things, but I think it's uncertain when we focus on hospitalized patients how findings in hospitalized patients relate to survivors of milder forms of COVID-19.

And so, one of the things that we're doing here at Yale, and I think many people are doing around the world, are trying to set up systematic studies that are focused on understanding these questions. With Dr Farhadian, Dr McAlpine, and others here at Yale, we're running something called the COVID Mind Study—again, I think there are similar studies happening at the NIH by Avi Noth and Northwestern by Igor Koralnik—where we're basically recruiting people who are presenting to our post-COVID neurologic clinic who are complaining of long-term complications of COVID-19. We're asking them to undergo a whole panoply of tests. Again, this is labor intensive and of a high commitment on their part, but many of these patients are really curious about understanding about what's happening with them and trying

to find answers. They're undergoing 3T MRI for structure and functional imaging; PET imaging of the brain including synaptic density and TSBO imaging; and really going through quite a number of neuropsychiatric, history, and survey batteries. Finally, we're doing a lot of work with blood and spinal fluid, which we've worked with for years studying HIV effects in the brain, including single-cell analysis and looking for novel immune profiling.

Our early findings really are mostly clinical and these suggest that many of the patients who are coming in to us are young, average age is 53 years. About 3 to 4 months after COVID is when they're coming in mostly with these complications. Only the minority were ever hospitalized with COVID-19, so most of them had mild disease. The majority of them were coming to us with cognitive symptoms. Again, this is a neurology study, so there may be many, many more people who have widespread psychiatric syndromes, but they're mostly coming to us with cognitive syndromes. Most of them have normal clinical MRIs.

What we've been doing is looking at some preliminary data from their blood, and at this point we don't have our control data yet back from the blood, but I'm showing you with the dotted lines the normal upper limit value in our laboratory for these different tests. You can see that blood markers of inflammation are mostly normal. The blood CRP is mostly normal; the blood ESR is also mostly normal. The absolute lymphocyte count in our participants 3 to 4 months after COVID is actually interestingly still a little bit low. Blood D-dimer and von Willebrand, which are markers of vascular inflammation, are slightly elevated.

CSF findings also show fairly normal findings. These are in comparison: the yellow is the COVID, the green is the comparison to prepandemic controls. You can see, though, there may be slight elevations in the CSF protein in some patients. This looks like it's more due to the production of CSF igG than due to blood-brain barrier breakdown, based on the CSF-to-serum albumin ratio. In most patients, there does not seem to be overt neural inflammation based on CSF white count, although the number of lymphocytes may be slightly lower, which is interesting.

Standard clinical and brain imaging in this cohort is mostly normal, but we're doing the research assessments. One interesting finding so far in one of the post-COVID-19 participants that we had who had psychosis is that, although his clinical labs were all normal, CSF IgG was slightly elevated. Working with Sam Pleasure, Michael Wilson, and Chris Bartley at UCSF, we found that there was potential detection of novel antineuronal antibodies in this patient, suggesting potentially an autoimmune-mediated psychosis. Those studies, of course, are ongoing with all the rest of our samples.

I'm going to end by saying there are many, many global studies on these syndromes. Fortunately the NIH has put a lot of investment in studying this with the PASC Initiative, now the Recover Study, which presumably has some really important neurologic endpoints; that will be a major focus of the study.

I think there’s just some final key questions on gaps that I want to end with. What are the main clinical laboratory biomarkers that associate with the presence of these syndromes? Is it neuroinflammation? Are there autoimmune syndromes? Is there still vascular inflammation?

Finally, I think the reason this is so important, honestly, is that when we see patients, many, many people have stigma-related issues; they have difficulty with work and employment. It's a major public health concern. Most people are able to function and do most of their ADLs, but many of them are not

able to get back to their normal lives. Clearly it's a key, it's really an important emerging area to develop interventions for these conditions.

Thanks so much for your attention. I'm going to again thank my colleagues, the entire COVID Mind team, all of my support at Yale, and study participants. I'm going to end my show so I can see people's faces if they're asking questions, and thanks for your attention.

Frances Jensen: Thank you so much, Serena, that was a fantastic talk. I have to say we've been very privileged in the neuroscience forum to have you present to us over the last couple of years very routinely, and so we've been staying updated with Serena's latest information about what's going on with the acute and post-COVID syndrome.

We have several questions; we probably have about 3 to 4 minutes to go through them.

One question, which I think a lot of people will ask is, in other severe systemic viral infections that do not directly invade the CNS, are there similar changes in inflammatory cytokines and cellular responses as seen in SARS-CoV-2, or does it seem like this is somehow unique in causing this response?

Serena Spudich: I think that's an incredibly important question. One of the only positive things about COVID is I think it's made the world a lot more interested in how viruses affect the CNS.

I don't think we have really a definitive information about those things. There have been some small studies where we've looked at people with HIV and it's outside of the park in terms of CNS inflammation. I think there have been some small studies in respiratory viruses as influenza that suggest there's not this sort of robust inflammation. I think these are some of the controls that we should be using for these kinds of studies.

It may be that we find new, important information about the pathophysiology of those diseases and how they may affect the nervous system. For example, the chronic fatigue syndrome field has been saying for years that many, many of the triggers for chronic fatigue may be viral infections, but there's really been a lack of information about that. Hopefully understanding this condition better, where there's a known pathogen and some known outcomes, we can actually shed light on how some of those other viruses affect the brain.

Frances Jensen: Great. Another question is how does the level of T cell and microglial activation in postmortem brain of people with COVID-19 compare to levels of inflammation associated with infectious diseases such as Zika or other neurodegenerative disorders?

Serena Spudich: I don't know about Zika, I have to say. I think it's a great question and I certainly will look into that now that you asked. I think in terms of neurodegenerative diseases, I know there's microglial activation in Alzheimer's and that's been something that's been a really interesting major focus, but the level of inflammation that's seen in these post-COVID brains is off the charts compared to

that. It's much, much, much higher. It's absolutely widespread, and it's the main pathological finding in these conditions. I think, although there's another question in that, which is that will this actually trigger worsening neurodegenerative disease, I think the jury's still out but it's a really important question.

Frances Jensen: Another question relates to, what do you think is the relevance of the ongoing lymphopenia in relation to ongoing neural symptoms and neural repair?

Serena Spudich: I don't know. Again, I'm showing you super preliminary data. I think that's a little bit of a maybe. Is there really ongoing lymphopenia?

It is interesting, because I think this idea that you may be having some long-term alteration in your immune status when you survive and recover from COVID is a question, but also the other thing to think about is that I don't have a comparison group here of people have COVID and no neurologic syndromes. It may be that everyone who recovered from COVID has some lymphopenia that's lasting for months.

Frances Jensen: The last question is, what do you think the relationship between age and the secondary complications—what are we learning about that?

Serena Spudich: I think that's really interesting. The suggestion of, particularly from that UK systemwide study, is that the complications that we think of as being typically age-related, such as stroke, is certainly seen in higher rates in older people. That relates, I think, to the underlying risk factors. But the complications of some of these more immune-mediated disorders are likely happening in more predominantly younger people, which I think goes along with our understanding of autoimmunity. Experts for that are on this call right now. But I think it does suggest a really robust immune response. While it's beneficial in helping you survive COVID-19, it may actually be potentially setting people up for a higher risk of neurologic complications.

Frances Jensen: Alright, well, thank you, I think we need to move on to the next speaker, but Serena, thank you so much, and I would direct you to the chat area where you might be able to address individual questions that have come in, because there have been a lot of them. Thank you so much.

The next speaker I'm pleased to introduce is John Gallagher who is the director of the Dementia Platform UK and Professor of Cognitive Health at Oxford University. He's an MRC-funded public-private partnership, and he is focusing on accelerating research into early detection and treatment of dementia.

He is going to talk about, as he's an expert, he's going to talk about big data and medical research, and he holds visiting professorship as well at the Imperial College London.

We are asking him to talk about, given he is the principal investigator of the CARE prospective study and member of the UK Biobank steering group, which is leading cognitive and psychological assessments.

He's going to talk to us about youth mental health and new tools for examining. This please welcome, John Gallagher.

John Gallagher: So very kind of you. Let me just share my screen.

I must confess that, following those two excellent whistle-stop tours of complex areas, they're hard acts to follow. But it's my great pleasure to be with you and thank you very much for joining us here in a very beautiful, lovely autumn afternoon in the UK.

I'm going to talk about the Brainwaves Study. We've just launched it last week, actually; we literally started our fundraising for this last week. It's in response to the growing epidemic of mental health issues amongst our young people in the UK. I'm going to give some, a little bit of context, because I think these issues will be different in different cultures. I suspect they'll be slightly different between the UK and the US, so it may be of interest to you.

Here's the size of the problem in the UK. We have two surveys of comparable methodology in 2017 and 2021 with an intermediate stage in 2020. What we see is in 6- to 16-year-olds, there is an increased, particularly in boys, in mental health issues and also in 17- to 19-year-olds, particularly then in girls. We see this growing problem using some comparable methodology, comparable sampling, comparable questionnaires across the last 4 years.

If we were to compare that in terms of a specific mental health issue, which you could pick any one of a number but we will pick eating disorder, again we see a growth over the last 4 years, mostly in girls but it's still there slightly in boys, and in the older age group as well, again some in boys but mostly in girls. This is a very worrying trend.

If we're going to look at a specific symptom that might be affected by mental health disorder, we could look at sleep disorder and, again, we have a growth in both age groups. Curiously, if we look at ethnic differences, we find that the most affected group are those who self-described as White. In ethnic minorities, we find some increase, but it is a small increase. Although, in spite of the very challenging socioeconomic conditions of ethnic minorities in the UK, it is very interesting to see that they do not appear to be as affected in terms of the mental health outcomes.

That's our context. These numbers have not gone unnoticed in the UK, and therefore the government is putting money into adolescent mental health studies. And there are other initiatives ongoing as well.

What I'm going to describe to you now is one which has just launched last week called Brainwaves. It's a population-based school partnership with journalism in terms of developing classroom intervention. It's a partnership looking at. not just the etiology and the causes of adolescent mental health problems, but also a context for developing interventions and educational materials.

The design is that we are looking for a population-based sample, and we're going to base it in schools. Schools are the best place to access young people; that's where you can deliver most professional and educational supports; and more importantly, from an etiological point of view, it gives us population distributions, both of outcomes and the risk factors.

We're going for ages 11 to 18, because that's really the period of greatest risk of the first episode. We're looking for a cohort design, because we need follow people over time to give us information on causality. We're going to adopt what we describe as a living laboratory approach of which I shall be describing more detail shortly.

And the value of covert data accrues over time, because if you go at scale that means you have outcomes and exposures accessible over the life course. So effectively we'll get to establish something now which we can fund for 5 to 10 years, which will then run until the children become adults and go into older age.

Let's look at another design feature. We want to do this work at scale now. This is very interesting actual data. We have a sample of 500,000 people, from whom 50,000 were sample, from whom 5,000 were sampled. If we look at 5,000 people—you might look at the impact of age and blood pressure on cardiovascular outcome—and it would be very hard to tell any difference between the two age groups with any sense of confidence. If you then take a sample of 50,000 people, well then we do seem to see some differences in age between the association of blood pressure and cardiovascular risk, but it's really difficult in terms of working out precisely what that relationship is; for example, you might see there's a bit of a J-curve there in the 40–49's, and you might suspect that those curves are reflected in the other age groups.

However, if you take 500,000 people, then you see it as a very simple log linear relationship. This finding is definitive; you actually don't need to do it again. Okay, you might want to look at ethnic differences, you might want to look at cultural differences, but within the population sample, you can move on. This is a sort of scale that we do need in order to investigate not just mental health but most epidemiological factors, and this is the thinking underlying UK Biobank but it equally applies to mental health.

We'd like to adopt what's called a living laboratory design. The UK is in a very advantageous position with its National Health Service. In principle we can access, although it's very difficult in practice, I have to say—that's mostly due to governance issues rather than practical issues. In principle we can access the health records of everybody within the UK. What this means is you can take a population-based cohort, schools or otherwise, which is not necessarily representative. It has to be large as I showed you in the previous slide. It has to be large, but you can take a population cohort, do your assessment, and then you can relate them back to the population distribution of the country as a whole. Then that gives you some basis for generalizing beyond your sample.

Our goal is to recruit a population-based schools cohort, allowing us to have repeated assessments over time with the same individuals who are identified so we can link up all the data. We are going between 50 and 100,000 students from schools. Within that sample, we then invite the students to register for consent for recontact, and that allows us to recontact them with their consent for further studies. Those further studies might in the fullness of course, fullness of time according to funding, include genetics and imaging.

What this research register does allow is that we can then recruit to specific interventions. So we can then go and say, okay, we have so many partner schools, we can do cluster randomized trials in schools, we can do online trials, we can do in-person interventions. The secret here is to have sufficient numbers who are reconsented and phenotyped, if not genotyped, prior to recruitment to allow you to have targeted intervention. You can restratify your population at scale and frankly, have a little machine—it's

an industrial process, really, which allows you to conduct intervention after intervention after intervention. You don't really need a particular program because who knows what emerging research questions there will be. What you need is an infrastructure which allows you to do this.

Moving on to infrastructure, this is an economics-based graph, which is it's worth thinking about, although I don't suppose, many of us have had the chance to. Effectively, collaboration comes at a cost, and that cost may be described as transaction costs. Effectively, if you're going to collaborate with one person, that gives you a cost of getting to know them, trusting them, having a legal basis for collaboration, sharing the data, etc. If you're going to collaborate then with two people, four people, or six people, the complexity increases. There comes a point, and we've all been there, there comes a point when the net benefits for collaborating with someone just do not outweigh the costs. At that point collaboration stalls. It's really simple, we've all been there, it's really simple.

However, if you set up your infrastructure so that by design you've addressed complexity, effectively you've simplified it. What that does is lower the transaction costs and extends the upper limits of collaboration. That's effectively a major design principle for us: how can we streamline, standardize, automate the whole process from beginning to end, not just in terms of data collection but in terms of third-party data access, legal agreements, consents, security, end-to-end audit of data use? The whole thing, we intend to automate.

Now, at one level this sounds ridiculous; I completely understand that. But at another level, what we're doing is learning from infrastructure, which already does this. Here is the data portal of the Dimensions Platform UK. We take in data as is, and then we curate it to a research-ready standard. This is a long process and its ongoing, but that's what we do.

The fact that we have a defined process means that we can work interoperably with other platforms; so Dimensions Platform UK works with Dementia Platform Australia, it works with the outside Alzheimer's disease the data initiative initiated by Gates Ventures; I can name several other platforms that it works with. The point is, you can have access, you can have third-party access to data from wherever you are via multiple platforms.

But the data has to be discoverable, so within this platform there are data discovery tools. Of note, I'm not convinced that they're particularly sophisticated, but we're working on that. Then we broker access to the data. For example, let's say that you want to access five data sets to increase your statistical power; typically you would make five applications to five different data controllers. We offer the service of having one application, which we then send automatically out to the data control; so we broker the access.

We then have standard legal agreements. Now the standard legal agreements are really tough to negotiate, let me be honest, but once they're negotiated, everybody understands them, they're familiar with them, they're nonnegotiable, and frankly they go through quite well. We find that most of our cohorts—we have about 50 cohorts now totaling about 3- or 3.5 million individuals—most cohorts accept standard legal agreements because they understand the pros and cons, and therefore they can turn them around quickly.

We also use our data to develop recontact registers. So the different elements that we would use for the mental health cohort exist.

We provide for analysts a secure data environment. This involves analysis, analytic tools software. It involves personal workspaces; you could log on and get registered and work within our data environment this afternoon. If you so wish, we can configure those workspaces for consortia, and they can be configured to run on various sorts of containers and API'S for federated analyses.

We are building all over. The first six layers are in existence, but the seventh layer we're building, which is a knowledge management environment; effectively, we could help you, assist you intelligently in your research, because if you're looking at this, we know that 500 other people have looked at this and, therefore, we can suggest data sets and code that you could also use.

This exists. All we would need to do is to effectively clone it, lift it, rebadge it, and reapply it for adolescent mental health.

What this allows you to do is to provide at relatively low cost a multimodal analysis environment. For example, if you are a geneticist, you don't really need this if you're an expert geneticist, and if you're an expert imager, you don't really need this at all. But if you want to bring together cohort data, imaging data, genetic data, electronic health records, you need some preprocessing of these highly specialized, often high-order data sets in order to make them functionally useful for analysts. That's what we do.

It's in some ways it's a thankless task because we're doing things that everybody else wants done but nobody else wants to do. That's fine, we can live with that, because to bring these things into a virtual laboratory, we think will have fantastic scientific utility over the years to come. We expect other people to copy this model and maybe even be better at it than we are, and that's absolutely fine. Nevertheless, that's what this environment allows us to do.

We also are going to work within established school networks. We have two networks we're working with. One is *The Day*, which is the largest-circulation school newspaper in the UK. It reaches roughly a million students in that—I tell you a lie, that should be 1,400 schools not 11,400 schools, so forgive the typo there. I'm also working with the Oxford Schools network, which has schools in the Oxfordshire area but also reaching out to schools in more deprived areas, and that attracts 31,000 students in 180 schools. The point is, we have synergy between the academics and the education lists.

Let's just look at the potential for this system. These are data from the Dimensions Platform UK. Every month I have to report to MRC our performance—I can be sacked over these figures, so they're not exaggerated at all. These are the studies that we have, sorry, these are the projects we have from PIs around the globe. The point is you can have a central data repository, the data cannot be removed but people from around the globe can come and access it—so we can have researchers from Manchester in the UK or Malawi in Southern Africa and they can all access the same data with the same standards of security, the same standards of statistical tools, and the same level of support. I think there are few other ways to democratize science as simply as doing this.

Currently we've had over the last 3 years, 835 individual cohort access requests, and our median time for decision is around 23 days. It works quite well, it works quite well. The point here is that this system can be used equally well for mental health, and that we would be delighted just to clone it, lift it, and repurpose it.

It's not just a matter of looking at potential causes; I think you have to be looking at the translational pathway as well. The point is to use these data to make them available for the translational pipeline.

Effectively, we can use genetics imaging cohorts—and this is what we do in Dimensions Platform UK for mechanism discovery—and then we can recruit from the research registers to proof-of-concept trials and efficacy trials, and using the EHRs we can look at effectiveness over time.

Our strategic partnerships, which are critical to success here, is that we work with philanthropy. I think why people like to work with us is that we offer a high trust, precompetitive ethos, and this is really important. Within the partnership we share best practice, we share knowledge, and we expect those confidences to be kept. I suppose my job as Director is really just to make sure this ethos is there in the Dimensions Platform—if I find a partner not really playing the game, I just got to have a quiet cup of coffee and suggests that the rules are kept—and they are. It works very, very well.

We've started talking to philanthropy, and last week we raised our first million dollars. We're open to talking to industry and then to major research funders.

We have an established infrastructure and technologies, which means the project is low risk. We do not have massive development costs or massive development risks. We've learned from UK Biobank and Dimensions Pathway UK, and our informatics model and partnership model are literally just clones of those.

We're focused on treatment development. With our partners we've considered co-design to be really important. I think that offers a sense of trust; we do not have the, what is a frequent academic model of obtaining support from industry and then effectively doing what's academically interesting. What we really like to do is to have full disclosure of goals, align the goals, and then work together on succeeding that. Then we're looking for biomarker development, risk-stratified trials, and target interventions. At one level this is very aspirational, I fully accept that; at another level the technology and the thinking are actually quite mature.

I look forward to seeing how it goes, and I welcome your questions.

Marina Picciotto: Thank you very much for talking about this important resource and sharing it with us. I'm open to questions in the chat, but I would like to start with a question that's very logistical, really. In my understanding, one of the biggest issues of working with these kinds of basically enormous data sets that are not under our control is cleaning the initial record. Particularly, I understand that from electronic health records, that's the slowest, most painful part of the task. So it looks like that would be in layer one, data ingestion. Is that correct, and how challenging is this in the UK? Have you come up with strategies to overcome this at the larger scale?

John Gallagher: Well, you've obviously tried to do this. It's an incredibly difficult task.

We've broken it down into two levels. For the research data, we ended up having to design our own data model because the multiplicity of data models just made everything unworkable. We've done that, and there's a preprint just submitted to the *European Journal of Epidemiology* last week describing our data model. but I won't go into it now, but it was absolutely essential to go to do this.

Secondly, we do not have the resources to curate electronic health record data. The UK is only just in a position of centralizing its access to these data. We are working with another partner who is much more interested in curating those data than we are. We anticipate receiving curated data into the data portal once it is available.

It's interesting that they only became available because of COVID. It's because of the big pressure in the UK to get COVID research done that all of a sudden the governance bureaucracy has been streamlined beyond recognition. And so it now means that access to large data sets is so much easier, and therefore the curation is so much more important.

Marina Picciotto: Thank you. That's interesting that COVID actually has many unintended consequences.

There are few questions here in the chat. Can you comment on the management of patient consent—if it's monitored if at all, and what if a subject changes their permissions?

John Gallagher: Yes. With all of our studies, the subject can withdraw anytime; it's as simple as that. In terms of consent, it's as simple as that. In terms of data retrieval, typically, it is much more difficult once a data set has been given to a researcher.

Our solution to that is we actually do not allow data to leave the data portal. You have to conduct research within the data portal; however, that doesn't alter the fact that it's very difficult, that you cannot really remove data from an analysis, which was done 5 years ago. And so we would just defend our cause; as soon as you say that you no longer wish to have your data used, then it is withdrawn with relative ease.

Marina Picciotto: Thank you. The next question is, given the recent negative publicity around Spectrum 2K, can you comment on the communication strategies around using patient data for studies? Note that this is sort of related to that consent question.

John Gallagher: Well, this is very difficult for me to answer because I'm not aware of Spectrum 2K—that may be particularly US issue.

Marina Picciotto: Dr. Martin, would you like to unmute and maybe make a comment there?

Kelsey Martin: Thank you. It is a UK study, and it's around using newborn screening for autism. It's really hit… You know, one of the big benefits there is being able to take advantage of the National Health Service data and connect that. And so lots of questions on your virtual laboratory. You have genetic, and proteomic, and clinic—all this data—and that raises a lot of issues in the public arena that I think are challenging, especially around adolescent mental health.

So it hasn't been a problem?

John Gallagher: No, no. I think it depends what you consider to be the issue. For example, all the data in our portal is deidentified; we do not hold the lookup list. So even if you—and of course investigators are obliged not to try and identify—so the lookup list is held by the National Health Service, so there is very little risk in people's identity becoming known. That does go a long way to allay people's concerns.

Marina Picciotto: Okay, thank you. Please join me in thanking our speaker again, and we'll move on to our next speaker of the day. Thanks so much.

Our next speaker is Dr Deanna Barch. She is the Gregory B. Couch Professor and Chair of the Department of Psychological and Brain Sciences, as well as Professor of Radiology and of Psychiatry at Washington University. Professor Barch studies cognitive and language deficits, and disorders such as schizophrenia, and the neurobiological mechanisms that contribute to such deficits. Her research includes behavioral, pharmacological, and neuroimaging studies with normal and clinical populations and is focused on understanding the interplay among cognition, emotion, and brain function to understand deficits in behavior and cognition found in brain illness such as schizophrenia and depression.

Her group uses functional and structural MRI and cognitive neuroscience methods to focus on the ways in which early adversity shapes brain development and subsequent risk for mental health challenges.

Dr. Barch will be talking to us today about early emotional development and the Adolescent Brain Cognitive Development, or ABCD study. Thank you for being with us today, and I will hand it over to you. We can already see your screen perfectly.

Deanna Barch (she/her): Great, thank you so much, and I appreciate being able to speak today. I'm going to kind of continue in the theme of large-scale studies and in particular large-scale studies that might help us understand risk factors or early detection or prevention of mental illness.

I just want to take a moment in the theme that Victor highlighted yesterday about kind of highlighting emerging leaders in the field and much of the work I'm going to be talking about today has been done in close collaboration with my colleague, Nicole Karcher, who is an assistant professor at Wash U. Just a quick disclosure of interest, I don't have any conflicts of interest.

I'm going to focus today on early detection and risk for psychosis. I do that because we know that this is one of the forms of mental illness that is most debilitating, and it has the largest burden on both individuals and society. But it is, in its most manifest form, a fairly low base rate disorder, which makes it relatively challenging to try to identify risk factors.

I think much of the research to date has illustrated that there's a progressive course to the development of psychosis where; think of this line as onset of diagnosable illness. We are often working to try to treat people once they have already been diagnosed with the illness, but most of the evidence to date suggest that treatment is not as effective as we would like it to be if it doesn't start until then.

There is a growing line of research that is focused on trying to identify and treat people in the prodrome of the illness, sometimes that's called clinical high-risk research, and the hope is that intervention and prevention might work better, if it is occurring before the full onset of the illness or the disease. But the challenge here is that the folks we are identifying in this prodrome phase are often already very ill and have been ill for years and are already accumulating illness burden, both for themselves and for society.

Ideally, what you'd really love to be able to do is to identify people in a premorbid state, before they've developed very serious and significant symptoms, and to work on prevention and intervention early on. As I noted, when it's a relatively low base rate disorder, it's very challenging to do this. We have really been hoping to be able to do more population-level studies of psychosis. One of the holy grails is to be able to do a study where you could really identify early predictors of later psychopathology.

Today I'm going to talk about work from the Adolescent Brain and Cognitive Development study, which is a nationwide study that's been going now for a little over 5 years, that starts to try to do this, albeit at a somewhat smaller scale than the previous talk, and that may be able to provide very unique data that informs early identification and potentially prevention of psychosis.

The ABCD study recruited approximately 11,874 youth nationwide, 9 to 10 years old, and we are following them for at least 10 years. The sample is reasonably diverse in terms of race, ethnicity, and sex to try to promote generalizability of any findings.

The goal of this study was really multifold. We wanted to identify normative individual developmental trajectories of brain, cognition, and emotion and understand the factors that can impact those trajectories. We wanted to look at the role of genetics versus environmental factors; we have an embedded twin substudy. We wanted to look at the onset and progression of mental disorders. We wanted to look at things like exposure to substances and how that might affect development, and also to look at social determinants of mental and physical health and understand those factors.

This is just an illustration of the sites that have been involved in the ABCD study. Relatively broad distribution across the US, although admittedly we do not do as good a job covering rural parts of the US as we ideally would be able to do so. That is in part tied to the need to be close to a site that has a research-grade imaging center in order to be able to do the brain development component of the study.

I want to just briefly give you an outline of the kinds of data that are being collected as part of this study; because one of the things that's reasonably unique about the ABCD is all of the data is publicly released annually. It's a very, very broad range of data with many, many different federal and nonfederal partners who are contributing to data collection. There is a very diverse array of measures being collected.

The way this is set up is it's showing you the participant age. We do in-person assessments—COVID did put a wrench in things and we could talk about that–but annual in-person assessments with touchpoints by phone or online every 6 months. We collect all kinds of data about substance use and related factors, including both self-report and parent report, and saliva hair samples that give us important indicators of exposure to substances, both environmental exposures and their own potential use. We collect extensive information on mental health and related factors, including both youth and parent report in teacher reports of the full range of mental health symptoms. We collect a variety of information about physical health including, again, parent and youth report; we're doing Fitbit studies collecting

information on actigraphy and sleep; we get saliva for hormone assessments; we started collecting blood, both for measuring biological factors and for genetics. We measure a range of cognitive factors as well as school performance. We measure things related to gender identity and sexual health, culture and environment. And then also we do an extensive brain imaging assessment every 2 years that includes multiple modalities—structural, functional, diffusion imaging. A very broad range of data, and all of these data are publicly released every year for anybody who can get IRB approval to use; so it's very broadly available.

What I'm going to talk about today is the work that we've been doing in the sample looking at psychosis risk in children, because it was a large enough sample for us to really believe that we could start to go after something that, in theory, has a relatively low base rate in the population. To do so, we adopted existing validated measures from measuring what people might call "psychotic-like experiences," so experiences that people may be having that are analogous to, or perhaps precursors to, what we might consider to be diagnosable psychosis.

We used a modification of a measure called the Psychosis Questionnaire-Brief developed by colleagues at University of California-San Francisco. They had already begun to adopt this measure for use in 9- to 10-year-olds in studies of 22q11 deletion syndrome, which is a genetic syndrome that increases risk for psychosis by about 50%. We have kids fill out this measure starting at ages 9 and 10. It asks questions like, do you feel like you have special, unusual powers, things happening by magic, magically knowing what's in another person's mind, feeling that people might want something bad to happen to them, or that they couldn't trust other people, or being able to see or hear things that other people couldn't see. We have follow-up questions to understand what they're referring to so we can rule out normative childhood experiences. Then we also ask them to tell us about how much it's just stressing them, because, I don't have time to talk about all the data we have with this measure, but it is clear that the degree of distress and the degree of time over which they're experiencing these things are going to be really important indicators of risk for psychosis.

We have looked at this measure and its validation in a number of ways. For example, we've looked at it in relationship to family history of mental illness—so we have families report on their own family history of schizophrenia, depression, bipolar disorder—and what we see is that we see higher self-reports of distressing, psychotic-like experiences in youth who have a family history of psychotic disorders and we see less evidence of that in youth who have family histories of depression or mania. That would be consistent with what we'd expect of a measure tapping into potential risk for psychosis given the known genetic and environmental contributions.

We've also been looking at whether kids who report elevated distressing experiences of psychotic-like symptoms show impairments similar to what had been reported in the literature for adults with diagnoses of schizophrenia. For example, if we look at youth who have speech delays, which are known to occur amongst individuals with schizophrenia, we see higher reports of psychotic-like distressing symptoms in children who have speech delays, as well as children who have motor delays; again, both of which have been seen in in adults with schizophrenia. If we look at IQ, which is unfortunately often lower amongst individuals with schizophrenia, and we look at no psychotic like experiences, low and high distressing, severe psychotic-like experiences, we see a decrease in IQ levels, both for fluid IQ, which we might consider to be like problem-solving skills, as well as verbal IQ, which would be like reading and vocabulary skills.

When we look at specific cognitive functions, we also see that children who have higher psychotic-like experiences, especially distressing ones, show worse working memory, processing speed, episodic memory, and reading. Again, all of which are impairments that we see in adults with schizophrenia as well.

You can also look at a variety of brain factors that have been associated with schizophrenia in adults. I'll just give you an example of one of those, which is functional brain connectivity. Functional brain connectivity is looking at spontaneous fluctuations in what's called blood oxygen level–dependent brain responses, which are an indirect measure of neuronal activity. In many, many, many studies, we see that there are networks of brain regions that show similar patterns in these spontaneous fluctuations over time. They seem to form networks that are that are important for a range of cognitive and affective functions.

I'm going to focus in particular on a few networks today, what's called the fronto-parietal network, which includes the dorsolateral prefrontal cortex and the dorsal parietal cortex, which is thought to be important for a variety of higher order cognitive functions. There's also the cingulo-opercular network in purple, which is the anterior insula and the Dorsal anterior cingulate cortex, also thought to be important for higher order cognitive functions. As a comparison, the auditory core network, which is more involved in auditory processing.

In adults with schizophrenia, we've seen consistent evidence for reductions in connectivity amongst these brain regions, particularly the fronto-parietal network and the cingulo-opercular network, and less so the auditory network. We see that the degree of reduction in conductivity among these networks relates to cognitive functions among adults with schizophrenia.

When we look at our kids who have psychotic-like experiences, what we see is that reduced connectivity, particularly among the cingulo-opercular network, is associated with the severity of psychotic-like experiences. That is more so, that is more strongly related to psychotic-like experiences than it is to other mental health challenges that kids might be having at this age—including depression, anxiety—and externalizing problems like attention-deficit disorder or conduct disorder. There’s at least some evidence of specificity or stronger relationships to these brain network disruptions amongst kids with psychotic-like experiences.

I mentioned earlier that we had looked at family history of psychosis. We now have a process, the GWAS data from the Adolescent Brain and Cognitive Development study, and we have started looking at polygenic risk indicators for different forms of mental illness and how that relates to different symptom manifestations in the study. We call these PRS scores, or polygenic risk scores, and we can look at a range of these.

These initial analyses are looking at youth of European ancestry because the polygenic risk scores were developed in samples that have European ancestry, although there's much work going on now to try to generate more diverse samples that can give us more generalizable polygenic risk scores.

When we look at our psychotic-like experiences, either total scores or significant distress scores, what we see is—and this is the proportion of variance accounted for by that polygenic risk score in predicting these psychotic-like experiences—we see that polygenic risk for schizophrenia accounts for significant variance in significantly distressing psychotic-like experiences. We also see that educational attainment

scores and polygenic risk scores for psychotic-like experiences themselves all account for significant variants, as does a cross disorder polygenic risk score, which is really kind of risk for mental illness in general.

We don't see evidence that polygenic risks for things like birthweight or CRP, which is a very nonspecific measure of inflammation, account for significant variance in these psychotic-like experiences. So again, a little bit of evidence, at least, for specificity.

I focused mostly on biological factors here; I focused on genetic risk or illness; I focused on cognitive function; I focused on brain networks. We also know that there are very important environmental contributions for risk for psychosis across the full spectrum; we know that things like growing up in households with lower income is associated with a greater risk for the development of schizophrenia later in life; and it certainly is associated with increased psychotic-like experiences or increased risk for psychotic-like experiences in this sample.

But importantly—sorry, got ahead of myself here. Before I get to that, we've also been looking at what factors might be part of a pathway by which polygenic risk is associated with increased likelihood of experiencing psychotic-like experiences. Importantly, what we see is evidence that both cortical brain volumes and cognitive function are part of a pathway that may be linking at least some of the polygenic risk relationships to psychotic-like experiences. If you look at the relationship between educational risk, you know polygenic scores for educational achievement, and risk for psychotic-like experiences, we see evidence consistent with it being mediated by cortical volume and cognitive function, reduced cortical volume and reduced cognitive function in particular, which relate, in turn, to increase risk for psychotic-like experiences.

Returning to the environment, I already mentioned that there's robust evidence that lower-income households are associated with a greater risk. But there's actually really important evidence accumulating that broader environmental risk factors are also associated with increased risk for both schizophrenia and, in the ABCD sample, for psychotic-like experiences. Things like neighborhood levels of deprivation based on Census block estimates of median income in neighborhoods parent and child perceptions of the safety of their neighborhood, more objective measures of neighborhood safety like things like numbers of drug offenses that are occurring in neighborhoods, and things like exposure to environmental toxins like lead-exposure risk. All of these things are associated with an increased risk for experiencing psychotic-like experiences even when you control for family income, parental psychosis, depression, anxiety, a host of other factors. This is accounting for increased variance over and above these other factors. Critically, the evidence again is pointing to the potential for disruptions in cortical gray matter development as part of that pathway by which these early adversity neighborhood deprivation, you know, kind of potentially the stressors associated with living in a higher-crime neighborhood, might be increasing risk for psychotic-like experiences.

In the interest of time, I will summarize. I think this data is providing really novel and important evidence that we can identify psychotic-like symptoms in children. As I said, we have newer data suggesting that it's particularly important if those experiences are distressing and if they last over time. This, I think, is not something we would have been able to see without the power of large-scale studies with deep phenotyping that allow us to ask these questions in much larger samples than have been previously possible. I think it also provides increasing evidence for the idea that there's a spectrum of psychotic

experiences that go from fully diagnosable schizophrenia to things like psychotic-like experiences that may start earlier in life.

In terms of next steps, we really need to be identifying these children for whom these experiences will persist or get worse and be starting to think about what kind of safe and effective interventions might be helpful. I emphasize safe, because I think there's a lot of concern about the possibility of medications early in life when we don't know what effects those will have on normative brain development. We are going to want to look at interactions with substance abuse, particularly cannabis, because there is great concern that cannabis use may either exacerbate preexisting risk factors for psychotic-like experiences or be a risk factor in and of itself. And we want to be able to determine which kids are really at risk for progressing to a more clinically diagnosable psychosis so that we can understand where we should be devoting our resources in terms of identification and intervention, and then, obviously, to try to develop those interventions.

if this all works, I think this is a call potentially for broader screening than we have previously done; although I think it will be important for that kind of screening to be able to be longitudinal in nature, because we know that there are transient psychotic-like experiences that can be pretty normative and are not indicators of risk. Again, it's really when it's distressing and continues over time that we think that really presages more concerning experiences later on.

I will stop there; I think I hit my time target.

If anybody has any questions?

Danny Pine: Absolutely. Thanks a bunch for a wonderful talk, Deanna; like all the talks it both combined a broad spectrum but also rich levels of detail.

There's one question about a relatively detailed finding that you reviewed concerning the reduction in connectivity in the cingulo-opercular network. The questioner notes that, while there was a relationship, there also seemed to be a large number of children who had particularly low connectivity but no symptoms. The question was about longitudinal outcomes, if you know anything about the degree to which that can predict outcomes.

Deanna Barch: I indeed do; we just had a paper accepted looking at exactly that question. Indeed, reduced conductivity in the cingulo-opercular network was a risk factor for… We looked at intercepts and slopes of psychotic-like experiences over time, and so you can think of the slope as either increases or new emergence of psychotic-like experiences and that connectivity was indeed a predictor of that over time.

Now, truth in advertising, the effect sizes were not huge. This is not, we are not going to be able to use brain connectivity in isolation to identify which kids are at risk, but it's potentially informative as a mechanism. We're starting to look at whether, if you combine multiple risk factors, we might start to be able to get into a range of clinically useful prediction. Because by itself, the brain network connectivity is not going to be clinically useful as a predictor.

Danny Pine: We had another question about social media, and I know that early on one of the first papers out of the ABCD got a lot of press about talking about the cross-sectional relationship with social media, and I wonder if you could just talk about both those cross-sectional findings, but also in terms of longitudinal outcomes about what we know about social media and its relationship to health, either broadly or mental health in particular.

Deanna Barch: That's a great question. I don't have a lot to say about it specifically in relationship to psychosis, as we haven't looked at that strongly. We certainly have seen cross-sectional relationships, particularly with depression, less so with anxiety, or at least less so with anxiety if you control for depression, so it seems to be more associated with depression, and we also do see it associated with ADHD.

In our own work, the only longitudinal things that we have looked at is in relationship to ADHD. We actually do see there, I was pretty surprised to see this finding and I don't want to make too much of it, that we see that baseline use of, we call it electronic media usage broadly not just social media, is associated with a greater likelihood of increased ADHD symptoms over time, even when you control for the kind of cross-sectional relationship between ADHD.

But those analyses are almost entirely based on parent and child self-report of their electronic media usage. We have subsequently gone on to start to do more things where we're actually capturing cellphone usage and social media usage in kids, so we can get a more fine-grain estimate. I suspect it's going to be a very mixed picture. There are going to be components of electronic usage and social media usage that actually may be associated with better function for kids, you know, getting access to social support in ways that they might not have otherwise. There are ways in which it is a connection for them, but then there's going to be, likely, a lot of evidence for it iatrogenic effects, too.

It's not my specific area of research, so I can't say much more beyond that, but I would keep an eye out in the next couple years as these actual phone-based metrics come out, which may give us a more of a deep view into what kids are actually doing on a daily basis.

Danny Pine: You know, Deanna, in the interest of time, I think I'm going to turn it back to Husseini in 1 second, but there are a couple of other, more questions in the chat that you might want to have a look at. In the remaining 10 minutes that we have, maybe you can respond through the chat box.

With that, I'll thank you again, Deanna, and I'll turn it back to you, Husseini, for the last remaining 10 minutes.

Husseini Manji: Thank you, Deanna. Thank you to all the outstanding presenters. Sheena, if you wouldn't mind projecting the closing slide, we'll just walk through that. Great, thank you.

I think what this slide is meant to encapsulate is something we all know, that in addition to the tremendous pain and suffering that our diseases and disorders cause, they also have a huge impact on

what we might call “cognitive and mental capital.” That's to say that society's greatest resource isn't oil and minerals, it's our cognitive and mental capital.

This slide basically tries to detect the many factors during the lifespan that can either maintain or unfortunately impair cognitive and mental capital. And as you can see, early in life factors like neurodevelopmental disorders, even things like maternal perinatal depression, or something Deanna just eloquently touched on, things like childhood poverty and the stress of that can have a deleterious effect. In some ways that makes it challenging for people to break out of the cycle and reach their full potential, etc.

In the middle of the slide is probably where we see the biggest impact, and that's, unfortunately, mental illnesses. Because as you've heard you're already, by and large these strike individuals when they're relatively young, and then they are lifelong; so they are the chronic diseases of the young. They have a major impact not only on pain and suffering but also on productivity, especially in our knowledge-based economy.

And then if we move to the right, we see we have the major neurodegenerative diseases. This slide is articulating dementia but this would be true of all the major neurodegenerative diseases, and I think as all of us know with our growing, global aging population, these have been called ticking time bombs and are going to have a huge impact on society. I think what we also recognize is that even things like age-related cognitive decline, more and more it may well be that many societies are going to have to have people work longer, delay retirement age, etc. That might especially be true in countries like China or Japan, where you've got this aging population and a very smaller population of young people. And so this is going to be a huge problem.

I think what's also true on this slide with all these diseases and disorders is that these don't affect the individual; these affect whole families. We all know that the impact of caregivers’ stress and burden, etc., is huge. To help try and address some of the societal challenges, I'm delighted that a range of stakeholders, including the NAM, One Mind, and others have come together to launch a new initiative called the Healthy Brains Global Initiative.

Victor Dzau, the President of the National Academy of Medicine, is co-chairing this effort, and he was going to be providing a brief overview. At the last minute, unfortunately, his schedule precluded it, so I'll just make a few comments.

What we think that HBGI has the potential to do is make a significant contribution to tackling some of these major, major, major pressing health, economic, and social issues of our time. What HBGI is going to attempt to do, and obviously any of you can follow up with us and we can provide more details, it's going to attempt to generate breakthroughs in the prevention, diagnosis, and treatment of both mental and neurological health conditions by doing a lot of what you heard around this session, namely extensively characterizing individuals or look at holistically, importantly, who represents the world's diversity, whose data are connected, and also who are involved in a global collaborative approach to research.

We think that tackling this complexity requires going beyond classical research methods and allow you to look at patients or people where you follow them longitudinally and you study them extensively because, as we know, these are very complex disorders that arise up at the inheritance of multiple

susceptibility genes, arguably protective genes, sociodemographic and other environmental factors. Can we do something collectively to focus beyond a single ecological agent? That's what HBGI is trying to do, a longitudinal approach that, through cohorts, attempts to capture the full set of factors that influence brain health. These would include genetic, other biological factors, social, environmental, cultural, and even medical comorbidities that we think are going to be important.

Obviously such an endeavor is going to cost a lot. HBGI plans to finance the development of these cohorts by both looking at different stakeholders that could help really bring, the ambitious goal is $10 billion, of new research funding to tackle this in its totality. While HBGI will be focusing on brain health globally, it's going to start with a population that has been unfortunately neglected, which is adolescents and young adults aged 10 to 29.

The hope is that, in addition to doing this novel research as I said, we're also hoping to elevate new voices, so bring to the table the voices of people touched by these illnesses; that would include patients themselves as well as their caregivers, because we really want to know what matters to them, what change is going to really make a difference for them.

We’re going to hopefully try employing new financing approaches, and this would certainly include financing from government both research and development assistance budgets; for example, things like sovereign funds, philanthropic organizations, and the private sector. One model that many of you may be familiar with is from the California Institute of Stem Cell and Regenerative Medicine, where they launched a bond toward really trying to advance the field of stem cell research, and that has turned out to be very powerful to really drive research in stem cell and regenerative medicine with a tremendous ROI, return on investment, not only in terms of more private investment, but a lot of clinical trials for stem cell diseases. HBGI is thinking about some of this in a similar fashion.

One of the important considerations is also to really try and be global, because these are diseases and disorders that know no geographic, ethnic, or racial boundaries, and we unfortunately know that most of the research has tended to focus on the western world, so we can be broader in our thinking. Hopefully we’re going to make a difference for humanity.

We're hoping to in the coming months, update this esteemed group about more information as at HBGI gets going and hopefully be able to engage many of you in this very important share societal mission.

So with those words, I think we'll bring this session to a close. I'd really like to thank the National Academy of Medicine for hosting this very important session and really would like to thank all of our outstanding speakers. All the presentations were absolutely fantastic.

And a sincere thank you to all the audience joining in for your tremendous questions and your engagement. This was great to have you as part of this neuroscience behavior, brain function, and disorders session. What we're now going to do is take a short break, and I'd remind everyone that the next round of interest group sessions will begin at 1:45 Eastern.

Thank you very much again for your attention and look forward to working with you as we move forward. Thank you.