CDC's 23rd ME/CFS Stakeholder Engagement and Communication (SEC) Call

May 6, 2024, 3:00 p.m. ET

Christine Pearson: Good afternoon, everyone, and welcome to today's ME/CFS Stakeholder Engagement and Communications Call, which we call S-E-C or SEC. My name is Christine Pearson, and I'm the Associate Director for Communications in the division where the ME/CFS program is located within CDC.

As you may know, we host these SEC calls twice a year as part of our regular outreach and communication activities to provide information for people with ME/CFS, as well as their loved ones, clinicians, and anyone else who may be interested in the disease. Our goals during these calls are to provide updates on the work of CDC's ME/CFS program and for you to hear from external experts in the field. Today, we'll hear program updates from Dr. Elizabeth Unger, our Branch Chief for the viral -- Chronic Viral Diseases Branch. Then we'll turn it over to our guest speakers from the National Institutes of Health, National Institute of Neurological Diseases and Stroke, Dr. Brian Walitt and Dr. Avi Nath. After the presentations, we'll have a Q&A session.

During today's Q&A, you'll have the opportunity to ask questions through the webinar platform or by phone if that's how you joined today. We'll provide more information on that when we get to the Q&A session. Before we start, I'd like to remind everyone that this call is open to the public, so please consider that before sharing any personal information. We're also recording this call. Please disconnect now if you have any concerns about recording.

We'll post the transcript and video as soon as possible after the call is complete. If you'd like to access the closed captioning or to read along with the text of the program update, the links to both of those are in the chat box. Now, we'll turn it over to Dr. Unger to start with the program review.

Dr. Elizabeth Unger: Thank you very much, Christine, for that introduction, and welcome everybody to the 23rd SEC call. As we approach ME/CFS International Awareness Day on May 12th, I'd like to begin by recognizing the millions of people battling ME/CFS, as well as their loved ones, caregivers, patient organizations, and advocates. To begin CDC's recognition of this year's ME/CFS Awareness Week, our ME/CFS program will once again participate in a CDC Light Up event. During these events, CDC illuminates its Visitor's Center, one of its most prominent buildings, to bring attention and awareness to the impact of a disease or other public health issue. In this case, we're lighting up the building blue in honor of all people with ME/CFS, both diagnosed and undiagnosed.

Tonight we will be joined by members of the Georgia Chapter of #MEAction and their caregivers at the CDC campus. The blue lights will be on each night through May 12th. The CDC sign at the main entrance on Clifton Road will also announce CDC's recognition of ME/CFS

awareness. We have additional activities planned. Each day we will post a new social media message on X, and on May 12th, the CDC Facebook will post a message in honor of ME/CFS Awareness Day.

The ME/CFS program hosts a CDC ME/CFS Awareness Day webpage every year in support of Awareness Week. And this has just been posted. It can be found at www.cdc.gov/me-cfs. On this webpage, visitors can read about ME/CFS Awareness Day activities. We would like to share that #MEAction Georgia will be presenting the first Wilhelmina Jenkins ME/CFS Service Award to journalist, Ryan Pryor, and Emory University physician, Tiffany Walker, at a panel discussion and award ceremony being held May 8th. The award honors Georgians who made a significant difference in the lives of people with ME/CFS. I'm looking forward to attending this event and honoring the recipients. We are also really excited to recognize Jaime Seltzer, Scientific Director for #MEAction. She was just honored by Time Magazine as one of the Time 100 Health Award winners. Jaime is being recognized as one of the most influential people in health in 2024 for her work with ME/CFS and infection-associated chronic illnesses. Congratulations, Jaime, from all of us. We appreciate your work and dedication to the field.

Now I'll turn to sharing updates on our program's work since the last call. I'd like to start our updates by highlighting a recent publication from the Multisite Clinical Assessment of ME/CFS study. The study was published in the Journal of Clinical Medicine and is titled, "Heterogeneity in Measures of Illness Among Patients with ME/CFS is Not Explained by Clinical Practice." It addresses whether the clinical characteristics of patients with ME/CFS differed by the clinical setting and medical specialty background of healthcare providers. Seven specialty clinics led by providers who are experienced in diagnosing and caring for patients with ME/CFS recruited participants. Standardized questionnaires were used to evaluate ME/CFS symptoms. We found that the symptom profiles of patients did not differ between clinics. However, patients in each clinic showed a large range in the frequency and severity of all symptoms. The conclusion is that patients with ME/CFS differ due to the large number of symptoms and range of severity. The patient differences indicate that subgrouping on standardized measures of illness characteristics could bring more consistency to finding across studies.

Our program is continuing outreach and education activities for healthcare professionals and the general public. One of these projects was the posting of two videos from our collaboration with WebMD. During the past year, these videos reached more than 28,000 members of the public and 300 physicians. The videos highlight how knowledge, attitudes, and beliefs about ME/CFS can affect patients and healthcare providers. The videos can still be viewed at Medscape and WebMD. Based on what we learned from this project, some questions were adapted and included in CDC's rapid survey for evaluating the public's knowledge of and attitudes towards Long COVID. Data from the first round of that survey were released in February and provided some meaningful results. For instance, we found that 32% of adults had never heard of Long COVID, but among those who had heard about Long COVID, 82% at least somewhat agree that Long COVID is a real illness.

As noted in prior calls, our branch is funding the program called Infection-Associated Chronic Conditions Understanding and Engagement, abbreviated to ICUE, which is a partnership between the CDC Foundation and patient and community-based partner organizations. A short public report was published in February of the first year's work. The report summarizes opportunities for collaboration among the participating organizations, including promoting comprehensive research, enhancing patient and caregiver quality of life, advancing public awareness of infection-associated chronic conditions, identifying healthcare needs and gaps, and supporting clinician education. Additional information about the ICUE project, along with the report, can be accessed on the CDC Foundation webpage, and I should mention that when we post the transcript of this call, we will also include hyperlinks to this and other resources to make it easier for you to find them if you need them.

We continue to partner with the National Association of School Nurses, or NASN, as it's abbreviated, not only to collect information about ME/CFS in school children but also to train school nurses to recognize ME/CFS symptoms and help children with possible ME/CFS and their families find appropriate medical resources. There are currently 30 schools across nine states participating in phase two of the school-based active surveillance project. During the 2021 to 2023 school years, a total of 139,440 students at these 30 schools had chronic absenteeism. Preliminary school-level data showed that among absences due to health concerns, 3.2% were due to symptoms that can be found in ME/CFS. Also, in collaboration with NASN, we have submitted questions about ME/CFS for the National Examination for School Nurses Certification. The National Board of Certification for School Nurses Examinations Committee will consider whether to add these questions to the exam given to all nurses before they receive their certification.

We are also continuing our work on the Long COVID and Fatiguing Illness Recovery Program, or LC&FIRP. This is a collaboration with the Family Health Centers of San Diego, the ECHO Institute at the University of New Mexico, the University of Washington Post-COVID Rehabilitation and Recovery Clinic, and the University of Colorado School of Medicine. As you may remember, this project is aimed at empowering primary care providers to manage the health of patients with complex post-infection illnesses like Long COVID and ME/CFS. On March 14th, 2024, the LC&FIRP team hosted a webinar on patient resources and support. The speaker was patient advocate, Alison Sbrana, who was a member of the board of Body Politic before the group disbanded. Webinars are available online through the ECHO Institute's online software platform, which is called the iECHO platform.

In the last SEC call, Christine Pearson from our division explained CDC's Clean Slate Project to update and streamline the CDC's website. Our program continues to work closely with CDC communicators on this project, and the relaunched CDC.gov website is expected to go live on May 15th. We think that the public will find the new website easier to use, especially on mobile devices.

In April, I had the pleasure of participating in the first international conference on clinical and scientific advances in ME/CFS and Long COVID, which was held in Portugal. The conference was organized by ME/CFS and Long COVID lived experience experts to address the critical need to educate healthcare providers about these conditions. Many well-known researchers and clinical experts presented in person or virtually via the internet. I presented on CDC's public health approach to these conditions, and there was interest in leveraging CDC's educational materials for use in Portugal and Brazil. The organizing committee is continuing its strategic campaign to raise awareness and improve clinical care in Portuguese-speaking countries.

Finally, I'm excited to announce that on September 18th, Emory School of Nursing will be hosting a panel with CDC and #MEAction Georgia. The panel event is called ME/CFS Voice of the Patient and will feature volunteer ME/CFS lived experience experts who will be telling their stories. The event will take place at Emory School of Nursing located at 1520 Clifton Road.

Before I turn the call over to our guest speakers, I'd like to remind you that if you have suggestions for speakers or ideas for other topics for upcoming SEC calls, please email us at mecfssec.gov. This address can also be used if you'd like to be added to our email notifications about upcoming calls. And finally, just a note that the transcript of the entire SEC call will be posted on our website as soon as we can. Now I'd like to introduce our guest speaker.

Our first speaker will be Dr. Brian Walitt. Dr. Walitt has been collaborating with the National Institutes of Neurologic Disorders and Stroke, NINDS, as a clinician with the National Institute of Nursing Research since the launch of the NIH Director's Initiative study of ME/CFS in 2016. He officially joined the NINDS Clinical Neurosciences Program as a Staff Physician in 2021. Dr. Walitt earned his MD degree from the State University of New York Health Science Center at Syracuse and a master's degree in public health at George Washington University. His research protocols focus on deep phenotyping people whose symptoms developed after exposures such as infection. Currently, he's working with patients with ME/CFS, Gulf War illness, and post-acute sequelae of SARS-CoV-2 infection.

Our second speaker will be Dr. Avindra Nath. Dr. Nath is the Director and Senior Investigator with the NINDS. Dr. Nath earned his MD degree from Christian Medical College in India in 1981. He joined NIH in 2011 as the Clinical Director of NINDS, the Director of Translational Neuroscience Center, and Chief of the Section of Infections of the Nervous System. His research focuses on understanding how retroviral infections affect the brain and on developing methods to diagnose and treat those infections or treat these illnesses. He applied his expertise on the interaction of infections with the nervous system to understanding ME/CFS and other post-acute infection syndromes. Dr. Nath has also been recognized by Time 100 Health. His citation is as an innovator, demystifying exhaustion. Today's presentation will focus on deep phenotyping of post-infection syndromes and the way forward. Welcome, Drs. Walitt and Nath.

Dr. Brian Walitt: Good afternoon. I hope everybody can see my screen. I'm Dr. Walitt, and our talk today is called Deep Phenotyping of Post-Infection Syndromes and the Way Forward.

I think everybody on this call is familiar with what's pictured here. SARS-CoV-2, from its initial outbreak in early 2020 impacted all of our lives, and all of us experienced the ups and downs of the pandemic together. In the early days of the pandemic, people were very concerned about getting it, what would happen to you if you got it, what should you do, and how do you treat people who are acutely ill? But there wasn't a whole lot of thinking about what comes next after nearly the whole planet would be infected with this virus. It took until around January of 2021 for the idea that there were people who would never fully recover from COVID-19 to come into sort of the media zeitgeist, and this article here is from the New York Times Magazine on January 21, 2021. But people started to realize that not everybody would just turn around and get better.

The first studies of what came to be known as Long COVID, or PASC, post-acute sequelae of COVID-19, was actually done by the patients themselves. Lambert and Survivor Corps published the first paper, which categorized and provided qualitative numbers of how frequent symptoms are in about over 1,000 patients who had suffered from COVID-19, and you can see this long list of all the different types of problems that people have that followed their infections, but I put a red box around the most common ones here for you, and if we look at what those are, they are fatigue, muscle and body aches, difficulty concentrating and focusing, inability to exercise or be active, headaches, difficulty sleeping, memory problems and dizziness, amongst others. And when you step back and you look at those symptoms, it sounds a lot like myalgic encephalomyelitis/chronic fatigue syndrome.

On the right, is a cartoon that was drawn by one of the participants in our ME/CFS study at the NIH, and sort of how she illustrates all the different symptoms that she had. And you can see all the check marks that are very similar to what is reported in the Survivor Corps paper, including muscle aches, fatigue, headaches, brain fog, non-refreshing sleep, and dizziness. What is not characterized here is a post-exertional malaise, pictured here by her as a dark hole.

However, some of us realized that there was going to be Long COVID, and in July of 2020, Avi Nath, who will be speaking after me, is on record saying, "I think people, agencies, Congress, everybody, should be really focused on the possibility that some COVID-19 patients will develop ME/CFS." And we knew that this was likely going to happen because we knew a little bit about history.

And now I'm just going to take you all through the post-infectious persisting fatigue and syndrome history from 1934 to 2021. So, before 1860, there really wasn't a concept of infection, and without a concept of infection, it is hard to have post-infectious disorders. In 1860, Louis Pasteur completes his experiments that demonstrate that bacteria cause diseases for the first time. While that was difficult to show with the technology he had, about 40 years later, Loffler and Frosh developed a filter that was able to filter out the agent that was the cause of foot and mouth disease, showing that there was -- that you could isolate the cause of the disease for the first time, this infectious agent.

To actually visualize infection was first done in 1939 by Kausche and Pfankuch, who were able to visualize the tobacco mosaic virus using electron microscopy, which is pictured here on the right. And so it took a march of about 80 years from the initial idea that there are infections to being able to really characterize them with our technology. However, once we were able to characterize them with technology, the idea that infections caused lingering problems afterwards immediately came into being.

Pictured here is Alice Evans, and she was in the public health service serving as a scientist, and she was studying brucella infection and actually got infected with brucella on her own as well, and she described for the first time chronic brucellosis, a disorder characterized by exhaustion, insomnia, irritability, aches and pains for which no objective signs can be found. And she went on to say patients would typically carry a neurasthenia diagnosis, which was the label used for fatiguing disorders of the time.

She was actually a sufferer of chronic brucellosis, also infected, I believe, as part of her work. After her initial description of a post-infectious disorder, more followed, and from 1934 through 1957, there was a period of time with epidemic neuromyasthenia. At that time, polio was a rampant virus and caused great fear in the community, and there were a number of outbreaks of what looked like polio but really wasn't quite polio. The first being in 1934 at the Los Angeles County General Hospital, where 198 employees became ill with sensory disturbances, crushing fatigue, and muscle pain, but when they were evaluated, there was nothing there to suggest that they had polio. It was just polio-like. This was seen again in Iceland as Akureyri disease, simulating poliomyelitis, in 1937. In 1949, there was cases reported in Adelaide, Australia, of 800 people having such an illness, again in 1956 in Punta Gorda, Florida, and then even in 1957 in Washington, D.C. amongst student nurses.

Around this time in 1955, there was a similar epidemic at the Royal Free Hospital in the United Kingdom, where 292 staff members developed muscle fatigue and severe fatigue. Their cases started with a generalized respiratory, gastrointestinal, and vertiginous symptoms that evolved into chronic fatiguing syndrome and symptoms, and it became known as benign myalgic encephalomyelitis, where the term was coined, the term myalgic encephalomyelitis was coined.

In 1984 through 1985 there were two epidemics in the United States which introduced the term chronic fatigue syndrome into the vernacular, the first being in Incline Valley, Nevada, where 160 residents became ill over two years and the second in Lyndonville, New York, where 200 residents became ill, again, over two years of time. And so, our current term myalgic encephalomyelitis and chronic fatigue syndrome harkened to these two epidemics that came before it.

The idea of post-viral fatiguing syndromes continued to grow in understanding over time. It was first defined as a thing in 1985 by Behan and Behan as they described its principal symptom is severe muscle fatiguability, but there may be a range of secondary symptoms such as the aching of muscles, disequilibrium, and psychiatric manifestations. On the right, I show a cartoon

of all the different symptoms that are associated with post-viral fatiguing syndromes. Knowing that these things happen, it was decided that some groups would try to prospectively study these illnesses to understand them better, the first occurring in 1996 with the UK Viral Meningitis Study which followed 159 confirmed infections for up to 24 months, and they found that amongst the people they followed, the prevalence of chronic fatigue syndrome was around 12.6%.

In Dubbo, Australia, a similar study looking at a variety of infections looked at 253 people over a year, and they looked at the rates of chronic fatigue syndrome at different points in time. Six weeks out, chronic fatigue syndrome rates were as high as 35%, and they fell over the course of a year to 9% at one year of time.

Of course, SARS-CoV-2 COVID is not the first of the SARS viruses to have epidemics, and so people have studied SARS epidemics and MERS epidemics in the Middle East. And they found in 181 survivors followed over 41.3 months, that 40% of those folks had persistent fatigue, and that 27% of them would meet the 1994 CDC criteria for chronic fatigue syndrome. So, to us, it was pretty obvious that there was a high likelihood that there would be Long COVID. And so, prior to COVID, we had already started to study the chronic fatigue syndrome, myalgic encephalomyelitis, that occurred after infections, and this was with our 16-N-0058 protocol, myalgic encephalomyelitis, chronic fatigue syndrome at the NIH.

This program was announced in 2015, as shown here, and its overall hypothesis was that post-infectious ME/CFS is triggered by an infectious illness that results in immune-mediated brain dysfunction, and our aim was to conduct a cross-sectional study to deeply phenotype PI-ME/CFS to define its pathophysiology and to create new hypotheses to understand the disease. And to do this, we performed a lot of different measurements listed here. Some of these are traditional medical evaluations, such as histories and physical exams, neurologic assessments, neuropsychological assessments, measurements of patient symptoms. Some of these were more about energetics, such as diet, body composition, and whole-body, direct calorimetry. We looked at sleep. We looked at people's neurophysiology and autonomic status, and we collected a large number of biological samples to perform wide-ranging measurements using those samples.

We also conducted an exercise stress test using a cardiopulmonary exercise test where we measured participants at baseline and then followed them over 72 hours to help us better understand post-exertional malaise and its biologic basis. For our study, we used a very tight filter. We wanted to make sure that our participants truly had post-infectious ME/CFS. We talked to 484 individuals to do such. I ended up interviewing 217 individuals to bring 27 ME/CFS participants to campus and 25 healthy volunteers. We developed an adjudication process using experts in the community to independently review each of the cases that we saw to adjudicate whether they thought they were post-infectious ME/CFS. Only participants that were unanimously considered by all of the adjudication panel to be adequate patients were entered

into the analysis. And so, ultimately, we ended up with 21 healthy volunteers and 17 PI-ME/CFS participants.

We have recently published our paper, our initial paper of these results, "Deep Phenotyping of Post-Infectious Myalgic Encephalomyelitis Chronic Fatigue Syndrome" in Nature Communications in February of this year.

And this is our figure 10, and I'm going to take a moment here to review this because this provides you an overview of our thoughts about the genesis of post-infectious ME/CFS. As you can see my arrow here with infection, we believe that infection causes two things to occur simultaneously. First is an immune dysfunction, right? We saw that in participants that they had increased numbers of naive B cells and decreased numbers of switched-memory B cells, which suggest that there's a blockage in the maturation of B cells, that something is sort of blocking the typical course of an immune reaction.

We felt that this may be due to persistence of virus remnants, or infectious remnants, that may be playing a role in that blockade. Further evidence of this was alterations in adaptive T and B-cell processes that were suggestive of immune exhaustion. Our second major finding in the immune system was that there are striking differences in the immune reaction in male and female ME/CFS participants that is not the same. And so, the idea that there is a singular immune response in ME/CFS doesn't seem to be likely.

On the other hand, we also saw that there was microbial dysbiosis, where we can see that there were differences in the composition and the regularity of the microbiome in the participants with ME/CFS. We also saw that there were some alterations suggesting decreased in butyrate-producing bacteria and metagenomic potential, which we saw also in the cerebrospinal fluid metabolic analysis that we performed.

And so, we suspect that both of these arms are working through their respective neuroimmune and microbiota gut-brain axes to create alterations in the metabolic function and metabolic content of the central nervous system. On analysis of cerebrospinal fluid samples, we found a number of different metabolites being decreased, including citrate, glutamate, spermidine, tryptophan metabolites, butyrates, and some alterations in catecholamines, such as a decrease in DHPG and DOPAC, which are relevant for the production of norepinephrine and dopamine.

We believe that these changes impact the function of the brain itself, and again, going in two different directions. In one direction, it impacts the function of the hypothalamus, leading to a decrease of a function of an area called the temporoparietal junction, which is an area which detects mismatches between how we are performing and how we feel we should be performing to some degree. And we believe that this interferes with the ability of the brain to send out motor signaling, leading to decreases in the ability to activate the motor cortex and decreases in the activation of the musculoskeletal system, leading to decreased force output. Of course, when you have decreases in your ability to engage with your motor system, this is going to reduce your activity.

A second arm relies on alterations in catecholamines to impact the autonomic nervous system. And we saw in several measures that there are alterations in autonomic nervous system function, including decreased heart rate variability, and decreased baroreflex cardiovascular function that are suggestive of decreased parasympathetic function. There is a hint of increased sympathetic function, but not as rich as the data suggests a parasympathetic alteration. That alteration in autonomic system function looks like it has an impact on cardiorespiratory performance, as shown on exercise with a decrease in peak VO2, a decrease in their patient's heart rate reserve, decrease in the anaerobic threshold, and the finding of chronotropic incompetence in the participants during exercise.

Of course, decreased cardiorespiratory capacity is going to lead to a deep reduction in activity as well. And both of these different arms put pressure on the participants that were infected and push them into the ME/CFS phenotype. I would like to thank all the people that were part of the program. All the authors are listed on the left. We'd like to acknowledge all of the individuals on the right, in particular, Francis Collins and Walter Koroshetz for their support of this project. We would also like to thank the adjudicators that were essential for ensuring that we pick the most appropriate participants including, Anthony Komoroff, Lucinda Bateman, Benjamin Natelson, Andy Kogelnik. And of course, we'd like to thank all of our ME/CFS and healthy volunteer participants. For without their volunteerism, none of these would have been possible. And with that, I will turn over the floor to Dr. Nath.

Dr. Avindra Nath: Thank you. Yeah, thank you, Brian. Let me see if I could share my screen here. See my screen?

Dr. Brian Walitt: Yes. You just want to put it in presentation mode.

Dr. Avindra Nath: Okay. So, I'm going to talk about Long COVID, and as you know, this syndrome is caused by SARS-CoV-2. The problem is that although we all know the term Long COVID, when you start distilling down to actually what it means, it's quite complicated. Nobody really knows how best to define it. And so the term Long COVID was coined by patients, which was pretty simple. They got COVID, and then they recovered to some degree, but the symptoms were persistent. They said, well, I got Long COVID. But then people tried to define it. The NIH tried to do it, and the term post-acute sequelae of COVID-19, that's kind of a mouthful, and it's still used, but it's difficult to, you know, make it mainstream. So people call it PASC for short. WHO came out with a term just calling it post-COVID-19.

And so the WHO definition seems to stick, and so what they call it as they say that the post-COVID-19 is a continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation. The problem with all these definitions is that you really have to take into account two types of individuals. And in the simplistic plot here, one way to look at it is that if you have individuals who get admitted to the hospital, they are extremely sick, okay, and they end up in the ICU. Now, when they come out, they're not going to be the same. It's going to take them a

long time to recover, or they may never recover completely. So, they have this post-ICU syndrome or post-acute syndrome, which is, so which is really to be expected, but it doesn't mean that there is new activity ongoing, right?

Then you have this second subset of individuals who had relatively mild symptoms. They recovered either completely or almost completely. Then after some gap, either days, weeks, then they start developing new symptoms. But they are related to that infection that they had because they never had other problems. So, this is a -- the pathophysiology of this is going to be very different than the pathophysiology of this. So I think this is where we need to really focus our attention. So I like dividing them into these two different categories.

Now if you look at this data from the CDC, what they show is that in this duration of time, that if you look at the entire U.S. population here, you can see almost 5% to 6% of the adults of the U.S. population have symptoms of Long COVID, right? And of those individuals who had prior COVID, you're looking at about somewhere close to 11% or so. And it varies a little bit by the age groups and the middle aged here, populations seem to have a much higher incidence of Long COVID.

Okay, so what are the symptoms of Long COVID? And so, I said if you take out these individuals who have the post-intensive care syndrome, right, and you just look at these other individuals here, you can divide them into four buckets. And they're not distinct buckets because they do overlap with one another, but they are individuals who may have predominantly complained of exercise intolerance, others that complain of more cognitive sleep disorders or mood disorders. Then there's a third group that has largely dysautonomia or POTS or milder forms of POTS, right? And then you have a subset of individuals who complain of pain syndromes, and amongst the pain syndromes, I like to take out headaches as a separate category, because here you could have underlying CNS pathology that can account for headaches, like cerebral venous thrombosis and stuff, although has to be taken very seriously.

Okay. All right. So, we tried to look at individuals that had predominantly neurological symptoms, and we brought them here to NIH. And what we did was we wanted to be sure, just like we did with the ME/CFS, we wanted to make sure that these patients were absolutely clean, that the only explanation would be the infection that they had, and they didn't have prior pre-morbid conditions, and so on and so forth. So, we started off with a cohort of 173 individuals, and we finally brought in 12 individuals to NIH. And when we looked at them, what we found was that 100% of them were complaining of exhaustion, and 100% of them were complaining of cognitive dysfunction, and then about nearly half of them had other types of neurological symptoms. And so -- but if you look to see how severe were these symptoms, they're actually pretty significant symptoms.

They were quite disabling, as you can see. So a lot of them had, you know, affecting their daily lives, cognitive difficulties. Some of them were pretty severe, and some of them also had peripheral neuropathies that were moderate. Okay, now how does this compare to other types

of infections? Is SARS really unique compared to other respiratory infections? SARS-CoV-2 is certainly much more severe than a lot of the other respiratory infections.

And if you were to look at the development of neurocognitive dysfunction as minor cognitive disorders, based on various type -- COVID versus other respiratory infections, at these younger age groups, there is more so in patients who develop COVID, which is this blue line here, compared to other respiratory infections, except at the age group of greater than 70. There's bad news. It doesn't matter what infection you get, the outcome is bad. So unfortunately, aging poses its own problems. So, what are the underlying possibilities as to what is it that can really cause this kind of a syndrome? And there are broadly three different categories which you can derive these things -- divide them. And one is this possibility of viral reactivation. You have other viruses that can get reactivated. The other possibility is that the original infection you got, you actually never got rid of it. The third possibility is that maybe there is immune dysregulation.

So now if you look for reactivation of the virus, what you find is this is a study from Yale, and what they showed was that in these patients, LC is Long COVID, CC are individuals who have recovered from COVID, and then you have healthy individuals here. So individuals who have Long COVID have reactivation of Epstein-Barr virus, and that's been shown by several groups now, that you can get a reactivation of Epstein-Barr virus. Now does reactivation alone, is enough to cause Long COVID? That we do not know. So it's just association, not necessarily causation. The only way you would know the difference is that you've got to suppress it and then see if it makes a difference to the clinical course or not. But it's still important to know that, yes, other viruses can get activated, and that's if you have any inflammatory syndrome, it can happen, actually. The inflammation itself can reactivate resident viruses.

Okay. What about persistent viruses? And I'd like to include the possibility that you may not have complete virus. You could also have remnants of these things. So where does the virus really reside? We know it goes up the nose, and what it does is it infects the olfactory epithelium. And what it infects is largely these cells called sustentacular cells, okay? So, these are support cells sitting right next to the neurons themselves. Because you have neurons, olfactory neurons, sticking in the nose, and they go up to the cribriform plate into the brain, okay?

So, originally, we thought that what's going to happen is it's going to infect these olfactory neurons and you're going to get a lot of encephalitis and it'll be bad news. It turns out that's actually not the case. You get a lot of virus in the nasal mucosa. You can see all these black dots over here, all full of virus, okay? And if you look at the olfactory mucosa here, each of these dots indicates that there's presence of virus and it's a log scale. So, you know, even this much virus is a lot of virus.

So, you find it in the olfactory mucosa. If you go to the olfactory bulb, which is right at the base of the brain here, most of them, you don't find anything. There are only three individuals here

with small amounts of virus, oops. And if you look at the olfactory tubercle, again, you don't find anything. So, the virus doesn't enter the brain that easily. We still have a really good defense mechanism to really maintain it within the nose itself. So, my colleagues here at NIH did a very extensive study looking for the virus in various organ systems, okay? And what they found was if you just look at the respiratory tract and you look at individuals who had less than 14 days post-infection, you can actually find a lot of virus, 9,000 some copies of virus per nanogram of RNA.

But if you just go to a month later, there's less than a copy. There's not a lot of virus left around. All of these patients have long-term symptoms. If you look at the brain, even at less than 14 days, there's only 32 copies and greater than a month, less than 0.39. So, there's not a lot of virus around, very little stuff, but is that sufficient to do anything is the question?

So again, our colleagues here at the National Institute of Aging looked at the tongue and they published a beautiful study and here's an individual who's 45 years of age and 40 weeks post infection. Okay. They looked at the papilla, and here the green staining is for the spike protein and red for nucleocapsid, and you can see that there is staining for viral antigen. But I like to differentiate viral antigen, it doesn't mean that there's a replicating virus. These patients are not infectious. Okay. So if they were to kiss anybody, you're not going to transmit the virus. But viral antigen can persist without replicating virus, and I think that's the important thing to remember.

Now this is a group from Boston, and what they found was that if you look at the spike protein, so there's the S1 protein, spike protein, and nucleocapsid, they didn't find much of nucleocapsid or S1, but when they looked for the spike protein, they found that some individuals had presence of the protein in the blood, right? So, if it was replicating virus, you would find all these proteins. If you find only one protein, that tells you only some of it is being shed, so you don't have complete viral replication.

Okay, so what about immune dysregulation? What is the evidence that there is immune dysregulation? Two things to consider, antibodies and macrophages. So, this is a study from Canada, and what they did was they used a PET ligand, so these radioactive ligands that you can give to the patient and then measure it in the brain and see what happens to it. And this ligand binds to these activated microglial cells. That would suggest that there is inflammation within the brain. And what they found was that a T-score is a cognitive score so that those individuals who have low score, that means they're cognitively impaired, have increased amounts of binding of this ligand, suggesting that there is inflammation within the brain. So, this is one way to look for innate activity within the brain itself.

And this is a study from the Netherlands, and they looked at only two individuals, but nonetheless, they showed very dramatic, you know, binding of this ligand. They used a slightly different ligand, but again, it binds to the same activated microglial cells. And what you find is that increased activity in the brain compared to controls here at the bottom.

We looked at the brain at autopsy, and what we found was that in this COVID brain, all these brown cells here are all activated microglia. So, there was a lot of activated microglia, both in the gray matter, more so in the white matter, and compared to controls, and we would quantify it and show it the same way.

Okay, we also looked at the brain at autopsy using very high-resolution MRI scans. And here, if you look at the brain stem, what we found was the blood vessels were involved. So we then cut sections to the same area of the brain, immunostained them, and what we found was that there's a lot of fibrinogen leaking from the blood vessels that suggests to you that the blood-brain barrier is broken down, and these very large proteins that should never enter the brain start to enter into it. If that happens, that usually is bad news, okay? And we looked at the olfactory bulb, and again, we found the same thing. This is an olfactory bulb on an MRI scan, and here's the sections that we immunostained.

They also looked at the substantia nigra, and what we found, again, was abnormalities here. You can see the really gorgeous anatomy on these very high-resolution MRI scanners. This is an 11-Tesla scanner, and that pointed out to us that there's something abnormal. We then immunostained them and found that there is leakage of fibrinogen. All the red stuff here is fibrinogen this time, okay, and that's what's causing the damage. We looked for other inflammatory cells, and what we found was that there were perivascular macrophages here, astrocytosis. It just keeps switching, I'm sorry. But what we did not find is T-cells.

Okay. So, we found very few T-cells around the blood vessels, nothing in the parenchyma. If there was virus in the brain, you would find a lot of T-cells, and we never found them. What we found was that there were activated platelets sticking to the blood vessels. And I think that's very important because it’s suggesting that the pathology is at the level of the blood vessels themselves, and if you look at the different parts of the brain, we found that most of the pathology was in the lower parts of the brain, which is called the hind brain.

So we looked at the blood vessels more closely to see what is really happening. And on top of the controls at the bottom is this COVID-19 patient. And as you can see, this PCAM-1, that's an adhesion molecule expressed on endothelial cells. It is very highly expressed in these COVID-19 brains. Okay. So that tells you the endothelial cells are activated, and once they are activated, they start binding things. Okay. So here I show that they're binding complement, and they're binding immunoglobulins. So what it is it's an immunoglobulin-mediated damage to the endothelial cells. What the antibodies are recognizing is not entirely clear, but I'll show you some hypotheses, okay?

Important thing is that there is more IgM than IgG, and I think that's a problem in these COVID patients, and this coefficient is the exact same thing we found in our ME/CFS patients. That they have class-type switching is a huge problem for these individuals, okay? And I think that's the innate immune abnormality in both syndromes. Okay. Going back to those patients that we

brought here to NIH, we looked at their immune system, and what we found was that if you look at these Long COVID patients, they have B-cell abnormalities. Okay.

So the B-cell frequency is increased. You actually see antibody-secreting B cells are increased over here in these patients, and they have immune exhaustion markers on their T cells, okay? And I think this is very important because when we compare them to our ME/CFS patients, we found pretty similar abnormalities in them as well. Okay. So you can see the naive B cells are increased. There's an abnormality in switching to the memory B cells, and we found T-cell exhaustion on these T-cells in the ME/CFS patients. So the Long COVID and ME/CFS, at least immunologically, have a lot in common.

Okay. Now with regards to the Long COVID patients, I told you it was an antibody mediated phenomenon. Question is, what are they actually binding because we never found any spike protein or virus in those endothelial cells? So one possibility is that they develop what is called anti-idiotypic antibodies. That means you form antibodies against the antibody. So if you have an antibody against the spike protein, the antibody, if you develop an antibody against the first antibody, that will look like the spike protein, okay? So it doesn't have to be the spike protein itself. It's just that conformational changes on the antibody will mimic those of the spike protein, and that will then bind to the ACE receptor and cause disruption on the endothelial cells.

It's important to remember that if you look at the vasculature of the brain, I mean, there's lots of blood vessels in the human brain, and there's no cell that is distant from the blood vessels. It's in very close vicinity. So, if you damage the blood vessels, it can cause a lot of damage to the brain.

Okay. So what can we do about this? And there are a lot of things one can do. These patients, even though you may not have things that you can intervene with to change the course of the disease, physicians can treat patients symptomatically and actually make their lives better than what it is. Important that we also exclude other kinds of underlying diseases because sometimes they have other comorbidities that need to be treated, some they may not be even aware of, or they may get unmasked during the infection.

So, it's critically important that these patients be followed closely, be studied thoroughly to look for other treatable causes, and then treat them symptomatically. So I've listed a whole bunch of other potential interventions that can be done for a number of these symptoms. What about immune-modulating drugs? So, I do think this is the way to go because it's very clear that both Long COVID and ME/CFS have these immune abnormalities, and so intervention there would be useful to see what it does. But I would caution that these drugs are pretty nasty drugs. So I wouldn't just use them empirically. They should be done only in the context of clinical trial because they have pretty profound side effects, but there are multiple opportunities to impact either of these types of immune cell types. And one needs to stratify the population, try and see who has what type of immune abnormality, and then target them accordingly.

And so how to do it? I think what we need to do is we need to study multiple drugs at the same time and use a single placebo. That's at least one way of doing it. This is not the only way of doing clinical trials, but I think more and more with most diseases now, people have started thinking about this kind of strategy, and that is called a platform study, okay? It has its own drawbacks, but it also is at least one way of looking at it. Another way to do that is to do a crossover, a placebo-controlled study, and we are currently doing one with Dr. Walitt, who is leading a IVIG study for Long COVID patients at the moment. That's a crossover study.

Okay. The other thing is vaccinations. Do vaccinations prevent? And the answer is yes. More and more data suggests that those people who have multiple doses of vaccinations, their chances of developing Long COVID goes down, as shown in this meta-analysis. So, more dosages, the better. So, anything towards the left of this line suggests that it's preventing Long COVID.

So we have several ongoing clinical studies here at NIH. One is a natural history study for Long COVID. This is based on what we did with ME/CFS. We're doing very similar kinds of studies of Long COVID, so we can compare the two. I just mentioned that we're doing this IVIG trial. There's a study in development just looking at viral reservoirs. Now we know here what the infection is, the question is are the remnants of the virus still present? So we're going to do a deep dive, trying to collect tissues as much as possible, and body fluids, to try and see where we can find it. And then we want to look at the innate immune activation in the brain. I think that remains an unanswered question in both Long COVID and ME/CFS. And so Bob Innis who has developed a pretty novel ligand against COX-1. So we've been talking to him about developing a protocol here.

So I'd like to conclude and say that direct invasion of the brain with SARS-CoV-2 is rare and may not explain the neurological complications. Neuroimmune dysfunction is driven by activation of innate immunity, immune exhaustion, and antibody-mediated phenomena, and clinical trials and immunotherapies could be considered in patients with Long COVID. And I'd like to acknowledge a number of people. So here are the pathologists who helped us with all the analysis of the autopsy cases, and Serena Spudich and I wrote an article in Science on the pathophysiology of Long COVID. And this is the group in my lab that did all the histology here. This is the clinical group over here that have been studying all these patients, and this is the MRI group here, and Walter Koroshetz is the director of our Institute who supported these studies. So I'll stop here and take questions.

Christine Pearson: Hey, everybody. This is Christine Pearson again. So I wanted to mention that we will now begin the general Q&A portion of the call. There's three ways that you can ask a question. If you're joining on Zoom, you can raise your hand or put it in the Q&A box, or if you are on the phone, you can enter -- if you're on the phone only, you can enter star 9 and then join the question queue that way. I did want to mention that we already have quite a lot of questions. We'll do our best to get through as many as possible. So we'll just hit it straight

away. This is for Dr. Walitt. "Do you believe the effort preference may play a similar role in other neurological diseases such as MS, Parkinson's, and ALS?"

Dr. Brian Walitt: Well, thank you for that good question. It's an important question, of course. The evaluation network of the brain, which is the circuits of the brain that underpin measures like effort preference, is relevant to all neurologic diseases. Currently, people have been looking at effort preference in other disorders like Parkinson's and frontotemporal dementia, where they have seen alterations occur. Understanding how the evaluation network is impacted by a range of neurologic disorders, including ME/CFS, Parkinson's, frontotemporal dementia, MS, and ALS, all of those things will produce new insight into the function of that network and help us understand the role it plays in all of those disorders.

Christine Pearson: Thanks so much. So our next question is for Dr. Nath. It says, last week you recommended the need for a platform trial where multiple drugs can be studied simultaneously as the next step. Is any funding currently in place to pursue this aspiration? If not, how can NINDS encourage and solicit grant applications on this proposed plan to help make it a reality? What are the next steps needed to accomplish this goal?

Dr. Avindra Nath: Okay. So, I don't manage funding, so I can't answer that part, but I do think that platform trials is the way to go, and a number of diseases are already looking into it. One of the diseases that I study is ALS, and so there's an ongoing platform study in ALS, and one can learn from that experience. So Merit Cudkowicz at Harvard is the PI on that. It's a multi-center study. I think for platform studies, you need large sample sizes. So you're going to need multiple sites to enroll patients, and they are very expensive. So pharmaceutical companies usually fund these things. Federal agencies don't have that kind of bandwidth. Most of the funding for clinical trials usually come from pharmaceutical companies because they have the deep pockets to do these things. Their budget is 10 times that of NIH or more. So I think what you need is probably some kind of an advisory committee that can go and design these things, try to raise funds from pharmaceutical companies that conduct these studies, and learn from the ALS platform study. That's what I would suggest.

Christine Pearson: Okay. So the next question is also for you, Dr. Nath. "How do the findings of the ME/CFS intramural study comport with the phenomena that people with ME/CFS decline after exertion? Many patients start out mild and go to moderate or severe after continued exertion. Additionally, will you do further research on muscle issues? Maureen Hanson has shown your metabolite anomalies and Rob Wüst has shown that the muscles are damaged in PEM. Will you try to replicate these findings?"

Dr. Avindra Nath: So, I think there's a lot of activation of the innate immune system. My hypothesis is that a lot of this post-exertional malaise is probably activation of cytokines and that's probably what drives it. I am more focused on, really, modulating the immune system and conducting clinical trials. There are other people who are interested in muscle, so we have Paul Hwang who presented data at our -- and published a paper at PNS, so he's continuing to

study the muscle. That's his area of expertise. Urine metabolites, we don't have any expertise in that. We can certainly collect it and make it available to Maureen if she wants to study them. It doesn't make any sense that everybody do everything. You should do what your areas of expertise are, and that's where you're the productive.

Christine Pearson: Okay. Thank you. So the next question is for Dr. Walitt. Apologies, everybody. Let's try this again. Is that working now? Okay. All right. Sorry about that. So the next question is for Dr. Walitt, and this is from regarding your presentation. It says, "With the figure being shown that was a summary of abnormal findings, the findings are portrayed in a cascade-like order, but this is a hypothesis, correct? That is a chicken versus egg order of abnormalities aren't necessarily known."

Dr. Brian Walitt: Yes. It is just a hypothesis. Our program is an exploratory program, and the goal of exploratory research is to generate new hypotheses, not really to test hypotheses. And looking at all of the data combined, it seems to be the most compelling story to explain how one goes from having an infection to having PI-ME/CFS. Everything that we did is worthy of replication by other groups.

Christine Pearson: All right. I think this one would be for either of you two gentlemen. It says, "At last week's PI-ME/CFS symposium, Dr. Anthony Komaroff expressed that the findings from this study concludes that ME/CFS is a brain disease induced by chronic immune activation. What are your thoughts on this assessment?"

Dr. Avindra Nath: So yes, that's right. I mean, it is a -- we've showed humongous amounts of data showing that it's an immune-mediated disorder. I mean, there's no doubt it is, and so I don't think we are in -- I don't know what else to tell you. I mean, the paper shows huge amounts of immune disorders and immune dysfunction. We showed in all of our slides, there is immune dysfunction. There's no disagreement there.

Christine Pearson: Thank you. All right, so the next one, either -- also for either of you two gentlemen. "The fMRI component of the study was very small. There were a few parts of the brain that had lower blood flow in the ME/CFS group, possibly due to chance. Why the focus on one of the TPJs? Even with one TPJ, and even assuming the finding is not just noise, there are other ways to interpret the finding of reduced blood flow to that part of the brain. Is it true that the investigators were determined to apply a preconceived interpretation to very scant data? Do the investigators accept that their interpretation is not the only possible one?"

Dr. Brian Walitt: Well, a couple of things. In terms of what we thought or how we designed the experiment, you know, we didn't really expect to see the temporoparietal junction to be the place in the brain that would come out of those experiments. The way that the experiment was set up is really to investigate the muscle itself in the M1 region of the motor cortex. You know, the real purpose of those experiments were to understand how muscles and how the motor cortex itself were activating or not activating, and in that we were kind of surprised by the results because usually people talk about peripheral fatigue and central fatigue as being

phenomenon related to the activity of those two areas. The idea that the alterations that were playing a role in our ME/CFS participants were coming from a different area was a little bit of a surprise to us. While the sample sizes are small, usually in this kind of research, the sample sizes are small, and the fact that we saw such a large effect size makes it worthy of note. It is not really the only thing that our study shows, and our study shows a wide range of different types of physiological alterations, but it is certainly one that's worth noting and looking into a larger cohort.

Christine Pearson: Thank you. And then the next question is, I think, for either of the speakers. It says "What is the placebo in the Long COVID IVIG trial? Dr. David Bell stated past studies used normal saline, and he stated saline makes patients feel better, so not a true placebo?"

Dr. Avindra Nath: Yes. I think he is absolutely right. That's what you want to know. You want to know if IVIG is any better than saline or not. If they're equivalent, then just give people saline. Why bother with a very expensive treatment there? So, yes, it is saline, and it's good to compare saline versus IVIG. It makes a lot of sense.

Christine Pearson: Okay. Great. I think also another one for either of the speakers. "How do findings of this study comport with the patients who decline slowly after repeated exertions? If the patient continues to exert and decline, are they overcoming effort preference? Doesn't this warrant further research into" -- oh, sorry. I think that we've already -- I already asked that one. Sorry. Okay. So the next one is "With EBV, did anyone look for it in salivary glands where it tends to hang out? Is anyone interested in replicating the work of Maria Ariza at Ohio State looking at EBV dUTPases or their antibodies in ME/CFS or Long COVID patients? Also figuring out the activity of these antibodies, if any."

Dr. Brian Walitt: Well, I think I can give some of the answer to that, but Avi may want to chime in afterwards. We are moving forward with a tissue procurement protocol, as we mentioned, to look at antigens throughout the entire body, including all those with SARS-CoV-2, but we also plan to look at other viruses, including EBV. We will be collecting minor salivary glands at the lip, along with a number of other oral pathologies, and we'll be able to at least provide some insight into EBV persistence, or remnants, within salivary glands with the completion of the protocol that is about to get started.

Christine Pearson: The next question is for Dr. Nath. "What about the role of other anti-inflammatory drugs that are safer?"

Dr. Avindra Nath: Yeah, I think it can be tried. I'd, you know, see what happens. I mean, there are a lot of potential choices, and one could certainly try, and I would just do it in the context of a clinical trial. That, I think, is the most important. So as you have all these anecdotes, and you don't know what you're really doing in the end. So, you can try lots of different things. I get lots of emails from people who want to use all kinds of things, and I think that all is perfectly fine. You just do it in the context of a clinical trial, so we know, really, what to use ultimately and what not.

Christine Pearson: And then "Are there any thoughts regarding next generation COVID-19 therapeutics being promising regarding viral reservoirs and persistence, i.e., vaccines, monoclonal antibodies, and antivirals?"

Dr. Avindra Nath: Yeah, I'll take it. I don't think they're going to work. So, if you have -- there's no evidence that in Long COVID you have transmissible or replicating virus. So, I think these Paxlovid-like things and antivirals are not going to do anything. If they are remnants of virus, antivirals won't do it because they're not replicated. What you need to do is get rid of that remnant. I think that's why I've been proposing the checkpoint inhibitors because I think that activates the immune system, which is the exhausted part of the immune system, to go and find those reservoirs and get rid of them. And so I think that's really the way to go on that. What was the other part of that question? Sorry. Just something?

Christine Pearson: I'm looking for it. I'm sorry. We have so many questions.

Dr. Avindra Nath: Oh, okay.

Christine Pearson: Yeah. I think it was just looking at other options in terms of reservoirs.

Dr. Avindra Nath: The antiviral reservoirs? I think the other antivirals just don't make any sense. I think what you really need to do is develop new antivirals.

Christine Pearson: Okay. So the question is "I developed ME/CFS seven years ago following a chemical exposure but have the exact same symptoms as most Long COVID patients I've spoken with. Has there been any thought to pathological driver of symptoms outside of viral persistence? In my experience and from people who have seen improvement I've spoken with; they've had tremendous improvement when they moved to places with significantly better air quality. Coupled with the increase of self-reported chronic illness prevalence from 6% to 60% in the past 100 years, has there been consideration of chronic exposure to man-made substances in nearly every household as drivers of these symptoms and viral exposure just being an initiator to the susceptibility to these toxic or hazardous substances?"

Dr. Avindra Nath: Yes.

Christine Pearson: Beth, would you like to start with that?

Dr. Elizabeth Unger: Yeah. I think this is a good question for all of us to comment on, and particularly with ME/CFS it's recognized that patients see many different triggers, not just infections or they might not recognize the infections. And it's also clear that the environment does interact with infections, as does the host status in terms of the stress response at the time of infection. So this is part of the reason I think why it's really difficult to come up with a one-factor pathogenesis. So, we're doing our best to separate out each of the factors. And so, Avi and Brian, you should comment as well.

Dr. Avindra Nath: No, I couldn't agree with you more. So, you know, I think it's a really important question and really one that needs to be addressed, which is that if you have other

types of triggers, can you end up with the same syndrome? I would love to be able -- for somebody to look at those patients, compare them to the infection ones, see if you see the same kind of immune dysregulation or not. You know, it's quite possible just because you have fever, it doesn't necessarily mean the cause is the same, all right? Your clinical manifestation could be the same, but the underlying pathophysiology could be very, very different, or some parts of it could be very similar, so I think teasing that out could be a very important to do.

Dr. Brian Walitt: What I would add to that is the hope is that by studying post-infectious individuals, there will be pathways and new understandings that will apply to everybody. While we can try to study everybody out there at the same time, it's very difficult for one group to do everything. But the idea that one group can find a solution for a group that they're studying closely, that solution may apply across all types, and that's sort of a hope, at least that I have.

Dr. Elizabeth Unger: I do want to respond to a comment that we got that this meeting is going over and that the patients are tired, and we do apologize for that. The recording will be available, so I encourage you to leave if you don't have time, but we are trying to answer as many questions as possible, so we have sort of a dual goal here. So I apologize that it has gone later than some of you expected.

Christine Pearson: So maybe we'll just take one or two more questions. That would be good. Okay, so the next one I think is available for anyone. It is "Do you think that ANS [autonomic nervous system] retraining can help with ME/CFS? If so, who has the best program?"

Dr. Brian Walitt: Well, that's a difficult question. I do believe, you know, that training, you know, whether it be the autonomic nervous system, you know, whether it be any sort of neuromuscular training that people can do, all of the different ways that we can impact and change how we respond to our environment can be helpful. In terms of which is the best system, that's a difficult question because none of them have been really well studied to date. You know, people like the Levine system for slow exercise, and it's pretty good for POTS, which is a type of sympathetic retraining system. Some people like the visualization methods to try to control their breathing and control their feelings through sort of guided measures, which some people really think helps them. I was a big fan of this book, “Breath," which talks about the power of breath training to alter autonomic function, and I found that very compelling. I don't really think that there is a particular method that has been shown to be better than any others, and I would implore people that are interested to understand the different methods and choose the one that makes the most sense to them because that's probably what will be most successful for them.

Christine Pearson: Great. Thank you so much, and then I think for our last question, the question is, and maybe we'll start with you, Beth, and then if the speakers would like to jump in as well, is "How can I educate multiple provider specialists about the problems caused by ME/CFS?"

Dr. Elizabeth Unger: Right. And that is something that CDC is very committed to doing, and the materials that we have on our website for healthcare providers, feel free to share the links with your healthcare provider. We are looking to distribute and amplify our message as widely as possible. The Mayo Clinic Proceedings recently published a very nice CME that was done in conjunction with #MEAction that could be shared as well.

Christine Pearson: All right. Gentlemen, did you have any thoughts on that?

Dr. Brian Walitt: No. That sounds good. Yeah.

Christine Pearson: All right. So, I think I will go ahead and close it now. I did want to remind everybody that we will be posting a video and also the transcript as soon as possible. And as Beth mentioned, we will put links in there to try to make it easier to get to any of the items that were mentioned. Thanks so much for joining us and have a good afternoon.

*Dr. Brian Walit*t: Thank you.

Dr. Elizabeth Unger: Thank you.

Dr. Avindra Nath: Thank you, everybody.

Christine Pearson: Oh, and thank you to our speakers, sorry.