CDC's 22nd ME/CFS Stakeholder Engagement and Communication (SEC) Call

December 18, 2023

3:00 p.m. ET

Christine Pearson: Good afternoon, everyone, and welcome to today's ME/CFS Stakeholder Engagement and Communication 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 communications activities, to provide information for people with CFS as well as their loved ones, clinicians, and anyone else 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, the Branch Chief for the Chronic Viral Diseases branch at CDC, where ME/CFS is located. Then we'll turn it over to our guest speaker panel. After the presentation, we'll have a Q&A session. We have a really full schedule today, so we ask that our speakers stick to the timing as much as possible, and we'll -- so that we have as much time as possible for questions. 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. We'll provide more information on that when we get to the Q&A session.

Before we start, I'd like to remind everyone the call is open to the public, so please consider that before sharing personal information. We're also recording this call. Please disconnect now if you have any concerns with the recording. We'll post the transcript and the video as soon as possible after the call is complete. If you would like access to the closed-captioning, or to read along with the text of the program update, the links to both of those are posted in the chat box.

Now, before we get to Dr. Unger's remarks, I'd like to share a short update on a CDC-wide initiative to improve the agency's website. As part of this project, CDC communicators and scientists are currently hard at work reviewing, updating, and reorganizing pages on cdc.gov. The goal of this is to create a more readable, user-friendly cdc.gov that meets all of our audience's needs.

Now, a little bit about why our director's office created this initiative. First of all, CDC's entire website is huge, over 200,000 pages, and is extremely hard to navigate. Some pages are duplicative, others are outdated. Our research shows that web users can't find the information they need, and they struggle to find the information they're looking for. With a fresh start, we're hoping to focus on improved communication for all of our audiences, whether general public, partners, healthcare providers, or state health departments. We know that the CDC's

ME/CFS website serves a need for this community, and it's imperative to help raise awareness about ME/CFS and the disruption it causes in the lives of people affected by it. We're dedicated to making sure that the ME/CFS information is available for you, for healthcare providers, and for people who may be diagnosed in the future. Rest assured that nearly all of the ME/CFS current content will continue to be available on the CDC website.

Some of the changes that you may anticipate or may notice are a more mobile friendly layout, easier navigation, pages that are easier to read. In some cases, you may notice shorter sentences, shorter paragraphs, more plain language, and less jargon. Pages for healthcare providers will continue to use a higher reading level language than general public pages. In addition, some information for meetings held more than two years ago and some of our older "Voice of the Patient" features will be put into an archive. This information will continue to be publicly available on our archive called the "CDC Stacks" and in a new archive website which is archive.cdc.gov. This is a separate environment from the cdc.gov main site but will be a place that you could easily access the information that we currently have. We'll be redesigning the website now through the end of March, when CDC plans to launch the new cdc.gov. We're excited about the new site and hope that it can provide benefits for all of our users.

If you have questions on Clean Slate, which is the name of this initiative, you may ask them during the Q&A section of this call or by sending an email to our ME/CFS mailbox at mecfssec@cdc.gov. And now before we turn it over to Dr. Unger, I'll remind you that if you have suggestions for speakers, or ideas for future SEC calls, you can also send them to that same mailbox. And you could also use this address if you would like to be added for email notifications about future calls.

Now I'll turn it over to Dr. Unger to start the program.

Dr. Elizabeth Unger: Thank you so much, Christine. We really appreciate that you took the time to tell our audience about CDC's Clean Slate program. We hope that will improve our online information, and we look forward to continuing to work with you and other CDC communicators on this initiative.

I'd like to welcome everybody to the 22nd SEC call. To allow time for our speakers and the question-and-answer period, I plan to keep my remarks short, but I would like to share some brief updates on our ME/CFS program activities.

We entered into a cooperative agreement with the CDC Foundation in December of 2022 to launch an effort called the "Infection-Associated Chronic Conditions Understanding and Engagement" project, or "ICUE" for short. The project brings together patient partner groups and community-based organizations who are actively working to help people with ME/CFS, Long COVID, and other infection-associated chronic illnesses, and to raise awareness of these conditions. The ICUE project team is made up of members of the CDC Foundation, the Long COVID Alliance and Commonality Incorporated. The project leaders include members of Solve M.E., Dysautonomia International, the COVID-19 Long Hauler Advocacy project, and the Patient

Led Research Collaborative. In 2023, the ICUE project brought together more than 60 key partner organizations to identify and prioritize the community's needs and shared goals. The CDC Foundation worked with the Long COVID Alliance and Commonality to organize and host an ICUE National Webinar titled "Opportunities for Action: Infection-Associated Chronic Conditions" on October 24, 2023. The webinar featured an overview of the priorities and goals identified during meetings with participating organizations this year and was attended by 375 attendees.

Prompted by the increased recognition of unexplained post-acute infection syndromes resulting from Long COVID, CDC launched a new webpage in October titled "Chronic Symptoms Following Infections." This webpage gives an overview of the possible causes of chronic symptoms following acute infection and how they affect people. It briefly addresses talking with your healthcare provider about your symptoms, and also touches on the disease agents that have been linked to chronic symptoms. There are many similarities in the post-acute infection syndromes and those experienced by people with ME/CFS; CDC's experience with ME/CFS guided development of this new webpage. We believe that by looking for similarities and differences between ME/CFS and chronic symptom syndromes that develop following a variety of known and unknown acute infections, we'll be able to learn more about how often and why they occur, as well as how to diagnose and treat them.

CDC continues to partner with our collaborators on a variety of ME/CFS and Long COVID projects. We've started sharing our findings from various studies and projects that our ME/CFS program supports. At the 2023 International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Conference, CDC and its partners collectively presented five abstracts and conducted two workshops. Two abstracts contained data from the Multi-site Clinical Assessment of ME/CFS or MCAM, to look at how often patients had comorbidities such as dysautonomia and chronic overlapping pain conditions like fibromyalgia, irritable bowel syndrome, or chronic lower back pain, and how these comorbid conditions affected patients.

We found that the NASA Lean Test and COMPASS-31 Questionnaire were useful tools to identify orthostatic intolerance in other dysautonomia. These comorbid conditions were often present and were associated with worse symptoms and functions in patients with ME/CFS. In addition, we shared early findings from several of our Long COVID projects, including an oral presentation entitled "Addressing ME/CFS-Like Symptoms in Long COVID Patients," and another presentation entitled "ME/CFS-Like Illness Among Patients at Three US Post COVID Clinics," which discussed the overlap in clinical presentation between ME/CFS and Post COVID conditions. For surveillance activities, we continued to partner with CDC's National Center for Health Statistics to track ME/CFS and Long COVID through the National Health Interview Survey.

The September issue of NCHS' Data Brief provided nationally representative prevalence estimates of Long COVID in adults and children. Using 2022 data from the National Health Interview Survey, we estimated that 6.9% of adults ever had Long COVID, and 3.4% had Long

COVID at the time of the interview. The prevalence rates were lower in children; 1.3% of children ever had Long COVID, and 0.5% of children had Long COVID at the time of the interview. We also used 2021 through 2022 National Health Interview Survey to track ME/CFS. The data brief report was just released in the December issue of NCHS Data Brief. Based on self-reported diagnosis by a healthcare provider, we estimate that 1.3% of adults had ME/CFS in those years. We will continue to use this survey to track ME/CFS in 2023 and 2024.

Now I'll turn to an update on our program's educational activities. The newest online course introduced during the last SEC call launched in September is titled "ME/CFS Diagnosis and Management in the Age of COVID: Expert Insights" and will be available for continuing education credits for three years. The ME/CFS experts who participated include Drs. Anthony Komaroff and David Systrom from Harvard Medical School, and Dr. Lucinda Bateman from the Bateman Horne Center, an ME/CFS specialty clinic in Salt Lake City, Utah. The course is being promoted by WebMD, the National Association of School Nurses, and other partners, through their member list serves and networks. Through the seven online Medscape courses, we've reached more than 120,000 learners, had 49,000 test takers, and issued about 40,000 certificates.

For our final update, I'm tasked with making the bittersweet announcement that Dr. Jennifer Cope from our Chronic Viral Diseases Branch has accepted a new position and promotion within CDC. We wish her well in her new role and thank her for her time and service to CDC's ME/CFS program.

Now I'd like to introduce Dr. Vicky Whittemore. Dr. Whittemore received a Bachelor of Science in zoology from Iowa State University, and a PhD in anatomy from the University of Minnesota Medical School. She did a postdoctoral training at the University of California Irvine, and at the Karolinska Institute. She was on the faculty of the University of Miami School of Medicine until 1994, when she began her work with nonprofit organizations, including the Tuberous Sclerosis Alliance, Genetic Alliance, Citizens United for Research in Epilepsy, and the United Coalition for Health Professional Education and Genetics. Dr. Whittemore joined the staff of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health in August 2011. In this role at NIH, she oversees a grant portfolio focused on the underlying mechanisms of the epilepsies, including the genetic causes, animal models, translational and clinical epilepsy studies, and sudden unexplained death in epilepsy, as well as grants in ME/CFS. She is a well-known leader in the trans NIH working group, as well as in the ME/CFS Research Roadmap project.

Thank you so much, Vicky, for joining us today and for your leadership in bringing new researchers into the field of ME/CFS research.

Dr. Vicky Whittemore: Thank you very much, Beth. And thank you for the kind introduction and for inviting me to participate in this webinar today. So, just briefly, I just wanted to inform those of you who may or may not have tuned in last week, so on Monday last week we held a very

successful one-day workshop on ME/CFS for young and early career investigators so we had individuals all the way from someone who was a high school student, a couple of undergraduate students, some graduate students, post-docs, some junior faculty, and then we were joined in the afternoon by some individuals who were not so junior but we welcomed them to join our workshop for a one-day meeting to really exchange ideas about the research that's going on, to network with one another, and to establish those collaborations between the young investigators that will carry them forward into careers in ME/CFS research.

So there were several presentations that touched on the role of viruses and viral infections in ME/CFS and a couple that -- of individuals who spoke on Long COVID as well. There were both oral presentations and posters, and so between the individuals in the room and the individuals who joined us by Zoom from around the world, there were about a hundred young early career investigators, which is quite exciting to have that pipeline of new investigators in the field. So, following that one-day workshop, we had a two-day NIH ME/CFS conference that was organized and supported by NINDS, the National Institute of Allergy and Infectious Diseases that brought together investigators to present on their updates and progress on ME/CFS research, again, many of them touching on the role of viruses and viral persistence in ME/CFS and in Long COVID.

So it was for us I think really an excellent conference that showed the progress that we've made since the last conference that we held in 2019, which I think has really brought us a long way toward understanding the underlying etiolgy of ME/CFS and really helping to shape and address the questions going forward, which is something that we're also addressing, as many of you know, in our strategic planning process to develop an ME/CFS research roadmap. So, the video recordings from the conference last week will be available soon, and we'll send out an email announcement as well as post them on the NIH website when those are available.

Today it's my pleasure to serve as the moderator for the two speakers that have been invited to present their research. The first presenter is Dr. Bhupesh Prusty, who is a senior researcher and principal investigator at the Institute for Virology and Immunobiology at Julius Maximilian University in Wurzburg, Germany. He earned his doctorate in biosciences from Jamia -- if I'm saying this right, Millia Islamia in New Delhi, India. He was a postdoctoral fellow at the German Cancer Research Institute in Heidelberg, Germany, and his research is focused on innovative methods to understand molecular mechanisms of HHV-6 and 7 latency and reactivation. He will join us today to give -- well before I give you that, I did want to add that Dr. Prusty was one of the inaugural recipients of the Solve ME/CFS Ramsay Award for a project on HHV-6 mediated mitochondrial modulation and its association to ME/CFS. So, with that, I'd like to introduce Dr. Prusty to give us his presentation, "Understanding Infectious Origin of ME/CFS Through the Recent Pandemic." Welcome, Dr. Prusty.

Dr. Bhupesh K. Prusty: Thank you very much.

Dina Garrett: Dr. Prusty, you should be able to advance slides now.

Dr. Bhupesh K. Prusty: I'm trying. It's not working.

Dr. Vicky Whittemore: We're still seeing that introductory slide.

Dr. Bhupesh K. Prusty: Yes. So good afternoon, everyone. First of all, thank you for inviting me today to this webinar to discuss some of our recent work on ME/CFS. As you might know, my name is Bhupesh Prusty, and currently I'm located at Institute for Virology and Immunobiology in Germany.

Dina Garrett: Dr. Prusty, could you request remote control again, please? Give it just a second and try again, please. Try again, please?

Dr. Bhupesh K. Prusty: It's slow. Can I just click "next"?

Christine Pearson: Okay.

Dr. Bhupesh K. Prusty: It seems to be -- yes okay. Okay, so as we know, ME/CFS is a systemic disease and without any known biomarker, or even without clear knowledge of the mechanism of the disease development. One of the reasons behind this probably lies in the fact that majority of the patients are actually diagnosed very late with ME/CFS. And sometimes this diagnosis takes years. And by this time, we mostly missed the very early stages of the disease development. During the late states of the disease, we only see the chronic aspect of the disease with several varying clinical features from patient to patient.

Today I'm going to share some of the key findings from one of our recent papers, which is currently available in a med archive for your information. And is under revision at this moment. The study actually includes roughly around 100 ME/CFS patients. And today I will also share some of the data, which is not a part of this preprint, but it includes also additional independent cohort of patients. We have studied different aspects of ME/CFS disease development in this paper, but today I'm just going to focus on the one aspect, and I'm going to compare them with what we studied in ME/CFS patients with healthy controls.

We believe in infectious origins of ME/CFS, hence, to understand the very early stages of ME/CFS development, we have compared our ME/CFS results with SARS-CoV-2 infected patients after six to 12 months of their first infection.

This is very important to understand these results. We have divided these patients into three different groups. The first group we can call it as a “no Long COVID” group. Basically, these patients had once the COVID-19 infection, and within six to 12 months they have more or less recovered without any clinical symptoms. The other two groups include the “mild Long COVID” group. We can also call this “mild to moderate Long COVID” group. And the last group is “severe Long COVID” group. And these patients are separated; the different grades of Long COVID is being separated by a scoring system which was published by our own German colleagues in 2022, and also by the cohort study from USA in 2023.

So the philosophy of my lab is based on one topic, which my friend and the mentor, Bob Naviaux postulated, and that's called the "Hyperactivated Cell Danger Response" in ME/CFS patients. What it means is that possibly only a very small number of cells in a human body is carrying the actual disease condition, whether it's infection or any other mechanism. It's not the whole body which is carrying the disease, rather only a very few number of cells which are carrying the disease. And these few cells can actually communicate this threat to the other nearby healthy cells through this cell danger response, and thereby this process amplifies the sickness response.

Rob Phair also calls it as a mosaic disease. And when we say that only a very few number of cells are actually infected or carrying the disease, it means that what we are searching is actually a needle in a haystack.

So first Ron Davis and then Øystein Fluge from Norway raised the idea of something in the serum. Because serum from ME/CFS patients can actually recapitulate some of the aspects of the disease in healthy cells. We in our lab also focus on the same thing, and we also observe the same thing. My lab is focusing on finding these factors. I believe it is not a single factor, rather it is a combination of many factors. And one such factor that today I'm going to focus is immunoglobulins.

When I say, "Immunoglobulins," it doesn't simply mean the antibodies. Rather, it is the complete immune complex including both the antibodies and the bound antigens to these antibodies. To understand this process, we have started purifying immunoglobulins from the patients and the control serum. We have established a biochemical pipeline for this, and we are building sort of an immunoglobulin biobank in our lab. What we do is we take these immunoglobulins, and we do different types of experiments. So for example, when we exposed immunoglobulins isolated from severe ME/CFS patients to healthy cells, we observed a dramatic collapse in the mitochondrial network. If you look into the figures on the left-hand side of the screen, you can see immunoglobulins isolated from healthy individuals exposed to primary human endothelial cells, and on the right side immunoglobulins isolated from severe ME/CFS patients.

And you can see that the mitochondrial network which is basically green and yellow in color is collapsing and coming to the periphery of the nucleus. We not only quantify this using confocal microscopy and looking into average mitochondrial surface area, we could also show by western blotting, for example on the right side, that when we expose immunoglobulins from the CFS patients, we see a decrease in mitofusion 1, and MitoPDL or PDL6 which are the proteins which actually keep the mitochondria fused and elongated.

So these results suggest that the immunoglobulins from severe ME/CFS patients are capable of changing the architecture of the mitochondria in the target cells. Sorry.

So the obvious question which is coming from this is, "What is there or what is not there in these immunoglobulins that is causing this mitochondrial phenotype?" To understand this, we

are carrying out mass spectrometry analysis of these isolated immunoglobulins to not only see what the percent of IgG and IgM is there in it, also to understand what are the different proteins which are there in it. In this type of study, we see some of the proteins which are present in a higher amount within the immune complex of ME/CFS patients. And some of the proteins are also significantly less within these immune complexes.

Here is one example. One of the proteins called the "ficolin 2" or "FCN2", which is present in a higher amount within the immune complex of the ME/CFS patients; not all ME/CFS patients but quite a substantial proportion of ME/CFS patients. We verified this, so you can see here that one of the dots over here is FCN2. And this is one of the patients versus one of the controls.

Here in the middle figure, you can see that when we combine all the healthy control versus all the ME/CFS patients, we see that ME/CFS patients on average have a high amount of FCN2. So, we verified this data using ELISA and found that FCN2 levels are high in the subset of ME/CFS patients. And you -- on the right-side graph you can see. However, when we compared some other autoimmune diseases, for example, sclerosis patients, we also saw that quite a large number of these patients also have high amounts of FCN2 -- or high amount of FCN2 in their serum. So probably this increase in FCN2 or ficolin 2 is just because of the autoimmune nature of ME/CFS.

Now, coming to the -- sorry; coming to the next slide, as I mentioned, there are only very few proteins which were actually increased in the -- within the immune complex of these patients. At the same time, some of the proteins were also decreased. And three of the proteins which attracted our attention is transferrin or serum transferrin, alpha-2-macroglobulin, and fibronectin. So in this heat map you can see that healthy controls normally have a higher amount of these proteins within the immune complex; and not all again, but majority of the ME/CFS patients that we have studied so far had a lower amount of these proteins within the immune complex.

Today I'm going to focus on only one of the proteins that is called "fibronectin" or "FN1." The mass spec study showed that fibronectin is decreased to a different degree within the immune complex of these ME/CFS patients. Now, this raises the question, "Is there an overall decrease in fibronectin amount in the blood," that's one possibility, or there is a decrease in the antibodies that can bind to the fibronectin. Just to let you know that fibronectin binds to C1 antibodies and C3 antibodies, and other antibodies. So we checked both IgG and IgM against fibronectin in our purified immunoglobulins by western blotting. On the lower band you can see that the western blots--so just a representative western blot here showing healthy control versus severe ME/CFS patients, and you can see that there is actually no change in the amounts of IgM or IgG against fibronectin.

So this means that potentially there is some sort of translational modification. This is, again, a hypothesis from outside that possibly some post-translational modifications are going on within

fibronectin. And those posttranslational modifications are preventing the fibronectin to be -- to bound to these active immune complexes.

Now, next we decided to measure the fibronectin amounts in the blood. Now, here comes the question where to measure the fibronectin. Now, we can measure in plasma as well as we can measure in serum. Now, I'm bringing this topic over here because this is very important to understand what we are measuring and what is the function of fibronectin in serum in plasma. There is a basic difference in amounts of fibronectin in plasma versus serum. As fibronectin is a part of the blood clot, the amount of fibronectin in serum only represents the circulating fibronectin that is not incorporated into the blood clot. So when we prepare the serum, we let the blood clot, so a part of the fibronectin goes into the blood clot in process. What we isolate is the free circulating fibronectin.

But when we talk about plasma fibronectin, that actually includes both clottable fibronectin as well as the free fibronectin. This means that plasma fibronectin amounts are always higher than the serum fibronectin amounts. So we first took an independent cohort of samples from Sweden, where we compared 40 healthy individuals versus 40 ME/CFS patients, and we took the serum and plasma selected at the same time, and we tried to see what we see in serum versus plasma.

Each dot in this figure or in this graph represents fibronectin amounts from one individual. As I mentioned, as expected the plasma fibronectin in healthy controls as well as in ME/CFS patients was substantially high in comparison to the serum amounts. However, the plasma fibronectin amounts in ME/CFS patients particularly was highly variable. Interestingly, the serum fibronectin was significantly higher in ME/CFS patients, so we can compare to serum of healthy control -- healthy control serum to the ME/CFS serum. We see a significant increase in the fibronectin amounts in the serum. However, when we do the same in plasma, healthy control plasma versus ME/CFS plasma, even though the trend is there, the statistical significance goes away.

Now, this data is very important for us and it's also -- it's corroborating the data which is already known in the field of ME/CFS that probably there is a clotting defect is there in the ME/CFS patients' blood. And these results trend in the previous observation in this regard. Now, this data is based on a fully independent cohort of samples from Sweden. So the next step was to look or to check the results in other cohorts of samples. For example, here what I am presenting is our own cohort of samples from Germany. And if we compare the healthy controls versus ME/CFS patients, once again we see a reproducible data where ME/CFS patients have a high level of circulating fibronectin compared to healthy controls. Once again, henceforth all the fibronectin studies were done in serum not in the plasma, as we see the results in the serum, yes.

So when we divided this total group of healthy control versus ME/CFS into male and female genders, we observed a significant difference in fibronectin amounts in the male. And this is

simply because males have normally low amounts of fibronectin in serum in comparison to the female. We also found that the severe patients, severe ME/CFS patients with a very low quality of life have very high amounts of circulating fibronectin in the serum.

Once again, coming back to the infection-induced ME/CFS theory, we all know Long COVID patients have plenty of similarities to ME/CFS, even though there are differences in the disease development process. Some of the critical features of ME/CFS overlaps with Long COVID, hence, we studied the serum fibronectin amounts in our COVID-19 cohort of patients.

We found that increased amounts of fibronectin in the serum of severe Long COVID patients within the first 12 months of SARS-CoV-2 infection when we investigated some of the patients these “no Long COVID,” “mild Long COVID,” and “severe Long COVID” patients we did a follow-up cohort and picked some of the patients after 18 to 24 months of first COVID infection, we saw that the fibronectin amounts are even increased in these patients. And as usual we compared these results with the sclerosis patients, just divided them into groups as sclerosis patients without fatigue and with fatigue, where we did not see any increase in the serum fibronectin amounts.

During this time, we had an opportunity to study around 20 ME/CFS patients who had actually developed ME/CFS post SARS-CoV-2 infection. So let's call them as "PCS ME/CFS group." These patients saw the maximum increase in serum fibronectin amounts. If we separated them into male and female groups, we can also see that both male and female they so increased in the serum fibronectin amounts. And I predict that if we measure serum fibronectin in these patients after another three to five years, like we do in the severe ME/CFS patients, we probably will not see much difference in the amount of fibronectin in the serum because the body has been adapted to these changes over the period of time. Hence, the early time of the disease development is possibly the best time to identify these markers and to understand their contribution to the disease's development.

Now, I will wrap up these results with two more slides discussing on the potential outcomes of these types of changes in the immunoglobulins. Now, one must be wondering what these immunoglobulins are actually doing. Obviously, immunoglobulins are when we are exposing cells how the cells with immunoglobulins isolated from patients, are they entering into the cells and doing something? Immunoglobulins rarely enter into the cells. However, they can bind to antigens and help in complement activation. And these activated complement proteins can then bind to the cell surface receptors, and they can regulate the physiology of the cells. However, recently it was shown that antigen antibody -- sorry; antigen antibody binding is essential for the functioning of the – many of the cells, particularly the B cells. Now, Fc receptors on the surface of the cells they can bind to the antigen antibody complex, and thereby regulate the functioning of the B cells. And in the absence of the antigens, antibody may not function similarly.

So it is known from the literature that fibronectin -- different fibronectin components can actually have different roles on the mitochondrial architecture. So if you expose cells to a full-length fibronectin or fragmented fibronectin, depending on the type of fibronectin, they can cause mitochondrial fragmentation or mitochondrial fusion. So we predicted that these IgM and IgG bound fibronectin they have a pro-survival function. They help in better mitochondrial architecture. And when the fibronectin is not there with the antibodies, they might cause a mitochondrial fragmentation phenotype. We need more experimental evidence for this. However, this is one of the hypothesis.

And one of the -- I'm missing a slide over here. One of the recent papers which came out in the Cell showed that Long COVID patients have a low amount of serotonin in these patients. And it's very perplexing to know that serotonin can actually be used to modify fibronectin. This process is called "serotonylation" of fibronectin. So it will be a future topic for us to understand if the serotonin which is low in the Long COVID patients can actually be used by the fibronectin to modulate this fibronectin in a way that this is not incorporated anymore into the active immune complex, as well as in the clotting process in these patients.

So with this, I would like to thank my collaborators, my funders, and the entire patient community who support our work, and all of your support and encouragement. And thank you very much. I will be happy to take questions now or at the end of this hour now. Thank you.

Dr. Vicky Whittemore: Thank you, Dr. Prusty. We'll take questions at the end after Dr. Li's presentation.

Dr. Bhupesh K. Prusty: Thank you; yes.

Dr. Vicky Whittemore: So, thank you very much for that interesting presentation.

So the next speaker is Dr. Dawei Li, who's an Associate Professor at Texas Tech University Health Sciences Center in the School of Medicine in the Department of Immunology. He's a principal investigator for the Bioinformatics and Computational Genomics Lab, and Director for the planned Center for Genomic Medicine and Bioinformatics. He received a doctorate in genetics from Shanghai Jiao Tong University in China and has been trained in human genetics genomics and bioinformatics.

He completed postdoctoral training at Rockefeller University and has been a research scientist at Yale and on the faculty at the University of Vermont. So his current research focuses on developing innovative genomic and omics research methods and applications to ME/CFS. In 2018, he was awarded the Solve ME/CFS Ramsay Award for endogenous retroviruses and their expression in chronic fatigue syndrome, which is what we're going to hear from Dr. Li about today.

So welcome, Dr. Li.

Dr. Dawei Li: Thank you. Thank you, Dr. Whittemore and Dr. Brimmer, and Dr. Unger, for the -- for giving me the opportunity to present today. Next slide. Oh.

Okay, there was; thank you. So we just learned the virus may trigger ME/CFS such as Epstein Barr virus and SARS-CoV-2. Most people have these viruses, but not everyone has ME/CFS. So I suspect the endogenous retrovirus, briefly, ERV, is a key factor here. Possibly only people with certain genetics are predisposed, such as with certain ERV virus. So all ERV transcriptional activation can develop a chronic disease after acute infection.

Today I will introduce the possible link between ME/CFS and -- between ERV and ME/CFS. So what is ERV? ERV are derived from ancient retroviral infections and the virus integration into our ancestors' germ cells seven million years ago. ERVs are now fixed and a part of our human genome. We insert it in -- the ERV insert in our genome being that every single cell we inherited from parents into our every single cell. The protein-coding genes account for about 1.5 percentage of human genome. By comparison, ERVs account for eight percent. Each human genome has about 20,000 protein-coding genes. By comparison, ERV genome has at least about 600,000 ERVs, which that is about 30 times more than protein-coding genes. So, these ERVs have various cell functions in human health. For example, some ERVs can produce viral proteins or non-coding RNAs. And some ERVs can fuse with nearby genes to make fusion transcripts. ERVs have promoters and enhancers and can upregulate the expression of nearby genes. Methylated ERVs can silence downstream gene expression. Because of ERVs' repeat sequences, ERVs can facilitate a homologous recombination, leading to copy number variations. Because ERVs have inserted in a human genome for several many years, so the human genome has cooperated with ERVs for various benefits. Here is one example.

In early embryo development the placenta needs ERV proteins for its cell-to-cell fusion of the placenta. ERVs also regulate a key hormone gene important for pregnancy. So some ERV proteins mediate cell-to-cell transfer of mitochondria, as showed in the red color in this slide. We can imagine if this ERV protein is dysregulated, the cells will not be able to transfer mitochondria fast enough from a soft tissue to the destination, such as muscle. So, we know ATP productions run in ME/CFS. Research is needed to examine if ERVs are related to ME/CFS energy production.

And ERVs are also the only biological material that is derived from viruses, and also can pass from parents to children in a Mendelian inheritance model. ERVs are typically silenced by methylation, but ERVs can -- ERVs are viruses by nature, so they can be reactivated to produce viral products.

ERVs do not need to make a live virus or viral protein. Viral RNA is sufficient to trigger a new response because once activated, ERVs can make a double strand RNA, which will be recognized by the human cell double strand RNA censored as foreign RNA which then triggers type I interferon leading to inflammatory immune response which we observe in the ME/CFS.

ERV also has hormone responsive elements adjacent to enhance and promote that you can see here. So ERV activation can be additionally enhanced by female sex hormones. So we know three out of four ME/CFS patients are women, and so to study the ME/CFS -- ERV, ME/CFS link, the first question is how to detect ERVs in ME/CFS patients. So ERV detection is very challenging. For the ERV variant -- the ERV variants are not captured by SNP genotyping array, and not in the GWAS imputation database, not in standard NGS pipelines. And the ERV expression is not in the standard RNA-Seq pipeline also, the RefSeq database. Existing ERV detection methods are very limited.

So we developed a novel method, what we call the ERV caller to introduce the next generation sequencing to genome detection, genotype each individual ERV on the genome level. ERV caller can accurately detect and genotype each individual ERV using raw sequencing data and achieving about a 90 -- 97 percentage of accuracy based on our simulation data.

So, I -- we used the ERV caller into the various cells for existing genomic sequencing data, including the 1,000 genome samples. Our methods identify novel ERVs that cannot be identified by other approaches. We did a PCR on the Sanger sequencing to validate those novel ERVs we identified. Other genotypes were verified by Sanger sequencing. This figure shows just two randomly selected samples. In short, our method the accuracy is very high.

So, our ERV caller the platform processes each sample one by one, generally a standard format of genotype data that are ready for genome-wide association study in any human samples, so we used this platform to analyze our existing ME/CFS sequencing data. We first used the ERV caller to analyze whole genome sequence data from 20 severely ill ME/CFS patients. We found many distinguished individual ERV variants. Here I only show eight of them. This patient data is patient only without controls. So I compared the patient's blood measures by ERV genotypes. As you can see from the sample here is one copy, zero copies. This group of patients have no ERV, this has one copy, they have two copies.

So, as you can see here, the genotypes of the ERVs are associated with several cytokines or blood measures. Some of -- actually some of the cytokines were reported to be important to ME/CFS. For example, Dr. Mark Davis's group found the three, the top three here are positively associated -- correlated with ME/CFS severity. We found the same three are also positively associated with ERV genotypes in a same direction.

So we also analyzed our existing RNA-Seq data from ME/CFS control samples. In this figure, I use the differentially expressed ERVs should do a principle component analysis, as we can see here. As we can see, the patients are clearly separated from controls. The blue here is the patients.

We also found a number of ERVs uniquely expressed only in patients but not in controls. Use of this ME/CFS specific ERVs or subset of them can distinguish ME/CFS versus the healthy status of our exam subjects. So I also analyzed the publicly available RNA-Seq data of ME/CFS versus control before and after CPET exercise. We found a number of the differentially expressed

ERVs. Here I only show one example as you see on the right side. You know, in the controls this ERV expression was low in the day one baseline. Its expression went up with a first exercise and then came down to baseline after a few days of rest. By comparison, in the ME/CFS the day one baseline of this ERV is already high and did not come down.

We found a lot of differentially expressed ERVs. Those ERVs are novel. Nobody has annotated them before. So we do know there the exact functions. So, I checked what are the genes co-expressed with these ERVs. So our analysis produced an interesting network. So here I randomly selected one small part of the network here. And so the ERVs, as shown in the yellow color, are well-connected and centered in the network. When I checked the most connected genes, many of the genes are related to retroviral activation called "mitochondrial functions." The network that appeared there not at random, so we are currently examining the question, "Does ERV drive genes -- or the genes drive ERVs?"

So our samples are from -- mostly from Americans; are Americans. Our European colleague Dr. Elisa Oltra's group analyzed the ERVs in Europeans. So they got basically the same results as ours. They used a microarray to quantify ERV expression in ME/CFS, fibromyalgia, and the patients with both. They also used the differentially expressed ERVs to do a principal component analysis, as shown here. And the ERVs clearly separate ME/CFS from controls, also from the fibromyalgia. At the same -- but interestingly, the same procedure was done by using protein-coding genes. But as you can see, only ERVs can distinguish ME/CFS.

Similarly, they also examined the genes correlated with ERVs. They found several modules, among which the most significant modules of the genes are involved in the T-cell activation. And the co-expressed ERVs are low in controls and fibromyalgia but high in ME/CFS. In short, the data in Europeans are pretty consistent with our genomic sequencing study in Americans.

So a healthy normal cell should only have very low basal ERV expression. Long COVID mirrors major symptoms of ME/CFS. Originally research showed the SARS-CoV-2 virus can activate expression of many ERVs. By comparison, other respiratory viruses like flu can only activate immune responsive genes but cannot activate ERVs. And so COVID can cause Long COVID, but flu does not lead to long flu.

For many years we've known Epstein-Barr virus can also activate ERVs. We know that after an infection we first see IgM, the early stage and then IgG in the later stage. This paper found an increased ERV IgM in COVID patients, but in the ME/CFS patients the ERV's IgG increased. So this is consistent with our anticipated progression from COVID -- Long COVID to ME/CFS.

So this paper also concluded Long COVID can reactivate ERV expression regardless of if you have COVID symptoms or not. So the NIH ME/CFS Conference held last week had lots of great talks which together showed abnormalities in almost all aspects shown in this figure, such as brain neural inflammation, microbiome, metabolism, proteins, genes, et cetera. Some of the abnormalities may eventually lead to a diagnosis biomarker or even treatment.

I hope our future research allows the ERV link to add more data into the causal mechanisms of this disease. Only if we know the cause we can better treat, reverse, even prevent the disease. With -- I thank patients and their caregivers for donating their research samples. The samples used in this talk were from Dr. Ron Davis, Dr. Xiao's groups, and the Hanson groups. Our research is supported by the Solve ME/CFS Ramsay Award, the Open Medicine Foundation.

Thank you very much!

Dr. Vicky Whittemore: Thank you, Dr. Li. I'll start with a question for you. So what makes your ERV detection methodology and your research different than what's come before the previous research?

Dr. Dawei Li: Oh, thank you, Dr. Whittemore, for the great question. So in the past, the ERV detection was mostly based on the probes such as PCR. So if we design a PCR probe, we will -- actually we will catch a lot of ERVs because those -- although human genome has about -- or more than 600,000 ERVs, but those ERVs share a lot of sequencing similarities. So a probe is -- typically will count -- will catch a lot of ERVs. So we will see -- in the past recent mostly, they are starting a pool of ERVs.

But my -- I suspect that those ERVs are different, though. Although they are sequencing, they have similarities, but they are from a different chromosome. Think about the chromatin three-dimension structure, they may have very different functions. So in our research we use the next generation sequencing to do a non-hypothesis driven, screening. Our bioinformatics approach we're trying to distinguish each individual ERV. So we find the right solution on the chromosome. Nucleotide is the resolution. We know this ERV is in this chromosome from database -- from nucleotide, 1,000 to 2,000, for example. So that's what -- that makes a huge difference regarding the -- so we are trying to separate each of the half million ERVs one by one. Thank you.

Dr. Vicky Whittemore: Yes, thank you very much for that explanation. Dr. Prusty, if you could turn your camera, and --

Dr. Bhupesh K. Prusty: Yes.

Dr. Vicky Whittemore: I have question for you. So at the very end of your talk, you talked about serotonin, and I'm just interested if you would say a little bit more about how fibronectin levels are regulated and the role of serotonin, if you could just give us a little bit more explanation of that.

Dr. Bhupesh K. Prusty: Yes, I had a slide. I don't know exactly why this slide is not there. But anyway, so fibronectin is in an essential component of the extracellular matrix. And it's a huge 420 kilodalton -- no 210 kilodalton protein and presents in the form of tetramer. And it undergoes many different types of modifications. And one of the modifications which seems to be very interesting is this sort of the sense that -- so normally serotonin is produced in a limited

amount in the body, and it has its own function as a messenger controlling different types of physiological activities.

But it is interesting to see that serotonin under specific conditions yet unknown is recruited directly to the fibronectin protein. It binds to fibronectin and makes the fibronectin -- serotonylated fibronectin. Now, the -- it's just a hypothesis at this moment is that the paper which came out in the cell that serotonin is decreased in these patients. And what we see is upregulation of the circulating fibronectin in the patients. It just makes a hypothetical understanding at this stage is that probably the serotonin is recruited

We have some experimental evidence that yes, it is possible, but we need more data for this. What happened is that when the -- when fibronectin is circulated, it is circulated in sites, specific sites, which might inhibit its function as an antigen, because the antibody binds to that site. And by these changes, we believe that the antibody binding site is not available anymore to the protein, yes. But again, we need more data for -- experimental data to support this.

Dr. Vicky Whittemore: Yes. Thank you very much. That's very interesting.

Dr. Bhupesh K. Prusty: Yes.

Dr. Vicky Whittemore: Yes. So at this point, I'll turn it over to Christine to moderate the Q&A.

Christine Pearson: Thanks so much, Vicky. So just to remind everybody, we'll do the Q&A now for the general Q&A portion. There are three ways to ask a question. If you're joining on Zoom, you can raise your hand by clicking the "raise hand" button under the webinar controls at the bottom of the screen, or you can type your question in the Q&A chat box that's being monitored by one of our team members here. If you're joining by phone only, you can enter "star nine" on your phone to join the question queue and when we announce it's your turn, you can press "star six" to unmute yourself. So I think -- let me start here. So the first question that I have is a question for Dr. Prusty. It says, "Patients with Ehlers-Danlos or joint hyper-mobility frequently have comorbid POTS, ME/CFS. Do you see a link with the work you are doing on fibronectin elastin?"

Dr. Bhupesh K. Prusty: Yes.

Christine Pearson: Sorry.

Dr. Bhupesh K. Prusty: Yes, I saw the question; yes, thank you. We have not tested the EDS patients at this moment. We do not have any clinical collaborations where we can get these patients. But during the last six months, we have been -- so basically, we have been asked by the reviewers to validate our results in a completely independent cohort of patients. And we have been doing it going into multiple different centers in -- within Europe and having well characterized cohort of patients and trying to see it. And we have started to look into sclerosis and some other like cancer patients with fatigue and things like that.

But we never got an opportunity to look into the EDS patients. We are open to all sort of collaborations and looking into other types of disease conditions and to compare it if this is the case. But one thing I would like to mention it here, today's talk was only 15 minutes, and I could not cover the other part of the talk where we look into the IgM against fibronectin. And this seems to be very interesting that the IgM against fibronectin is capable of differentiating infection-induced ME/CFS from other types of ME/CFS triggers like trauma, stress, or the cranial nerve-related ME/CFS, which is completely noninfectious trigger ME/CFS. It is capable of differentiating, which is very interesting for us. And this also brings us to the point that anything which is probably an infectious trigger, including the COVID-induced ME/CFS is proliferating more to the fibronectin hypothesis rather than any other trigger of ME/CFS. Yes, thank you.

Christine Pearson: Thanks so much. I'm sorry for flubbing that. I am a communicator, not a scientist. The next question that we have is, "How is CDC getting word out to the medical community and healthcare data systems about the new ICD code for ME/CFS?" Dr. Unger, would you like to take that one?

Dr. Elizabeth Unger: Sure.

[Electronic Echoing]

So sorry. Okay, the -- where were we, oh, the question.

Yes. So we have -- I think we mentioned the new code in our last SEC call. It was very new at that point. And we have included the information on our website, and we will be including it in all of our educational materials. We think that it is really important to get the word out, and we'll do what we can to think of other ways to get it out.

Christine Pearson: Okay, great; thank you. So the next one is for Dr. Li. It says, "I'm a longtime person with ME. I thought it was triggered by a flu. Now you are saying flu doesn't trigger ME. Was it perhaps triggered by an EBV?"

Dr. Dawei Li: Thank you for the question. So I think they have found out there is no evidence that shows that flu can trigger ME. And also I think that the data is not also sufficient due to prove that EBV can -- really is a cause or trigger. But I personally think that there will be a very -- probably a very wide range of triggers, the factors that can trigger the ME/CFS. But for now we don't know yet what they are. But SARS-CoV-2 it looks like is one of the triggers. But what are the others before the COVID pandemic we don't know yet. That's what we are looking to -- we are trying to find out.

Christine Pearson: Great; thank you so much. So, the other one isn't -- the next one is not directed to a specific person, so if either of our guests would like to respond, or both of you, that would be great. The question is, "Are any of your findings pointing towards specific treatments or experimental trials?"

Dr. Bhupesh K. Prusty: Yes, so I can answer this question. The results at this moment suggest that just in the form of the fibronectin, it's a protein which is produced in response to inflammation. We have some initial evidence from our collaborators in the US that fibronectin is also produced in response to - - due to particularly from EBV. So we believe that any treatment condition which takes care of the infection probably will also take care of the increase in fibronectin. At such at this moment, nothing is known about the treatment for high fibronectin amounts, but we have to keep in mind that fibronectin is also essential for the normal healthy body. So I guess the root cause of the increase in fibronectin probably should be taken care of in terms of treatment rather than increase in fibronectin. Yes.

Christine Pearson: Great, thank you. Dr. Li, did you want to answer that question as well?

Dr. Dawei Li: So --

Christine Pearson: I can repeat it if you'd like.

Dr. Dawei Li: Yes; so regarding the possible treatment, so I guess like for example, if the ERV ME/CFS link is proven, then it's possible we might be able to repurpose FDA approved generic antiretroviral or anti-inflammatory drugs to reverse ERV effects. So -- and also, we know the -- I think there is already ongoing antiretroviral clinical trials to suppress ERVs in multiple sclerosis and also in [….]. Maybe we could sometime test this in ME/CFS as well. I think probably we should. And also, I learned from several patients they -- I learned from them they used some of the antiretroviral drugs and that they see there, and they have improved the symptoms. The second is about I saw some literature about epigenetic nutrients. So the use -- the ME/CFS patients they use the epigenetic nutrients. Actually, they even improve the -- the symptom improved regardless of the deficiency of the status of this. Yes, thank you.

Christine Pearson: Okay, thank you.

Dr. Dawei Li: By the way, I also want to mention regarding the specifics for the ERVs, I see from literature, the ERVs also, they are emerging targets for immunotherapies, which there are a lot of -- in the cancer treatment. Because ERVs are different. If we find that the ERV's in the ME/CFS, there could be -- so immunotherapy could be one of the approaches in the future.

Christine Pearson: All right, excellent; thank you. So the next question is about ICD codes. It is, "Is there a way to encourage Long COVID clinics to screen their patients for ME/CFS, and if they qualify for ME/CFS diagnosis, as many will, also put in a code for ME/CFS in their record?" Would you like to take that, Dr. Unger?

Dr. Elizabeth Unger: Sure. I can start at least. It's a really good question. We have included information about ME/CFS in our Long COVID and Fatiguing Illness Recovery program. And I think that it's pretty clear that it's very difficult to talk about Long COVID without mentioning the similarities to ME/CFS. So we do encourage the physicians to identify ME/CFS in their patients through their diagnostic workup and to be aware of the similarities. We -- the post-COVID condition code also encourages physicians to diagnose other conditions that are

identified in these patients and list ME/CFS, I believe, as an example. But CDC does not direct anybody how to code things, that really is up to the clinicians. We do point out that it will be much easier for us to track the illness in the population if people use the codes correctly.

Christine Pearson: Great, thank you. So the next question is, again, for you, Dr. Unger, which is, "CDC released their new prevalence survey which inflated the number of people with ME. Why did CDC use a telephone survey asking people about tiredness and fatigue, rather than assessing people with viral and biomedical evidence to determine the prevalence? And why did CDC not use experts' criteria, MEICC, which would capture the accurate prevalence?"

Dr. Elizabeth Unger: Thank you. We really wanted to get a national estimate of ME/CFS. And the only way to do that practically was through the National Health Interview Survey. Now, the National Health Interview Survey does not ask how the healthcare provider made the diagnosis, so we don't know what method was used or what case definition was used. And we do know that there are limits in using a self-provided report of a physician diagnosis. Nonetheless, it's a baseline for us to evaluate and make other important health connections through the National Health Interview Survey questionnaires. And the Canadian National Health Service used a very similar approach.

Christine Pearson: All right, thank you. So the next question I have is, "One clinician researcher reported not diagnosing ME/CFS in Long COVID cohorts when it was present because certain research studies would not accept those patients. Any ideas on how to address that?"

Dr. Elizabeth Unger: Hmm. That is an -- I had not heard that as a problem. And I think, you know, study protocols have their own rules, and I don't think there's a way for CDC to address that. Don't know if anybody else would comment. Sorry; yes.

Christine Pearson: Okay. So the next question is for Dr. Prusty. It says, "If clotting defect tends to show up early in ME, but if the body adjusts later, does that mean clotting issues are unlikely to show up later in disease progression?"

Dr. Bhupesh K. Prusty: Yes, good question. No, it's not the case. What I meant that the body adjusted the amount of the fibronectin particularly is that over a period of several months to years when -- as I mentioned, the fibronectin is a mark of inflammation over the period of time when other types of chronic conditions appear and patients go on different type of treatment and things like that. So the increase in fibronectin what we see in the initial period goes down. But that doesn't mean that all the functions of fibronectin, whether it's a defect in clotting process or its incorporation to the immune complex, it changes.

It's just that the sudden increase in the fibronectin that we see just after the infection like in COVID-induced ME/CFS is diluted over the period of years. It is increased over a period of time. Like I said, within eight to 12 months it was increased, but it increased even further with 18 to 24 months. But as we see in ME/CFS patients, most of the times patients are sick for several

years, sometimes 20 years, 30 years, so it's very hard to see the similar significance in those patients, yes.

Christina Pearson: Okay. So the next question is, "When are we going to see clinical standards for Long COVID clinics; so they might be improperly diagnosing their ME patients and also finally stop them from harming patients diagnosed or not with outdated anti-science therapies like GET graded exercise therapy?"

Dr. Elizabeth Unger: Well, the -- there -- as you probably know, HHS has established a Long COVID office-- within the Office of the Associate -- Associate Secretary -- yes, Associate Secretary for Health. And they have issued reports. I don't think they are ready to give a national mandate or guide to diagnosing Long COVID, but they certainly are making sure that information about the reality of the illness and the importance of understanding the impact that exercise can have through post-exertional malaise.

Christina Pearson: So, "Does the CDC have plans to help mandate or at least encourage and publicize use of the new Mayo Clinic proceedings guidelines for managing and treating ME?"

Dr. Elizabeth Unger: Well, that will be a good reference that we -- I don't think we currently have it in our references for healthcare providers because it's new, but that is one that we can include when the new webpages are up. That would be the best way for us to refer to it.

Christina Pearson: All right. Oops, I'm scrolling. Other -- okay, Eileen. So, Eileen, I think your hand is raised. I'm sorry, I've got multiple screens up here; but go ahead and unmute yourself or try and then you can ask your question.

Eileen Holderman: Hi, this is Eileen Holderman. Can you hear me?

Christine Pearson: Yes.

Eileen Holderman: Well, first of all, thank you so much for this presentation. And also, I submitted a question in the Q&A, and I thank you so much, Dr. Unger, for answering that. I have a quick follow-up regarding that survey. And Dr. Unger, you and I worked so long, so many years on the CDC website, and I'm gratified to hear that you're going to be making more improvements to it. But the recent press that centered around the survey's release had me very concerned because it was recycling old myths, debunked information about ME, buzzwords like "patients report", the word "fatigue", the word "tiredness". We didn't hear anything about viruses and infectious disease as our esteemed presenters Doctors Prusty and Li talked about. Can you talk to us a little bit about CDC's interactions with the press regarding all of that very bad press?

Dr. Elizabeth Unger: Well, let me -- I'll start by saying we did do an interview about it. We were asked just a very few questions. It was really very brief. And then we don't have a lot of control over how it gets promulgated. And I'll turn it over to Christine who helps coordinate this.

Christine Pearson: Sure, yes. So I'll just mention that, you know, Beth is right, we did not actually get media queries. Most of the reporters who were covering this just wrote from the report. And you know, we've been trying to -- you know, well we did talk to the one or two reporters -- I can't remember, yes it was very, you know, sort of like, "What does this mean, and what can you tell us?" But they didn't have a lot of specific questions for us.

And then, you know, as far as once we talked to them, we don't have any control over what their headline is or even how they cast it. You know, we try to give caveats when we did the interviews about, you know, what the study meant and what it doesn't mean, and how, you know, the numbers and things are different than you might see if you were looking at a population of people who go to some of the specialty clinics with the experts, or if you, you know -- or if you did the survey a different way. And so, you know, we try to provide sort of the benefits and drawbacks from doing a survey that's just a national survey like that.

But again, I mean, I used to be a newspaper reporter, and I will tell you that, you know, a lot of times, they are given very little space and not a whole lot of time or background on it.

Dr. Elizabeth Unger: And yes, and I will say I was disappointed often that I saw chronic ME/CFS just abbreviated as "chronic fatigue." It just pained me every time I saw that, so I knew the community would be hurt by that. And so the good news is at least it got a -- some attention. And I hope that this will keep the interest up in this very, very significant problem.

Christine Pearson: And you know, I will just say as someone who has been working on communications for ME/CFS for about 15 years here, that is probably the most that any reporters have paid attention. So I'm hopeful that potentially, you know, if other reporters see it, you know, we can keep up the good fight of trying to use the -- you know, use the right words and explain to them about it and, you know, hopefully see some more interest. In addition, you know, now that Long COVID is out there, that is I think also drawing people's interest, so I'm hopeful that those things will help keep it in people's minds.

Let me see. Hold on a second, let me -- I was talking so let me see if I can scroll down and see if there are additional questions.

Dr. Elizabeth Unger: Ed Yong had a very, very thoughtful commentary recently. He's a reporter for The Atlantic, and he did the commentary I think in the New York Times. And he really understands. And so there are reporters that hear it and learn from that, so we just hope that there's going to be more and more of them.

Christine Pearson: Okay, so the next question says, "Wouldn't more specified press releases be acceptable by the media to target the important points of ME/CFS?"

So I will say that most reporters get probably hundreds of press releases in their inbox every week, and it is incredibly hard to try to get them to be interested. One thing that we have done that has I think sometimes been helpful is to reach out to specific reporters who have been interested in the past, or to try to reach reporters, like say, healthcare reporters or other sort of

targeted ones. You know, a lot of reporters basically are generalists who may write about, you know, city planning commission one day and education the next, and ME/CFS the following. And I think that's -- that is something that we have difficulty turn -- you know, dealing with because they are generalists, so they don't really necessarily know a lot about, well, really any of the things that they are writing about. And that's really the best we can do is just try to educate them when we talk to them.

Oh, and then the next question I see is, "Where can I get a written transcript of this presentation?" So, we will get a transcript, and we will be getting it cleaned up, and we'll get it posted on our website just as soon as possible. If you go to the website, which is www.cdc.gov/me-cfs, and then go under the section that says "meeting", then you'll be able to find it there.

All right, so this one looks a little bit more like a comment, and it says, "Your explanation for media using incorrect terminology underscores the need to change the terminology on your end. 'Fatigue' is an inappropriate word, use of scientific language only. Please, respectfully, you have the power to change the language for our community and can command great change for ME."

So, thank you for that note. I will say that, as I mentioned, we are working on revising and updating our -- fully our webpage, and we will -- you know, we'll listen to any and all input that we receive, and we'll work on assessing it.

Dr. Elizabeth Unger: Right, and there was a comment before, and Vicky and I discussed this prior to the call. During the NIH Conference, a suggestion that we move away from the term "ME/CFS", which HHS as a whole has adopted, and move strictly to "ME". And that's a decision that the government as a whole has to make through the agency. So, the naming convention we'll move together. Thank you.

Christine Pearson: All right, and we're closing in on time so this will be the last question. It says, "Will previous information about SEC meetings still be available in the archive website? Please retain this information. It's important in the historical record. Thank you."

Yes, absolutely, we will not be taking anything that's currently in the archive site out of it, and we will be archiving any old meetings that are not going to be moved over to the new site. And then the plan is that, you know, as we have these additional SEC calls, basically the oldest one will roll off and the new one will be posted, but they will always be available. And we'll also post a link that has the how to find that stuff in the archive so that everybody can find it if they need it.

All right, well thank you so much, everyone, for joining us today. We thank you to our speakers and to Dr. Whittemore for your help, and to Dr. Unger for your remarks. We will be posting a transcript and slides and a video just as soon as we can get them prepared. Thanks, everyone, have a great day.

Dr. Bhupesh K. Prusty: Thank you.

Dr. Dawei Li: Thank you.