**CDC's 16th ME/CFS Stakeholder Engagement and Communication (SEC) Call**

**September 23, 2020**
**3 p.m. ET**

Coordinator: Welcome and thank you for standing by.

At this time, all participants are in a listen-only mode until the question-and-answer session of today's conference. At that time, you may press star 1 on your phone to ask a question. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I will now turn the conference over to Christine Pearson. Thank you. You may begin.

Christine Pearson: Good afternoon everyone. My name is Christine Pearson, and I'm the Associate Director for Communications in CDC's Division of High Consequence Pathogens and Pathology, where the ME/CFS program is located. On behalf of the program and our division, I'm pleased to welcome you to today's ME/CFS Stakeholder Engagement and Communication conference call, known as the SEC call. I'll be serving as your moderator today.

Our primary purpose today is to share information with anyone interested in ME/CFS as part of our regular outreach and communication series. First, we will hear from Dr. Elizabeth Unger, who is branch chief of CDC's Chronic Viral Diseases Branch, which houses our ME/CFS program. She will provide

some program updates. Dr. Unger will then introduce today's guest speaker, Dr. Maureen Hanson from Cornell University. Dr. Hanson will be providing what looks like a very interesting presentation on emerging data from a study that her group is doing on immune dysfunction in ME/CFS. After Dr. Hanson's presentation, we will open the line to questions. The operator will provide information about how to ask a question after the introductory remarks.

Before we start, I'd like to provide a brief disclaimer. These calls are open to the public. Please exercise discretion in sharing personal information as confidentiality during these calls cannot be guaranteed. This call is being recorded, and transcripts will be posted on the CDC website.

I would now like to turn the call over to Dr. Unger for a program update. Welcome, Dr. Unger.

Dr. Elizabeth Unger: Thank you. And I'd like to welcome everybody to our 16th Stakeholder Engagement and Communication call, CDC's forum for regular communication with the ME/CFS community. As Christine indicated, today's call will follow the format we used for our most recent call. I will provide brief updates on some of CDC's ME/CFS activities and then Dr. Hanson will share her presentation.

We truly appreciate her willingness to volunteer her time for this call and I will formally introduce her before her presentation. Following her presentation, we'll have time for listeners to ask questions to Dr. Hanson or to CDC. When we get to that portion of the call, please follow the operator's instructions to ask a question. If you have suggestions for speakers or topics for future calls, please send them to the SEC call email and that address is

mecfssec@cdc.gov. This is also the address to use if you would like to be added to the listserv to receive email notification about upcoming calls.

Now moving on to updates on CDC's ME/CFS program. As many of you are probably aware, CDC and NIH co-hosted the first interagency ME/CFS working group meeting on August 11. This workgroup of federal agencies, NIH, CDC, Department of Education, Social Security Administration, Congressionally Directed Medical Research Programs in the Department of Defense, and Veterans Affairs all participated.

The group is intended to facilitate interagency coordination to advance work on ME/CFS. After agency introductions and updates, the first meeting focused on the impact of COVID-19 on those living with ME/CFS, as well as those who have called themselves “COVID-19 long-haulers.” Long-haulers chose the name to reflect that they, rather than fully recovering from COVID-19, developed persistent and profound fatigue and an illness with some similarities to ME/CFS.

Workgroup members benefited from the input of representatives of three invited stakeholder groups: The Open Medicine Foundation, Solve ME/CFS Initiative, and MEAction. CDC is in the process of funding studies to learn about long-term complications of COVID-19 and to determine risk factors for and natural history of post-COVID fatiguing illnesses.

Our program has also been providing information about ME/CFS and approaches to identifying and managing post-COVID fatiguing illnesses to CDC's COVID response teams. One outcome of the interagency meeting is that we have added a brief section to the CDC ME/CFS website on what we know about the relationship between COVID-19 and ME/CFS as well as some practical guidance for people with ME/CFS. We have also provided a link to

the webcast of the interagency workgroup meeting on our ME/CFS homepage under the “ME/CFS Meetings” tab.

At the interagency workgroup meeting, I introduced the new project we are beginning with California's Emerging Infections Program (EIP) and Kaiser Permanente Northern California. I'd like to take this opportunity to provide more information about that project.

California's EIP program is part of the EIP network of ten state health departments and their academic collaborators. This network is a national resource for surveillance, prevention, and the control of emerging infectious diseases. EIP projects impact policy and public health practice. EIP has been quite fruitful in its contributions to surveillance, prevention, and control in a variety of areas such as bacterial infections, influenza, food-borne diseases, and HPV.

We had the first planning meeting with staff from the California EIP program and Kaiser in July, and the project is currently in the design phase. Project goals include developing and initiating methods for surveillance to identify new onset ME/CFS, identifying risk factors for progression from prolonged fatigue to ME/CFS, and characterizing ME/CFS subgroups.

The project has been officially named Surveillance to Optimize Protocols for Early Identification and Sub-grouping of ME/CFS, with the acronym of STOP ME/CFS. The Kaiser team includes two physicians, Dr. Jamila Champsi and Dr. Jacek Skarbinski. Both of them are Kaiser physicians who are involved in caring for people with ME/CFS. Their direct clinical experience will add a vital perspective to the study design.

While on the interagency call, I also introduced a new initiative we are working on with CDC's National Center for Health Statistics on the National Health Interview Survey, NHIS. NHIS is a survey of households designed to represent the U.S. civilian non-institutionalized population. Participant-reported survey data has been used since 1957 to analyze health trends and track progress towards achieving national health objectives. The two ME/CFS questions developed for the Behavioral Risk Factor Surveillance System will be added to the 2021 NHIS survey. Once completed, this will provide national data on whether those surveyed had received a diagnosis of ME/CFS from a healthcare provider and whether they still have ME/CFS.

In response to the coronavirus pandemic, this year, some NHIS interviews have been conducted by telephone instead of in person. The results will be complementary to the Behavioral Risk Factors Surveillance Survey as there are differences in survey designs. Because NHIS surveys are based on households, information will be available on persons of all ages. On the other hand, the national sampling framework of NHIS may limit the estimates for state, county, or smaller geographic areas.

We are continuing to make progress on finalizing data from our multi-site clinical assessment (MCAM) study. COVID has impacted our ability to complete follow up and full enrollment in the pediatric and ill comparison cohort portion of the study. We will make use of the information that has been gathered.

We had abstracts accepted for the International Association for Chronic Fatigue Syndrome Myalgic Encephalomyelitis conference, IACFS/ME. As you know, this conference was changed to a virtual meeting due to COVID. The virtual meeting was very successful, but it restricted the number of presentations. Unfortunately, ours were not selected. We still plan to have

three manuscripts into CDC clearance by the end of the year. They will address the following topics: description of patients with ME/CFS by clinic, a methods paper on our NK cell function study, and a description of the results of cardiopulmonary exercise testing.

Finally, I would like to discuss the plans for ME/CFS clinical guidelines. As you know, diagnostic criteria were strengthened by the 2015 Institute of Medicine report. However, there are no government guidelines on ME/CFS management and treatment. Health care providers newly recognizing their patients with ME/CFS are often left wondering what to do. Practice guidelines could help fill this gap. The process of guideline development needs to be evidence-based, transparent, and open. Preparing a systematic review of the scientific literature on the management of ME/CFS is the first step of this process.

The Systematic Review Report from Oregon Health Sciences University has been delivered to CDC and is under CDC review. We are currently identifying a process that we will use to collect public comments and are planning for a 90-day timeframe for comment once the document is ready to be shared.

Now I would like to introduce our guest speaker, Dr. Maureen Hanson. Dr. Hanson holds a PhD in cell and developmental biology from Harvard University. She is a Liberty Hyde Bailey professor in the Department of Molecular Biology and Genetics at Cornell University in Ithaca, New York, and director of the Center for Enervating Neuroimmune Disease. The Center's mission is to promote research to identify causes, biomarkers, and pathophysiology of ME/CFS in order to lead to prevention and effective treatments. She is also the Principal Investigator of the Cornell ME/CFS Collaborative Research Center, one of three NIH-supported ME/CFS research

centers. The title of Dr. Hanson's presentation is “Immune Dysfunction in ME/CFS.” Welcome, Dr. Hanson.

Dr. Maureen Hanson: Hello. Can you hear me?

Dr. Elizabeth Unger: Yes.

Dr. Maureen Hanson: Okay. Good. All right. So as Beth just told you, I'm going to be telling you about some of our work at the center, and this first slide shows you a photo of Ithaca and the campus, which we're actually going to look like this in about three weeks.

So I know that there may be some people who are interested in long-haul COVID on this call so I thought I would just introduce ME/CFS to anyone who is not familiar, though I realize most of you are well familiar with these unfortunate facts. Now, the fact that very few people with the illness can work full time and that a large number are housebound or bedbound. The most severely ill victims can't speak, eat, or tolerate light and sound and a couple of these victims are shown in the photos, the one on the right requiring a feeding tube.

The prognosis is poor. Unfortunately, it's rare for an adult to recover, although more children are able to recover than adults. There's no FDA-approved drug for treatment, and the majority of patients indicate an onset after a viral-like illness. You can see more information about the disease at the IOM report available for free at this URL at the bottom.

Okay. So the fact that there have been outbreaks of ME/CFS implicate the possibility that there is - that this is a post-viral illness. It's much - it's most likely that a virus caused these outbreaks. We don't know if it's the same virus,

the same family of virus or multiple different types of viruses, but it's certainly possible that a single family of viruses is causing all of these outbreaks that have occurred in the past, and therefore it's definitely of interest to know whether or not a virus is still involved.

Unfortunately, at the time, we didn't have the molecular biology methods that we do now and these - whatever caused these illnesses we really don't know. But what could cause continued symptoms following an acute infection? It's certainly possible that it's a chronic infection and that the chronic infection could either be the inciting organism, which is still present and has not been able to be detected. Perhaps it's in a reservoir in the body that we don't have access to.

But it's also possible that there's a loss of control of known chronic infections such as EBV. Almost of all us have been infected by Epstein-Barr virus chronically for the rest of our life and of course we all have endogenous retroviruses in our genomes, which could become activated. It's certainly also possible that there's been some damage from the acute infection. And as a result of that acute infection, there could be some epigenetic alterations in our DNA in response to the infections that are still there and are promoting an abnormal immune response or abnormal function of the body in other ways.

It's also possible that autoimmunity might be induced after an acute infection and certainly there could be disruptive microbiomes, the gut microbiome as well as other microbiomes. And even more complicated, it could be a combination of some of these different possibilities.

The immune system, however, seems to be playing a major role in this illness and therefore we think it's a very important system to study. There's a lot of components to the immune system, but most people are currently studying

because there's access to blood as a reasonable bodily fluid that one can obtain. A lot of work has been done on cells in the immune system.

We are particularly interested, you know, for this talk in the T cells, shown here. There's a variety of T cells that we've been interested in examining but we're also examining other types of cells as well.

So the - we believe that it's important to analyze specific cell types in the peripheral blood because that can reveal features that you can't see when you've got mixed cell populations. The blood, white blood cells are actually a complex population of a variety of different cells types. Most of the studies in the field have been done with peripheral blood mononuclear cells. This is just a small sampling of the cells that are actually present in this complex mixture.

And we think that sometimes you can miss what's happening if you've got an entire population analyzed together. So, we are right now analyzing T cells, different types of T cells, the NK cells and different types of NK cells as well as B cells, but my talk today is going to focus on T cells.

T-cells are really key elements of the immune system. The two main types that are easily separated and that we can access are CD4 T cells and CD8 T cells. Both of these have important roles, with CD4 signaling an immune response and CD8 cells, which can cause death of pathogen-infected cells or cancer cells. These cells become activated and start doing their job when they interact with the dendritic cell that tells them that there's a foreign antigen present in the body. And of course unfortunately, it can also be a self-antigen that has been erroneously presented to the T cells.

T cells use various types of energy sources to maintain themselves and also to respond. So a quiescent T cell that might just be circulating in the body is

primarily using glycolysis, fatty acids, amino acids for fuel, but after it starts to proliferate, glycolysis is up regulated in order for the cell to gain energy and to take on biosynthesis in order to multiply.

We can detect - we can study the energetic functioning of T cells by measures of metabolic pathways and mitochondrial characteristics. We've been using the Agilent Seahorse device to measure the activity of oxidative phosphorylation in mitochondria, glycolysis, and fatty acid oxidation. I'm going to tell you a bit about OXPHOS and glycolysis today where we have studies on fatty acid oxidation that are currently in progress. We can use flow cytometry to examine single cells and find out by having them pass through a detector mitochondrial size, shape, and membrane potentially using a variety of fluorescent probes. We can also use fluorescent microscopy to examine these different parameters.

So, the patient population for our T cell study consists of 45 controls and 53 ME/CFS patients, both male and female. These individuals were largely from the practice of Dr. Daniel Peterson in Incline Village, Nevada and most of these individuals had a rather long illness duration.

Looking at their SF-36 surveys, one can see that the ME/CFS patients are rather ill. Their physical condition is poor as one can see that the blue bars, the lower they are, the worse condition of the population that's being examined. So, in comparison to controls, especially the physical health, is particularly poor in these patients.

Now this work has been published and so I'm not going to go into it in detail. You can consult the paper shown at the left. It's freely available if you Google it with that title. So, I'm just going to summarize it here. We separated CD4 T

cells and CD8 T cells, and we found that the mitochondria had normal mitochondrial mass in these two types of cells.

There were no significant differences in oxidative phosphorylation in the CD4 T cells. The mitochondrial membrane potential, however, in the CD8 T cells was lower, indicating that the mitochondria in those cells is not functioning properly. The CD4 T cells had lower glycolysis, and after they were activated, the CD8 T cells had low glycolysis as well as before they were activated. So the CD8 T cells seem to be particularly impaired in the ME/CFS patients. You can learn more about the details of this study also by looking at some videos, one of them produced by the first author of this paper, and you can find all of these on our website in our News tab.

One note of caution that I would like to put out there is that you can't conclude that because, for example, mitochondria are impaired in CD8 T cells that that's actually what's happening in muscles and brain and all the other parts of the body. What we know by studying immune cells is about the function of the immune system. Not necessarily applicable but I've been somewhat alarmed to see people concluding that because they found some difference in immune cells, that difference is applicable to every tissue in the body. The peripheral blood mononuclear cells that a lot of people analyzed is a mixture of many cell types using different fuels and what we find out in these cells doesn't mean that's what's happening in the body. It's only telling us about the immune system.

Immune cells also communicate by releasing and uptake of plasma cytokines and extracellular vesicles. So, a cell will receive a stimulus. It will release cytokines, and another cell will respond to those cytokines. Similarly, there'll be a stimulus causing a cell to release extracellular vesicles. These vesicles can be taken up by other cells and then there can be a response. And the cells

that take them up are not necessarily only immune cells. They can be cells in tissues in the body. There are three types of vesicles that are released: micro vesicles, exosomes, apoptotic bodies, and we analyze and assay then all together by obtaining them through a precipitation method.

The precipitation method is shown here. You start with some blood, do centrifugation, add a precipitation agent, and then you can collect these extracellular vesicles, which I'll now refer to as EVs. Once you have these EVs, you can carry out nanoparticle tracking analysis. This allows us to determine the size and number of these extremely small particles.

We then carry out immunoblots. This is basically a way to examine what proteins are present in your preparation. We want to make sure that proteins characteristic of EVs are there and proteins characteristic of other parts of the cells, such as a nuclei, are not there, and then we can also use transmission electron microscopy to verify that we've done a good job isolating the EVs.

The study population for this study is different than the previous one. These are subjects recruited by Dr. Susan Levine in Manhattan, New York. We had 28 females [patients], 28 female controls, 7 male controls, and 7 male patients with approximately the same age. And again, if you look at the SF-36, you can see that the physical health, the lower the bar, the worse off the person is. They physical health of this patient group is quite poor.

What we found by doing nanoparticle analysis is that the overall size and concentration of the particles in the blood did not differ between patients and controls. However, by size, the smallest particles, these are so-called exosomes here, the concentration of the smallest particle type is actually higher in the ME/CFS patients than in the controls. Now we don't know the

significance of this, what it might mean, but it is an observation that there's a difference between the patients and controls.

We took samples from 38 of these subjects to analyze them for the cytokines that were in the EVs and then the whole plasma. And this is just a list of all the cytokines that were examined in this particular experiment. We used a technique called principal component analysis to find out whether the cytokines of each individual person were different depending on whether they were an ME/CFS patient or a control, and you don't really need to understand how this technique works. It's basically a way to display data.

Each one of those triangles or circles indicate - is a statistical reduction of all the information about the cytokines that we obtained. And you can see that the blue and the red are mixed together and so there's really no separation. We don’t see a difference in the cytokines, in either the EVs or the plasma. However, we could see that the cytokines in the extracellular vesicles are different than the cytokines in the plasma.

Now that's extracellular vesicles from both patients and controls and plasma from both patients and controls. What this is telling us is that the EVs really are a different compartment in the plasma. So, if an EV, a batch of EVs were diffused with a cell, the cell would respond differently than if it was merely bathed with some of this plasma.

So, one thing we wanted to know, since we saw no real difference in the amount of cytokines or the types that were present, is whether the cells are communicating normally. Cytokines actually are in a network. They - one of them signals to another and then that one - that cell will signal another and release different cytokines.

So, we asked the question when a particular cytokine's level is high is another one also high or when one's high, is another one low? What are the relationships between cytokines in these different preparations? What we found is that in the plasma we could see a dysregulation of the cytokine-to-cytokine interaction. So this is a very complex figure.

The blob at the left where you see a lot of pink names of cytokines, each gray line that connects those different cytokines is a positive correlation. So they - so for example if one is up, the other is up, and we found in fact that there were 483 positive correlations in the controls and 522 in the patients, but surprisingly there were actually 13 negative correlations in the patients that were not present in control. So IP-10 seems to be involved in numerous negative correlations in ME/CFS, indicating there's a real difference in the cytokine networks between patients and controls.

We can also see the same kind of thing in the EVs. Again, the positive correlations are shown in gray and the negative correlations are a large black bar, and you can see right away just looking at this that there are many fewer positive correlations between cytokines and the ME/CFS EVs. We don't know what this means, but it's certainly a striking difference, and it definitely means that the immune function in ME/CFS patients is different than in controls.

So here's our conclusion. We don't see a difference in EV size between ME/CFS and controls, but there were more exosomes in ME/CFS. We don't see differences in the cytokine levels. This is something that has been seen in a lot of studies. It's very difficult to find differences in cytokine levels. Very few reports have found such differences, but we are seeing dysregulation of inter-cytokine associations. Our work on this topic has now been submitted to a journal. It's under review, and it certainly will be out soon.

So, our current studies are now using samples before and after provocation. The previous studies I described, those were samples collected at one time and assayed, you know, after only a single collection. Now we are using a provocation to see if we can learn more about the disease.

So, a healthy person when they're in good health and they exercise, they're still in good health. They might even be in better health. But an ME/CFS individual who's already ill--after exercise, they start experiencing post-exertional malaise. So, we compare what happens between a healthy person before and after exercise and an ME/CFS person before exercise and after they're experiencing post-exertional malaise and see what's different.

We of course can also look at the differences at baseline between the ME/CFS person and the healthy individual and also their state after they've exercised. So, one of the questions that my lab is analyzing is to find out how the cargo carried by extracellular vesicles can change before and after exercise.

So there's a number of different cargoes that are carried by these extracellular vesicles, not just cytokines. Cytokines are a protein, but they have other proteins in them as well. They have small metabolites in them, and they have messenger RNAs, and they also have a class of RNAs called micro RNAs, which are able to profoundly affect gene expression. When you have a lot of micro RNAs delivered to a cell you can really turn off some gene expression.

This is being studied by two of my colleagues, Andrew Grimson and Jen Grenier. That study is currently in progress. What I'm going to talk to you today about is some preliminary cytokine data from these - from exercise subjects. Before the pandemic shut down our assay facility, we were able to look at 22 ME/CFS subject samples and 17 controls collected in three different locations: Ithaca, New York City, and Los Angeles.

And these individuals had done two cardiopulmonary exercise tests. So, we had samples before they exercised on Day One, post exercise Day One, pre Day Two that we were able to analyze for cytokine content. And we could see that exercise affects the inter-cytokine cargo correlations. If you look at the controls pre Day One, the controls are having an effect. You can see more positive correlations than at post Day One.

And then the controls pre Day Two you're seeing fewer than post Day One but you're also seeing a negative correlation arising. And if you just look at ME/CFS, you can certainly see that the ME/CFS patterns look very different than the control. Again, we can't interpret exactly what this means other than the fact that there are differences in the cytokine correlations between patients and controls before and after exercise. And this is still under analysis, and we hope to test a lot more samples as well.

We're also analyzing other types of protein cargo in the EVs. As I mentioned, it's not just cytokines that are in there. There are other types of proteins, which potentially could be affecting other cells or actually telling us something about the cells from which they were derived. So, if a cell is different in ME/CFS than in a control, it will release different cargo in its extracellular vesicles.

The current data we have available is for 90 samples that came from 15 female ME/CFS patients and 15 controls and, as we speak, additional analyses are being done on EV proteins. 194 proteins were detected in the EVs, and we found 33 that were detected only in controls and 22 only in ME/CFS. We could also see that the protein content changes with exercise, and it changes differently for the ME/CFS patients than the controls. We could see that there are 34 proteins lower in controls at baseline in the ME/CFS but it becomes 57 proteins in the ME/CFS subjects that are lower than controls and one that are

higher, and 73 proteins that are lower than in controls and one higher after post-exertional malaise has been induced.

So, we're currently analyzing what these proteins are and what pathways they are involved in in order to actually understand what significance or differences in the EVs may be giving us.

I'd like to move on to another study that we are - also have in progress just to mention that we are looking at plasma metabolite comparisons between ME/CFS and controls because that could actually reveal differences in functioning of tissues and organs since plasma is derived and flows through a lot of different tissues and organs in the body.

So, we might be accessing information about what's happening in a variety of locations in the body. So now for this sample - for this study we're using blood samples from the four different times: before exercise and after exercise the first day, before and after exercise the second day. The plasma metabolites were analyzed by Metabolon.

The samples were collected in Ithaca and New York City and Los Angeles and had 30 sedentary controls, 45 ME/CFS subjects that we fortunately had obtained. These are females. When - they had all performed the two-day exercise test before the pandemic shutdown of a lot of these subject visits.

What's interesting is that exercise increases the number of metabolites that are significantly different between controls and patients. The Q value under .05 is actually a good statistical significantly - indicates a good statistically significant difference. There were seven that were different before the exercise, 24 after and then the next day during post-exertional malaise, there

were 30 that were different, and then after the second exercise, 56 that are different between patients and controls.

The majority of the metabolites we detected are lower in the ME/CFS patients versus the controls. So the yellow shows the number that are higher in the patients than controls and the orange the number that are lower. So you can really see that of these ones that are different, there's more that are lower in the ME/CFS versus the controls.

Now, those were so-called global metabolite analyses done by Metabolon. But they also analyzed lipids and fatty acids in a separate panel. And what was interesting about the lipid species is that in that case the ME/CFS patients had higher abundance of the lipid species and the fatty acids than the controls. So you can see a dramatic effect of the second exercise.

So while there are only a few lipids and fatty acids that are differentially present before and after the first exercise and before the second, there's a huge increase in the number of lipids and fatty acids that are different after the second exercise.

Again, we don't yet know how to interpret this. But it is clearly something that is telling us something about the disease. So what we have to do now is perform pathway analysis to see what metabolic pathways are disturbed. The data I've been presenting you on the EV proteins and on the metabolites is very recent data. We have to analyze the proteins - what proteins are - how those proteins fit into different pathways in the body.

We have to do the same thing with the metabolites. And we also need to integrate the physiological measures that we have -- how people performed on the two-day CPET -- and also all the clinical information to find out whether

some of these differences might be correlated with particular symptoms, their severity, the length of time that individuals have been ill - all of that clinical information that the patients kindly gave to us as they volunteered for the study.

I'd like to end with my acknowledgements. As I mentioned, the samples for the first study were kindly provided by Simmaron Research and our collaborators there. All of the samples for our two-day exercise test are collected through the NIH Center. All of these individuals participated in the collection of the samples from the three sites.

My laboratory is shown at the top, obviously in better times when we could gather together and have a photo taken. Two of those individuals -- Alexandra Mandarano and Ivan Falstyn on the right have now gone to their next position, continuing their career in science. And we also need to acknowledge that this work is supported by NIH, by Cornell, the Sloan Foundation. We've had some kind private donors, as well as Simmaron Research. Thank you.

Christine Pearson: Thank you, Dr. Hanson. So, now we will move on to the Q&A portion of the call. Terri, can you please remind the callers how to queue up for a question?

Coordinator: Yes, thank you. If you would like to ask a question, please press Star-1, unmute your phone, and record your name clearly. Your name is required to introduce your question. If you need to withdraw your question, press Star-2. Again, to ask a question, please press Star-1 and record your name. It will take a few moments for the questions to come through, so please stand by. So our first question comes from Denise Lopez-Majano. Your line is now open.

Denise Lopez-Majano: Good afternoon. There's evidence that COVID-19 long-haulers at risk of developing ME/CFS will experience harm if they undergo cognitive

behavioral therapy and graded exercise therapy. Yet medical entities continue to recommend them, which increases the risk of additional harm. How soon will CDC issue a firm statement refuting GET and CBT treatments, knowing their potential to do harm? It's not enough to get Mayo to take down recommendations for GET, though we're glad that's been done. These recommendations are on many, many Web sites, and the recommendations are continually being made to many people. How soon will CDC widely disseminate the statement to ensure that all healthcare providers are aware and informed?

Christine Pearson: Dr. Unger – Would you like to address that question?

Dr. Elizabeth Unger: Sure. Thank you, Denise. And as you know, CDC's Web page recommends activity management. It cautions against the harm of exercise beyond the energy envelope. We do not have the ability to dictate to everybody what they do, but our message is very clear. We have recommended the energy envelope and pacing as the very best option for controlling the symptoms.

Christine Pearson: Okay, next question, please?

Coordinator: All right. Our next question comes from Mandy Kramer. Your line is now open.

Mandy Kramer: Thank you very much. I just want to point out about the previous answer before I ask my question that it's not enough to publish guidance about what should be done. It's crucial to publish guidance about what should not be done. And we're not suggesting here in the ME community that CDC should direct that at any particular individual organization. But CDC does need to disavow this nonsense.

My question today - during the interagency meeting this past August, CDC told us that, as of June 30 of this year, 9,000 people took the April 2020 CDC sponsored continuing medical education course -- or CME -- on Medscape. There is significant misinformation in the CME that is not evidence-based.

Here are just two examples. Number one, quote, "Maintaining a positive attitude is not an independent predictor of symptom improvement." The implication in that quote is that for people with ME, maintaining a positive attitude can be a predictor of ME/CFS symptom improvement, just not an independent predictor.

Second quote from the CME sponsored by CDC. "One frequently studied rehabilitative approach is GET, graded exercise therapy, which is often paired with cognitive behavioral therapy," end quote. My comments are as follows. One, the combination of GET and CBT is derived only from the discredited PACE trial.

Two, the theory behind combining GET and CBT for ME is to use CBT to convince people with ME that they are not physically ill, and to use GET to reverse their physically deconditioned state. We know that this is entirely false, unproven, and cannot be reconciled with the 2015 Institute of Medicine report on ME/CFS, nor can it be reconciled with findings of biomedical research on ME, including the beautiful work of Dr. Maureen Hanson, whom we hold in the highest regard.

So, my two questions. First is a rhetorical question. Why did CDC sponsor an educational course for physicians that is so profoundly incorrect, stigmatizing, and rife with misinformation?

And two, when will CDC ensure that all errors about ME/CFS are corrected so that they are based on science and not whatever opinions the author based them on? Thank you.

Dr. Elizabeth Unger: Well, thank you for the opportunity to explain this problem. The example that you talk about, the combination of GET and CBT, is provided as an explanation for why that was not the recommended course of action for caring for the patient that was described in the case description. The references are provided, clearly show the problems with the PACE trial, and yet we need to acknowledge [physicians have seen] the publications that are out there, that have found some benefit from graded exercise therapy.

The CME article, as well as our Web page, clearly state that ME/CFS is a biologic illness. We do not believe that it is anything to do with a misunderstanding or misperception of illness, and it's not going to be cured by any changing of understanding.

And so that particular CME, using case-based learning, I think will be very helpful. And explaining that while GET and CBT has been used, it gives the reference why it's a problem, and it also states the limitation of the description of the patients and the harm that over exercise can do. It clearly shows that pacing is the recommended course of action.

Christine Pearson: All right, Terri, next question, please.

Coordinator: And our next question comes from Claudia Carrera. Your line is now open.

Claudia Carrera: Thank you. Before I ask my question, I'd also like to respond to that response. So you said you need to acknowledge studies that have shown benefit, but the study you're referring to -- the PACE study -- we all know is hugely

problematic and doesn't actually show benefit when analyzed in a statistically appropriate way, especially given that some…

Christine Pearson: Claudia, if I could jump in, please. We've got a whole bunch of people queued up, and I'd like to be - I'd like to allow time for them, too. So could you - if you could just ask your question, that would be appreciated.

Claudia Carrera: Right. In your update, you mentioned the CDC's plan to investigate post-COVID fatiguing illnesses. As you know, studying post-COVID fatiguing illnesses is not the same thing as studying post-COVID ME/CFS specifically, which includes the symptom of fatigue but is better characterized as a complex, multisystem disease. We are concerned that we have not heard specific strategies that CDC will use to measure specifically ME/CFS across long COVID studies. We want the CDC to use this opportunity to learn about ME/CFS arising from acute viral illness, about which so little is known, especially considering the likely spike in ME/CFS cases due to COVID.

In what specific ways are you working with the domestic COVID-19 response team in designing long COVID studies, as well as other relevant teams to ensure that ME/CFS -- specifically ME/CFS -- is accurately, reliably, and consistently taken into account and measured in all long COVID research?

Dr. Elizabeth Unger: Okay, thank you. The problem you describe is one that we recognize. Not all fatiguing illness is ME/CFS, and we don't fully know whether post-COVID fatiguing illnesses -- the problems that long-haulers have -- we don't know yet the similarities and differences between their - what they experience and what ME/CFS experiences.

So we have just recently issued a contract through CDC's broad agency announcement to Nova Southeastern University. Dr. Nancy Klimas is the PI.

She's very familiar with ME/CFS. And her study will be a three-year follow-up of patients - of people who were diagnosed with COVID who recovered versus those who did not recover. And there will be a detailed characterization of their illness as well as risk factors.

There are other groups that are studying long-term sequelae in ME/CFS, and we have been consulting with them to be sure that they're asking questions. Not the full set of questions that are in the NIH/CDC common data elements, but a representative set of questions so that we can understand all of the elements that are required for the case definition of ME/CFS, as well as additional characterization of the illness that they may be experiencing.

So, one of our biggest concerns is going to be how to tease out actual organ damage that may occur uniquely related to COVID versus other kinds of damage that are more like the other post-infectious illnesses that are very ME/CFS-like. So, we have a lot of work to do, and we are - unfortunately, there are a lot of people that are potentially subject to this problem. Thank you.

Christine Pearson: All right, Terri, next question, please.

Coordinator: And our next question comes from Therese Russo. Your line is now open.

Therese Russo: Hi. People struggling with lingering symptoms for months after COVID need information now on the best ways to support their health and prevent themselves from getting worse due to potentially harmful treatment like the graded exercise therapy mentioned that some medical entities still offer. Can the CDC's Vital Signs Program promote public education on ME?

If not through that avenue, what is the CDC doing to educate the public about ME/CFS in a proactive way that extends beyond Web site updates? What efforts are underway to systematically and aggressively reach out to the press regarding the risks of developing ME/CFS from COVID-19? Thank you.

Christine Pearson: Thanks so much. This is Christine Pearson. I can take those. So regarding Vital Signs, that - Vital Signs has a lengthy process for applying for topics, and CDC's Office of the Director is only able to take ten a year. However, that is one thing that we're looking into. I think, to be honest, that there's - it's very competitive to have it, and so it's sometimes difficult to get ideas through. But it is one that we're looking into.

Related to the media, we have been brainstorming on ways that we can get more interest to ME/CFS. Right now, any topics that we present to the media that are not COVID and specifically COVID are really - the reporters are just telling us that they don't have time because they're all being pulled to cover COVID. So, we are looking at ways that we could maybe try to fold in these persistent post-infectious fatigue cases to maybe get some more interest in it.

But it really, honestly - anything except for COVID is pretty hard right now. We are also working to put together a list of potentially some niche media, who may have a little bit more bandwidth to cover things that are non-COVID. And if not, we'll basically just keep our list together, and as soon as it sort of starts to loosen up a little, we'll work on trying to promote additional information.

Dr. Elizabeth Unger: Yes, and - this is Beth. I just wanted to add in that we have been in contact with the COVID domestic response clinical team, and we know that they're preparing an educational module for presentation at the Infectious Disease

Society of America on this topic. And so, we are working with them about this presentation, and we'll include as much information as we can.

We have repeatedly emphasized -- and there's a lot of interest in the COVID response teams -- about the importance of carefully managing activity, particularly during the recovery phase. But in general, that this is not an illness that gets better by exercising.

Christine Pearson: Okay, Terri, next question, please.

Coordinator: Our next question comes from Billy. Your line is now open.

Billy: Good afternoon. Given the increasingly alarming long COVID crisis, it is more important than ever to carry out a widespread ME/CFS clinical education campaign. Please tell us, what are you doing to actively engage the leadership of medical associations, public health departments, hospital systems, and medical schools to promote the ME/CFS education needed to address the post-COVID ME/CFS crisis on an aggressive timeline.

How will you include expert ME clinicians as well as people with ME/CFS and COVID long-haulers in the planning of future curricula?

Dr. Elizabeth Unger: Thank you. I think that we appreciate the importance of stakeholder collaboration and getting input. And as I mentioned, the EIP project is benefitting from clinicians who are actively caring for ME/CFS patients. Kaiser has an ME/CFS workgroup that has patient input, and we are really looking for ways to elicit additional input from experts and the stakeholder community.

We've been working with the National Association of School Nurses, who - they are working with us on a pilot survey of children. And as part of that project, they have educated their members. And we are not doing - we don't have another big national group that we have an active contract with at the moment, but we are - we always have that in mind.

Christine Pearson: All right, Terri, next question.

Coordinator: Our next question comes from Robert Bugel. Your line is now open.

Robert Bugel: Yes, hello, thank you. This question regards standardized measures. There's still no standardized ME/CFS diagnostic criteria for research or clinical purposes, nor is there standardized validated instrumentation. As projects launch across the globe to study long COVID, we're deeply concerned that there's no standard way for researchers to study ME/CFS arising from COVID-19.

How does the CDC plan to address this alarming limitation on the aggressive timeline needed to address the post-COVID ME/CFS crisis? Thank you.

Dr. Elizabeth Unger: Yes, thank you. This has been a continuing problem. We certainly recognize it. And the first start to this problem was establishing the common data elements project with NIH and with extensive input from researchers and throughout the world. Now, those first set of data elements are just a start, because then we have to look at what the thresholds are for each of the responses. But at least we have now started to collect systematic measures of this illness.

And so part of our publications related to MCAM are to evaluate the instruments that we have used so that we can clearly show what the

thresholding will do for the case definition. This is not going to be really fast. But I think even using the measures, you can always change the thresholds, if everybody uses very similar measures.

And so we are working with the community to develop a more standard set of instruments that could be used for ME/CFS as well as in the study of post-infectious fatiguing illnesses.

Christine Pearson: Terri, next question, please.

Coordinator: Our next question comes from Eileen Holderman. Your line is now open.

Eileen Holderman: Yes, hi. Thank you, Dr. Hanson, for an excellent presentation. My question is for Dr. Unger. For decades, advocates have challenged CDC for redefining and renaming ME with flawed criteria, most recently IOM SEID criteria, which downgrades a serious neuroimmune infectious disease by defining the disease with four symptoms, removing the flu-like viral symptoms.

My question is, why is CDC suddenly comparing and studying COVID-19 with ME? Does this mean that CDC is reversing or revising the criteria for ME, adding back in the viral-type symptoms, making them mandatory?

Dr. Elizabeth Unger: Thank you, Eileen. I did not mean to imply that we were changing any of the criteria. Just to be clear, the IOM criteria are for clinical use, and there are different kinds of criteria that you can apply depending on what your research question is. So, research could use a lot of different criteria. But following the established elements of one or more case definitions.

So we are envisioning that the post-infectious fatiguing illnesses have many - could possibly have symptoms that match the IOM case definition. They are four basic symptoms, and it was meant to be clear enough and useful enough for routine clinical use.

Christine Pearson: Next question, Terri?

Coordinator: Our next question comes from Wilhelmina Jenkins, and your line is now open.

Wilhelmina Jenkins: Good afternoon. Dr. Unger, the CDC has reported widely and repeatedly on the disproportionate impact of COVID-19 on people of color. And we know that also many studies -- especially Dr. Jason's studies -- have found that the rates of ME/CFS are higher among Black and Latino respondents compared to the general population.

Given this enormous need to reach out to these populations, could you address what concrete steps the CDC ME/CFS program is taking to reach doctors who serve people of color, including outreach to historically Black medical associations and schools?

This week, the National Medical Association -- which as I know you know is the historically Black equivalent of the American Medical Association -- talked about how necessary it was to reach Black patients with COVID-19 concerning vaccination. They needed to find doctors who they could trust in order to enter any kind of a vaccine or treatment program. And the National Medical Association emphasized that.

Could we not work with the National Medical Association and many other associations, the historically Black medical schools -- like Morehouse right here in Atlanta and others -- to see that the correct information goes out to our

doctors who treat primarily minority communities? Eighty percent of Black people go to Black doctors. Those doctors just don't have the information that they need.

Dr. Elizabeth Unger: Thank you, Wilhelmina. Your points are very excellent, and we've taken them very seriously. When we issued contracts for the BAAs, we tried to make sure that the setting for recruitment would include a really diverse community. And the Neuro-Immune Institute at Nova Southeastern University will be recruiting from those tested by the health department and by federally qualified health centers. So we believe that study will be very representative of people of color.

We need to do more, and we have that as one of our top priorities. We've reached out to Morehouse School of Medicine to begin planning for some educational activities. That's still very early on. I don't have - I can't say exactly when it is going to happen, but we're really early on in the process.

And your suggestion of the National Medical Association is really excellent. And if you have any contact information, please do send them. Because that's one of the hardest things that we have. While we have an idea, we don't necessarily have a connection or a right person to talk to. And as everybody knows, it makes a difference when you reach out if you have somebody that's ready to listen to you. So that would be very helpful if you could provide any names that we should reach out to.

Christine Pearson: Okay, Terri, next question, please?

Coordinator: Our next question comes from Sharon Cohen, and your line is now open. Sharon, we cannot hear you. Do you have us on mute?

Sharon Cohen: Can you hear me now?

Coordinator: Yes, we can.

Sharon Cohen: Okay, sorry. I didn't realize my phone was still muted. Thank you for that presentation. I did participate in both the Cornell Weill study and the Cornell study (unintelligible) and I know there's some ongoing research as well. So thank you for that. Everybody was really very kind and responsible when they did that. So I was happy to be able to participate.

One of my frustrations with dealing with this whole process is regard to the diagnostics. And it does seem like the CPET is the diagnostic. The Social Security Administration does look at that, and that's actually what got me approved for disability. Why isn't that more clear -- or actually at all written up -- in the CDC diagnostic and the SSR diagnostics? That would really help people. There's actually probably a five-year delta from when I should have been diagnosed to when I was actually diagnosed for a permanent disability. That's a huge financial expense, obviously.

Dr. Elizabeth Unger: Okay, thank you. I think that there's a difference between a diagnostic test and a test that is used to determine disability. And the Institute of Medicine (IOM) felt very strongly that the CPET test could be used to evaluate and qualify for disability but should not be required for a diagnosis. And that's a balance that we feel is important, to make the diagnosis as inexpensive and as easy to access as possible. And CPET testing is still not really widely available. Although as you note that it is accepted by the Social Security Administration I believe at this point.

In addition, the two-day CPET test really is very, very difficult on patients with ME/CFS. And we have been told by many of severe, severe relapses as a

result. So it's something that needs to be undertaken with a great understanding of the risks and should be done in consultation with your healthcare provider.

Christine Pearson: All right. Thank you, Dr. Unger. We did receive a question in our SEC box that's for Dr. Hanson. It says, "Will it be possible to use metabolites in blood as biomarkers to diagnose ME/CFS?" Dr. Hanson, would you like to take that one?

Dr. Maureen Hanson: Yes, thanks. We and others have compared the metabolites in blood between patients and controls, and it's typical to perhaps find 80% to 85% of the ME patients being identifiable from these - just by looking at their metabolites. That certainly isn't a completely definitive test. It's probably not as important to use this as a diagnostic test versus actual biomarkers for us to learn about the disease.

So we think - you can have a biomarker that tells you, oh, this person has got disease X, Y, Z. You can also have a biomarker that says, oh, this is what's wrong with this individual, that this is - this tells us that this system has gone wrong, or this characteristic. So I don't know that metabolites are going to be allowing us to diagnose ME/CFS, but it's still - the jury is still out.

And the other thing is, it's certainly possible that plasma proteins might be suitable for diagnosis of ME/CFS. There has to be more research. But we may eventually have that desired diagnostic test, that you merely go to the doctor, have your blood drawn, sent off to a lab, and then the diagnosis is made so that the doctor does not need to be expert in the disease.

I'd like to make another comment, since I can't really ask a question. But I'd like to make a comment about some of the previous questions. I'm hearing a

lot of people say that, "Oh, we can learn a lot about ME/CFS from studying COVID-19." I would actually like to say that it's probably the reverse. I think that ME/CFS is going to tell people about long-haul COVID, rather than vice versa. Beth alluded to this when she mentioned that a number of the patients who have long-haul COVID also have other problems. These individuals have heart damage in some cases, lung damage, kidney damage. They have leftover damage from the acute infection.

One thing that concerns me is that it may be very difficult to figure out what's causing these individuals to have fatigue and post-exertional malaise and all of these other symptoms that are characteristic of ME/CFS when they have this actual outright damage? Instead, ME/CFS patients provide a population of individuals who have similar symptoms, but they don't have this frank damage. And I actually think ME/CFS is going to be more informative for long-haul COVID than vice versa.

Christine Pearson: Thank you so much, Dr. Hanson. Terri, if you're still there, we have time for one more question, if you'd like to pull up the next caller, please.

Coordinator: Okay. So our next question comes from Lisa Rasinger. Your line is now open.

Lisa Rasinger: Yes, hi, everyone. Thank you so much for doing this call today, and everyone who's trying to help everyone else get better. I am - unfortunately have been sick with COVID-19. I'm a long hauler for what will be seven months this week. And I would like to know what could possibly be done to help those of us that got sick at the very beginning of this and were denied testing, so we have no positive COVID test.

And we require multiple specialists working in conjunction with one another, and we're not eligible for any of the long-haul COVID clinics. For instance, I

have lost 22 pounds. I'm down to 101 pounds, and I can't eat 95% of the foods that my body suddenly thinks I'm allergic to. And they're triggering vascular symptoms. And I've consulted over a dozen specialists for months. I've spent thousands of dollars trying to get help. None of the specialists think it falls under their category. It's all under somebody's category, and I need somebody to help me. I obviously need to be able to eat food and digest it properly to be able to live. So these are very concerning problems, and we're falling through the cracks.

I'm in a group with 17,000 other long-haulers from over 25 different countries, and we're all - there's a whole subset of us that have sudden food allergies to foods that we're not allergic to, that are dropping tremendous amounts of weight. We're going to doctor after doctor after doctor and not getting any help.

I would like somebody to start researching this. I would like to have someplace to go where somebody - the specialists could work in conjunction with one another instead of just passing us back and forth and saying, "It's not my problem." Is there anything that you guys can do to help us?

Dr. Elizabeth Unger: Well, your story is very, very concerning, and I think that probably most of the ME/CFS patients will identify with you in the difficulties in finding care. As far as documenting COVID infection, the antibody tests are becoming available, and that may be able to be used to help document that you were affected by COVID.

And then as far as the care goes, I think the best thing that we as a community can do is to continue to document that this is a long-term consequence, that there are no easy answers, and I really don't have a clinic that I can refer you to, but there are clinicians that understand how to care for patients and provide

supportive care. And a lot of ME/CFS patients improve with supportive care, sort of symptomatic management.

But you do need to find a clinical team that will support you. And I hope that you will be able to do that.

Christine Pearson: All right. Thank you, Dr. Unger. This brings us to the close of our call today. Thank you for your time and interest and for joining us. We hope you'll be able to join us for our next call, which is currently planned for early spring 2021. And again, just a reminder that a transcript of today's call will be posted on the CDC website as soon as it's ready. Thanks so much.

Coordinator: And that concludes today's conference. Thank you for participating. You may disconnect at this time. Speakers, please allow a moment of silence and stand by for your post-conference.

END

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