CDC's 17th ME/CFS Stakeholder Engagement and Communication (SEC) Call

May 13, 2021

3 p.m. ET

Christine Pearson: Good afternoon, everyone. My name's Christine Pearson. I'm Associate Director for Communication in the division where CDC's ME/CFS program is located. On behalf of the program, welcome to today's ME/CFS Community Engagement and Communication Conference Call, known as the SEC call. I'll be moderating today's call.

As many of you know, our primary purpose in the SEC calls is to share information with anyone interested in ME/CFS, and this is a regular part of our regular outreach and communication series. First, we'll hear from Dr. Elizabeth Unger, who is the branch chief for CDC's Chronic Viral Diseases Branch, which houses our ME/CFS program. She'll program some program updates. Dr. Unger will then introduce today's guest speaker, Dr. Dane Cook from the University of Wisconsin-Madison. Dr. Cook will provide what looks to be a very interesting presentation on data from exercise testing in the MCAM study. After Dr. Cook's presentation, we'll move on to the question-and-answer part of our call.

We've received numerous inquiries about asking questions via the Zoom webinar versus the phone. We have been exploring how to make this call as seamless and equitable as possible and will be allowing for the most people to get their questions answered within the time we have today. So, for today's call, those of you who have joined us via Zoom, we ask that you type your questions in the Q&A box at the bottom of the Zoom window. If you're not on Zoom, please email your questions to mecfssec@cdc.gov. Our staff are monitoring the box and will share questions in real time with me so [you] can be added to the queue. Before we proceed, we'd like to acknowledge the issues that have been raised regarding the call format and assure you that we're continuing to work to try to make the process as easy and seamless as possible.

Before we start, I need to provide this disclaimer. As you know, these calls are open to the public. Please exercise discretion in sharing any 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'd now like to ask Dr. Unger to start the call. Welcome, Dr. Unger.

Dr. Elizabeth Unger: [Unmuting] You'd think I would be used to that by now. But thank you very much, and welcome, everyone, to the 17th CDC ME/CFS SEC call. I'd like to give a special welcome and thanks to Dr. Dane Cook. We are

most appreciative that he volunteered his time and expertise for this session.

If you have suggestions for speakers or topics for future calls, please send to the SEC call email, which is mecfssec@cdc.gov. This is also the address to use if you would like to be added to the listserv to receive email notifications about upcoming calls.

Now, moving to CDC updates. The CDC ME/CFS program is currently working on the third roundtable project. This builds on our previous two roundtables that fostered dialogue among partners with diverse perspectives, including advocates, healthcare providers, researchers, foundations, and government. CDC's toolkits for patients and for healthcare providers are a direct outcome of this partnership and demonstrate the value of working together. Patient handouts are designed to help patients, their families, and caregivers manage their doctor visits. The healthcare provider handouts include information on assessment, management of ME/CFS symptoms, and other supportive strategies to improve patients' quality of life. Both toolkits can now be found on our website.

We recognize the value of working together with community members affected by ME/CFS and other individuals and organizations that support them. The upcoming roundtable meeting will extend this work and is planned to identify opportunities to build and strengthen existing ME partnerships, as well as to engage new partners to advance [the] ME/CFS program. We expect this project will provide insert—insights leading to stronger, broader, and more effective partners. McKing, our contractor for this roundtable, will be planning the agenda for a virtual meeting in the fall, based on information they gather through interviews and conversations with a variety of groups. These groups include existing partners, potential new partners, and the organizations that have established successful partnerships with other CDC programs that could provide models for strengthening and developing partnerships for CDC's ME/CFS program.

We have also continued our healthcare provider educational offerings. We've renewed the continuing education on our three existing Medscape courses for another year, and we're planning a new Medscape course—a spotlight course—with expert faculty from the Icahn School of Medicine at Mount Sinai and Harvard, Stanford, and Emory universities; specifically Doctors Benjamin Natelson, Donna Felsenstein, Mitchell Miglis and Dale Strasser. They are developing course content about ME/CFS recognition and [will] emphasize patient-centered management.

Course is planned to launch in the fall and will include information about similarities of ME/CFS to post-COVID conditions and other post-infectious syndromes.

In previous calls, we've mentioned our new collaboration with the Emerging Infectious—Infections Program in California and Kaiser Northern California. This is the STOP ME/CFS project, standing for Surveillance To Optimize Protocols for early identification and subgrouping of ME/CFS. Most patients with ME/CFS are diagnosed after experiencing symptoms for many years. So, identifying individuals much closer to the time of illness onset is a key priority. The first phase of this project is well under way and involves a retrospective look at Kaiser medical records to explore what distinguishes patients with prolonged fatigue who've progressed to ME/CFS from those who do not. This analysis is being used to plan phase two that will follow patients who have unexplained prolonged fatigue limiting their activities. This will allow us to describe the onset and early phases of ME/CFS. We expect phase two to start in early 2022. We've just learned that our collaborators at Kaiser are planning a regional Grand Rounds ME/CFS webinar for Kaiser physicians this summer. This will raise awareness of ME/CFS and describe the collaboration with CDC on the STOP ME/CFS project.

Additionally, we're working on five manuscripts for publication. The topics include a paper comparing the function of natural killer immune cells, or NK cells, in people living with ME/CFS and healthy controls. And this will describe the association of NK cell function with other measures of ME/CFS illness. A second paper focuses on the work Dr. Cook will present today on the response to exercise. Other papers in progress include one describing the differences among patients with ME/CFS in MCAM clinical sites, and a paper describing medical conditions that tend to occur together with ME/CFS. As well as a paper reporting on the use of PROMIS measures of sleep and pain to describe the experiences of people living with ME/CFS. We expect to have at least three of these manuscripts submitted for CDC clearance by the end of this year.

In recognition of ME/CFS International Awareness Day—which was yesterday, May 12—our program published a webpage to support the ME/CFS community. The webpage describes our new patient toolkit and highlights a new CDC resource for medical students that will help prepare the next generation of healthcare providers to diagnose and care for people with ME/CFS. Students can visit the webpage to learn about ME/CFS through videos, a case study, continuing medical education, patient stories, and more. Medical students can also share these resources with their schools and their peers. We're highlighting these new resources all month

using promotional channels such as Twitter, the CDC features homepage, and through the CDC Learning Connection. We anticipate the Federal Register Notice for the systematic review report for diagnosis and treatment of ME/CFS will be published within the next week. At that time, it will be open for public comment for 90 days. This systematic review adds to the 2014 systematic review and evaluates evidence from 1988 to January 2019 regarding diagnosis and treatment of ME/CFS in adults and children, considers treatment of the symptoms, stratifies findings by ME/CFS case definition, and assesses harms and benefits of diagnosis and treatment. The final report will incorporate new studies identified from an updated search in 2020 as well as the comments from the public and peer review.

Finally, the CDC ME/CFS program has been collaborating with other CDC programs to better define and understand long-term symptoms following COVID. In addition to coordinating across workgroups within CDC, we're collaborating with the National Institutes of Health, the World Health Organization, and others on the response to this problem. CDC is partnering with clinicians to understand the healthcare needs of patients who have symptoms long after the coronavirus infection is typically resolved. These efforts have helped to describe the type and frequency of long-term symptoms and the patients who are most likely to be affected. CDC staff working on the emergency response to COVID are analyzing

the electronic health data, including medical records, laboratory results, and administrative data to rapidly describe health outcomes over several months after COVID-19 diagnosis. We're also establishing studies with external partners to understand the duration of COVID-19 illness and risks for complication. As of February 2021, there are eight multi-year follow-up studies that have been funded through CDC broad agency announcements, and these have already started enrolling or will enroll soon. These projects were not funded by CDC ME/CFS program, but the Chronic Viral Diseases Branch that houses the ME/CFS program is leading the effort for two of these. One of these projects that's underway is COVID UPP, which stands for COVID, Understanding the Post-Viral Phase. This is a four-year follow-up study of individuals who tested positive for coronavirus infection and reported that they have not recovered three to four months later. COVID UPP is a collaboration with Dr. Nancy Klimas and her team from Nova Southeastern University, and its objective is to describe the nature of long-term symptoms, their frequency and severity, and difference in overlap of these symptoms with ME/CFS. This project has an approved protocol and is just beginning enrollment this month. The second study is called RECOVER, which stands for Research on COVID-19 Long-Term Effects and Risks. This project is a collaboration with the University of Washington to examine medical records of patients with coronavirus infection in the University of Washington Health System and to collect specimens for biomarker and

genetic testing from a subset of these patients. The primary goal of the RECOVER study is to document and compare a wide range of risk factors for COVID-19 severity and outcomes like hospitalization and long-term complications. The protocol is currently under development. In addition to these two studies, our program has recently solicited proposals through a broad agency announcement for applied research. The announcement called for design and evaluation of multi-disciplinary team approaches to identify and disseminate those practices most effective in providing medical care for people with long COVID, ME/CFS, and other post-infectious fatiguing illnesses in primary care settings. This research is expected to start this summer. We're committed to ensuring that these efforts to improve care are inclusive of patients with ME/CFS and that they address potential health inequities and include diverse populations. The ME/CFS program staff have also lent their expertise to several other CDC studies of COVID long-term symptoms, such as the INSPIRE study, which stands for the Innovative Support for Patients with SARS-CoV-2 Infections Registry. This study is enrolling patients from multiple health systems and collecting clinical information, as well as surveying patients about their symptoms. The questionnaires that are being used for INSPIRE include some in the ME/CFS common data elements list. Another study with Tulane University will follow infected individuals at 3, 6, and 12 months, and include screening for ME/CFS symptoms at each follow-up using an instrument adapted from our program studies of ME/CFS. A

study in collaboration with the Johns Hopkins School of Public Health is looking at COVID-19 in high-risk American Indian communities in the Southwest and will also screen for ME/CFS symptoms. CDC is pursuing population-level approaches to help provide estimates of the long-term impact of COVID-19. Last year, the ME/CFS program added questions on ME/CFS diagnosis to the National Health Interview Survey, which is a nationally representative survey of the non-institutionalized U.S. population. This will allow tracking of ME/CFS diagnosis along with COVID-19. Our ME/CFS program is consulting on questions on COVID long-term symptoms to be added to the National Health Interview Survey in 2022. Funding was also recently approved to add questions on COVID long-term symptoms to the 2022 Behavioral Risk Factor Surveillance, which can provide state-level estimates. The ME/CFS program also provided input on two new CDC [web]pages about post-COVID conditions for the public and for clinicians, published last month.

Now, I would like to introduce our guest speaker, Dr. Dane B. Cook. Dr. Cook holds a PhD in Exercise Science from the University of Georgia. He completed a post-doctoral fellowship in neuroscience from New Jersey Medical School. He's a Professor of Exercise Psychology in the Department of Kinesiology at the University of Wisconsin-Madison and a Health Science Specialist Research Physiologist at the William S. Middleton Memorial Veterans Hospital. Dr. Cook also holds an adjunct

appointment within the War-Related Illness and Injury Study Center at the New Jersey VA Healthcare System. In addition to being director of the Exercise Science Laboratory at the VA Madison and Codirector of the Exercise Psychology Laboratory at UW Madison, he is the current sitting chair and director of the Marsh Center for Research in Exercise and Movement. The title of Dr. Cook's presentation today is "Exercise Testing in the MCAM Study." Welcome, Dr. Cook.

Dr. Dane Cook: Thank you, Beth, and good afternoon, everyone. I want to thank Dr. Unger and the CDC for inviting me here today to talk about exercise testing in ME/CFS with a focus on some of the data that we've been collecting in the MCAM study. Next slide, please.

So cardiopulmonary exercise testing, or CPET, has really been an integral part of ME/CFS research. It's been used as a standardized physiological stressor to try to uncover pathophysiology among different systems, such as the central nervous system, the autonomic nervous system, and the immune system that may not be apparent at rest. It's also used as a direct measure of the function of the cardiopulmonary system to determine and measure the integrative response to physical effort. Next slide, please.

So before I get to the data, I thought that I'd give you a very brief overview of some of the standard measures and indications of CPET. So,

we use metabolic carts to directly measure oxygen consumption—so the energy component of the body—and carbon dioxide production—which is the byproduct of metabolism during exercise—as well as ventilation, and broken down into its component parts of breathing frequency—so how many breaths you take per minute—and the depth of breathing, T underscore V here, called tidal volume. We also add direct measures of heart rate, work rate, and oxygen saturation. And from these directly measured variables, we can calculate and derive dozens of indirect measures that help us to understand the exercise response of the participant and determine whether or not pathophysiology is present in that exercise response. For example, my lab has been recently interested in what we generally call measures of exercise efficiency, and here are a few examples. Here we have the ventilatory equivalents of oxygen consumption, VO2, and the ventilatory equivalent of carbon dioxide, VCO2. So, these measures are how much you have to breathe or ventilate in order to utilize oxygen for energy, and to dispel or eliminate carbon dioxide, which is the byproduct of metabolism during exercise. Importantly, higher measures of these are indicative of inefficient pulmonary ventilation. So if you have high levels of VE VO2, you have to breathe more in order to utilize oxygen for energy, and you have to breathe more in order to get rid of CO2 that is being built up during metabolism. We also look at the relationship between VO2 and heart rate; so how much oxygen do you consume per beat, as well as the relationship

with work rate. CPET is also used clinically to examine exercise tolerance, where low tolerance can be indicative of cardiopulmonary disease. It's used to look at heart and lung disease, as well as symptoms, during exercise. It's commonly used as a measure of impairment or disability ratings. And then from a real—a very practical standpoint, it's used perhaps most commonly to prescribe the dose of exercise for rehabilitation. Next slide, please.

So there has really been an increase in the utilization of exercise testing in ME/CFS, and it's been used in its standard way, to test the cardiopulmonary system, similar to what I'll be presenting to you today, and to determine exercise tolerance, and in some cases to guide exercise prescription. But it also has a unique role in ME/CFS research – and that is, as I mentioned earlier, to challenge physiological systems. So we can use this exercise stressor to challenge the autonomic nervous system, to challenge the central nervous system, to challenge the immune system. We can measure these during exercise, but we can also measure the consequences of that challenge post exercise to see if we can uncover pathophysiology. For example, that might be representative of post-exertional malaise. Next slide, please.

So a critical element of exercise research in general—and certainly, particularly for when looking at disease—is determining whether or not

exercise responses are indicative of a low fitness response or are more associated with disease pathophysiology. This is really critical for interpreting the data. With that being said, a recent meta-analysis found clinically meaningful differences in peak oxygen capacity between ME/CFS and controls. So, a meta-analysis is a study of studies. So it's kind of a taking all of the responses and finding the mean difference of an outcome between two groups. In this case, they were looking at the mean peak oxygen consumption for ME/CFS and controls – so how fit the two groups were. And they found for ME/CFS here in the red box, they were about 25 mls (mililtters) per kg(kilogram) per minute. That's a standard measurement metric that we use. And the controls were around 30. And this difference of 5.2 mls per kilogram per minute was found to be clinically meaningful a difference. It's important also to note though that we know very little beyond peak and threshold responses in ME/CFS. The vast majority of studies have reported responses at the ventilatory or anaerobic threshold and peak responses, and very little of the research has looked at the dynamic response that occurs between these two points. Next slide, please.

There has also been quite a bit of interest in cardiac responses to exercise in ME/CFS. So, here's another meta-analysis that showed large effect size differences between ME/CFS and controls for their peak heart-rate responses. So, an effect size is the size of the difference between the two

means. So anything over 0.8 is considered large. Here, their effect size was 1.37, so they found large differences between ME/CFS and controls, with controls achieving about 94% of their age-predicted heart rate, and the ME/CFS participants about 82%, which is suggestive of chronotropic incompetence. In other words, the heart is not able to adequately respond to the physical stress of exercise. Next slide, please.

So this brings us to the—at least the exercise portion or purpose of the MCAM study. So, one purpose of the MCAM exercise study was to determine the exercise capacity of the MCAM cohort. So, this is—would be very similar to previous research in ME/CFS, looking at their exercise capacity. Another purpose was to more comprehensively examine the cardiopulmonary, metabolic, and perceptual responses during exercise in ME/CFS. And that's what I'm going to be presenting to you today. And a third very important purpose was to determine the role of aerobic fitness. So, as you'll see, this is one of the larger studies that's been conducted of exercise in ME/CFS. So, we were able to find a large subgroup that was closely matched on aerobic fitness. And why this is important is because it allows us to determine more specifically—when differences occur and they're matched on aerobic fitness—that we can say this is not due to differences in fitness. This is more likely to be due to having the disease ME/CFS. Next slide, please.

So for the methods—next slide. So we were able to evaluate 403 exercise tests and compare 348 participants in the study, 179 ME/CFS, 169 controls. Testing was conducted in a controlled laboratory environment, and participants were asked not to smoke for two hours, consume caffeine or food for four hours, or exercise for 24 hours prior to the test. We used a 12-lead ECG, or echocardiogram—electrocardiogram—to measure resting heart rate as well as to monitor heart rate during exercise for participant safety. Next slide, please.

So this is a sample of our protocol. So, as I mentioned earlier, we're using a metabolic cart. We're directly measuring oxygen consumption, carbon dioxide production, ventilation, heart rate, and work rate. Here's a sample test. So we have watts, or the amount of work that they're doing on the bike during exercise, and then the protocol is here on the x-axis, the ramped protocol. So we had them sit for two-minutes rest—two minutes of rest on the bike to acclimate to the equipment that they're wearing to measure the metabolics. We then had them conduct a—do a one-minute warmup at no load on the bike. And then exercise intensity increased at 15 watts per minute, or 5 watts every 20 seconds, until what's called volitional exhaustion – so this is a point where either the participant says they can no longer keep going or they're unable to keep up with the pedal rate of 60 rotations per minute. Next slide, please.

So, from the CPET test we, as I said earlier, we determine their threshold and capacity. So, we're looking at the ventilatory or anaerobic threshold VT here, their peak VO2. If you move to the right, under efficiency, we're calculating their ventilatory equivalents of carbon dioxide and oxygen - so this is how much you have to breathe to eliminate carbon dioxide and utilize oxygen for energy. We're also looking at the relationship between VO2 and heart rate. Slide to the right for work rate. We're looking at the relationship between VO2 and work rate. And then lastly, for ventilation, we're looking at its components, the tidal volume, so how deep you're breathing, and your breathing frequency, the fR there, so how many breaths per minute. And then finally, we're calculating what's called the oxygen uptake efficiency slope, or OUES. This is the relationship between oxygen consumption and ventilation, and it's a common measure in exercise physiology to look at exercise efficiency and fitness. Next slide, please.

So for our data processing, it's important to note that this was conducted independent of who conducted the exercise test and blind to clinical status. So we made—we ensured that the systems were calibrated prior to testing. And then we looked at and removed obvious data artifacts. We then determined how many participants met standardized criteria for a peak effort. These criteria are from the American College of Sports Medicine and the American Heart Association. So that's a respiratory exchange

ratio—or RER—of 1.1, reaching greater than or equal to 85% of age-predicted peak heart rate, and an RPE of 17 or greater. And I can tell you now, before we get to the data, that 90% of our participants met peak criteria. So that's a testament to both the participants and the data collection sites. We then took the data in its absolute form and we calculated relative exercise intensities from 0 to 100%. And this just simply allows us to compare individuals and groups to one another. Next slide, please.

So for the results, I'm going to show you the entire sample, so all 348 participants, and then I'm going to show you how the results change or don't change as a function of our fitness-matched subset. Next slide, please. So here we have the demographic data on the left three columns, we have the entire sample of 348 participants. So ME/CFS, controls, and then the ES stands for effect size, and its confidence interval. So, effect sizes are the how meaningful or large the differences are again, 0.3 is small, 0.5 is moderate, 0.8 or larger is large. And then the confidence interval tells us whether or not it's significant. So, any time you see stars on the results that I'm showing, that means that there's a significant difference between groups, in this case based on their effect size. On the right, you can see that we were able to match 99 ME/CFS one-to-one to controls on their fitness within one milliliter per kilogram per minute. So they're very tightly matched on fitness, and within plus or minus five years

of age. Here we're showing their age, their height, their weight, and their BMI. For the entire sample, the ME/CFS were older, slightly heavier, and a small effect, larger for their BMI. And so for any of the entire samples, because this was a moderate effect difference, we are controlling for age in all of our analyses. When you look for the over to the fitness-matched side, all of these differences go away when we match on fitness. Next slide, please.

So these are the clinical indications from the study of their ventilatory and cardiac performance during exercise. So same thing, the entire sample is on the left three columns for ME/CFS and Controls. The fitness-matched sample is on the right with their associated effect sizes. Here we have the VE/VCO2 nadir. So this is a common clinical measure of ventilatory efficiency. So how well are you able to eliminate carbon dioxide at its nadir? The OEUS, again, is the oxygen uptake efficiency slope. So that's a measure of fitness and efficiency. And we have this both in its standard form and controlled for body surface area, so BSA. We have percent heart rate reserve and percent predicted max heart rate that they achieved. Higher—higher values for the VE/VCO2 are bad, meaning you're less efficient at exercising. And then lower measures on the rest are also indicative of poor exercise efficiency. And so we see for the entire sample, ME/CFS have a higher VE/VCO2, lower OUES, lower percent heart rate reserve adjusted, and achieved a lower percentage of their predicted

maximal heart rate. When we looked at the fitness-matched subgroup here, what we see is that they continue to have a difference in their VE/VCO2, with the ME/CFS having a higher value, and having a lower percent heart rate reserve during exercise. The other—the other differences were eliminated when matching for fitness. Next slide, please.

So now I'm going to show you the dynamic responses. So all of those responses I showed you previously, that's one point in time, or a slope. Here I'm going to show you how these are changing during exercise, and how the two groups compare. So the first set of graphs I'm going to show you are the oxygen consumption during exercise and the wattage that they can complete during exercise from 20 to 100%. So here we have VO2 on the y-axis and then their percentage of peak on the x (axis). The top graphs are over the entire sample. The bottom two graphs are for the matched sample. And as you can see that throughout exercise, ME/CFS in red are consuming less oxygen all the way through to peak. So they are less fit in general compared to controls. And as a result, they're completing less work, or doing—or able to produce fewer watts than the controls. When we matched them on their fitness, you see these differences completely go away. So this is what you would exactly expect. So we matched them on their peak fitness here at the 100% line, and you see that throughout exercise, the groups are now matched on VO2 during exercise and they're producing the exact same amount of watts. So this one shows us that our

manipulation of fitness matching worked and that when you match on peak responses, the entire dynamic response is also matched. Next slide, please.

So here are the results for ventilation. So again, the top graphs are for the entire sample. The bottom graphs are for the matched sub-sample. We have ventilation here on the far left graph. So this is in liters per minute. And as you can see, throughout exercise, after 20%, the ME/CFS group are having lower—a lower ventilatory response to exercise. When you look to the right, this lower ventilatory response—if you look at breathing frequency, breaths per minute—they have a lower breathing frequency throughout exercise, but no difference in their tidal volume. So they're breathing slower throughout the test, but they're breathing—but the depth of their breathing is the same as controls for the entire sample. When we match on fitness, we see that this ventilation response on the bottom left here goes away. So now the two groups are matched on their ventilatory response to exercise, meaning the volume of ventilation between the two groups is the same throughout the exercise test. However, that does not tell the whole story. Because if we hadn't broken ventilation up into its components of breathing frequency and tidal volume, we would have missed a very interesting finding. And that is that even when they match for fitness, the ME/CFS participants are breathing slower throughout exercise, and they're breathing deeper. So they have a deeper ventilatory

response and a slower ventilatory response. This is a unique and inefficient breathing pattern for exercise, and it can't be explained by fitness because it only showed up when we matched for fitness. Next slide, please.

And then finally, for the dynamic exercise responses, we have our ventilatory equivalents of oxygen consumption and carbon dioxide production. Again, the entire sample on the top. The matched sample on the bottom. This is, again, how much do you have to breathe to utilize oxygen for energy? And how much do you have to breathe to expel carbon dioxide? We see for the entire sample that the ME/CFS throughout exercise have higher values for their ventilatory equivalents for both VO2 and VCO2. And if you switch down to the matched subsamples, you see those differences remain even when we match for fitness. So we think that this has something to do with the pathophysiology of ME/CFS because it cannot be explained by having low fitness. Next slide, please.

Okay, so for the discussion, next slide. So in summary, if you look at the entire sample, all 348 participants, we have reduced oxygen uptake, reduced cardiac performance, inefficient pulmonary ventilation, and increases in perception of effort, which I didn't show today. When you match on fitness, the oxygen consumption and cardiac differences for the most part go away. And what we see that is maintained is an increase in

the ventilatory equivalents of carbon dioxide and oxygen consumption. So you're not able to utilize energy well. You're not able to expel the bad byproducts well. This is associated with a decrease in breathing frequency and an increase in tidal volume, which is a unique breathing pattern. And we maintain the perception of effort. Again, not shown. Next slide, please.

So we think that these ventilatory responses are indicative of a problem with gas exchange. So VE/VCO2 is usually suggestive when you have high levels of poor perfusion. You're not able to get rid of and transfer the gases across different tissues and then expel them into the environment. The VE/VO2 is suggestive of poor extraction of oxygen to active skeletal muscle. And so you have a hard time getting rid of these byproducts,and even if you can deliver oxygen to the muscle, it's difficult for the muscle to use that oxygen. We think this unique breathing pattern may be a strategy to improve what's called alveolar ventilation. So you have these air sacs in your lungs where gas is collected and then transferred to the blood to send to active muscle. And so if you breathe slower and deeper during exercise, you might be trying to bring in as much oxygen as you can to improve ventilation. We also think it might be—another explanation would be respiratory muscle fatigue, which could lead to what's called a—what's called a metaboreflex. So the release of neurotransmitters that cause vasoconstriction at the exercising muscle, which is not what you want. You want vasodilation. You want lots of

blood to be sent to those exercising muscles. And we think that you get this vasoconstriction because the respiratory muscles need more oxygen because they're becoming fatigued. This is what's called the Robin Hood effect in exercise physiology. So the system is robbing the oxygen-rich exercising muscle to pay the fatigued and poor respiratory muscles. Next slide, please.

We saw very little evidence of overt chronotropic incompetence. Most of the cardiac differences went away with fitness matching, and none of our—none of our metrics met criteria for chronotropic incompetence. So fitness matching appears to be very critical if we're going to determine what is specific to the disease and then what could be a consequence of just comparing people on different fitnesses or different exercise time. We also think that these relationships that we're seeing—in cardiopulmonary inefficiencies it would be very interesting to look at the relationships between symptoms, disease severity, cognition, and sleep. Next slide, please.

So just as a take-home message, I want to stress that we observed clinically relevant indications of a compromised cardiopulmonary response in ME/CFS. We found inefficient exercise ventilation, even when directly controlling and matching on aerobic fitness. I also want to stress that ME/CFS is not a disease of low aerobic fitness. That is a false

narrative. That has been propagated by non-exercise scientists. In my opinion, it's been damaging to the ME/CFS community, and it's presented a lot of noise in the research that is really unnecessary. I can't think of a plausible biological reason why someone who is low fit would have a heterogenous and complex disease like ME/CFS. It just—it doesn't make logical sense. However, understanding how the cardiopulmonary system operates and interacts with other physiological systems I think is critical for understanding disease pathophysiology. Next slide, please.

So I'd like to acknowledge my laboratory and collaborators. I want to acknowledge and a big thank you to all the MCAM study participants who volunteered their time, their effort, their health for this study, as well as all of the sites that participated and collected the data. Thank you for your attention.

Christine Pearson: Thanks so much, Dr. Cook. That was really interesting. So now we'll move on to the question-and-answer portion of the call. Just a reminder for—for our attendees, if you would like to ask a call within the Zoom platform, please click on the Q&A button at the bottom of your screen and then type your question. For those of you who are on the phone only, you can submit questions by emailing mecfssec@cdc.gov. We're monitoring that inbox in real time, and we'll add your question to the queue. So let me switch over to the questions.

Dr. Elizabeth Unger: While Christine is organizing the questions, I'd like to ask Dane one of—one myself. I think that finding in the breathing changes are really, really interesting. Has this been reported before? And do you think that breathing training could help patients with ME/CFS?

Dr. Dane Cook: So the ventilatory equivalents of oxygen consumption and carbon dioxide production have been reported previously by us many, many years ago. Has not been followed up until this study. So this was a—a wonderful opportunity for that. The breathing frequency and tidal volume, I believe that is a unique finding. I'm aware of only one other study that has examined this, and that is in Gulf War veterans with Gulf War Illness. And wouldn't you know it? They saw the same thing. So I think it's—I think it's a unique finding. It needs to be followed up. I can't—I will say that it is consistent with some of David Systrom's work that shows that there are subgroups of ME/CFS that show either a reduction in their cardiac output—so a poor delivery of oxygenated blood to muscle, as well as poor oxygenation of blood. So these findings are consistent with that. As well as—I'm sorry, can you say your second part of the question again?

Dr. Elizabeth Unger: That breathing—could breathing training help patients with ME/CFS reduce their symptoms?

Dr. Dane Cook: I would say breathing training at rest may not translate to exercise. But if you did breathing training during exercise, you could train the ventilatory system to not have that inefficient response, and maybe improve exercise tolerance. I'm not sure. That's definitely an interesting and empirical question that could be tested.

Dr. Elizabeth Unger: Thanks.

Christine Pearson: Okay, great. So, Dr. Cook, we have a bunch of questions for you. I think hopefully you can answer them quickly so we can get

Dr. Dane Cook: I'll try.

Christine Pearson: through a lot of them. So, one of them says: "Interesting results. So, is this evidence against the deconditioning hypothesis? And also is this a one-day CPET, i.e. not a two-day CPET?"

Dr. Dane Cook: Yes, and yes. So, very supportive of refuting the deconditioning hypothesis. So let me restress this. This is not a disease of deconditioning. That—that does—that does not make scientific sense. As far as it was a single day, so we were able to find really clinically meaningful differences with a single exercise test.

Christine Pearson: Okay. I apologize if this is repetitive. I'm trying to—I'm not sure.

Dr. Dane Cook: That's okay.

Christine Pearson: if you—if this is included. But the next one is: "What additional information is gained when a two-day CPET is done versus a one-time CPET?"

Dr. Dane Cook: Yeah, so—so if you were to do this in a two-day CPET, you could test a lot of really interesting things. Could they—the standard two-day CPETs show—can test whether or not they can reproduce the same work, the same oxygen consumption, the same heart rate at the ventilatory threshold and at peak. So if we had—if we did an add-on study here and did a two-day CPET, we could see, do these ventilatory inefficiency measures get larger? Do they get reproduced? It really determine whether or not the system responds the same when it's serially challenged.

Christine Pearson: And so another question is: "Are there any differences in the recovery time of ME/CFS versus the control group?

Dr. Dane Cook: So, in terms of recovery of the metabolics, we have not looked deeply at that. And so that would be a very interesting test, to see whether or not the

heart rates are recovering slower, whether the oxygen consumption is recovering slower. So, if you're talking about metabolics, we have not looked, and that is something that we're very interested in. If you're talking about, are they recovering as an individual, they're definitely taking longer to recover. We know that from the literature, that when they do an exercise test, there's a cost, that it is not—that the controls just don't have.

Christine Pearson: And so, the next one: "Have you tested the breathing in the same individuals during sleep?"

Dr. Dane Cook: Personally, me? No. I don't know if the MCAM study has any sleep-related breathing data.

Dr. Elizabeth Unger: No, we don't.

Dr. Dane Cook: So, no.

Christine Pearson: Okay. And then there's a question about: "What—when—or will these be—these findings be published soon, or when?"

Dr. Dane Cook: They are in submission.

Christine Pearson: Okay. Hang on, sorry. There's so many. I'm trying to comb through. So, it says: "To Dr. Cook. Are there differences in testing for true ME patients versus CFS patients since CFS could be caused by a number of fatigue diseases?"

Dr. Dane Cook: Yeah, I'm not aware of any individualized protocols for distinctions among the diseases. Certainly, if you think about disease severity and where that might fall out, you would consider that there are certain types of protocols that can't be completed by someone with the disease, but I'm not aware of any that have been categorized in that fashion.

Christine Pearson: Okay. All right, I'm going to try not to mess up this question here. So the next one says: "You study O2 and CO2, but can you add sensors to also monitor NO, nitrous oxide, NH3, ammonia, perhaps acetic acid, lactic acid, CO, carbon monoxide, to assess nitrogen oxidative stress and if anaerobic?"

Dr. Dane Cook: Yeah, so you can—I don't know the—I don't know the sensor technology for all of those. There are certain sensors that you could put on the skin that measure some of what—some of the variables in that question. We could also draw blood serially during exercise to examine some of the either—you know, either depending on the frequency, some of those

outcomes. We did measure lactate during exercise, and found no differences in the lactate response between ME/CFS and controls, either for the entire sample or the fitness-matched subsample. But that nitric oxide and that stress is important, I think. I would also add that if I had my way, we would have also looked at mitochondrial function in every possible way that we possibly could, but you know? There's only so much feasibility you can do in a multi-site study, so.

Christine Pearson: Okay. Next one: "Is there any difference in duration of CFS and performance?"

Dr. Dane Cook: So that is another research question that we're very interested in, both severity and disease duration, and whether or not their exercise performance varies by that. We have not looked. So great question. Sorry, I don't have an answer for that one.

Christine Pearson: Okay. So next one says: "Fascinating presentation. It's clear that people with ME/CFS are significantly disabled. How do long COVID patients compare? Given that PEM is reported in 72% of long COVID patients, I'd imagine it would be similar."

Dr. Dane Cook: Yeah, so this is something that I'm very interested in doing. I don't know of any cardiopulmonary exercise testing data in long COVID yet, something that my group is currently planning to do.

Christine Pearson: Okay. So there is one that actually I can answer because it's actually about communication, so I'll jump in and do that one real fast, which says: "Yesterday, I noticed that there are new handouts posted for healthcare professionals linked on the ME portion of the CDC website. Thanks for posting them. One quibble, only one page seems to mention that ME can affect people of any age. This is information that is likely should appear on most the pages as many healthcare providers are unaware of this. And if they only look at one of the handouts, might not realize that, for instance, children can get ME. Also, when will the recently posted handouts for healthcare professionals be posted in Spanish?" So, I'll just mention that briefly. Thank you for bringing that up. In some cases, we were constrained by space in the layouts of them, but we will definitely take a look at that to see if that might be something that we could add. As to the Spanish, we actually have Spanish versions in the works for both the patient handouts and the healthcare provider handouts. They're just—they're—I think we've recently gotten the translations back, or we should have them back soon. And we'll get them posted just as soon as possible, but we do have plans to have both of those posted. Okay. Let's see. For Dane Cook: “Can these one-day tests translate to diagnostics?"

Dr. Dane Cook: So, depending—diagnostics, I would say, that would be a big lift. I don't think that these are pathonomic of the disease in terms of just saying, if you have this ventilatory response, you have ME/CFS or ME or CFS. It's not specific enough for that.

Christine Pearson: "Do ME/CFS patients have a low anaerobic threshold?" Sorry about that.

Dr. Dane Cook: Yes, they do. Lower anaerobic thresholds are seen in many different cardiopulmonary conditions, pulmonary cardiac conditions, as well as those with low fitness. That's another non-specific measure that we're trying to stress in this paper. We have to get beyond just looking at that because the anaerobic threshold is something that is a—it's a key indicator of fitness, but its pathophysiological significance is not clear.

Christine Pearson: All right. So, we've gotten quite a number of questions related to long COVID and how it—how it relates here. I'm going to—in the interest of time—try to condense them into one question since they're all basically asking the same question, which is—so it says, "NINDS Director Dr. Walter Koroshetz has stated COVID's clearly one of several infections that can drive ME/CFS. And I think that over time, long COVID and ME/CFS will become one and the same. Yet Dr. John Brooks at CDC has said that they are two separate conditions. Dr. Brooks gives two reasons

for his stance. One, long haulers know what caused their condition. And two, a number of long haulers have organ damage." And so the question that they are asking is: "What is being done in terms of how CDC educates Dr. Brooks and/or how we talk about this issue of whether or not they—of how they are related to each other?" Dr. Unger, would you like to address that one?

Dr. Elizabeth Unger: Sure. And as I tried to indicate in my remarks or updates of what our program is doing at CDC, we've been interacting a lot with the response teams that are involved. And while it does sound like the two scientists said something very different, I think that they're closer in their thought process than it appears. And I think the truth of the matter is we want to be very sure to document what is going on in each of—this outbreak has been so kind of unprecedented in its demands on healthcare and public health and everybody that everyone is learning new things every day, and we want to be sure that we document exactly what is going on with these patients. And each patient has a whole complex array of things that could be going on. And that's what Dr. Brooks was talking about in terms of, you know, direct organ damage from the viral infection, like lung scarring or infarcts from the thrombotic events. At the same time, the patient reports and the symptoms that are in the medical record have striking similarities to ME/CFS. And those of us working with ME/CFS definitely see the parallel and want to work with the scientists and the physicians

that are caring for these patients and studying these patients to be sure that we get the data that we need to demonstrate similarities and possible differences between patients that we're seeing as long COVID patients—for lack of a better term at this point—and those that we recognize as ME/CFS. It won't be surprising if there are some differences because most of the ME/CFS patients we see we know have been ill many, many years. And so we feel like this unfortunate pandemic is giving us a whole group of patients that were affected kind of acutely, and now we're able to see early on which—what are the factors that predispose to going on to this picture of ME/CFS-like illness? So I hope that answers your question. We are dialoguing with NIH regularly, and WHO, and each other, and working to be as clear as we can in our communication.

Christine Pearson: All right, so for the next question, “in your opinion, for disability application purposes, is the one-day CPET test going to be sufficient rather than two-day invasive a test given your results?"

Dr. Dane Cook: No. I think the two-day is—unfortunately, for the person with ME/CFS—is the better test for disability. If you can document that someone cannot reproduce the same aerobic capacity, or that their ventilatory threshold changes and that they can go from above a disability rating for their exercise performance to below one, that's very valuable information.

Dr. Elizabeth Unger: Yeah. And I would just like to emphasize that two days—not everybody needs a two-day CPET test to document their disability.

Dr. Dane Cook: That's correct as well.

Dr. Elizabeth Unger: Social security has been trying to work with the community to be sure that their physicians are educated about ME/CFS and ways to document the illness. So just wanted to add that.

Christine Pearson: All right. "Knowing how damaging exercise is for ME/CFS patients, have you followed up with participants to identify longer-term effects from testing on controls and participants?"

Dr. Dane Cook: I'll speak for my research first. Every exercise test I've ever conducted in ME/CFS we've followed up with participants. We always do. And it's usually part of our study is the follow-up aspect of it. I know the MCAM had multiple days post the exercise tests, but I'll let Dr. Unger speak to the follow-up for participants here.

Dr. Elizabeth Unger: Yes, that's correct. We did have what we call a visual analog scale for patients or participants to record their symptoms. We also—and we didn't really talk about this yet; we're still analyzing the data—had done

cognition testing. And so we do have follow-up information. But in addition, we got information from the clinicians caring for these patients that some were really ill for months. And so we retrospectively went back to try to collect information to figure out how often that kind of illness resulted. So we're in the process of seeing how much of that information you can get. But we at least have a short-term data on illness exacerbation, or worsening, as a result of the testing.

Christine Pearson: All right, so for the next question, it says: "I'm glad to hear there are multiple manuscripts being prepared by CDC. I think there were blood draws during exercise as part of the MCAM exercise sub-study. Are those findings part of the manuscript CDC is preparing for submission?"

Dr. Elizabeth Unger: Yes, there were blood draws. And other than that just the lactate—which was a finger stick which will be part of, I think, Dr. Cook's manuscript—the other samples are not being included. We have not analyzed those yet.

Christine Pearson: So, Dr. Cook, feel free to tell me if this was already asked and answered. I'm trying to make sure we get these handled.

Dr. Dane Cook: Sometimes redundancy is good.

Christine Pearson: Okay. So, this one says: "What are your thoughts on second and/or third CPET to confirm diagnosis and/or treating someone with ME/CFS?"

Dr. Dane Cook: Well, as has been pointed out by many, it's—the exercise testing research is a double-edged sword. It's necessary, and we've discovered really important things with it, but it's also a huge burden. I can't imagine a three day, nor do—nor would I—I'm not sure how ethical a three day would be to conduct. The two day, I think we need—I think that there's now quite a bit of data. There was last year a recent—a meta-analysis showing that the aggregate changes were significant and meaningful in terms of a decline in aerobic capacity from day 1 to day 2. And really, the exercise test that is conducted is driven largely by the research question. So if you want to understand whether or not capacity changes from one test to another, you have to do a two-day test. If you want to determine whether or not the—being able to specify from the data who has ME/CFS and who is control, the—there is an increase in specificity from day 1 to day 2 on the serial tests. But if you want to challenge a physiological system and look for pathophysiological responses, oftentimes you only need a single test. And we've done—we've done multiple studies where we've found brain abnormalities, brain function abnormalities with—and cognitive function abnormalities, and symptomatic responses to a single exercise test. And it has really uncovered some really interesting physiological differences

between ME/CFS patients—those with ME/CFS and controls. So it's really driven by the research question.

Christine Pearson: Okay. I think this is sort of a follow-up, which was asking if it was a one-day. But then it says: "If so, doesn't this underestimate the exercise capacity problem?"

Dr. Dane Cook: Yes. And this is why this study is not just an exercise capacity study. What this is, is what is the dynamic cardiopulmonary response to an exercise test in ME/CFS? Which has not been looked at in this way or in this depth ever. So, these are really novel data that we hope will, you know, be viewed by, you know, physicians so they could understand that it's—that this is different. But you need to understand this cardiopulmonary response if you're going to incorporate any time—any type of physical activity into the lifestyle of someone who has this disease.

Christine Pearson: So, this one says: "This is probably a very basic question, but it's a mental block of sorts for me. I am able to exercise, but I know I will pay a price thanks to PEM if I go beyond a minimal amount. How does this habit figure into the findings from your research?"

Dr. Dane Cook: So that's a fantastic question. So, there's two parts to this. One is we're very interested in looking at the post-exertional malaise response to the maximal test, but that we're also conducting research where we're looking at the dose response of exercise with post-exertional malaise. Looking at whether or not there is a general threshold—we know there's going to be a lot of individual variability to this based on disease severity, based on what people's capacities are. But that is a huge gap in our knowledge of post-exertional malaise, is the dose of activity, whether this be mental activity, whether this be physical activity, that is both necessary and sufficient to trigger post-exertional malaise. There are studies out there showing that even minimal, walking 1 mile an hour for, you know, a low number of minutes can exacerbate symptoms. So we need to see if that's true for the majority of ME/CFS or is this—is this the most severe? There are a lot of unanswered questions to this that we're actively looking at right now.

Christine Pearson: Okay. So the next question is, is: "How can my local doctor not familiar with this disease receive a copy of Dr. Cook's report?" I would assume they mean post publication.

Dr. Dane Cook: Well, post publication, I'd be happy to send it to them. Pre-publication, you have to talk to Dr. Unger about that one.

Dr. Elizabeth Unger: Well, and this—these slides will be—I mean, not the slides, the webinar will be available online shortly after. I mean, at some point. Christine, you can correct me on when it will be available. So that's another place you could forward it to your—forward a link to your healthcare provider.

Christine Pearson: Yes. We will be—as soon as this is over, they'll start the process of processing it, and we will work on getting it posted just as soon as we can. So, you may want to check back on our ME/CFS website. Okay, so—so the next question: "Is there any similar exercise data that compares ME/CFS patients to patients that have POTS autonomic dysfunction without ME/CFS?"

Dr. Dane Cook: Ooh, I'm trying to think if Peter Rowe has ever published any of that data. I am uncertain of that. I'm sorry. Off the top of my head, I don't know if there are direct comparisons of that particular combination, looking at whether or not someone has POTS and no ME/CFS, ME/CFS plus POTS, ME/CFS without. I'm going to—I'm going to say probably not.

Christine Pearson: So, the next question is: "Do you know anyone who has died from this disease?"

Dr. Dane Cook: Me personally?

Christine Pearson: I don't know if that is the intention.

Dr. Dane Cook: No. I don't know anyone personally that was—that I had a friend or acquaintance relationship with. I do know that we've—we have honored those when I was part of the working group. But no, no one that I was personally related to, or personally—friends with.

Christine Pearson: Okay. So, the next question is: "Is there an actual ME versus CFS medically accepted distinction? This is not my understanding as a well-read patient. This only adds to the confusion."

Dr. Dane Cook: Let me just wholeheartedly agree with the end of that. Adds to the confusion. There are case definitions for CFS, ME/CFS, ME. There are multiple case definitions. And just—I'll just add for my own perspective, we gather as much information as we can on each participant in our studies so we know what diagnostic criteria they meet, including the ILM criteria as well. So, there are multiple criteria out there. They have definitely—that has contributed to some of the confusion. Our approach has been to measure as much as we possibly can.

Dr. Elizabeth Unger: Yes. And I guess I will echo that as well. So that we have really emphasized the use of questionnaires for each of the domains of ME/CFS.

We've collaborated with the international community to create common data elements that are available on the NINDS common data elements webpage that are specific for ME/CFS. And we feel that there are likely more than one condition, which is—gets to the STOP study, where we're trying to optimize protocols to identify subgroups, and that have biologic basis that we can start targeting therapies for. So we agree that this is not an ideal situation to be in. From a clinical point of view and discussions with our clinicians, they are using sort of what they find works for them. It's usually kind of a combination of a couple of case definitions. And then they are all requiring the care of really good clinicians that are able to evaluate all the potential differential diagnoses that need to be considered.

Christine Pearson: So the next one says: "As you know, a percentage of patients report chronic health problems following a bout of COVID-19, and many now fit an ME/CFS diagnosis and/or may have become permanently disabled. Does the CDC have plans to proactively educate the public about this additional life-altering possibility and/or use this information to further encourage vaccination among the hesitant?"

Dr. Elizabeth Unger: I don't know about the vaccination question. But I do know that CDC's been working on webpages about the long COVID and is working on some guidelines for clinicians about caring for patients with post-COVID conditions.

Christine Pearson: And I think I know—I don't think we have the answer to this, but I will go ahead and ask it, which is: "What is the timeline for testing long COVID patients?" I'm not clear if that's addressed to you, Dr. Cook, or to you, Dr. Unger.

Dr. Elizabeth Unger: And I'm not sure what—sorry, what testing might be. These studies are—that are collecting data have started, and then the studies that I mentioned that are going to be collecting biospecimens will be not happening this fiscal year, for sure. They'll be a little bit later.

Dr. Dane Cook: For us, the exercise testing, we hope to begin this in the summer.

Christine Pearson: Okay. It's a little bit long, but: "I agree. Exercise should not be recommended for this at this time. But for future research," quote, "any type of exercise, I find there's different tolerance if I exercise while flat or with certain braces, like neck brace. Have you reviewed different postural positions during exercise with regard to exercise impacts? And what about passive muscle fascia stimulation, like massage or other modalities?"

Dr. Elizabeth Unger: Yes. We don't have studies directly on those. But as on our webpage, we report that many patients find that massage therapy can be—can help them with their symptom management. We are also aware that the position

during exercise can be very impactful, particularly for those patients that have any component of a POTS, so lying flat can be very helpful. And we've been in discussion with clinicians that are caring for patients and they have been emphasizing that individualized response is very, very important. So that would be—that would include positions of exercise, and all of these options, so thank you.

Christine Pearson: So the next question is: "Where can I find the new," oh, "the new ME/CFS patient website?" I will provide that URL, and then I'll just—in the Chat—in the Q&A box.

Dr. Elizabeth Unger: And I should just say, it's not a whole new webpage. It's new sections.

Christine Pearson: Yes. Yes. It's a toolkit of a number of different things that people can use for different things. So, I will hit that so everyone can see that. All right, so then I think we're getting close to time, but I think we can do one or two more. "Is there any push to get medical schools to train on ME/CFS information, as it still not taught in most medical schools? And new clinicians are coming into practice every day who are harming patients with their lack of knowledge from the start."

Dr. Elizabeth Unger: Yes, this is—this is a problem. We are aware of it. That's one reason why we included the special new section targeting—or trying to get—the interest of medical students. And we will continue to work on this issue.

Christine Pearson: Let's see. Okay. "What kind of challenges does the CDC foresee with regard to introducing clinical definitions and protocols to clinicians to promote ME/CFS awareness?"

Dr. Elizabeth Unger: Well, you know, the challenge that we've had up until now, I would say, is relies around—lies around getting clinicians to listen to us. And I would say that one of the biggest differences that I have myself experienced is that, all of a sudden, clinicians are starting to be interested because they're seeing so many patients that—as a result of the COVID pandemic resemble ME/CFS, and they're starting to realize they need a way to learn how to manage these patients. So, I think we'll have an easier time, that we are really looking forward to the start of our broad agency announcement, which is all about therapy and evaluating therapy and has an educational component built into it. And by that, I mean we have asked that the—that the contractor include a way to disseminate their findings. And so that would be clinicians speaking to other clinicians, and so that's another way to increase the outreach.

Christine Pearson: Okay. Well, thank you all. So that brings us to the close of our call today. Thank you, Dr. Cook, again, for joining us.

Dr. Dane Cook: Thank you for having me.

Christine Pearson: I was glad to see that you—that there were a lot of questions for you. I think that always speaks to people being very interested in your presentation, so appreciate that. Thanks, everybody, for your time and interest. We will be getting a video recording and the transcript just as soon as we can posted on the CDC website. And we hope that you'll join us again for the next call, which is currently planned for the fall of this year, 2021. Thanks, all.

[END OF TRANSCRIPT]