

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder and Communication Conference Call

September 16, 2019

3:00 pm EDT

Coordinator:

Good afternoon and thank you all for standing by. At this time I would like to inform all participants that your lines have been placed on a listen-only mode for the duration of today's presentation. I would now also like to inform participants that today's call is being recorded. If anyone does have any objections you may disconnect at this time. And I would now like to turn the call over to Ms. Dana Brimmer. Thank you. You may begin.

Dr. Dana Brimmer:

Thank you. Good afternoon everyone. My name is Dana Brimmer and I'm a contractor working for the ME/CFS Program at the Centers for Disease Control & Prevention (CDC).

On behalf of the program I'm pleased to welcome you to today's Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, ME/CFS, Stakeholder Engagement and Communication Conference Call, known as the SEC Call. Our primary purpose here is to share information with a large number of people with interest in ME/CFS as part of our regular outreach and communication activities. Before we get started I want to review how the SEC call works.

As a reminder there's no need to register or RSVP for the call. Participants can still dial in using the 800 number and use the participant code provided in the SEC announcement email. Or the one found on the ME/CFS CDC Web site. To participate using the webinar format click on the link that can also be found on the SEC announcement or the CDC ME/CFS web site. Please note that if you do participate using the webinar format you may need to use headphones plugged into your computer to hear the audio portion. Or use both the 800 number audio-only and the webinar to see the slides of the presenter.

Notification of calls will be sent by email and information is also posted on the CDC ME/CFS Web site. Due to the large number of call participants we are unable to have call lines available in speak mode. We will take questions via email using the ME/CFS SEC call email system. Please note that this email address is used only for these calls and not monitored at other times. Please note due to time constraints CDC staff and the guest speaker may not be able to answer all questions that are submitted. But please be assured that those of us in the CDC ME/CFS program read all of your questions and comments.

Our guest presentation today is entitled The Biology of ME/CFS the Emerging Model by Dr. Anthony Komaroff. Before Dr. Komaroff begins lets first here from Dr. Unger Chief of the Chronic Viral and Diseases Branch. She will provide updates about CDC's ME/CFS program.

After Dr. Unger and our guest speaker finish we will answer questions submitted via email. I will first read the questions out loud and then our speakers will answer them. Before we begin I need to share a disclaimer that these calls are open to the public and please exercise discretion in sharing sensitive content and material, as confidentiality during these calls or items submitted via email cannot be guaranteed. Today's call is being recorded by CDC and transcripts will be available at a later date on the CDC ME/CFS web site. The views of non-CDC presenters expressed during this conference call are their own and do not necessarily represent the views of the U.S. Department of

Health and Human Services or the Centers for Disease Control and Prevention. I'd now like to ask Dr. Unger to begin her remarks. Welcome Dr. Unger.

Dr. Unger:

Thank you Dr. Brimmer. And welcome to everybody. It's hard to believe but we've been having these calls since August 2012. Our first call speaker was Dr. Leonard Jason. We began these calls to have a forum for regular communication and engagement with the ME/CFS community about CDC's activities and as well as a way for the community to hear from external experts about their ME/CFS related work. While we've used the same basic agenda, we have made changes to improve the usability of these calls. Starting in 2017, transcripts of each call were prepared for the CDC ME/CFS web site and in some cases we are able to provide an audio file as well.

In 2018 we gave the presenters the option of using a Webinar format allowing them to share slides with the audience. The next addition will be to move to a format that allows participants to ask questions through the call line. We've heard from many of you that this is very important. The live call in format for the question and answer session will be part of our next call. The information shared by our outside speakers is very important and we are extremely appreciative of our speakers willingness to accept our invitation to participate.

Our outside speakers are volunteers who independently prepare their remarks. If you have questions for speakers and or topics for future calls, please send them to the SEC call email address and that is ME/CFSSEC@cdc.gov. This is the also the address to use if you'd like to be added to the list serve to receive email notification about upcoming calls.

I'll now shift to give you an update on some of CDC's educational activities. As mentioned before, our current continuing education is the Medscape Continuing Education spotlight course entitled "Diagnosing ME/CFS: The Experts Weigh In," was first made available February 25, 2019. It will be available through February 2020 and

we plan to extend its credit for another year after that, February 2021. About 6500 learners accessed the course within the first 5 months. Over 2200 of these learners took the test with a 98% pass rate. We've been happy to see this many learners and that they are getting accurate information about ME/CFS that they can use in their work.

We've asked several medical professional organizations to help promote this course as well as posting information on our ME/CFS Web site. The Georgia Chapter of the American Academy of Pediatrics, the National Associations of School Nurses, and the Association of American Medical Colleges are sharing this information with their members through their list serves and networks. We're hoping this additional promotion will allow our course and website to reach a broader audience.

We are also working with Medscape to prepare two additional ME/CFS continuing education courses. One will be a clinical practice assessment course. This course will use a series of 20 questions to assess the clinician's attitudes, knowledge, and competence in diagnosing and managing patients with ME/CFS. ME/CFS Expert Clinician Dr. Nancy Klimas is serving as the Lead Faculty Member for the Clinical Practice Course and is supported by a Medscape physician and a medical writer from the Medscape team.

The other course will use the test and teach method. Two patient case scenarios are presented with interactive questions that test knowledge on a topic, followed by discussion of the main teaching point. The areas include medication management and comorbidity such as sleep disorders and depression and POTS (Postural Orthostatic Tachycardia Syndrome). Dr. Stephen Gluckman from the University Of Pennsylvania is the lead faculty member for this course.

The Medscape team conducted its kick-off meetings with Doctors Klimas and Gluckman in July. Educational content has been guided by the faculty as well as by topics suggested by test takers of the spotlight course. While timing is not certain we are expecting the Clinical Practice Assessment Course will be available by the end of

December. We will use course takers feedback to refine the test and teach module. And we will continue to update you on the status of these two courses in future calls.

Now I will shift to updates on the Multi-Site Clinical Assessment of ME/CFS Study, also referred to as MCAM. The MCAM study at the original 7 clinics included participant follow-up and allowed new enrollment during the follow-up periods. With new enrollment largely focusing on people with ME/CFS who are homebound or who had a recent onset of ME/CFS.

We understand that it seems as though it's taking a long time to get information published. However we believe that the longitudinal information is particularly useful in understanding the course of disease. The unfortunate downside of doing this is that it takes longer for us to have the data to analyze. We do have some good new though. We have closed out the enrollment for adults with ME/CFS in healthy controls from the 7 original clinical sites. We are still working on obtaining and cleaning data but have been able to analyze preliminary data from these early stages.

We have presented some of this at the 9th Biomedical Research into ME Colloquium held in London at the end of May 2019. The most recent publication using MCAM data is available online in the Journal Quality of Life Research. It's called Psychometric Properties of the Promised Fatigued Short Form 7A among adults with ME/CFS.

The study findings support the reliability and validity of the Promised Fatigue Short Form as the measure of fatigue experienced by patients with ME/CFS. This information will be used by our collaborators to submit the instrument through FDA's drug development tool to qualify it as a measure of therapeutic effect in ME/CFS clinical trials. We have a number of other manuscripts in the work.

Our description of ME/CFS illness, characteristics based on many of the new common data elements is being prepared for publication. The exercise in cognition have been shared with our expert collaborators Doctors Dane Cook and Gudrun Lange who will be

leading the analysis and publication of these findings. And the results of the NK cell function testing on a sub-set of MCAM participants will be ready for analysis by the end of the year.

We have plans for additional publications that will provide validation of a questionnaire, measuring fatigue, and comparing different approaches to measuring post-exertional malaise. We expect to have 4 to 6 manuscripts ready to submit to journals by the end of 2020. As we discussed, we have extended the MCAM study protocol to additional clinics to supplement the numbers of children and adolescents with ME/CFS enrolled as well as adults with other illnesses that share features with ME/CFS, such as Rheumatoid Arthritis, Multiple Scoliosis, and post cancer fatigue. We are still enrolling people in these two categories.

The base-line data collection of both of these study groups is expected to continue another year. And then we will proceed with follow-up data collection for another year. For children and adolescents with ME/CFS the clinicians that have been contributing data are Doctors Lucinda Bateman, Nancy Klimas, Andy Kogelnik, Patricia Delamora, and Amy Smith Nurse Practitioner. While Dr. Peter Rowe was unable to participate through enrolling his patients, he is supportive of the study and has agreed to consult with us. Based on his advice we've submitted an amendment to the IRB protocol to add a few measures.

The pediatric part of the MCAM study uses a similar standardized approach as was used in the adult MCAM study but with more age appropriate questionnaires. The physical examination includes the NASA lean test as well as the Brighton Score for joint hyper mobility.

Through Dr. Rowe's introduction our contractor is now seeking Dr. Jullian Stewart's participation in the pediatric data collection. While it will take a while to sort out the logistics and local IRB approval, Dr. Stewart has indicated his interest. We are looking forward to moving, advancing work in all of these areas of the MCAM study and to

sharing what we found as soon as we possibly can. This concludes CDC's updates. And thank you very much for your attention and participation. At this point I'd like to turn the call over to Dr. Brimmer so she can introduce our guest speaker.

Dr. Dana Brimmer:

Thank you so much Dr. Unger. Dr. Anthony Komaroff is the Simcox/Clifford/Higby Professor of Medicine at Harvard Medical School and Senior Physician at Brigham and Woman's Hospital. In the past he's served as the Chief of General Internal Medicine at Brigham and Woman's Hospital, the head of Harvard Health Publishing, the arm of Harvard Medical School responsible for all of the books, and newsletters, and Internet content for the general public, and is the founding editor of New England Journal of Medicine Journal Watch General Medicine a publication that keeps practicing doctors informed about the latest biomedical research. For 35 years as both a practicing doctor and researcher, Dr. Komaroff has dedicated himself to the problem of ME/CFS. We asked him to talk today about the "Biology of ME/CFS: Emerging Models." Welcome Dr. Komaroff.

Dr. Anthony Komaroff:

Thank you so much Dr. Brimmer. Let me know if you hear an echo. I wanted today to go over a large body of data and so it may go a little fast but I think I'll show you the information that is most important on each slide. We've known about this illness for more than one hundred years. But interesting it began ramping up a lot in the mid 1980's.

Back then what did we know? Practically nothing. We knew it was illness that was defined by symptoms. But it had no consistent objective abnormalities. No physical exam abnormalities. No diagnostic tests. No proven treatment. No information on prognosis. No evidence of underlying biologic abnormalities. In other words there was very little we knew about it and some people even wondered if it was a real disease.

Where are we now today in 2019? We know a lot more. Literally 1000's of published studies have compared people with this illness to healthy individuals of the same age and sex. And sometimes to people with diseases - other kinds of diseases that are characterized by fatigue. We know the following: there are many things objectively wrong in the brain, the central nervous system and in the autonomic nervous system, which is the part of the brain, and the central nervous system that controls vital functions of the body, like heart rate and body temperature. We know that there is something wrong with metabolism, particularly energy metabolism. That there is certainly wrong with both the cells, the cellular phenotype and the function of the immune system cells.

And there is growing evidence -- I wouldn't call it solid yet -- that the microbiome which we'll come back to is also abnormal. Neurologic changes. There are many, many studies of the brain, central nervous system and they fall into different categories. The endocrine system of the brain - the brain makes hormones that spread through the blood stream and affect all parts of the body. It's different in people with ME/CFS than in healthy people. Thinking, cognition, that's also different. Particularly information process speed, memory, and attention. The automatic nervous system that I mentioned a minute ago has two arms: the sympathetic and the parasympathetic arm. And both of those are not quite right.

MRI is the technique for imaging the brain. And there are many kinds of MRI's. All kinds of MRI that have been used to study ME/CFS have found abnormalities, a few of which we'll summarize. Spec scanning is another way of imaging the brain. So is PET scanning. And again all of these modalities when they've been used have found abnormalities in the brain.

And then finally EEG or brainwave abnormalities also have been found. Brain activation when it's challenged is now something that we can study in the living human brain with a technique called functional MRI. Look at the top row if you can see it [see slide 7]. These folks on the top row are the patients with ME/CFS being compared to healthy

individuals of the same age and sex in the bottom row, when all of these people are asked to do a particular test of thinking called the Stroop test. As you can see in the patients with ME/CFS a lot more areas light up in the brain than is true in the normal control subjects in the bottom row. What does that mean? It means that the brain has to work a lot harder in patients with ME/CFS's to do the cognitive test in comparison with the healthy individuals.

Another way of looking at the brain is MR Spectroscopy. This is a study recently published that - from Dr. Jarred Younger's team. And they found in people with ME/CFS abnormalities in several markers in several different brain regions. The metabolic marker levels that they measured and found abnormal correlated with the severity of fatigue, which increases the likelihood that those metabolic abnormalities actually had something to do with the symptoms of the illness.

The most prominent abnormalities that they found were an increased ratio of two molecules choline and creatinine, and in particular an increase lactate. Lactate has found to be increased in many other studies. But this was the most recent confirmation of it. And we'll come back to what that might mean in a little bit.

What about the metabolic changes that I mentioned. Here's a little background. Our bodies work and we remain alive because of a complicated group of thousands of different molecules or natural chemicals. In recent years it has become possible to measure the level of hundreds, even thousands of molecules in one small drop of blood or other body fluid. All of a sudden instead of doing tests for one - just one molecule, you can look at what's happening at hundreds or thousands at a time. And study how they might be interacting with each other. This is a powerful new tool.

Several things have emerged from what are called these metabolomic studies. The first is that energy production, ATP production is impaired. ATP is the energy molecule. It's the source of energy ourselves need to function. The cells of our body not only use ATP

and need it to function but they also make ATP. And make it from oxygen, sugar, fats, and amino acids.

There's growing evidence that in people with ME/CFS, people who say they don't have enough energy that their cells actually have a problem making energy, making ATP and using it efficiently. When this idea was first proposed about 15 years ago I and others thought it was pretty simplistic and unlikely. I'm here today to say we were wrong. It looks increasingly likely to me.

The second general abnormality, not quite so solidly established, is hypo metabolism that is an under production of a lot of molecules that all of us have in our body. And the third level that I won't talk about today is called oxidated stress, nitrogen stress. Here's the energy production, just one of hundreds of papers [slide 10]. It's complicated but the main point is under two different conditions, cells in patients with ME/CFS in the two conditions make less energy than in the cells of healthy people.

Immunologic changes. There are a whole bunch of different immunologic changes that have been found over the course of 30 years now. One is difference in the numbers of different types of white blood cells, and I'm going to go into some detail on that. There are abnormal levels of, well increased levels, of circulating levels of immune complexes. These are little packages of antibodies bound to antigens. All of us have some of them in very low levels but they're much higher levels in people with this illness.

People with the illness also have increased levels of immunoglobulin G, and decreased levels of certain immunoglobulin G subsets. Multiple studies show they have increased numbers of cytotoxic T-cells. These are T-cells that attack foreign things. The natural killer cells, another cell that defends us are not functioning as well as they are in normal people, as if they've been exhausted by some kind of chronic war that they're fighting. And then finally, many studies have found increase blood levels and increase lymphocyte production of what are called pro-inflammatory cytokine.

What are cytokines? Cytokines are chemical signals. When the immune system is activated, when it goes to war against something it's like an army. The generals need to send orders to the lower ranking officers, and the officers need to send signals to the troops, these orders are sent by chemical signals called cytokines. Blood levels of many cytokines are significantly higher in ME/CFS patients than in healthy control subjects, particularly in the first three years of illness but not after. Levels of many cytokines in the spinal fluid also distinguish patients from ME/CFS from healthy controls. And then finally, levels of many circulating cytokines correlate positively with the severity of the symptoms. So again, the fact that an abnormality that you can measure correlates with how severely ill people are, suggests that the abnormality you're measuring really does have something to do with the suffering of the illness. And it's worth knowing more about.

The microbiome. Over the past ten years evidence has emerged that the human microbiome may affect the risk of many human diseases and ME/CFS may be just one example. So what is the exact - microbiome and how could it affect the risk of ME/CFS. The human microbiome, of all of the micro-organisms that live inside us and on us there are trillions of them with each of us. We've known that there were a lot of them for a long time. But we only have discovered recently is that they collectively have one hundred times more genes than we do. They are in effect the second human genome.

More than just the huge number of genes they have, many of these genes of these microorganisms produce molecules that affect us - that affect human physiology. They make hormones, they make neurotransmitters, they make molecules of inflammation. They make molecules that stifle inflammation. And when there's inflammation for instance in the gut, it causes the gut to become leaky. And bacteria and toxins produced by bacteria leak into the blood stream where they're not supposed to be. Here's an example studied several years ago of what happens to ME/CFS patients when they exercise shown in the blue line compared with health individuals [slide 16]. As you can see after exercise in the ME/CFS patients the levels of bacteria in the blood go up

whereas they don't go up in the healthy controls because apparently the gut is leaky in patients with ME/CFS.

Post exertional malaise. We've known for 35 years that people with ME/CFS have an unusual symptom that not's seen in a lot of other diseases which is a flare of their illness following physical exertion, cognitive exertion, but we haven't known really what caused that. Here's an example of what physical exertion and cognitive exertion do to the ability to think in patients with ME/CFS and in healthy control subjects. This is a complicated slide [slide 18]. Hope I can take you through it. I'm looking for a curser here and it seems to have disappeared. Okay I'm going to walk you through with word. On the left side of this slide there are three groups. And then on the right side there are three groups. And each group has a red bar and a grey bar.

The red bars are ME/CFS patients, the gray bars are healthy controls. What the bars are measuring is the number of errors made on a test of cognition. The left three tests were all done before exercise. And the right three tests after exercise. What do you see? In the healthy people, the gray bars, each time they take the test before they exercise they make fewer and fewer errors. And after they exercise they still make fewer errors. And you'd expect normal people to make fewer efforts - errors because they're taking the same test repeatedly and they're getting better at it.

But what are you seeing in the ME/CFS patients? Here the errors go up even before exercise and after exercise continue to go up. A dramatic difference both in the effect of cognitive challenge as well as physical exercise challenge on how well people with this illness think. And here's how their brains are working [slide 19]. This is complicated but this study from Dr. Dane Cook shows that in ME/CFS patients, like I showed you earlier, the brain following exercise taking these cognitive tests is just working harder displayed in red compared with the patients who are our healthy controls where the blue areas are parts of the brain which are actually working less hard as time goes on.

So how do you put this all together on saying that there now reproducibly documented abnormalities involving the brain or central nervous system as well as the autonomic nervous system? Abnormalities of metabolism, of white blood cells in the immune system, and of the microbiome.

But the outstanding question is why? What ties them all together? Which leads to which? Which comes first? We're just beginning to get a handle on that very important question. And there are four alternative models that have been proposed. Because they're well established models in health and disease not only of humans but of all animals. And they may way apply to ME/CFS.

The first is the sickness behavior model. So what is that? We all know what we feel like when we get sick. Like for instance you get the flu. One phrase that we often use when we get the flu is "I feel like a sick puppy." Why do we use that phrase? Well because we've seen our pets get sick. And we've seen how they look and how they act. And they seem to look and act like we know we feel when we get sick. You look like a sick puppy. You feel like a sick puppy. Why? Why does that happen? We now know over the last 20 years that sickness behavior is something that's hardwired into all of us. You even see it in insects. And you certainly see it in every mammal like us. What is it? It has a biological purpose.

Our brain sends out signal that cause us to shut down a whole bunch of activities that eat up energy. And it does that by telling us to be lethargic and sleepy. To not spend a lot of time with friends in a social communication. It makes us achy which causes us not to want to move around a lot. It makes us sleepy. We lose our sex drive. Difficulty thinking gets us depressed. Lose our appetites. Appetites and digestion takes energy. All these things conserve energy so that our body has the energy fight whatever is making us sick. It's a biological protected response. It makes all sort of sense.

The question is could it be that this supposedly temporary response does get stuck. Doesn't get turned off properly in people with ME/CFS. Does it become chronic? What

causes sickness behavior? There's plenty of evidence in animals, and some in man, in humans, that neuron inflammation is at the root of sickness behavior. Somewhere in the brain, here is a picture of the basal ganglia [slide 26]. But there are several areas of the brain that at least in animals have been fingered as groups of neurons, brain cells that direct the sickness response. What signals those brain cells to tell a body to behave sick? Inflammation or activation of the brain's innate immune system is the prime thing that signals the sickness response.

The cytokines that I mentioned a minute ago, when they're produced in the brain signal the fatigue nucleus to do all of those things that we do when we feel sick. What triggers or activates the brain immune system? Could be an infection of the brain.

It could in other people be auto antibodies that stimulate the fatigued nucleus. Could be toxins, obesity somehow to ways we don't yet understand activate brains immune system. Chronic stress does. Increased levels of a molecule called leptin.

There are a bunch of things that trigger the nucleus in the brain that causes the sickness response. What we've learned it's not surprising that something like an infection or a toxin that gets into the brain directly could cause this. But what we've learned is that infection or inflammation elsewhere in the body, outside of the brain, can also do this.

This is fairly new information over the last 15 to 20 years. We know that - we've learned that a part of the body called the blood brain barrier which normally is a wall that prevents inflammation molecules from getting from the blood into the brain, that that barrier becomes leaky or porous. And allows the entry of immune cells, molecules, even microorganisms, tiny microorganisms.

The other thing that we've learned is that when there's inflammation somewhere else in the body, like in the gut, it sends signals up the nerve of the body that come out of the brain. It seems them backwards. Up the nerve - the vagus nerve being the main one up into the brain.

And the result of that is that the immune system of the brain gets turned on. In other words when there's inflammation in the gut, it sends signals to the brain that turn on and activate the immune system in the brain. So you can have nothing directly wrong with the brain but it could affect the brain.

What triggers neuro-inflammation? I've just gone through a few examples. The micro biome is one that has grown in increasing attention in this illness. Several studies now have reported that bacteria that tend to make pro-inflammatory molecules, so bacteria that tends to encourage inflammation in the gut are increased in people are increased in people with ME/CFS.

And bacteria that normally tend to discourage inflammation are reduced. So you've got one pedal on the accelerator. And the pedal that's not on the brakes. And so you have more inflammation in the gut. And that sends signals to the brain the hypothesis is. It also - the inflammation in the gut make the gut be a little leaky. This is a complex side.

I'm only going to talk about a part of it. This is the study from Dr. Hanson's Center - Maureen Hanson. She looked at a toxin made by bacteria called LPS. And she found that it was present in much higher levels in patients with ME/CFS than in healthy control subjects. And the same was true with two other molecules that are related.

Depressed metabolism. I said that the several of the metabolic studies show a depressed metabolism. This is like what you see in animals that are hibernated. And it's like what I talked about with sickness behavior in a way. Because why do bears hibernate in the winter? They hibernate because it's hard for them to get the food that they need. And therefore they need to conserve their energy in order to remain alive. And so they just go to sleep. They don't move much. They don't do much. They don't digest much. They - that would use energy. And they need the energy for other vital functions.

Worms also enter a state like hibernation. It's called dauer. That's important only because one worm in particular has been used to learn a lot about things that go wrong on - in humans. Maybe disheartening to learn that that humans are like worms in a lot of respects but we are. And therefore we have a lot to learn from it. In both states -- hibernation in bears and other animals or dauer in worms -- there are a series of things that are found. And I've showed them on this slide [slide 36]. I'm not going to go into the detail. But the point is that all of these things have also been seen in people with ME/CFS. That doesn't prove that people with ME/CFS are in a form of hibernation. But it's consistent with that possibility. And it indicates to me at least that we need to study this phenomenon more.

Can our different models be united? Well sickness behavior caused by neuro inflammation - ancient biological mechanisms that preserve energy in order to prevent or heal injury but there's a price to be paid. Temporarily impaired function anything that's not absolutely essential is shut down or greatly reduced to preserve the energy for healing. The micro biome might be causing inflammation and injury in some patients. And the micro biome also has been - is increasingly being shown to be involved in hibernation and even dauer.

Do the symptoms of ME/CFS result from activation of these ancient mechanisms? If they do we're beginning to learn a little bit about how animals turn on and turn off these mechanisms, these hibernation type behaviors. And as we learn more about that it raises the possibility that we'll be able to turn off this protective response that's stuck in people with ME/CFS.

Again let me be clear these are hypotheses. They are not proven but I'm saying that in my opinion there is now enough evidence accumulating from enough very serious scientific labs that they are deserving of the attention of a lot of other serious scientific labs. So in summary there's robust evidence of underlying biological abnormalities in people with ME/CFS.

These abnormalities have considerable overlap with several well documented models of disease. And more needs to be done to solidify and expand our understanding of each these abnormalities and with their relationship with each other and all of the triggers that set them in motion. So that's my quick fly over summary.

And I hope it's been comprehensible and I'm happy to answer any questions. Thanks very much.

[Dr. Dana Brimmer:](#)

Thanks Dr. Komaroff. We will go ahead and start with you for questions.

The first question is "Hello I am a 45-year old patient in Seattle with Fibromyalgia and Chronic Fatigue. Recently I took a broad panel of blood tests and was surprised to test a false positive to the RPR Quant Test, normally used for syphilis. I subsequently took the TPPA test which confirmed I do not have syphilis. My question is whether ME/CFS researchers are aware of a false positive tie to the RPR Quant Test. Could this be used to aid in diagnosis or treatment?"

[Dr. Anthony Komaroff:](#)

Well listen, first of all I'm very glad that you turned out not to have syphilis. You're right that there are many illnesses in which false positive syphilis tests are seen. In my experience I have seen this in people with ME/CFS. It's not very common but on the other hand we don't really know how common it is because syphilis tests are not done routinely in people with ME/CFS. Why is it? Well there's one other illness in which it's fairly often seen.

And that's acute infectious mononucleosis or mono. In mono the antibody producing cells, the p cells - plasma cells, are making all sorts of wild amounts of antibodies for a period of time. And the anti-syphilis antibodies are just one of them. Some people with ME/CFS have this - a similar thing to what you see in Mono where they have more B

cells than plasma cells making a wider variety of antibodies. At least there's several studies that suggest that. So that may be the explanation.

Dr. Dana Brimmer:

Okay thank you. A second question. "Thank you for your excellent widely read article, "Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome," in the Journal of the Medical Association publication 2019. Do you plan additional clear and concise articles and/or talks which educate, raise awareness, and counter bias like this one does?"

Dr. Anthony Komaroff:

Oh sure. In fact I and many other people in the field do this fairly often, publish articles that we hope are clear and concise. And give talks we hope are clear and concise. And certainly do plan to do it again. I think it's really important. There's still an awful a lot of doctors who just don't know much about this illness. And in particular don't begin to appreciate just what I've said today how much has been learned over the last 35 years about what's going wrong. So we're - all of us are working on doing that because it is very important.

Dr. Dana Brimmer:

Okay. Next question for Dr. Komaroff. "Are there any diagnostic tests for ME/CFS on the horizon?"

Dr. Anthony Komaroff:

Yes there are. There are several on the horizon. And whether they're going to really become real, time will tell. A good diagnostic test, understand it has to meet certain very stringent criteria. It has to be abnormal in practically everyone who has the disease that the test is supposed to be for. And it has to be normal in people who are healthy and it also has to be normal in people with other diseases besides the disease the test is designed for.

There are no tests currently that are so good in that respect that they constitute diagnostic test. But there are several that have - that are being looked at. Two for instance just in the last 6 months that Dr. Ron Davis at Stanford has published.

I turned on because I thought someone might ask this question. I turned back on the slides. I hope you're able to see them. Dr. Davis published a study a couple months ago with his collaborators about a test called electrical impedance. Basically the details don't matter. What he showed was in 20 very sick patients with ME/CFS there was a very different pattern in all 20. The red lines in the slide if you can see the slide [slide 41]. Then in the healthy controlled subjects which are the blue lines in this slide. So that's one test. But you need a lot more than 20 patients and 20 health controls. And you need more than healthy controls. You need people with other fatiguing illnesses. And to see whether the test is normal in them, making it truly distinctive in ME/CFS.

The second study [slide 42] is that the test of not white blood cells like that first one but of red blood cells. Dr. Davis and his collaborators found out that the red blood cells are, in people with ME/CFS, are stiffer. And that means that when they get into the littlest blood vessels, the narrowest blood vessels, they have trouble getting through those blood - they're not flexible. And so they clog up the little blood vessels. Actually this has been noticed for 25 years.

The first studies of this were from Australia in the early 1990's. But the technology now available to study this and prove it is much more powerful and that's what this study from Dr. Davis showed. So these are just two. And they're many more that I can tell you that I would call promising but they all need a lot more work before they can become - before they qualify as diagnostic tests.

[Dr. Dana Brimmer:](#)

Thanks Dr. Komaroff. I'm going to switch now and we have some questions for the CDC for Dr. Unger. The first one is "My ME/CFS has been made worse by a fall. Hitting my

head twice on the sheetrock wall in March of 2010. Evidence by auto fuse fractures at C3, 4, and 7, and 8. A three round of Fentanyl that was overdosing me each time. I tried to shower, cook, or take a walk. Didn't help matters. I just saw a rheumatologist. And each time he reluctantly prescribed the only functional medication that my kids can attest that makes me alert during the day. And I've take it for the past 17 years. It's Provigil or Modafinil. And it's just like gasoline for my car. My question is who do we see that takes notice of this disease and it's debilitating, life altering, and sometimes unknown and for how long, intermittently worse aspects on our life?"

Dr. Unger:

Thank you for that question. And I'm really sorry to hear that you've been having trouble finding a healthcare provider that understands this illness. This has been a focus of CDC for quite some time. We are really trying to get our educational materials out to healthcare providers so that they're aware of this illness. The NIH is also working on this. And of course you've heard Dr. Komaroff and his efforts today as well as his very clear publications, all focused on trying to explain this illness to healthcare providers. I think that Dr. Komaroff's talk today is a very good example of how the tide is changing. We are starting to be able to put all of the observations into at least a hypothesis that medical providers will recognize, and that's an important step in helping everybody understand this illness. So this is not a project that's easily just do one thing. This has to be a sustained long-term initiative. And that is why CDC is continuing to develop new educational materials.

Dr. Dana Brimmer:

Thank you. Second question for Dr. Unger. Last month on the NIH call you said that the adult portion of the MCAM study was complete. When will results be released to the public?

Dr. Unger:

Thank you again for that question. So as I indicted in the remarks that I did give, publication of the first part of this study is currently underway. We do have one

additional publication that has just come out, and we are planning subsequent publications as quickly as we possibly can. We are - have as part of CDC's data management and policy, some of this material will be available, and we will do that as soon as the data is cleared and standardized. And approved for release. I'm not sure how long that will take.

[Dr. Dana Brimmer.](#)

Thank you. And we have one more question for Dr. Unger. "What is CDC doing to prevent ME/CFS? Known to occur after mono, Influenza "the 2015 Norwegian study. And HPV vaccination parenthesis 2019 IIME conference." What CDC prevention projects are underway to address triggers? For example are you investigating what factors might predispose someone to develop ME/CFS after the HPV vaccine?"

[Dr. Unger:](#)

That's a very good question. And we actually - to date we and others have been whether the HPV vaccine in particular is associated with ME/CFS or other illnesses such as POTS. And to date we have no evidence that there is an association.

The problem is that these conditions can appear at - sort of at the same age. And so we are continuing to investigate this possibility using a medical case review. And part of - we have a project ongoing with the vaccine safety data link. It's just - I should say it's starting with the vaccine safety data link. And the goal of the project is to see if we can identify patients that have ME/CFS through a standardized medical record review. Because case ascertainment being sure that we have identified cases is a very important part of the project.

And then once we identify the cases then we will see if we can use this approach to - as another way of looking for whether ME/CFS is associated with a vaccination. As far as other risk factors for ME/CFS this was part of our portfolio in the past. And we have not found anything that we can actually make recommendations that people should or shouldn't do.

But we're making sure that people understand the illness and - as much as possible of course. And making it clear that the best management approach is to rest when your body indicates that you need rest. And that's particularly important early on.

Dr. Dana Brimmer:

Thank you Dr. Unger. This brings us to a close for our call today. Many thanks to Dr. Komaroff for being with us today and to our call participants for your time and interest. To submit questions or ideas for future topics and speakers please email MECFSSEC@cdc.gov.

More information can also be found on the CDC ME/CFS program Web site. Both of these links are listed at the bottom of the communication you received regarding today's call. And thank you for your participation. And we look forward to having you join us on our next call.

Coordinator:

Thank you. And that does conclude today's conference. All participants may disconnect.

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