Transcript

Lisa Newman

Hello, I'm Lisa Newman. I'm the project director for the Recover Administrative Coordinating Center and the moderator of today's webinar. Welcome to the Recover Research Review or R3 webinar series. The goal of this webinar is to catalyze a shared understanding of the research within the Recover consortium. I want to start by thanking everyone who submitted questions ahead of today's webinar. During the webinar, please submit any questions that arise using the Q&A feature in Zoom as Patrick recommended. We will answer as many questions about today's topic and presentations as possible. Some questions may also be answered online within the Q&A feature within the chat.

An FAQ document for this seminar will be posted with the recording of the seminar on recovercovid.org. It will include the answers for all questions relevant to the seminar that were submitted in advance or submitted during today's webinar. Questions about other scientific topics will be addressed in future webinars and answer to broader questions about Recover will be available in the faqs at recovercovid.org.

Today's speakers will discuss what is known about commonalities with other disorders and postviral syndromes with a focus on myalgic encephalomyelitis/chronic fatigue syndrome otherwise known as ME/CFS. Address gaps in our knowledge and how Recover will contribute to filling these knowledge gaps.

Our presenters today are Dr. Nancy Klimas, Dr. Ben Natelson and Dr. David Systrom. Nancy Klimas is director of the Institute for Neuro-Immune medicine and professor and chair of clinical immunology in the College of Osteopathic Medicine at Nova Southeastern University. She is also affiliated with the Geriatric Research Education and Clinical Center at the Miami Veterans Administration Medical Center. In partnership with the Miami VA Gulf War Illness Research Program, the Institute for Neuro-Immune Medicine is a multidisciplinary research and clinical institute that takes a systems biology approach to understanding complex medical illnesses, such as ME/CFS, Gulf war illness, and now long COVID or PASC.

Dr. Klimas has achieved national and international recognition for her research and clinical efforts in multisystem disorders, including ME/CFS and Gulf war illness. She is the past president of the International Association for chronic fatigue syndrome and myalgic encephalomyelitis, and a past member of the Health and Human Services Chronic Fatigue Syndrome Advisory Committee. She is co-lead in an ongoing CDC sponsored study of long COVID titled COVID, Understanding the Postviral Phase.

Dr. Benjamin Natelson received his bachelor's in medical degrees from the University of Pennsylvania and Philadelphia, and then did his neurology residency at the Albert Einstein College of Medicine in New York City. Following that, he did two postdoctoral fellowships, one in behavioral neurosciences at the Cornell University Medical Center, and one in physiological psychology at the Walter Reed Army Institute of Research. After you

years at the New Jersey Medical School and the Veterans Administration Medical Center, he left to join the Icahn School of Medicine at Mount Sinai as a professor of neurology and director of the pain and fatigue study center. Since heading one of the chronic fatigue syndrome centers in the early 1990s, his focus has been on medically unexplained pain and fatigue, such as chronic fatigue syndrome, fibromyalgia, Gulf war illness, and now PASC. He has over 250 papers published in peer review journals and has authored three books.

Our last presenter will be Dr. David Systrom. He's a member of the Brigham and Women's Hospital Pulmonary and Critical Care faculty and assistant professor of medicine at Harvard Medical School, where he directs the dyspnea clinic and the advanced cardiopulmonary exercise testing program. He has been on the Harvard faculty for over 35 years during which time he has received funding from multiple sources to study various forms of exercise intolerance. Over the past five years, he has used invasive cardiopulmonary exercise testing to investigate mechanisms underlying fatigue, shortness of breath, and orthostatic intolerance in ME/CFS and PASC. His recent work suggests commonality between the two in particular neurovascular dysregulation and related hyperventilation undergoing symptoms during exercise. He is the principal investigator of an ongoing $8 million study of limb skeletal muscle mitochondrial dysfunction and just completed the first ever randomized clinical trial. I'm going to have trouble pronouncing this, pyridostigmine in ME/CFS. So excuse that mispronunciation.

Finally, our discussant today is Dr. Anthony Komaroff. He is a highly distinguished professor of medicine at Harvard Medical School and a senior physician at Brigham and Women's Hospital. He is a clinician, teacher and investigator. He has served as director of the division of general medicine at Brigham and Women's Hospital, editor in chief of the Harvard Health publications division of Harvard Medical School and founding editor of the New England Journal of Medicine Journal Watch General Medicine. Dr. Komaroff has published over 270 research articles, review articles, book chapters, and two books. In the past 30 years, his publications have been primarily focused on ME/CFS and the biology and clinical consequences of infection with human herpes viruses 6A and 6B and more recently on the possible relationship between ME/CFS and long COVID.

And our first talk today, Dr. Klimas will compare ME/CFS and PASC or long COVID and lessons learned. Dr. Natelson will then discuss the implications of PASC, chronic fatigue syndrome, share data and next steps. Dr. Systrom will discuss the pathophysiology of exercise intolerance in ME/CFS and PASC. Finally, our discussant, Dr. Komaroff will conclude by asking a few questions of the panelists. Then I will open it up to questions for the presenters. Please welcome all of our speakers, and now, I'll turn it over to you, Dr. Klimas.

Nancy Klimas

Well, thank you very much and thank you for the lovely introduction. I'm going to go ahead and attempt to share a screen here, see how it goes. Yay. And then do this. Super. Well, anyway, thank you again for inviting me to be a part of this distinguished group. We've all known each other for a long time. We've all been trying to learn what we can about ME/CFS for a long time. And I was asked to lead so I've got some background slides. And because my personal background is clinical immunology, I got a few of those slides and then, well, you'll see as I go.

So first, I think a conversation of things that we've learned as we went is that caseness is tricky. Caseness is really, really tricky, and it really affects the outcome of our studies. And so over the course of the 30 some years that I've been doing this and a little before that, there've been a grand total of 25 ME/CFS case definitions, three of which have been primarily used in studies, but 25 different case definitions tells you that we don't have a consensus caseness. So it's important. And already in the short time of PASC, there've been eight case definitions that have been suggested in the literature. And as you know, whenever there's something new, it's hard to evidence base a case definition until there's a body of evidence. And so in the end, that's what drives things.

But the most important thing learned from this is that these are heterogeneous illnesses and ME/CFS, very much so, and that it was important. And we learned this the hard way early on, and particularly in our clinical trials efforts to have some sort of subgrouping strategy that tries to make tighter circles around the group that you're trying to study or that you're trying to intervene upon. And so that's important.

And the other thing that learned in the case things, and I can tell you with the exception of perhaps one of the US meetings, I was at all of them, it's really, really important to have the advocate voice in the room when you're discussing caseness and names. So having a representative scientific group that includes advocates is an important part of the process.

So we've tried a lot of different subgrouping strategies in ME/CFS. Duration of illness, mode of onset. There's definitely a subgroup that's postviral that was discussed in the very first CDC paper that attempted to do some subgrouping. Subgrouping by severity or subgrouping by underlying mechanisms or biomarkers. All these are valid strategies.

This is a paper I found that was not too long ago, that just mapped out all these case definitions over time. And that was an interesting historical reference. And I've copied it down there on the bottom, if anyone's interested.

Now, one of the things that's interesting about ME/CFS, and you all know this or you wouldn't have invited us to speak, is that the presentation of these two illnesses is very, very similar. Fatigue is a common though not absolute symptom in PASC. It's an actual case definition requirement in ME/CFS. Reduced exercise tolerance is common, and it's a required case definition element in two of the most research used case definitions in ME/CFS. Then there's a host of systemic symptoms that have to do with inflammation, poor sleep.

In the Institute of Medicine exercise to create an ME/CFS clinical case definition, the end requirement was fatigue with postexertional malaise and either cognitive dysfunction or dysautonomia. And this was a really important thing to say, because this was very much evidence based. This was a lengthy process. You know how the IOM processes go with the expert committee and then a second review panel and public comment and so on and so forth. And in the end, a very large document was the outcome of that. And these were the elements of the case definition that were felt to be the most evidence based.

There is also a lesson learned in ME/CFS and it's awful important early on. And you were trying to do that in the recovery program to use a common data element set so that you can compare apples to apples. This was not the case in ME/CFS for many, many years. And thanks to a combined effort of the NINDS and CDC group who led the charge and created a very large committee of experts to try to review all of the different types of instruments that are being used across all of these different domains of illness. And you can see there's 11 domains here. And again, a year plus effort, many, many, many, many, many meetings and reviews and the evidence review the common data elements was born. And it is now available to you. If you go on the NINDS website, just you can Google NINDS and ME/CFS common data elements, you'll go right to this page. And it's very self-explanatory and very helpful in designing studies.

So when you have something that has common symptoms, that you are hard pressed to tell one illness from the other. Our long experiences with Gulf war illness, which is a illness that happened after toxic exposures that crossed the blood brain barrier and had neuro inflammatory and oxidative stress responses that turned out to persist for decades, it's continued to persist in our veterans that went to the first Gulf war and had organophosphate and other exposures. The presentation is identical to ME/CFS, but the onset is extremely different. It's not postviral, whereas ME/CFS is very often postviral and of course, PASC is postviral. So you have to assume that the commonality of the symptom complex has to do with long term mediators of persistence. Perhaps not so much about how that button was pulled, but what the cascaded events that follow might be . And then it would be nice to know if they really are the same, or they're just a lot of common symptoms with different mediators underneath them.

And so those are the kinds of studies that have been going on in ME/CFS for quite some time. But there are a lot of similarities of signatures in PASC or long COVID, including chronic immune activation inflammation, inflammatory cytokines. Some early studies suggesting there might be defects in cytotoxicity or immune exhaustion. And then some really important papers came out just recently, the paper that ... by Su et al, that noted that when EBV reactivated at the onset during acute infection, that that was predictive of long COVID. The same paper predicted auto antibodies. And this was important from my old HIV days, viral load. Viral load at the acute infection in HIV absolutely predicted the outcome of people who were HIV infected. How quickly they lost their immune systems was predicted by the initial viral load and the viral burden post-acute infection.

So I keep coming back in my head to that when I'm reading some of these things in the past literature and going, "Oh." I said, "That's interesting. The viral burden early on during acute infection was so meaningful." Because there are other papers in past that say hospitalization may or may not be predictive, severity of initial infection may or may not have been that important, but this wasn't about that. This was about viral burden. And that I thought was very interesting.

So there are all these different potential biomarkers that are common across chronic ME/CFS and PASC. And you'll find in papers, again, early papers but important papers that are looking at bioenergetics, oxidative

stress, cell function, neuro inflammation, and so on. When you look at the literature of ME/CFS, you'll find that while all these systemic things are really important, these brain things are really, really important and that the combination of neuroinflammation and oxidative stress seems to be a key feature in the severity and the persistence of illness.

So we talked a long time about possible models of pathogenesis. This is so common to so many diseases. This is a very generic, why do people get chronically ill? And it starts with genetic predisposition, what was the triggering event exposure/infection, what are the mediators of persistence. And there's a big space in this mediator space, what happens early, what happens later, what happens as a result of being say deconditioned for years, and how much does that affect some of the things we're seeing, which is true of all chronic illnesses that are serious and cause a lot of housebound bedbound time versus things that are happening in an ongoing fashion that are driving immune activation, inflammation, neuro-endocrine dysfunction, dysautonomia. With dysautonomia, because really, I'm not going to speak to that because you got two expert speakers after me. But they're very interesting and important part of this whole chronic illness complex.

So I'm quickly reviewing here, the kinds of things people have been focused on, but I'm picking out and talk the next few slides the immunology, because that's been a lot of our work and we're very interested in it. So immune inflammation, cell function, regulatory cells in the immune system, immunosenescence, immune exhaustion. That role, as it might play into viral reactivation, this very important cell that we neglect a lot, mass cells and mass cell activation. Mass cells release a tremendous number of toxic mediators. And when they're in a slow leak instead of a massive sudden release like anaphylaxis, it causes a very serious and chronic and miserable illness, chronic mass cell activation. And there's some evidence that, that might be playing a role in both of these illnesses, the PASC and ME/CFS. And of course, as I was saying, how important the brain is in neuro inflammation and oxidative stress in that space.

We've done a lot of work in immunology starting way back. I think our first paper was in 1989 or something like that, where we published an early paper on NK cell abnormalities in chronic immune activation in a series of ME/CFS then called CFS patients. Since then, there's been a lot of different people working in this and the results are interesting. There are large end papers. I'm in a group with a CDC, the MCAM study, where they just did a very large series using a flow cytometric method for NK and they failed to see the level of NK cell dysfunction that we see. We saw very significant NK cell dysfunction using a functional assay with a K-562 cell and very, very fresh cells. NK cells are really tricky to study because they lose their function very rapidly in 24 hours in a test tube. So there's just a lot of work to make sure this is one of those comments about how important it is to line up our methods. But the CDC did a great job of trying to line up methods and they have a very different result than our large case series.

So saying that, but we and many others have shown pro-inflammatory cytokine expression, neuropeptide Y elevation, cytokine shifts, TH2 shifts, macrophage abnormalities, and so on.

This is some of our early work where we tried to do a rock curve for just NK cells. This is an large series, 176 patients. And this is our chronic fatigue cohort in white here. This is our Gulf war, even worse, the Gulf war cohort in terms of natural killer cell function. And we thought we had a respectable rock curve there.

So the other thing we see in some of these, this is the same paper and here's the reference at the bottom, the CD26 as a activation marker in T-cells is being elevated in ME/CFS. Interestingly, even though they're overactivated, their actual soluble CD26 in the serum was lower, which was a reflection in the function of those cells. Their inability to actually make enough receptor to bump up the soluble CD26 in the periphery. And so I thought there's some interesting observations that matter.

This is just a whole bunch of the line on the bottom was the mean of normal for these cytokines. You can see that we have ... and blue is Gulf war and red is chronic fatigue, but red is elevated. The neuro inflammatory panel was elevated and the TH2 panel was elevated. Whereas the cytokine IL-15, which promotes NK cell function was diminished. IL-8, which is a chemokine that draws cells into an area was diminished. So consistent with the story I just pictured.

Now, one of the things you're going to hear from the other speakers in our group two, and I mentioned in Maureen Hanson's paper at the bottom of this list, but it's just a lot of papers now that are using exercise challenges, a way to really increase the signal and really be able to look at these mediators, the postexertional malaise and chronic persistence of this illness. And we've done a lot of this work where we can use it to subgroup. We can find a different pattern for women than men for instance. We have a different pattern for people with abnormal HPA stress responses versus not, and so on.

And we've even been able to use that to propose models for intervention, where we can have a very granular, very impressive comprehensive dynamic model by drawing bloods at baseline on the bike and afterwards nine times in 24 hours and measure every gene turned on and off cytokine neuropeptide you can measure and so on, and let the computational biologists have at that to try to put the horse before the cart and help us determine where we might try to do an intervention so you're able to look with that kind of method at an intracellular level with gene activation, the cell populations in their activation, the cytokines that Hanson's group's paper was using exosomes, packaging, cytokine message as another place to look. We have never done that. That was really cool. And then linking that all to actual presentation and symptoms and severity and so on. And then put that all back into a computational model. When you do that, you see that these common illnesses that present exactly the same look very differently when you start doing this mapping. When you look at a normal person and all the ways they're communicating across this dynamic challenge, where this button is going over here and hitting that button, and then that's hitting this button and so on, and you can look at these network dynamics, ME/CFS looks like someone punched out the cobweb, that there's very few connections. It's just really a mess, but it's not signaling well. Whereas Gold War illness is a really intense signaling, over-signaling, going around alternate pathways.

So even though they present exactly the same, they are very different when we start doing this network analyses. So a lot of common mediators, but different communication. And we're able to look then at all kinds of subgroups. This was a paper by Travis [Cradick] in our group and Gordon Broadrick, and they're looking at male versus female and they find a premenopausal, a postmenopausal, a male set of network analyses that engage of the neuropeptides as well as the immune system and other systems. And they start seeing patterns that might predictive of the types of treatments we should use in these... In this paper, they actually have a lot of treatment predictions.

This is something that's actually gone on to clinical trial. We have Golf War illness model just the same way. And we were funded. And this instance funding is so nice, but funding to do the phase one study, not once, but twice. We were able to do two different phase ones tweaking this model, where we first suppress neuroinflammation with a bio... with... With a [intercept], and then try to block the adrenal axis ever so briefly to reboot the HPA access through this short block with a glucocorticoid receptor antagonist. And we have some very nice early data in Gulf [War], and we have some pilot money to get this study finally off the ground in ME/CFS after a long COVID pause.

So despite 30 years of study and a lot better understanding of what the mediators are, we have yet to have a successful clinical trial that was based on a biomarker that was based on a biologic target. And this is partly because at least in our own work, it would suggest that one target's not good enough, that all this stuff is homeostatically connected. And you can't just hit the immune system and hope to get the neuroendocrine system done align, but even that aside, and that's very hypothetical, it's really important to subgroup. And so when people have tried to do studies, like say the rituximab study that was done in Norway, a brilliant study, but they did it on the entire group and they didn't necessarily say pick out an auto antibody that you might have tried to identify an autoimmune subgroup with, or a biomarker that would lean into auto immunity.

So perhaps when we have seen some of these studies fail, it's because we tend to lump rather than split. And we have to be conscious of that. And that we've had a terrible problem just with primary outcome variable in our field. And you're going to have this trouble too in past, because you can either pick a functional... function or severity or a symptom or a cognitive function, or perhaps something that you can measure even better than that, perhaps a neural image or something. But we don't have a consensus on what this might be. And of course in our field, we've had terrible funding over the many years that we've been doing this. I mean, a great big year would be $20 million, might be flushed into the field. Thank you. And we haven't had that kind of success.

So I'm almost out of time. I'm going to bop through these last couple slides, and we'll be there. Just so you know, we're doing a CDC funded study called COVID Up, where we're comparing our historic ME/CFS cohort to prospectively and longitudinally followed cohort where we're phenotyping. This is a study with my colleague, Anna Palacio, and [our team at] also at the Miami [Grekin] at the University of Miami. And we're lucky because we're in south Florida. We have a very diverse population. So we're happily recruiting right now in this rich environment,

our past patients as we have a comparator group from the old COVID... From the old MCAM study that we just completed before the pandemic with the CDC. So it's a prospective cohort. We're collecting about 200 people prospectively for phenotyping additional people on a longitudinal platform. And we're comparing them to the CDC MCAM study, which was recently completed.

Dr. Natelson was one of the sites, seven export sites that pulled together about 700 plus patients longitudinally, prospectively followed and phenotyped and these are the platform. You'll actually see this platform. It plays... will sing to you if you've looked at the common data elements platform because this data helped evidence-base that data.

So this is my conclusions slide. We've learned a lot. The case definitions matter. Duration of illness impacts some of our mediator findings. Single lens approaches will fail to account for the multisystem nature of the illness and the homeostatic interactions of these systems that computational modeling is terribly important. Exercise challenge is a great tool for improving the signal and dynamically challenging people you might, and I'm sure you have that in your headlights. And that the heterogeneity needs to be embraced, exploring this heterogeneity presents challenges to all of us, but it's true that this is heterogeneous group and it will provide us greater insights. Certainly the very large end study you all have planned is going to help with that. So thank you very much, and I'll pass to the next speaker.

Lisa Newman

Thank you, Dr. Klimas. Dr. Natelson?

Benjamin Natelson

She... I think she needs to unshare her screen, so I can share mine.

Nancy Klimas

[inaudible] I'm doing it. Right now.

Benjamin Natelson

Thank you.

Lisa Newman

There you go.

Benjamin Natelson

Thank you.

Lisa Newman

Sure.

Benjamin Natelson

So let me start. Okay. By sharing my screen, where are you folks here?

So I want to thank the organizers again for asking me to participate in this recover seminar. And I'm going to talk about PASC-CFS implications data and next steps.

I can't get the next... Oh, here we go. So this slide really captured my attention. One PASC symptom across the world by time. So if you look to the left of the 150 days, which is five months, you see that many countries in the world are reporting a lot of PASC, but I'm most fascinated by the data to the right of the 150 or five months after acute infection, where we see the range of PASC to go from 25% in one US study to 75%. So we are talking about an epidemic of post-COVID disease. So the problem with that study is that mixed self-report data with lab abnormalities in hospitalized patients, and any one abnormality counted. And it was very unclear as to who had what. So there really was no definition of PASC in that study.

So I would like us to think about two groups of patients, one obvious, one who was hospitalized, needing oxygen or intubation and winding up with cardiopulmonary dysfunction, which certainly could produce long life symptoms. But the ones that I am most interested are the ones who were never hospitalized, have normal chest x-ray and echo. They have no medical explanation for their symptoms. So I would like to define PASC as at least six months of continuing problems with fatigue, brain fog, and/or post exertional malaise. Post exertional malaise is said to be the [inaudible] known for chronic fatigue syndrome, producing at least a substantial problem for these patients. But I also want to suggest rather than reinvent a wheel and come up with a case definition for PASC, that we use published case definitions to diagnose or define those who have ME/CFS. So here is a system we have used for many, many years, which allows us to diagnose CFS and determine whether it's in the severe category. In our research center, it's about 30 or 40% are severe.

And it's got two hunks. The first is that fatigue has to have produced a significant reduction in activity across one of those spheres: work, personal, social life, or if you're a student at school. And then we ask patients about these 10 symptoms, the IO with the IOM, we would add an 11 symptom of feeling worse when standing upright without moving, but using these symptoms, they're really three sets. They're infectious, which would be feverishness, sore throat, and tender glands. There'd be rheumatologic, which would be achy muscles and joints with muscle weakness. And then there'd be neuropsychiatric, which is unrefreshing sleep, brain fog. And then this ubiquitous symptom of post exertional malaise. And if you're interested in using this questionnaire to identify and make case definitions for CFS, just shoot us an email, info@painandfatigue.org, and we'll send you a copy of it.

So how do we define PASC? Well, using case definitions reduces heterogeneity imposed by long duration illness. And that's one of the problems with ME/CFS. Many of the patients I see in my practice have been ill for many years. So as Nancy pointed out, subgrouping strategies do help. And we've done several efforts of this using sudden versus gradual onset to infer an infectious onset, comorbid psych versus no psych as another strategy. But PASC obviously bypasses some of these issues. We have a short duration of illness, an infectious disease for every patient. So if there is an immune cause we should find hard evidence of that in the next year. And I'm assuming

that recover is going to be instrumental in such data. But in the meantime, for my purposes, in my research, I'm defining subgroups of PASC, that is patients with no medical cause for their symptoms.

I'm requiring them to remain symptomatic for at least six months. And those that fulfill criteria for ME/CFS will get that diagnosis and the patients who continue will for greater than six months, but do not fulfill criteria for ME/CFS, I'm calling PASC, not CFS. So I believe that COVID will do for the practice of medicine, what Lyrica did in the case of fibromyalgia. And there were arguments that existed, and for some doctors still exist, that CFS and FM are functional disorder. But when the FDA approved three jugs for fibromyalgia, that changed the stance of the practice of medicine because fibromyalgia was then treatable, and it became a medical problem for PCPs so that the great bulk of fibromyalgia is now handled by the primary care provider. I think the same thing is going to happen for CFS. I remember a paper in the nineties where psychiatrists and internists were pulled as to their belief as to what CFS was.

Was it medical or psychiatric? The psychiatrist said medical, and the internist has said psychiatric, but COVID is the corrector. We have an avalanche of the diagnosis ME/CFS in our hands, 50% of past patients that we've worked up fulfill criteria for CFS. So doctors are going to be obliged to consider and then try to ME/CFS PASC.

So where are the differences? Well, as Nancy pointed out, there are a lot of similarities, but in this collection of data that Lenny Jason pulled together of PASC patients and patients that he knows has ME/CFS, the top three are really different because the COVID PASC patient has more shortness of breath, more irreg... complaints of irregular heartbeat and more complaints of chest pain than the ME/CFS with the other cardiovascular variables being really no different between the two groups.

So what do we know about racial and gender breakdown? Actually pretty... Surprisingly pretty little. In our data set of 761 PASC patients, 60% are women, 19% are Latino, which is sort of what you'd expect in our catchment area. If you look on the right paper again, by Lenny Jason, where he compares PASC to ME/CFS of interest, he found more women in the COVID PASC group then in the ME/CFS group. And what you might expect is that COVID PASC is less of a problem for white, Caucasian women. Other races obviously play a role, but we don't have the racial breakdown yet. I'm expecting we'll get that in the next few months from recover. I didn't find much on race except this paper indicating that in the United States... Hang on. 20% of patients were black and there were... whereas about 11% of deaths were in black people, and that's higher than you'd expect across the United States.

So we're waiting for those data and they should be emerging quickly. So what are differences? Well, here's a paper that came out of colleagues here at Mount Sinai led by a neuropsychologist, Dr. Becker on patients that were seven months after COVID. Really no data on what their symptoms were, but they were cognitively impaired. And she did formal neuropsych testing on these patients. Focus your attention on the outpatient. The two columns I'm interested in are outpatient, and the ones that went to the ER, and the things that strike me a

very... A great interest is the processing speed. 15% were abnormal. The memory in coding 16%, and processing speed and executive function were the big three. And these are the ones that we find to be abnormal in ME/CFS also.

So let me now tell you about a study we're just about to launch at Mount Sinai I'm very excited by because COVID, as I'm going to point out, has produced an epidemic of chronic fatigue syndrome. One important question is determined, if CFS unassociated with COVID is the same as PASC CFS. And so we have just received funding and our study is about to begin with funding from NDS, and it's me and a brilliant imager Dr. Xiang Xu.

And what we're going to do is bring in three sets of subjects: those with PASC CFS, those with classical CFS, and age match, healthy controls, and we're going to image all three of them and get out three sets of dependent variables, anatomic data, which will tell us about unappreciated lesions or differences in white or gray matter perfusion by ASL to see if we can replicate, once again, the findings that we had in classic CFS of regional reductions in blood brain flow. And another variable that I'm very excited by: venous oxygen extraction fraction, which... And these three dependent variables will tell us about structural abnormalities, perfusion deficits, and whether in fact, there's an energy... brain energy deficit, and then we will take those outcome variables and correlate them with the patient's fatigue status. So we're very excited by this and just launching it.

So we are now in the process of doing cardiopulmonary exercise testing in PASC, we've published a paper, Mancini et al. in JACC, in which we showed VO2 max and heart rate were lower than expected, but our colleague Dan Cook at Wisconsin using MCAM data has done a very large study comparing ME/CFS versus matched sedentary controls. And here, it's very important to emphasis eyes that what he's done is he's matched on a case by case basis, based on VO2 max, the value for the ME/CFS patient to the head... To the sedentary control. It's a big study. 99 in each group. And what he's found is that the heart rate differences that we found and others found disappear, but he does find increased ventilatory equivalents of oxygen and CO2, as well as decrease... Increased title volume accompanied by decreased respiratory rate, leading him to conclude there is inefficient exercise ventilation in the PASC patient... in the ME/CFS patient.

And we're going to see what we find in PASC, but we have done a study of 41 PASC patients published in JACC. And we found three things: chronic fatigue syndrome, hyperventilation in the baseline condition, and odd looking abnormal breathing. So what we found is we used the 94 case definition, and we found that nearly half of the past patients had CFS. We excluded for obesity, and we know that obesity as well as diabetes and hypertension are risk factors for PASC. And if we had included the obesity would have been about 55%, we found that half the patients had hyperventilation during baseline and a different 50% that I'll share with you in a minute had dysfunctional breathing during exercise and what's dysfunctional breathing? Well, here's a normal breathing. As the exercise goes on, the individual moves more and more air over time.

Whereas the patient with dysfunctional breathing, you see it even in anticipation of exercise, but in exercise, the patient pants, higher, moving more air, and then less air. This irregular pattern of breathing that

we're calling dysfunctional breathing in that until today, we've had to identify by the eyeball test, but we're in the process of developing mathematical algorithm that we will be able to pass through large numbers of datasets to pull out those with dysfunctional breathing. So we're excited by that. Not there yet, but it's an active work. So here's the hypocapnia, the range of hypocapnia. The arrow points to what we think is normal, which is 35 millimeters of mercury. Here's the PET CO2s at rest in blue and during exercise, at a low exercise intensity 25 Watts. And the thinking here is that if the hypocapnia is due to worries about being in a... Having to do cardiopulmonary testing or having had to come into the lab, not feeling well, exercise is a metabolic regulator.

And at 25 Watts, we would expect that the end title for those patients would go to above 35. And that does happen for some, but your eyeball shows you that the great bulk of patients who are hypocapnic before exercise remain hypocapnic at 25 Watts, and in indeed some who were normal capnic become hypocapnic. So there's a lot of hypocapnia, and most remain with exercise. Now, this is just a little slide, a very preliminary slide, that we pulled together to say, which PASC patients had which, so these are the ones with CFS. These are the ones that didn't fulfill criteria for CFS. Same numbers of dysfunctional breathing, and the hint that the CFS patient may have more hypocapnia than the non-CFS patients. And we're going to pursue this as I will explain in a minute. So here's an algorithm for working up patients with unexplained dyspnea, we'll bring them in, we'll make sure their ECG chest x-ray and spirometry are normal. If they're not normal, that obviously will lead that to the decision on the left, where they'll get worked up for cardiopulmonary disease. If not, we will do a CPET on them and the results of the CPET will provide one of three outcomes. Either they'll be normal, so we either can reassure them and discharge them, we find actual abnormalities, which report require cardiopulmonary intervention, or we find dysfunctional breathing, hypo, capnia, et cetera. And then we're going to try to come up with a physical therapy regimen, we haven't arrived at that yet, but to improve these patients' health related quality of life.

So where are we going?

Well, the first question is what does sleep do to hyperventilation and dysfunctional breathing seen in PASC? So we're going to now do CPETs on whatever PASC patients we can, identify those with hyperventilation or dysfunctional breathing, and then do overnight polysomnograms because sleep, like exercise is a metabolic regulator. If either of these breathing abnormalities is due to psychogenic or functional causes, it should disappear with sleep. And then the other important outcome from this study is, we ought to be able to learn the difference between PASC with no CFS and PASC-CFS. So then I found this paper on French subjects who underwent an open label trial of Vagus Nerve Stimulation, on the left are the symptoms on day 0, and then they underwent to periodic Vagus Nerve Stimulation on the auricula branch, I'll tell you about that in a minute, found significant reductions of symptoms and on this French fatigue scale, as you can see also improvement.

So for me, without a lot of treatments for PASC and PASC-CFS, I'm excited to determine whether VNS can help. So here's the Parasym device that attaches to the tragus of the ear. Because it attaches to the tragus of the ear, it allows long stimulation times, as compared to the device that you have to hold on the cervical Vagus, where

you really can only hold it for two or three minutes for each stimulation train, so longer stimulation times using the Parasym. And so the question for me that I'm very excited to try to answer, will Vagus Nerve Stimulation improve PASC? My colleague, Dr. Guchen Lang and I did a study some years ago, in which prior to any of these transcutaneous devices, we had to implant VNS in fibromyalgia patients, and we found improved pain and fatigue in that open label study. And now we're hoping to use auricular VNS for 45 minutes in PASC.

Our IRB has asked us to get FDA approval. The Parasym, just for your information is available without prescription in the EU in UK and has had no real risks of using it in many, many uses by individuals who are buying it overseas. So we're awaiting FDA approval as a no risk device. And then we're going to launch this little pilot. And if it's significant, we'll do a bigger study. So thank you so much for your attention.

Lisa Newman

Thank you, Dr. Nadelson. That's a good segue to Dr. Systrom so let's move on to you Dr. Systrom.

David Systrom

All right. Thank you very much Lisa. And it's my pleasure to speak today. A full disclosure, I am a lung doctor, pulmonary and critical care physician. And I think this session today is actually a testimony to the village that it takes to better understand ME/CFS and now PASC. We had Nancy Klimas of course, from the immunology ranks and then Benjamin Nadelson from the neurology ranks. And we're trying to put all of this together, of course, with help from other specialties and subspecialties, including infectious disease and rheumatology and so it goes. Along the way in the next 20 minutes, I hope to tell you how I got into this business. I had a longstanding interest in Exercise Capacity Pathophysiology. And what I'll do is end up telling you how we use some of the tools we developed about 30 years ago at Harvard and Boston to determine who has early pulmonary vascular disease and heart failure. We've applied those same tools and specifically the Invasive Cardiopulmonary Exercise Test to better understand in ME/CFS and now PASC.

I have no disclosures. This is what goes on in the basement of one of the buildings at the Brigham and Women's hospital virtually daily. We do about 10 of these a week and have a satellite facility that's just opened up. So this is what Dr Nadelson was just referring to as the Cardiopulmonary Exercise Test and this variety is the invasive one. And I'll give you some of our data that we think we can accrue from the use of two catheters. So like Non-invasive cardiopulmonary Exercise Testing, we have a pneumotachograph and sample line for expired gases, inspired and expired pulmonary gas exchange and from those things we get non-invasive variables. The invasive variety of this testing adds two catheters that are placed in the cardiac catheterization lab around the corner. One is the radial artery line shown in this gentleman's left wrist and the other is a pulmonary artery catheter placed in one of the internal jugular veins. From those catheters we derive pressure measurements and blood gases, both arterial and venous and from those things, we calculate a lot of derived variables.

Here's sort of an overview of the things that we can diagnose with Invasive Cardiopulmonary Exercise Testing, and rapidly focus on the things I think are relevant to most of our patients with ME/CFS and more recently

with PASC. So up here is a time honored assessment of overall aerobic capacity or impairment that's the Peak VO2 expressed as a percenter predicted, the independent variables that go into that are age, gender, and an assessment, or an estimate of lean muscle mass derived from the height. So we can say how impaired an individual is from whatever ails them, heart, lung disease, and other things that we'll talk about in a minute. Some of these things are relevant to the differential diagnosis of the severely compromised past patient, perhaps one who has spent some time in the ICU, intubated on a ventilator. There is of course, a subset of patients with PASC much less commonly with ME/CFS who have Parenchymal lung disease in the form of organizing pneumonia that may persist or perhaps fibrosis due to a RDS.

We can rule this out. This is a non-invasive variable that compares the amount of ventilation at peak exercise to the amount of ventilation one can do in the resting state, the so-called Maximum Voluntary Ventilation. But the rest of the world is explained largely by the Fick principle, which is shown over here and is explained by either impaired oxygen delivery shown over here or its subsequent uptake in utilization. So please remember all of this will come back to this and this repeatedly in the course of the next few minutes. Also relevant though, to PASC, especially the severely ill patient, perhaps in the ICU or perhaps with a cardiomyopathy, would be the ability of this testing to rule out or rule in a left heart limit to exercise, we measure a Fick cardiac output every minute all the way up to peak exercise by measuring the VO2, and every minute the arterial and mixed venous oxygen contents and calculating a Fick cardiac output.

And when that's abnormal and it matches as a percent predicted the Peak VO2, as a percent predicted, we're allowed to infer that there's a central pump problem and we can differentiate left from right heart disease and PASC left heart disease occurs occasionally, especially in younger individuals who may have had mild disease with a cardiomyopathy. We can rule that out. And then of course there is a thrombophilia that can occur with PASC and sick patients, including pulmonary emboli and occasionally chronic pulmonary emboli we can rule out pulmonary vascular disease with this. But the vast majority of patients we see with both ME/CFS and PASC have these other things. One, we're going to call preload failure, it's a colloquial term, come back to that a bit. It's low filling pressure, it's feeding the right heart in the upright position and I would emphasize the upright position where gravity is the enemy.

And this is ubiquitous in our hands, in both ME and PASC as you'll see. The other abnormality that we've detected more recently and have focused on is an abnormality of oxygen extraction, normally the mixed venous oxygen content during incremental cycling exercise falls about threefold, down to about 5 ML per deciliter. We can normalize the difference between arterial mixed venous oxygen content for anemia, by dividing by the hemoglobin, and deficiencies in systemic oxygen extraction have a differential diagnosis. They're basically two and they're not mutually exclusive, they may coexist. One is peripheral left to right shunts. There could be intracardiac shunts but we ruled that out at the time of the resting right heart catheterization. And the other is an intrinsic

mitochondrial myopathy where the machinery of the mitochondrion is abnormal, cannot create a sump for oxygen delivery into the mitochondrion and of the muscle and there's failure to depress the next venous oxygen content.

So once again, I'm going to come back to these two repeatedly and I'll now turn to how we got into this about five or six years ago. Will Oldham was the first author on this paper that we published six years ago, basically asked the question that we had observed anecdotally. Are there other explanations for exertional intolerance, including dyspnea, but as it turned out fatigue and orthostatic intolerance that are not accounted for by classic problems with the heart or the lungs? And the short answer of course was yes, there is a group. We took this approach we had at the time, 600 plus patients in our Invasive Cardiopulmonary Exercise database. Essentially we ruled out everything else under the sun. This is left and right heart disease, this is pulmonary mechanical disorders, and we ended up with a group that was impaired by the Peak VO2.

Their VO2 max was less than 80% of predicted, almost 50 of them, they were symptomatic. A variety of symptoms as it turned out, in retrospect many of them met the IOM criteria mentioned by our two previous speakers for ME/CFS. And we compared them to a group of symptomatic normals, nearly 30 of them, patients who had come to our tests but we could find nothing wrong with them. And what turned out to differentiate the impaired group from the normal group was ventricular filling pressures. So here's the right atrial pressure at rest and at peak exercise in the non impaired group, the normal group and the impaired group, and especially at peak exercise and again, I would emphasize in the upright position, if one does this as many centers do supine on a cardiac cath lab to able you will miss this signal.

The other thing we found was that a surrogate for left atrial pressures, the wedge pressure that we get every minute at rest and throughout exercise also showed deficiency at peak exercise in the upright position. So biventricular filling pressures seemed to be the rule and this special group whose exercise intolerance was not explained by intrinsic heart or lung disease. We attempted to regress these filling pressures on both sides of the heart to the Peak VO2. And there was a loose association and ditto for the cardiac output. So our takeaway from this early study was that there was a group of patients whose exertional intolerance is at least partially explained by abnormalities of biventricular filling. And we call that preload failure recognizing fully that pressures are not volumes and the classic Frank Starling type of thinking.

So this is where these patients landed in our algorithm. They often had mildly depressed VO2 peaks and cardiac output peaks. They did not have any of these things or this, they ended up here. And again in retrospect, we determined that many of them met criteria for ME/CFS. So that's how the lung doc got into this business. So my interim summary is that preload failure during exercise is very important in old fashioned ME/CFS and as you'll see in a bit, we think also important in PASC. We took this a little further last summer when we published this study in Chest, one of our cardiopulmonary journals, Philip Joseph was the first author and we took a slightly deeper dive into the pathophysiology during exercise and here we required that the patients meet clinical criterias outlined in the last two talks for ME/CFS. This was pre COVID, but old fashioned as it were ME/CFS.

We also had increasingly recognized with the help of Ann Louise Oaklander or over at mass general, that there was a high prevalence of small fiber neuropathy by skin biopsy in these patients we were seeing with chronic fatigue who had preload failure during exercise. So we wanted to ask how relevant was that to our findings. We took a very similar approach to the Oldum paper. We now had a threefold increase in our invasive cardio pulm exercise database. We ruled out every thing else under the sun. We focused on those with preload failure, additionally those with a skin biopsy for small fiber neuropathy and then finally we only ruled in, or only included for this study, the patients who met clinical criteria for ME/CFS.

And what we found was a majority of patients met the clinical criteria for ME/CFS. And then we took a further dive into what ailed them. These are the skin biopsy results. This is minimally invasive skin biopsy above the lateral malleolus, just above the ankle. A definitive diagnosis of small fiber neuropathy is when the neuroi density by special stance is less than the fifth centile compared to Norma controls. Probable diagnosis is less than 15, and you can see that nearly half of the patients who met these criteria for ME/CFS, and additionally had preload failure on our exercise test had either definite or probable any, or a probable small fiber neuropathy.

We attempted to better understand the hemodynamic abnormalities by interrogating three different subsets of cardiac output versus VO2 slope. Classic finding in normal individuals and even in heart failure is that that slope is around 6ML per ML, cardiac output versus VO2 during incremental cycling. And then what was of interest to us? There was that this intermediate group in green. Well, we had two other groups. One was a low flow state with disproportionately depressed cardiac output versus VO2. And we think that was mostly what we had described in the olden paper, that I described a second ago, but the real interesting one was that there was a high flow group. And remember we're measuring Fick cardiac output, which is pulmonary blood flow. And this raised the specter of left to right shunting meaning we knew that their Peak VO2 were depressed. Focus on the red bar here.

So round 70% are predicted on average, but the cardiac output or pulmonary blood flow was disproportionately preserved. This is a hallmark of left to right shunting. This is what we know from septal defects in our cardiology colleagues, [inaudible] , when there's left to right shunting through an intracardiac deficit. But we knew our patients didn't have that because there was no step up in oxygen saturations from the SVC to the distal pulmonary artery during the rest in right heart catheterization. So what we inferred here was that we had a high blood flow group, a lot of pulmonary blood flow, but effectively not as much system blood flow, probably typical of left to right shunting. And we had associated impairment of systemic oxygen extraction. I was delighted to hear Dr. Nadelson is going to pursue some of this I'm not sure which venous compartment he is interrogating with his proposed study, but we think this exists at the whole body level, in a subset of patients with ME/CFS and by study design, all the patients compared to normal here on the gray had low right atrial pressures in the upright position.

So our take home message here was that there is, in addition to preload failure in ME/CFS, subset of patients with impaired oxygen extraction in the periphery and one possibility is that this is left to right shunting.

I'm borrowing this from Dr. Frank Rice, a colleague at Albany who has studied biopsies of the hypothenar eminence from the hand deeper biopsies that get the epidermis shown here. And then interestingly, what he can show in the skin is arterials and veins below the dermis with potential shunts between the two, and they're enveloped by small fiber nerves that secrete calcitonin gene related peptide, which is a known vasodilator. And it's interesting to me that in the clinic, I can ask patients and I can't believe how often the answer is yes. Do you get in the hot shower, have your legs turned red or purple and become lightheaded, and what we think might be happening there is opening up dynamic opening of these shunts, perhaps related to the small fiber neuropathy, the small fibers having both a pain function and an autonomic function.

So my next point, my interim point here is that in ME/CFS, in addition to preload failure that we find is pretty ubiquitous. There is an abnormality, at least in a subset of patients of systemic oxygen extraction, which may in turn be related to peripheral left to right shunting. There is something else in the differential diagnosis. This is that interim summary. We got to start on this and that's mitochondrial dysfunction. We got to start on this several years ago, when a senior medical resident at the Brigham helped us out with this study, very similar approach to the previous two, where we had an invasive cardiopulmonary exercise database excluded other things. And what Katie Melamed found was that we had a subset of patients with poor systemic oxygen extraction that was very severe and actually suggestive of intrinsic mitochondrial dysfunction. This got our attention because this may suggest in addition to that left or right shunting, that can give you the same finding.

There could be something wrong with the mitochondria and these two groups, some of whom known to Dr. Nadelson hyperventilated, and some of whom did not. We borrowed from the UT Southwestern muscle mitochondrial myopathy group published a paper back in the day where they had actual measures with muscle biopsies of the mutation load in a mosaic pattern of the limb skeletal muscle and did cardiopulmonary exercise testing made in a non-invasive way of getting to systemic O2 extraction. What they found was the greater the mutation load in the muscle mitochondrion, the more narrow the peak exercise, a VO2 content difference compatible with the findings we had and that I just showed you. So we took this a little further, these unpublished data and sent 11 of our patients with poor oxygen extraction during the invasive cardiopulmonary exercise test to Dallas, they had a muscle biopsy frozen sent over to Houston to Baylor and had the limb skeletal muscle mitochondria interrogated in particular the electron transport chain and 10 of the 11 patients had evidence largely by citrate synthase deficiency on that muscle biopsy of intrinsic mitochondrial dysfunction. So we thinking the differential diagnosis of impaired oxygen extraction in ME/CFS is in addition to the left to right shunting intrinsic mitochondrial disease. And the two may coexist.

We've launched, as Lisa told everyone at the beginning, an $8 million study here at the Brigham, investigating this with a PPAR-delta modifier, that's thought to enhance fat metabolism in the muscle and will be variant. And this is specifically in ME/CFS. We've not excluded PASC, we've already included some patients with PASC and we'll be very interested to see if they behave the same as pre-COVID ME/CFS. So more to come on this

one. So this interim conclusion is that there is a peripheral limit to exercise in some of these patients perhaps compatible with mitochondrial disease.

All right. And now I'm going to turn to PASC. We did an invasive cardiopulmonary exercise test with two of our alumni, Indy Singh And Phillip Joseph who are now at Yale. The help of Aaron Waxman and others. And this was an invasive approach, the very same protocol that I showed you in PASC. And we compared 10 PASC patients who were mildly affected about 11 months out from their acute illness to normal individuals had undergone this test. And to cut to the chase, the data are frighteningly similar to pre-COVID ME/CFS. The peak exercise VO2 on average is mildly to moderately depressed compared to our normal controls. The pulmonary blood flow, this is the thick cardiac output, is in the same range as the normals. This might suggest that left to right shunning and the hallmark of their problems at least, during our invasive exercise testing is impaired systemic oxygen extraction measured in a slightly different way, are about half normal. They also had preload failure, although with the numbers, there probably was a type two error here.

So there was one additional finding, but the interim conclusion here is that in PASC there is a peripheral limitation with severely impaired systemic O2 extraction by our testing, in addition to the preload failure. Both of these, of course, common to ME/CFS pre-COVID.

Now, last bit that I wanted to show you is again, a nod to Dr. Natelson and his findings of aberrant ventilation. And we would second that. So in this particular study, Indy Singh's Study, we also found ventilatory inefficiency. And that's defined as a high minute ventilation divided by CO2 output at the mouth. And it's usually measured as a slope, although occasionally as a fraction, at the anaerobic threshold. And the patients with PASC compared to normal normals were abnormal. They had ventilatory inefficiency. Now, inefficiency implies dead space ventilation in the lung docs world. But there is another reason for the so-called inefficiency or elevated slope, and that's hyperventilation. In fact, that's what we have found.

So this is the VE/VCO2. This is the ventilatory alveolar ventilation equation rearranged. There are two reasons for this fraction to be high. One is hyperventilation, a low PaCO2. We're directly measuring this. And the other is excessive physiologic dead space to tidal volume ratio. So what we found is what Dr. Natelson suggested. We found in the patients with PASC that there was hypocapnia directly measured by the A line in an associated relative alkalemia in blood. It's the definition of hyperventilation. These patients hyperventilated. VD/VT was not abnormal. It fell from a normal value in our patients with PASC to the expected value of around 20% at peak exercise in PASC. So the reason for ventilatory inefficiency, at least with a small cohort of past patients is hyperventilation, a depressed PaCO2, not excessive dead space.

Others have begun to recognize that dyspnea, this is as Benjamin suggested, I think one of the differences between PASC and old fashioned ME, there is a subset of patients with ME/CFS who have dyspnea, but many do not. It seems to be more prevalent in PASC. And part of this has been linked by others. This was published last summer to the preload failure. And then this quote from the ERJ also last summer comes to the same conclusion

we have come to. So my last summary slide here is that PASC is manifested by the very same things that we see in terms of hemodynamic abnormalities in ME/CFS. There is the preload failure. There's the suggestion of left to right shunting. There may be a mitochondrial problem buried here. And then there's a lot of hyperventilation presumably associated with dyspnea.

So that's all I have. My summary is that exercise intolerance and PASC is probably more similar than not to ME/CFS, a lot of commonalities that we need to explore further. And I thank you for your attention. And special thanks to a bunch of folks shown here on this slide, including research squad, MC Stovall, who will be a medical student at Tulane in this coming spring, Johanna Squires, who is a master's level exercise physiologist, Kristine Madsen, who's a visiting fellow from Copenhagen and others I've mentioned along the way. Special call out to collaborator Donna Felsenstein at MGH, Wenzhong, who's our statistician premier at Stanford and Harvard, Peter Novak, autonomic function specialist at Brigham Faulkner, and the late Ron Tompkins who put together this consortium. And a special thanks to all of our funding, including the Open Medicine Foundation who's been very active in all this. Thank you.

Lisa Newman

Thank you, Dr. Systrom. Dr. Komaroff, our discussant is going to ask a couple of questions of our panelists.

Anthony Komaroff

Actually we're running late and in the interest of time, just a couple of summary comments, and then throw it back to you, Lisa, for broader questions from the community of listeners. So what Dr. Klimas and Dr. Natelson did in particular is summarize the similarities between ME/CFS and PASC when it comes to symptoms and several categories of underlying pathophysiologies. Although as Dr. Klimas out within a category of abnormalities like cytokine network disruption, you may have very different patterns from one illness to the other. But there are many commonalities, symptoms and underlying pathophysiology, which says to me that it would be important as the recover study goes forward, to have people with ME/CFS serve as important disease comparison groups, along with healthy controls and COVID recovered controls. So those would be my overview comments. And then Lisa, I turn it back to you for more open questions and discussion.

Lisa Newman

Thank you, Dr. Komaroff. First of all, Dr. Natelson, would you repeat the email address that you provided earlier and I can put it in the chat.

Benjamin Natelson

Yeah. It's info@painandfatigue.org. And if somehow that doesn't do what it's supposed to do, Benjamin.natelson@mountsinai.org.

Lisa Newman

Thank you very much, Dr. Natelson. Okay. Dr. Klimas, I think this is for you. Why are we assuming that long COVID is postviral and not viral persistence?

Nancy Klimas

It's an excellent question. I like the question, because we don't know the answer straight out. It's too early in the world of PASC research to know if there is a large group, a subgroup or a whole group that has persistent infection. There's definitely some nice papers out in the first few months post-acute COVID that showed persistent in protected compartments and not still accessible by nasal swabs and whatnot. And so part of that's tricky because they were doing things like GI biopsies, which are invasive and finding evidence of COVID persisting in the GI compartment. And then there's those people that got better with vaccine, not everyone by any stretch, certainly in my clinical practice, I didn't see it, but there are reports of that. And there are some people reporting incidental improvement after say something like a monoclonal COVID infusion, which how they got that, I'm not sure. But there's been a couple incidental comments on that. So the point is we got to find out. It's really important.

Lisa Newman

Thank you. Okay. Dr. Natelson, assuming the vagus nerve modulation approach works, what do you think is the underlying mechanism of the pathophysiology of the vagus nerve or other neurologic dysfunction?

Benjamin Natelson

Well, one of the things that happens with pain, we don't know a lot about brain and fatigue, but pain, the descending pathways controlling pain are affected so that they don't work well. And so individuals with ME/CFS and fibromyalgia have body wide pain. And so the VNS targets those areas and we think opens up systems that are blocked so that descending control of pain, again, we don't know much about fatigue, are ameliorated by treatment.

Lisa Newman

And Dr. Natelson, are you accepting patients for your pilot study?

Benjamin Natelson

Damn right? 212-844-6665. We're looking for PASC subjects for our imaging study. Well, PASC/CFS, that is for our imaging study and of course, classical CFS, 212-844-6665 is the way to get into the research limb of the Pain and Fatigue Study Center.

Lisa Newman

Thank you very much. Okay. Dr. Systrom, do you have recommendations for patients who have a cardiopulmonary exercise test triggering a crash?

David Systrom

Well, it's not specific to the exercise test triggering a crash. It would be the recommendations that we might make for any form of crash. I will hasten to add that the number, we probably have done 2000 of these invasive tests in ME/CFS, and only a handful of patients have reported a significantly [inaudible] lung crash post. So it's not a real common problem for us. We give intravenous fluids after oftentimes to help hasten the recovery. But yeah, it would be the same recommendations as out in the field for a crash.

Benjamin Natelson

Lisa, if I can just say a word-

Lisa Newman

Go right ahead.

Benjamin Natelson

... my cardiologist colleague, Donna Mancini, and I have a NIH funded study to do two CPETs in a row 24 hours apart. And we are using the Daxor device to measure blood volume. And if blood volume is depleted on the first day, then we randomize them into getting either a leader of saline or [inaudible] saline. So we're going to try to sort that out in that RO1, and we're optimistic, we put in for a supplement to extend the identical studies to PASC. And so we're hopeful if we can do that, we can do what Tony's calling for, because I totally agree, Tony, we need to learn about ME/CFS from PASC/CFS.

Lisa Newman

Thank you. That was actually one of the questions. Okay. Dr. Systrom, what steps are being taken or will be taken to drive the results of PASC/CFS studies to further ME research and to help treat ME patients in a more timely manner? Actually, this could go to any of you.

David Systrom

Sure. Well, I think we all agree and I hesitate to use the term, but if there's any kind of silver lining to long COVID, it's the fact that it's helped out with research funding that I think will help out both disorders. And I say both disorders, not knowing that the two are totally different. I can defer to the others and their thoughts on that as well.

Nancy Klimas

I'm sorry. I had a break up on the internet. I couldn't hear the question.

Lisa Newman

The question was... Apologies. What steps are being taken or will be taken to drive the results of PASC/CFS studies to further ME research and to help treat ME patients in a more timely manner?

Nancy Klimas

Okay. That's my favorite question of all. And while the short answer is probably, I don't know, I am really hopeful that the PASC investigators will understand, first, the great benefit there is to including an ME/CFS sick control group in all of their studies. I know in the clinical trials that I am being asked to do for PASC, I am asking the people that fund that to allow me to, if it makes sense, do the same intervention in an ME/CFS group as well. So I'm sort of bargaining. But it is kind of sad. I mean, I've been doing this for more than 30 years, so it's been, well, that we've had so few clinical trials in our field, is so sad. I mean, people have had this illness and there are so many things we could be doing. And the answers, the reasons why are complicated, and we can't do that here, but I'm hoping that the pharmaceutical industry and certainly the federal funding agencies and everyone are seeing through PASC how horrible people's lives are when they have illnesses like this. And go ahead and make [inaudible] to give people back their lives. It's terribly important.

Lisa Newman

Dr. Natelson, anything to add?

Benjamin Natelson

No. Nancy has said it perfectly. The silver lining about long COVID for me again, is that ME/CFS is for real. I mean, we know it's real, those of us who cared for these patients over the decades. But now there's not going to be any argument because there's a avalanche of PASC/CFS coming down the pike.

Lisa Newman

Thank you. [crosstalk]. Tony? Yeah. Comments from you?

Anthony Komaroff

Nothing to add.

Lisa Newman

Okay. Dr. Klimas, I think this is for you. The 2012 international Consensus Criteria is one step in sub-grouping patients. We're now seeing how patient selection using the ME International Consensus Criteria is providing results specific to that patient group. Is the ME ICC along with the ME IC Primer being considered to screen PASC patients?

Nancy Klimas

I don't know the answer to the question, because I'm not really engaged in the recover program or the PASC planning. I'm sorry that I can't answer that question. I'm hoping that they at least know that it's there. It's reference was very thoughtfully done, engaged a treasure trove of worlds authorities. And it would be a shame not to include that information when you're thinking things through.

Lisa Newman

And Dr. Systrom, the findings on hyperventilation are very interesting. What are the current hypotheses on the mechanisms causing this sudden hyperventilation in PASC, for instance, and people previously not hyperventilating.

David Systrom

Yeah. It isn't known. We don't know and it isn't known and it's an area right for research and treatment because presumably that hyperventilation relates to dyspnea and is one of the cardinal PASC symptoms. I can tell you that some of the other diseases we've talked about are associated with hyperventilation and in particular mitochondrial disease, if there's no respiratory muscle involvement, hyperventilation is ubiquitous. In all forms of heart failure and pulmonary vascular disease, where there is a component of impaired oxygen delivery, there is also hyperventilation. And that signal may come from the periphery. There is not an error signal at the level of the arterial chemoreceptors. What we think, and this is a hypothesis, that what may be at play in some of these patients is muscle metaboreflex. So the group four afferents that come out of the interstitial fluid of muscle respond to the byproducts of muscle metabolism. And if the muscle is stressed because of O2 supply issues and/or intrinsic mitochondrial problems, hyperventilation ensues. But that's at the level of a hypothesis.

Lisa Newman

I think we have time for one more question. Have you seen any cases of ME with chronic active virus still present in the body?

Nancy Klimas

Well, I mean, yes. That's the real problem with ME/CFS work is the immune system's dinged enough to let viruses reactivate and viruses reactivate. And we have lots and lots and lots of papers in the field that have measured viruses reactivating. And they come and they go. You have to be longitudinal to really capture them very, very efficiently. And of course, methods for measuring them have changed, so the sensitivity's much better now. And it matters what compartment you're measuring. For instance, Dr. Chia's enterovirus work is seen in the gut, it's not seen in the circulation. So you totally miss enterovirus if you're looking in the blood compartment.

So the question is, the course and the CART again, do viruses reactivate and drive a lot of this down to immune exhaustion, cellular depletion, poor antiviral function, or is there mitochondrial oxidative stress bioenergetics thing that's more systemic and in every kind of cell driving the poor cell function that lets viruses reactivate, and that they're more like a flag than they are necessarily driving the illness, or is it just a big mush mash of all that, which is most likely that you can't ignore any of it. It's all important. Tony, you had a smile and you disagree with that?

Anthony Komaroff

No.

Lisa Newman

All right. Well, we're at the end of our 90 minutes, I want to thank the panelists and our discussant, again. We really appreciate the information you've provided today and to remind everyone that the next seminar is on April 26th, also from 12:00 to 1:30, Eastern Time. And it will focus on the clinical spectrum of PASC, the focus on pediatrics, including MIS-C. So thank you again. Have a great afternoon.