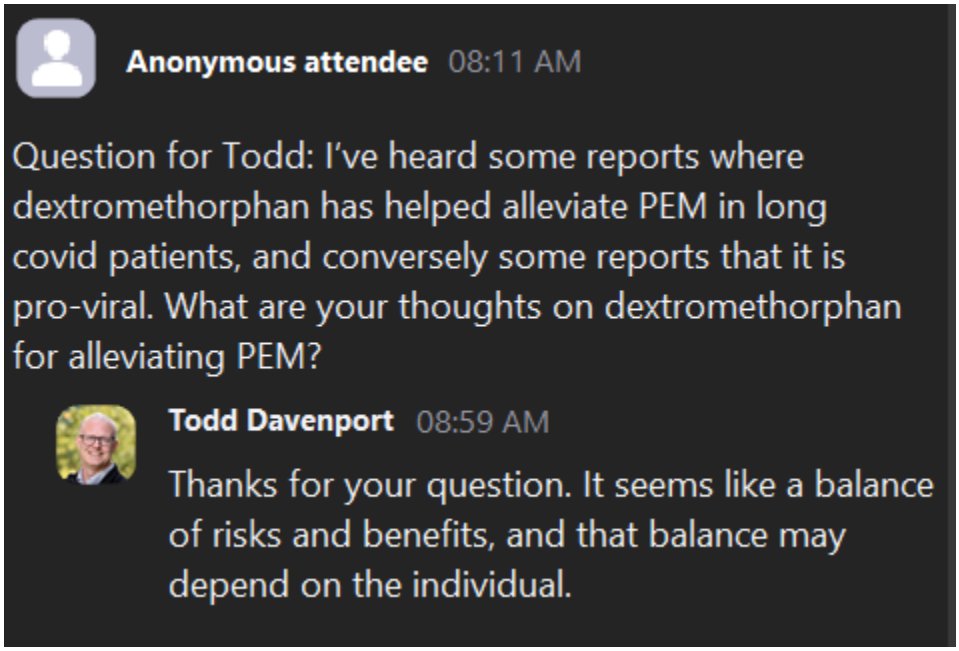
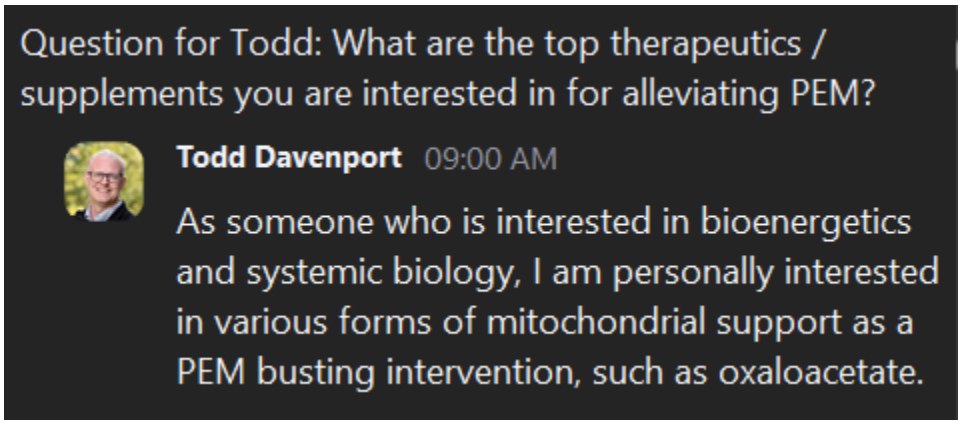
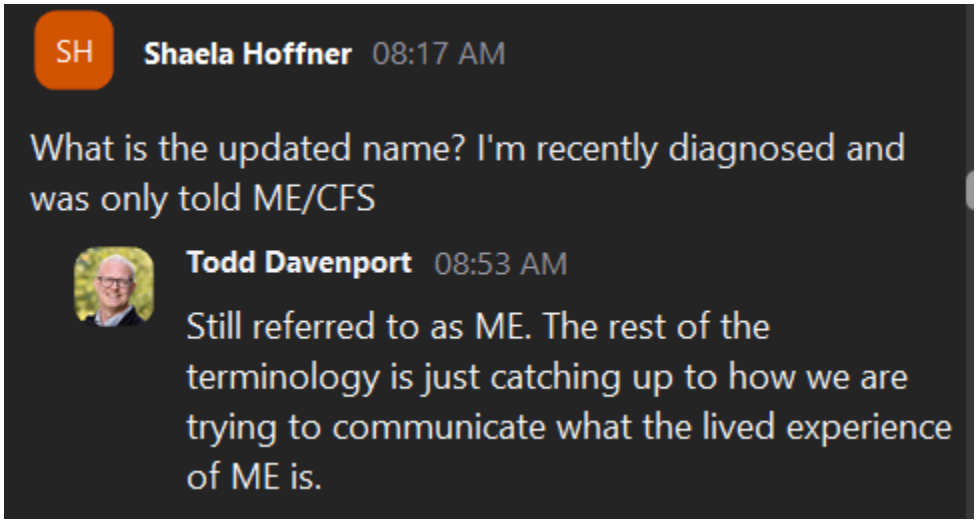
2026 OMF Community Symposium on the Molecular Basis of ME/CFS - Q & A







GW **Galen Warden** 08:20 AM

For speaker: is immediate exhaustion the PENE then? My very severe son experienced collapse immediately after exertion - or during - his is what ended the activity

Todd Davenport 08:55 AM

I am so sorry. Usually we think of the immediate response as PESE, but if the system is primed and/or the magnitude of exertion is high, there may be no/very little separation between PEM and PESE.

Anonymous attendee 08:27 AM

Q: Are there any commercially available mitochondrial tests that are showing promise in this area?

Todd Davenport 08:45 AM

There are a few patient-accessible mitochondrial tests available but the clinical applications (i.e., what to do next) are unclear.

IM **Iñigo Murga** 08:28 AM

Post-exertional malaise is nonspecific; multiple diseases present with this symptom. Subjecting a patient with ME/CFS to a bicycle stress test—or any other form of exercise—is dangerous and contraindicated, and it yields no molecular biomarkers. All research involves bioethics; non-maleficence and beneficence are among the fundamental principles.

We already know that when an affected individual exceeds their endurance threshold, they become severely ill and require a prolonged recovery period. This phenomenon occurs in other conditions as well, such as in rheumatology.

These tests are not the answer; they pose a danger to patients. It is not a universally applicable test; bedridden or housebound patients can barely support their own body weight—how could they possibly get on a bicycle?.

Todd Davenport 08:52 AM

Thank you for contributing your thoughts, friend. I would dispute your characterization of the ubiquity of PEM based on the definitions of ME relative to the other conditions you mentioned. Certainly all research involves a balance of risk and benefit, and this is no different.

RS **Rivka Solomon** 08:31 AM

Todd: should all past "CFS" studies that did not screen participants for PEM be disregarded? That is, should all studies prior to, say, 2014, be disregarded?

Todd Davenport 08:41 AM

I view these results with caution as unreliable. Specifically, the case definition introduces more noise than necessary that would seem to bias these studies toward the null hypothesis, so I am especially suspicious of any 'lack of differences' observed.

JI **Jason Isaia** 08:35 AM

Is their any science/advice towards using HRV monitoring to try to avoid PEM? Or atleast to use spoons when the risk is lower?

Thankyou

Todd Davenport 08:43 AM

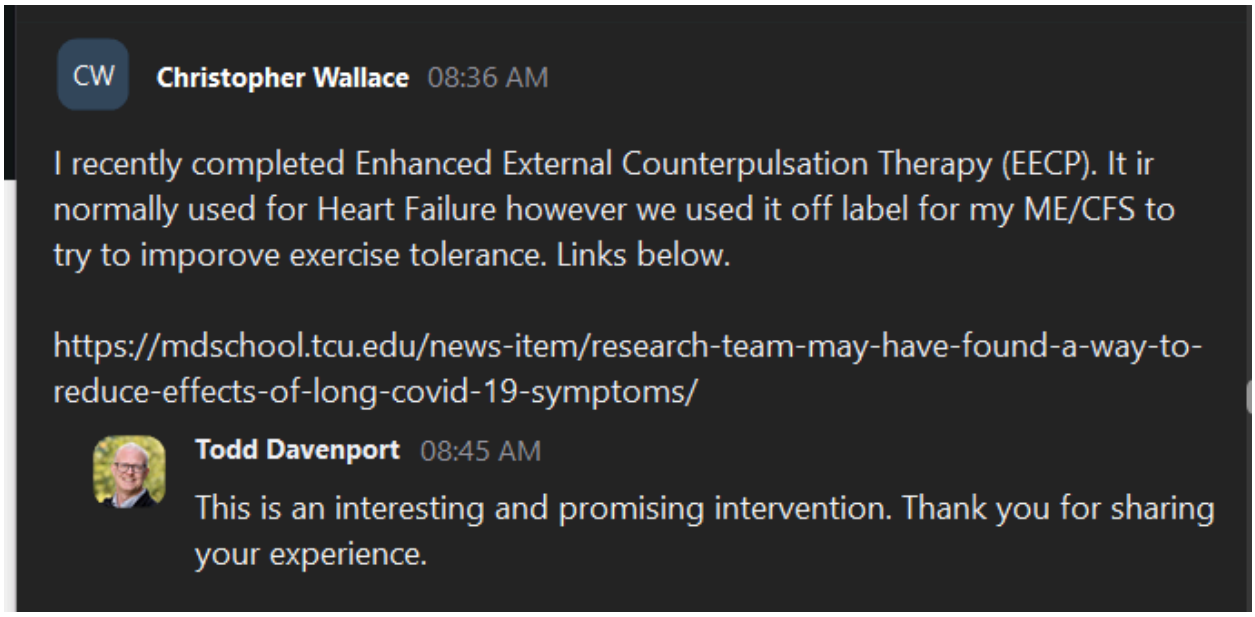
There is some information suggesting lower HRV during PEM, but that literature is hard to interpret based on the lack of transparency of all commercial devices. Our data (in preparation) suggests heterogenous autonomic responses to exercise, so the story may be more complicated than a wrist monitor gives. Hope to be able to provide more specific recommendations soon.

BK **Brynna Kelly** 08:35 AM

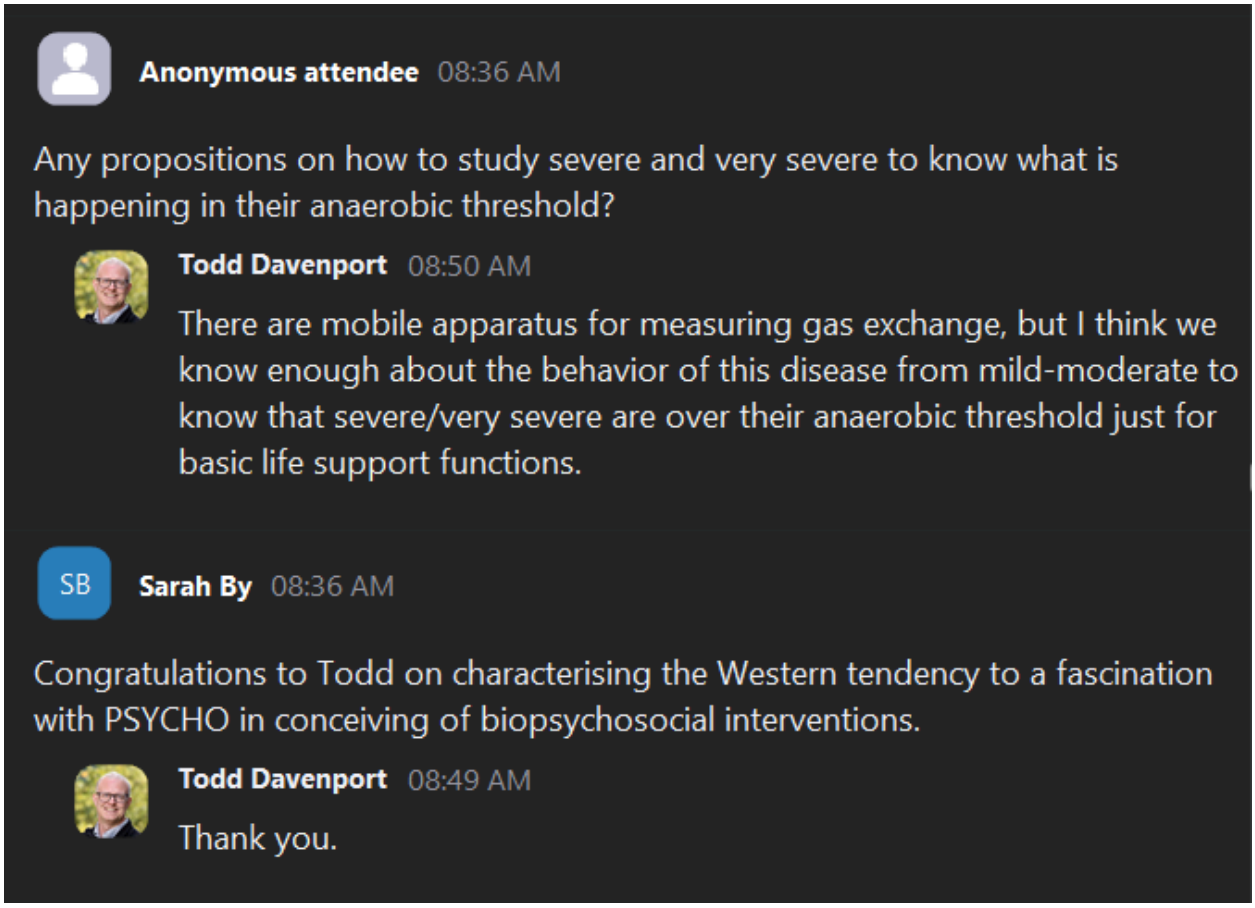
Prevalence of FND and ME together?

Todd Davenport 08:44 AM

The prevalence of PEM-related FND and no other atypical neurological findings must be zero by definition because the presence of PEM rules out FND.



https://mdschool.tcu.edu/news-item/research-team-may-have-found-a-way-to-reduce-effects-of-long-covid-19-symptoms/



JS **Jaime Seltzer** 08:41 AM

Todd brought up the need for mentorship for young researchers/scholars in the field. Wanted to point out that there is an EDS fellowship for people who want to become researchers in the field at the Norris Lab at the Medical University of South Carolina. It's particularly oriented to people living with EDS. Through a CIHR/ICanCME grant, I'm also running a mentorship program for MD/PhD, PhD, and MS Canadian students who want to study IACCs.

 **Todd Davenport** 08:48 AM

Thank you, Jaime! And thank you for your ongoing work in this space.

It is interesting to see the incidence of ME/CFS in Long COVID patients to be depicted as 10 - 30%. I more often read around 50% and even up to 58%.

KM **Kara Martin** 08:53 AM

Todd: Is there evidence of actual low blood oxygen during exertion? All heart and lung scans are mostly normal and no evidence of cause of my low oxygen with POTS. Frutrated with my care and lack of diagnosis. and doctors have offererred no clear next steps except supplemental oxygen and pt.

 **Todd Davenport** 08:57 AM

I am so sorry. We have not see desaturation at the systemic level. Oxygen saturation in the blood is something we measure on every test, and it is almost uniformly normal. Of course, that does not rule out the possibility of tissue level hypoxia.

Anonymous attendee 09:22 AM

If someone with long covid, POTS, ME , has no improvement with one bilateral SGB, does that likely mean multiple SGB's will not help?

LL **Luke Liu** 09:35 AM

SGB targets only one section of sympathetic chain. Have to evaluate other target sites, include celiac plexus, which I published on for long COVID. So, it really depends on the case.

MC **Marlon Couture** 09:27 AM

question for Dr. Liu: how frequently would be ideal to have SGB done for treating ME/CFS? (ie monthly, bimonthly) and should sides be alternated with each treatment or done closer together?

LL **Luke Liu** 09:39 AM

Closer together is the better approach, but doing so needs more technical expertise and experience, as well clinician availability. Cadence and frequency of the treatment depends on the individual case.

KG **Katherine Glass** 09:53 AM

Hello Sjoerd, thank you very much for your talk! I'm surprised the number of ME/CFS participants in All of US is so low with your criteria. Do you know the prevalence of ME/CFS based on your All of Us data and/or what was the total number of participants that you had available to select from?

SB **Sjoerd Beentjes** 11:05 AM

Hello Katherine, you're very welcome and thank you for your question, I should have mentioned this during the talk. We started with the All of Us cohort from our earlier work "Replicated blood-based biomarkers for myalgic encephalomyelitis not explicable by inactivity" (EMBO Mol Med, https://doi.org/10.1038/s44321-025-00258-8, please see the subsection "All of Us (AoU) cohort" in Methods). This consists of 903 cases and 75,943 controls.

From there, we restricted to participants (i) for whom their DNA variants (specifically, genotyped SNPs) are recorded, and (ii) that are of white genetic ancestry. To its credit, the AoU research program is set up to be far more diverse than UK Biobank, which is why our AoU replication cohort consists of 371 cases and 33,140 controls. So similarly a prevalence of 1.1%.

Just to note, our discovery cohort (UKB1) is the UK Biobank cohort defined in the same EMBO Mol Med paper (1,455 cases and 131,303 controls), and then subset to white British ancestry resulting.

https://doi.org/10.1038/s44321-025-00258-8.

LS **Laurids Stockert** 09:27 AM

@Luke: We have observed vagal cholinergic denervation of gastric mucosa in LC (Acanfora et al). Would it be interesting to test whether SGB partially alleviates that, or is there perhaps a more promising/ambitious marker you would consider in future studies?

LL **Luke Liu** 09:40 AM

Interesting finding. Email me for further discussion.

NW **Nicole Wenzel** 09:28 AM

I had good results with SGB in horses with sever CNS infections, esp. if they was hard to handle due to neurological deficiencies incl ataxia. I had often used it as part of treatement concept, and its funny to see it (20 yrs later) also works here, for me underlining, there is still an ongoing infection.

LL **Luke Liu** 09:42 AM

Thank you for the veterinarian experience. Curious how SGB was done on horses. Ongoing infection or source of the pathology should always be treated or removed.

WG **Will G** 10:28 AM

Are there any meds or supplements that you hypothesise could help to reverse the itaconate shunt or are beneficial?

Rob Phair 02:13 PM

Some patients have self-experimented with citraconate, an inhibitor of CAD. I've heard of only one who experienced benefit. We do not have any information on whether citraconate actually reaches the mitochondrial matrix where CAD is located.

PL **Patrick Lambe** 10:30 AM

For Phair, what is the suspected impact of the carbon/itaconate export into the cytosol derived from SLC25A10?

Rob Phair 02:15 PM

impact would be, in theory reduced ATP production per molecule of fuel,

Anonymous attendee 09:29 AM

I think that principal of early treatment, early exercise restriction, early intervention if at all possible seems critical to preventing long term and/or permanent injury. Should this principal be part of proposed treatment algorithms (if it is not already)?

LL **Luke Liu** 09:44 AM

I definitely agree! Earlier intervention, better prognocis and prevention o further downstream injuries.

WG **Will G** 09:30 AM

Roughly what percentage of long covid patients do you believe stellate ganglion blocks helps?

LL **Luke Liu** 09:46 AM

Depending on the severity and chronicity of the disease since initial Covid infection. Roughly 60-70% patients achieve meaningful improvement with just one set of the treatment. Rest require more repeated treatments and other forms of autonomic nervous system modulation.

LC **Lily Chu** 09:32 AM

Dr Liu: Do any of the patients you've treated have autoantibodies to adrenergic/ muscarinic autoantibodies? Or HRV evidence of sympathetic predominance at night or otherwise? Any possible ways to subgroup by sympathetic overactivity?

LL **Luke Liu** 09:48 AM

In clinical practice, it is difficult to study these autoantibodies due to resources. Would be great to look at these in future studies, in particular to see the treatment effect on these autoantibodies.

WG **Will G** 09:35 AM

Are there any particular symptom profiles that you think respond best to stellate ganglion blocks? Thank you!

LL **Luke Liu** 09:50 AM

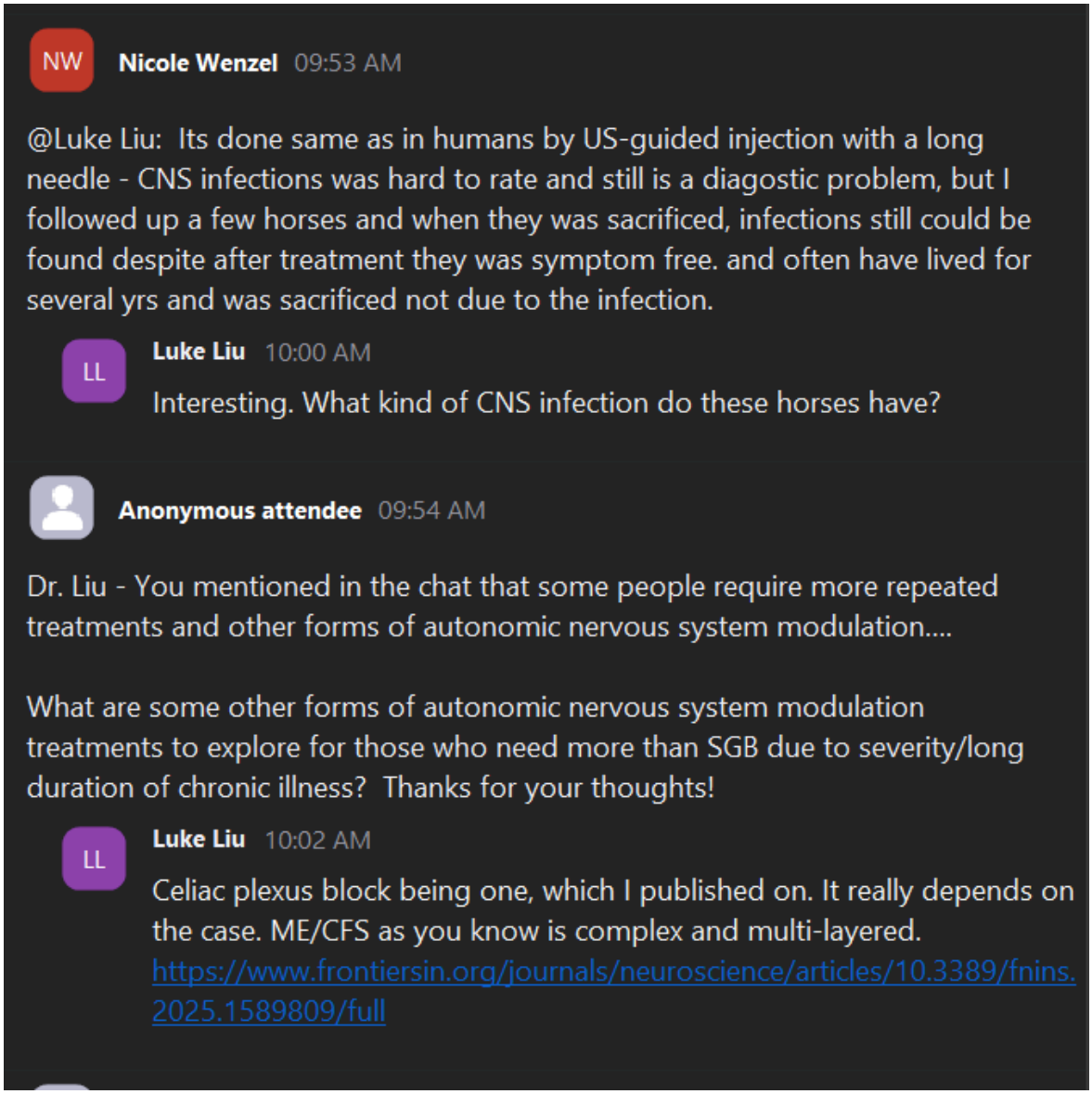
Symptoms of gross sympathetic hyperactivity. However, there are always exceptions.

JS **Julia Seidel** 09:35 AM

Question regarding Luke Liu & SGB: In your studies, did you differentiate between types of POTS? (hyperadrenergic, neuropathic, hypovolemic) Intuitively, hyperPOTS would be interesting. But also in terms of cerebral blood flow: 20 something % show reduced ceberal bloodflow for OI test even without increase in HR. Could that be potential biomarker? Was also wondering to what extent the presence of autoantibodies might interact with response to SGB? (because if there are autoantibodies, then blocking "native" SNS responses might not do as much?)

LL **Luke Liu** 09:54 AM

We did not differentiate between the different types of POTS. I think impaired cerebral blood blow is a major contributing factor in maintaining POTS symptoms. Optimizing cerebral and peripheral target tissue perfusion and function may be the key in treating hyperadrenergic / neuropathic POTS. Agree with autoantibody evaluation in studies. The question is would SGB decrease titers of these autoantibodies.



https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2025.1589809/full

MS **Marie Smith** 09:59 AM

Dr Liu: is there a fairly feasable way for ME/CFS LC patients to have a test done to get a sense for their cerebral blood flow? (What would that be? and would that build a case for SGB?)

LL **Luke Liu** 10:06 AM

In clinical practice, this is tricky. Transcranial doppler ultrasound is usually used in research setting. Not sure if MRA and CTA is worthwhile (risks/benefits) and cost effective for pre and post treatment evaluation.

TS **Toby Sawyer** 10:07 AM

Is a wearbable like the Lumia accurate enough to give us an idea of cerebral blood flow?

LL **Luke Liu** 10:16 AM

It is a superficial surface tracker. Not research grade to look at what's happening inside the skull.

AS **afiya sajwani** 02:57 PM

Dr Kilmas, what are your general recommendations for testing for mast cell activation, since the testing for it can be finicky?

Nancy Klimas 04:01 PM

i test - but negatives still end up on a test trial of mast cell stabilizers because it is hard to catch the tryptase/hitamine levels in a moment in time.

GB **Gerald Bourne** 03:07 PM

perfusion ?? What about oral nitrates (yes I an a cardiologist)

Nancy Klimas 04:00 PM

very reasonable in my mind - easy to test with the a cappliary scope

SB **Sarah By** 09:44 AM

Over what period of time were the data presented by Sjoerd gathered at UK Biobank? The diagnostic criteria for CFS was extremely broad and the graphic he presented changes from CFS to ME/CFS as if they are the same in the UK. The PACE Trial controversy was verified evidence they are not (and never were). 1.1% prevalence pre Covid is extremely high if the ME sample is screened for PEM.

SB **Sjoerd Beentjes** 10:23 AM

People will have self reported CFS or ME diagnosis from any time over their lives. UKB participants were sampled from older UK people (40-70).

The usage of CFS or ME/CFS reflects terminology used by UK Biobank (and/or All of Us) at the time. UK Biobank recruited participants between 2006 and 2010. At the time, the terminology "CFS" was used for the self-reported condition. The UKB pain questionnaire was sent out between 2019-2020 and completed by about a third of UKB participants. UKB used the wording "Have you ever been told by a doctor that you have had Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (M.E.)?" (the data field can be found here: https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=120010).

This is why we use "self-reported CFS" to describe the first strand of evidence found in the UKB, and "ME/CFS (Pain Questionnaire)" for the second strand of evidence. I agree they are not the same, and where possible we refer either to "people with ME" or "people with ME/CFS".

https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=120010

AH **Ashley Hoven** 09:41 AM

Why did the study exclude based upon ancestry/ race?

SB **Sjoerd Beentjes** 10:22 AM

Thank you for this important question. Differences in ancestry can create spurious associations between genetics and trait. Non-white British ancestry is, unfortunately, very low in number in the UK Biobank. We therefore restricted to white British ancestry to ensure our results are not due to ancestry differences. More broadly, you raise an excellent point: It is crucial that cohorts/studies utilise data from diverse populations where available.

Anonymous attendee 09:50 AM

For Sjoerd: Why is predicted white British ancestry required as a control?

SB **Sjoerd Beentjes** 10:21 AM

Thank you for your question! Since we restrict to predicted white British ancestry for our cases, we similarly do so for controls. This is to ensure that any results we find are not due to ancestry differences. In short, our entire cohort (case + control) is of predicted white British ancestry

CJ **Cynthia Johnson** 10:00 AM

What is the next steps with DeCode ME related studies?

SB **Sjoerd Beentjes** 10:51 AM

DecodeME is currently awaiting the reopening of the UK Biobank compute infrastructure; it has been closed to all users since April. Realistically - given that the infrastructure will initially have limited functionality - DecodeME will revise its preprint asap in 2027.

JS **Julia Seidel** 10:00 AM

Questions for Talk of Sjoerd Beentjes: To what extent were your selection criteria specific for only ME/CFS as opposed to PAIS more generally? (E.g. the PQ, iirc from the slide, only seems to question for PESE, instead of truly (delayed) PEM?)

SB **Sjoerd Beentjes** 10:51 AM

Thank you for this question Julia. The PQ in UKB specifically asks "Have you ever been told by a doctor that you have had Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (M.E.)?" (this can be found here on UKB's data browser: https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=120010). Only if a participants answers "Yes" here, they get asked the three follow-up questions I mentioned during the talk. We only include someone with the PQ strand of evidence if they provide the specified answers to all three questions. So the PQ strand of evidence is specifically about ME/CFS diagnosis and symptoms, not PAIS.

That said, we agree that there are no adequate questions fully specifying PEM in national Biobank cohorts; this needs to change.

https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=120010

PM **Paolo Maccallini** 10:11 AM

@Sjoerd Beentjes: will the summary statsitics of the discovery and replication cohorts (UKB1, UKB2, AofU) made available?

SB **Sjoerd Beentjes** 11:12 AM

Thanks Paolo. I forgot to mention during the talk that we have submitted a preprint with our results to MedRxiv a couple of days ago, so this will be able on MedRxiv early next week under the same title: "Seven replicated genomic association of myalgic encephalomyelitis/chronic fatigue syndrome: a biobank study". This includes the summary statistics of the discovery and replication cohorts, everything presented today, as well as further discussion on the 7 replicated variants.

IB **isaac bickley** 10:26 AM

having an 8 hour schedule with only one 15min break is inaccessible and exclusionary to people with ME who might want to watch this live (since it is about us!). posting recordings after the fact does improve accessibility but doesn't excuse excluding people with ME in this way. this could easily be improved in future by adding more frequent/longer breaks, or spreading the symposium over multiple days.

Ashley Haugen 10:31 AM

Unfortunately we are restricted by availability. We currently don't have the staffing and availability to run this over multiple days. We discussed having longer or multiple breaks but decided against it because it would greatly limit the number of speakers we would be able to have. We decided people would appreciate more speakers over more breaks with the ability to watch anything missed in the recorded version. I totally understand it feels exclusionary but we do discuss the best way to approach it to make it available to the most amount of people possible while also getting the most information out about research that we can.

Anonymous attendee 10:55 AM

Dr Davenport: If 2 day CPET testing reveals low Oyxgen Pulse, does this confirm oxygen is not getting to cells/muscles? Does this suggest a root cause at the mitochondrial level or are other factors likely at play?

Todd Davenport 11:57 AM

Excellent question. O2 pulse is a measure of oxygen delivered per heart beat. However, it is agnostic to the underlying mechanism. Two potential reasons are impaired peripheral oxygen extraction or cardiac pumping impairment. It may be artificially elevated by beta blockers that reduce heart rate, thereby decreasing the denominator of the equation.

RG **Robyn Goldstone** 11:28 AM

This is not a question and, I am aware that I am among many medical minds - however, as a layperson and someone suffering with X, Y and Z..

I would just like to take this opportunity to thank each and every one of you that is working tirelessly, having the passion and interest in the areas that you do and for giving me (and I know many others) hope.

I first attented your symposium virtually last year and every single time I am met with any kind of medical brick wall or get answers such as "they may never have any answers.." in general, all the work you all do has given me one of the most precious things - not only hope but belief.

Thank you so much.

Ashley Haugen 11:33 AM

Thank you for sharing. We absolutely know how hopeless it can feel. Many of us have personal ties to this disease. Just always remember there are hundreds of scientists across the world working tirelessly day and night to figure this out. It can feel like it will never happen but none of them have given up and we have new researchers in the field all the time bringing fresh perspectives and new research. Most of these scientists have dedicated their entire lives and existences to figuring this out for all of you and we have enough hope for a cure for everyone. We're happy you could be here today to restore a little hope to get you through.

VA **VERONICA ATHIE** 02:00 PM

To Daniele Medows: Do you think the reseacrhers running the RECOVER trials are open to go back and reanalyze the data considering patients profles subgrouping?

DM **Danielle Meadows** 02:07 PM

I certainly think it's possible they would be open to conducting subgroup analysis. And I also think there will be ways for non-RECOVER researchers to access de-identified data from those trials and do some of that work.

Anonymous attendee 02:02 PM

For Danielle: where can we as patients register for Me Cfs studies? thank you so much for your aggregated information!!

DM **Danielle Meadows** 02:05 PM

Thanks for your note! If you're interested in participating in ME/CFS research, you can sign up for the StudyME registry here: https://www.omf.ngo/studyme/

https://www.omf.ngo/studyme/

LB **Lucy Berlin** 02:04 PM

Is there a way to see if one has already registered into the Study ME database, AND to update one's information with added lab results or diagnoses that would be useful to precision medicine researchers?

DM **Danielle Meadows** 02:13 PM

StudyME serves as a connection between researchers and participants, so we don't maintain health information in the platform. But if you want to know if you have registered or if you need to update your contact or demographic information, please feel free to reach out to me at studyme@omf.ngo

Anonymous attendee 02:07 PM

With all these talks about finding the right subgroups or category of responders, how can we prevent null results from being ignored?
Don't you have to be extremely careful not to take the easy way out when dealing with negative studies—simply claiming that you included the wrong "subgroup" or didn't stratify enough?

It's something already happening with BPS "therapies" like Brain Retraining or physical rehabilitation, where the people pushing these always point to an ill-defined subgroup who profits from their "therapies" when being confronted with contrary evidence. I see a real danger that something like this could also happen in more serious biomedical ME-research.

DM **Danielle Meadows** 02:11 PM

This is a great question. This is partially why I personally prefer the pre-stratification approach. If you are testing a specific hypothesis. It becomes easier to interpret results as positive or negative (rather than mixed) and in some senses, as a researcher, it feels like a clearer answer to whether my hypothesis was correct or if I need to move on to something else.

Anonymous attendee 02:09 PM

Are there any commercial tests that would detect problems with neutrophils? Thank you!

Ron Davis 02:11 PM

Not that I'm aware of

EK **Elliott Karetny** 03:29 PM

Could oxygen consumption be different based on cells that don't have as much of a glycogen reserve (like neurons, from what I remember.) vs ones that do have access to glycogen like muscles?

Nancy Klimas 03:40 PM

that came up yesterday as an area that could be driving some of this. neeeds some study

CI **Christina Ignacio-Deines** 03:32 PM

In defining subgroups, have clear (or even fuzzy) cohorts emerged from patients whose total symptoms have been catalogued?

Nancy Klimas 03:44 PM

well yes - particularly in interventive trials that are targeting something specific (like a specific cytokine) but we also do gender differences, duration of illness differences. our modeling has a different treatment for post menopausal women from premenopausal which is difernt from men

Anonymous attendee 03:35 PM

If EBV vaccine was developed, would RFK Jr allow it?

Nancy Klimas 03:47 PM

it hs m been developed - by moderna. so will we get to test it? good quesiotn

MT **Maria Tribe** 03:37 PM

What are your views on the repurposing of GLP+GIP (Tirzepatide), as a microdosed therapeutic for stabilising mast cells?

Nancy Klimas 03:51 PM

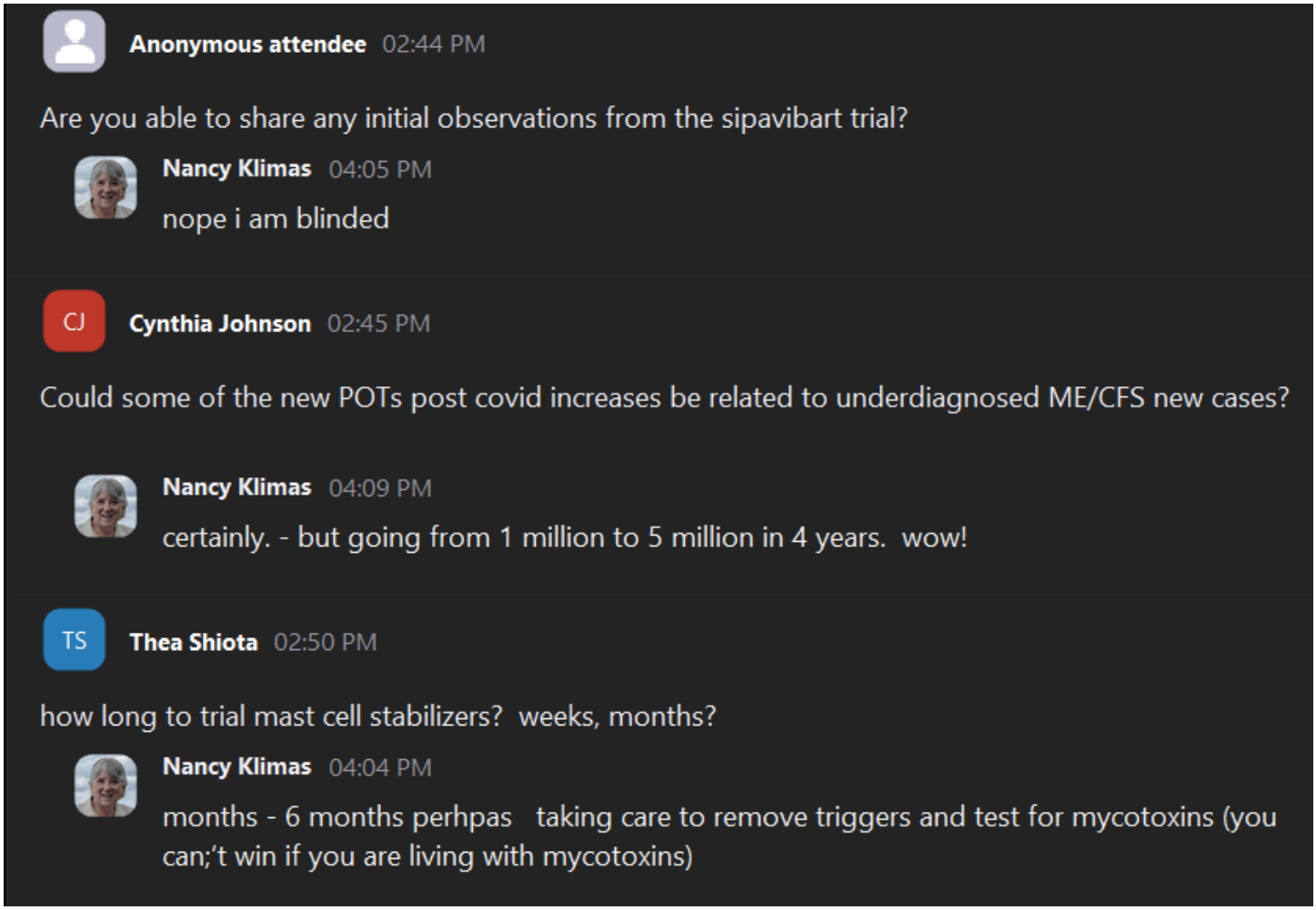
David should answer tis one but there is a mechanism that makes sense. The Scripps study is not microdosing but not advancing to max if the subject doesnt want to. thats 1000 patients! that should teach us sometihng

PR **Patricia Ritchie** 02:51 PM

Quercitin schmercitin! I've been taking it over a year with no observed result. Dies it really work for anyone??????????

Nancy Klimas 04:02 PM

one is rarely enough. luteolin, quercitin , rutin ketotefin plus pepcid .....



Speaker Discussion – Community Symposium

1. There are ~4 x 10^{13} cells in a human body. In a severe ME patient, how many cells are sick? How could we find out?
2. ME research is torn between a search for a global cure and a biomarker-based subgrouping of patients aimed at finding therapies that work for some. Do you see subgrouping as ideal or merely practical?
3. Diverse symptoms and patient heterogeneity may be due to different disease mechanisms or to different cell types expressing the same organellar dysfunction.
4. Some of our speakers and discussants see ME as an immune system disease, some as a disease of vascular biology, some as a disease of the CNS or the ANS, some see a disease of myocytes, and some argue that what all these have in common is central carbon metabolism and organelle function. How do we distinguish cause from effect? Primary from secondary?

See Recording for full answers

1.) ???

2.) Sometimes initial research is done with the thought that a subgroup may be identified for further research. Historically, research which has tried to find therapies that help everyone have not been that successful. But trials that don't focus on subgroups might not grant information on the foundational mechanisms of the disease.
3.) ??
4.) It is risky to try to look for a single cause. ~ Dr. Kaufman
Our capabilities to study ME/CFS are limited by capturing it when people are fully symptomatic. ~ Dr. Yellman

Speaker Discussion$_2$ – Community Symposium

1. There is a necessary tension between theory and observation. Do we want to design trials based on heterogeneity of patient symptoms/biomarkers, or based on what would help if a given theory is correct? Perhaps, some of each (suramin?).
2. One approach to animal models is to build an animal model of the hypothesis you want to test. When the Peterson lab expresses the human ACOD1 gene in zebrafish and observes an ME-like phenotype, we immediately test drugs that block the shunt, but should we also test drugs targeted at specific cell types or specific molecules? What do you infer from our zebrafish results?
3. In a serious infectious disease, 0.01% to 1% of body cells are infected. If we consider an ME-triggering infection,

Speaker Discussion$_3$ – Community Symposium

1. What do we know about the tropism of viruses associated with ME? Do the infected cell types matter? Or is it an aberrant interaction between the immune system and the microbe that sets the disease course?
2. Does GWAS tell us about predisposition? Should we expect GWAS hits to constitute molecules in the chain of cause and effect? Or should we look to GSEA to put us on the causal path?
3. What mechanisms might explain the fluctuating course of ME? Even on a time scale of days?

Above not answered due to time restrictions.