Dr. Bateman delivered a presentation to an audience of scientists and clinicians at the ME/CFS International Conference 2021: RID-Research Innovation and Discovery. The following is a transcript of her online presentation. The video can be viewed at:
https://youtu.be/5Gf40qzKC4A

The Clinical Presentation of Long COVID Subset Similar to ME/CFS

November 2021

Hi, it's great to be here with you. I'm really enjoying the conference and I hope you are too, and thank you very much for inviting me to speak. I'd like to talk now about the clinical presentation of a Long COVID subset that's very similar to ME/CFS. The Bateman Horne Center is a non-profit organization with a clinical research department and a full educational department for the dissemination of educational resources. Our mission is specifically to improve the lives of people with ME/CFS, fibromyalgia, post-viral syndromes, and the conditions that we find common in this group of people.

The principal goals of seeing Long COVID at Bateman Horne Center, and including them in research, has been really strategic to compare Long COVID, which is an early post-viral illness (at least at this point), to ME/CFS (a long-standing illness). It is known in the majority of cases to be a post-viral or post-infection condition. We want to learn about the clinical presentation of Long COVID and try to determine what is causing it, to help us understand ME/CFS better and to determine if understanding Long COVID can help improve ME/CFS diagnosis and treatment.

We're all familiar with this horrible COVID-19 pandemic and becoming increasingly aware of the many lingering consequences after infection. So, for the ease and simplicity of this short talk, I'm going to just talk about one of two main groups:

- There's a group of people who were in the hospital with severely impaired and lingering organ damage that's identifiable.
- Then there's another group of people that we're focusing on, people with mild to moderate COVID, acute COVID, but with apparent lack of recovery, or sometimes becoming increasingly worse in terms of symptoms and impairment after the acute infection, yet without apparent biological markers.

Keep in mind right now the world is calling all lingering unresolved symptoms of acute COVID-19, Long COVID, Long Haul COVID, Post-COVID, and similar designations. So, we don't know yet how many people will go on to be chronically ill and meet the ME/CFS criteria. Hopefully only a small number. The Long COVID participants at Bateman Horne Center have been carefully screened, recruited through a private Long-Hauler Facebook group in our state that has more than 3,000 members, and specifically screened to bring in people interested in coming to the

clinic who were never sick enough to be hospitalized, and who have an uncomplicated medical and psychiatric history prior to acute COVID. Those who have remained sick at least 3 months after COVID-19, and in the case of our first 50 or 60 patients, more than half have been sick longer than a year.

We have seen more than 60 Long-COVID patients at our clinic now, 40 of which have been recruited for NIH-funded research participation. Before coming to the clinic we had them fill out a number of questionnaires and one of these questionnaires was to screen for the U.S. Institute of Medicine, 2015 ME/CFS Clinical Diagnostic Criteria. These are the core symptoms and they must be scored in order to meet the criteria, and the symptoms must be frequent and at least moderate to very severe. So, those on the left, impaired function are associated with fatigue, post-exertional malaise (PEM), sleep disorders, cognitive impairment, and/or orthostatic intolerance (OI). And at least 60 percent of our applicants met the Institute of Medicine criteria for ME/CFS based on the pre-screening questionnaires. We also asked about other common symptoms: widespread pain, headache, POTS, allergies, and sensory sensitivities. You can see not quite as many as the core symptoms, which would make sense, but still a sizable number had these symptoms, by questionnaire, present at least 50 percent of the time and considered moderate to very severe.

We also took a symptom list from the WHO Long-COVID recommendations for research and other published literature to query our patients about whether they had these symptoms in the top box or those that were present in more than 50 percent of our applicants, and those on the bottom who are less common in our applicants.

I think it's kind of interesting that the common short-term consequences of COVID: a cough, wheezing, and long symptoms, as well as the loss of taste and smell were relatively less bothersome for this group of patients. So, after seeing these patients and doing pretty extensive evaluations and treatment in our clinic, I will say that these important comorbid conditions should be considered and cognitive impairment can definitely be very significant. We've seen many forms of orthostatic intolerance and dysautonomia, we've seen mast cell activation (MCAS), a ramped-up allergic response system, and we think there's probably a high-frequency of small fiber-neuropathy (SFN) based on clinical presentation, but we haven't done skin biopsies in this cohort. Many have sleep apnea or other primary sleep disorders, gastrointestinal problems, and of course meeting the ME/CFS criteria if their symptoms have persisted more than 6 months, and meet the established criteria usually using symptoms and symptom frequency and severity.

I want to point out a few individual things, the post-exertional malaise (PEM) reported by our Long COVID cohort is very similar to the PEM of ME/CFS in early 2021. We published a paper, it's referenced down below, looking at 150 ME/CFS patients enrolled in the NIH-funded Collaborative Research Center research. This was 75 patients whose illness was less than 4

years and 75 patients whose illness had been present more than 10 years. So, we compared early-onset and long-established illnesses in terms of post-exertional malaise. What I'm showing you here is the values from those patients in the ME/CFS column and the values of our first 80 Long COVID applicants when they filled out the post-exertional malaise questionnaire. You can see that the onset timing and the time to resolution of post-exercise is very, very similar between the 2 cohorts.

This is a little bit too small to be showing you, but this shows the more in-depth questions that were asked in this post-exertional malaise questionnaire and you can see on the ME/CFS in the second column and the Long COVID patients in the first column. So, the ones with the low p-values are the columns that were kind of different in our cohorts. You can see that inducing PEM with high physical exertion, I think this really came out this way because our ME/CFS patients don't go to high physical exertion, they avoid it. It's not showing up as often but some others fatigue and sleepiness was more common, respiratory complaints more common in the Long COVID, secondary mood symptoms much more common in this acute a confusing disorienting phase of illness, etc. And so while there are some really good similarities there are also some differences which we feel may relate to the virus but mostly relates to the early-onset nature of the illness and lack of adaptation. We know that orthostatic intolerance plays a primary role in the impaired function of our Long COVID subjects, especially those that meet ME/CFS criteria. We know this because every Long COVID patient in the clinic, and those who engaged in enrolled research, underwent a 10-Minute NASA Lean Test and a DANA Cognitive Test before and after the orthostatic stressor.

So, just as a reminder, this test is when the patient spends 10 to 15 minutes supine, in a quiet dark room, letting their heart rate and blood pressure kind of relax down to resting levels. Those are recorded then the patient moves a short distance, stands in a relaxed way with their shoulder blades against the wall while the heart rate and blood pressure are checked for the next 10 minutes. This is one Long COVID patient, a stunning example, but we have seen many like this, a male teacher aged 45, 6-7 months since his acute COVID and you can see in the resting state his heart rate is 65, climbs rapidly and that test was terminated at 8 minutes when his heart rate reached 138. You can see many, many symptoms relating to altered perfusion both centrally and peripherally. So, he meets the criteria for POTS with this rapid heart rate increase. But, these are symptoms from both groups that were assessed before, during, and after the 10-minute NASA Lean Test. The blue bars are the ME/CFS patients, the orange bars are the Long COVID patients, and the gray bars are those that matched healthy controls in the ME/CFS study. The first graph is fatigue, the first column is before the Lean Test, the second is just before the Lean Test ends 9 minutes into the standing portion of the Lean Test, and immediately after the Lean Test, a day later, and a week later they were able to just give a numeric score assessed to their fatigue, brain fog, feeling light-headed, and dizzy, nauseated, breathing discomfort, and pain anywhere**.** You can see the parallels with actually higher bars in

our Long COVID cohort relating to the orthostatic intolerance, brain fog, and breathing discomfort.

In 2020 we published a paper looking at our ME/CFS population in the Collaborative Research Center during the Lean Test. That again, as a reminder, there were 75 healthy controls, 75 ME/CFS patients ill more than 10 years, and 75 who had been ill less than 4 years. This is another way of looking at the effect of orthostatic stress during the Lean Test. This shows the pulse pressure and the ratio of pulse pressure to systolic pressure which surely shouldn't drop to less than 25 percent. Everybody drops a bit. The top line and this is going through the 10 minutes standing, healthy controls, long-standing ME/CFS illness, and you can see that the shorter duration illness patients really did not compensate as well and had a very significant drop toward the latter stages of the Lean Test. So, we took this same group of ME/CFS patients lumped them together and this graph shows our Long COVID patients during the Lean Test. These values here show baseline pulse pressure over systolic pressure and then you can see that in the healthy controls the perfusion, or this value, stays about the same in our combined group of ME patients. You can see that it dips but doesn't go below that 25 percent and you can see it's precipitously going down in our Long COVID patients. This is just normalized at zero to show and these are statistically significant differences between our groups.

The cognitive impairment of Long COVID subjects is also significant in our Long COVID cohort and may be even more severe than we've been seeing in at least the ME/CFS on patients well enough to enroll in our research protocols. So, before and after the NASA Lean Test we have patients undergo a very quick computerized cognitive test with 3 components: the simple reaction time, the procedural reaction time, and what's called Go-No-Go. But, I want to just show you the results of the simple reaction time in our Long COVID cohort compared to our combined ME/CFS patients and healthy controls in the same group. So we're only talking about now a score of cognitive efficiency based on simple reaction time. The first column is ME/CFS, this point would be before the Lean Test and this would be immediately after the Lean Test once sitting back down. Long COVID patients started lower and still went low and our healthy controls started higher and actually got a little better. So no orthostatic change, induced changes, on their simple reaction time. And we saw similar trends for the other tests as well.

We feel that studying Long COVID can bring us closer to understanding the underlying pathophysiology of ME/CFS, identifying biomarkers and diagnostic tests for ME/CFS, and hopefully bring us closer to using this information to move toward clinical trials, and specifically, treatment trials for Long COVID and ME/CFS.

What is needed next, massive funding to study people who've had COVID and haven't recovered and you may have heard that there the U.S. NIH Recover Initiative, which is just getting going, has appropriated 1 billion dollars; half of that will be going into studying Long

COVID longitudinally and doing as much testing as possible with the other half reserved possibly for treatment trials.

We need constant reminders to Long COVID researchers about what we have learned from studying ME/CFS and common comorbid conditions. So thank you to our team and people we work with. We have 6 clinicians, 2 of which are physicians at Bateman Horne Center. We have some very good outside collaborators at the University of Utah. I've put our research team here in red. We have substantial funding for this large study through the NIH as part of the Collaborative Research Centers, but also we're very grateful for the funding from private donors, the participation of our patients, and some of the other foundations that have been helping us with our research.

And while I close, these are some papers that we've been able to publish in the last 2 years based on the information clinically we've learned from our enrollment of patients in the Collaborative Research Centers trial.

Thank you very much for the chance to share my research and insights and I look forward to more time with the group and answering any questions that might be relevant or helpful.

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We advise viewers to carefully review and understand the ideas presented and seek the advice of medical providers with any questions you may have as it relates to your patient-specific situation.

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