Transcript

Dr. Christine Bevc:

Thank you for taking the time to view this recording. The webinar you're about to see features a panel for RECOVER investigators, Dr. Upinder Singh, Dr. Tanayott Thaweethai, Dr. Andrea Foulkes, Dr. Sairam Parthasarathy. As you're listening to the recording of this webinar, you'll hear their names fumbled and mispronounced. Names are powerful. They represent and reflect the principles of equity, diversity, and inclusivity that we strive for in this initiative. We wanted to take this moment to get it right and make sure that you have an accurate pronunciation for each of their names. Dr. Upinder Singh, Dr. Tanayott Thaweethai, Dr. Andrea Foulkes, and Dr. Sairam Parthasarathy. Thank you.

Dr. Upinder Singh:

Good morning, good afternoon, good evening everyone. Thank you so much for joining us. We're excited to present on behalf of the RECOVER Consortium, the findings from our first manuscript. Next slide please. So just to remind everybody that RECOVER is in fact national in scale and inclusive of participation. And so as the goals have been outlined there to predict, treat, and prevent long COVID and PASC, and in this effort, there's multiple different realms. There's autopsy and tissue pathology studies, a number of clinical trials at Wilson, becoming studies using electronic health records and studies using pathobiology. And then what we're going to focus on today are the longitudinal observational cohort studies of which there's both adult and pediatrics.

This discussion today will focus on observations from the adult longitudinal observational cohort studies. I do also want to mention that RECOVER is patient-centered and patient inclusive, and so a patient perspective has been utilized during the development of the protocol as well as the year has gone on with modifications. Next slide. This is just to remind everybody that in fact, RECOVER is a nationwide inclusive effort.

There's over 200 enrollment sites as are shown on the map in 33 states, Washington, DC and Puerto Rico. And so again, the goal is to have a diversity of sites, diversity of participants, and be wholly inclusive. I'll hand over to Dr. Sairam Parthasarathy for the next slide.

Dr. Sairam Parthasarathy:

Thanks Upi. I will be, if you just go to the next slide, I'll be covering the objectives of the RECOVER study.

So the Researching COVID to Enhance Recovery or otherwise known as the RECOVER study is a multi-site observational study of PASC in adults. And these are the objectives. First to characterize best prevalence, characterize the symptoms, organ dysfunction, natural history, and the distinct phenotypes of PASC. Identify demographic, social, clinical risk factors for PASC, onset and recovery, as well as define the biological mechanisms that are underlie, PASC pathogenesis. And specific to today's discussion, if we go to the next slide, we will be talking about what are the knowledge gaps that we'll be addressing today, which was generated by this JAMA paper. What symptoms are differentially present in SARS-CoV-2 infected individual six months or greater after infection compared with uninfected individuals? As well as what symptom-based criteria can be used to identify post-acute sequelae SARS-CoV-2, otherwise known as PASC cases? So with that, I'll hand it over to our next speaker.

Dr. Andrea Foulkes:

Thank you so much Upi and Sai. Please bear with the next slide. Thank you. So it's a pleasure to be here today along with my colleague Tanayott Thaweethai from Massachusetts General Hospital on behalf of the RECOVER Consortium authors and collaborators. I'm going to begin by providing a brief motivation and overview of the RECOVER adult study design and then Dr. Thaweethai will present the methodology we applied in some of the more significant findings of the recent manuscript in JAMA. And finally we'll wrap up with a summary of the limitations, significance and next steps. So next slide please. So the analysis we are presenting today was based on survey data collected on just under 10,000 RECOVER adult participants including approximately 8,600 and infected and 1,100 uninfected individuals. The principal goal was to derive an approach to identify adults with long COVID based on self-reported symptoms. That is we aim to leverage the available information on the full array of

symptoms reported by each of the approximately 10,000 RECOVER participants, both infected and uninfected to arrive at what we've been calling a working definition of long COVID.

And the term working definition is important here because it emphasizes two complimentary aspects of this work. First, the findings represent a significant step scientifically in that they provide a rubric or rule for researchers to identify individuals with long COVID. This step of defining this rule for identifying individuals is essential for characterizing sub phenotypes that is different manifestations of long COVID, evaluating potential risk factors, investigating mechanisms of disease, and ultimately developing and evaluating interventions. Secondly, the term working is used as the findings provide a framework that can and will be further refined through the integration of data on clinical and subclinical assessments, including laboratory tests and imaging studies. Further analysis that integrates data across these different realms to refine and update the definition of long COVID is a crucial next step. And importantly, based on the findings that Dr. Thaweethai will be presenting, we now have the groundwork or a framework for doing that integration and ultimately arriving at a more discriminating, inclusive and precise definition. Next slide.

So an overview of some of the important features of the RECOVER adult study design is provided here and in this visualization each line represents a person and the X axis that's shown at the bottom of the slide is the time from initial infection or a negative test for SARS-CoV-2. And one important thing to note here is that infected participants in RECOVER adult did not need to have a positive PCR test to be classified as infected. Rather, they needed to meet the WHO definition of probable suspected or confirmed SARS-CoV-2 infection. Well, hear that RECOVER adult is an observational prospective cohort study, which means that participants answered survey questions and had checkups and tests at regular intervals over time and they did not receive any treatments or interventions as part of the study. So the shaded rectangles in this figure are the enrollment visits that is the first visit in the RECOVER study and the ovals represent follow-up visits which occurred approximately every three months after enrollment.

As indicated on the left-hand side, there were two distinct cohorts. The acute cohort, which included participants with an enrollment visit, again, the shaded rectangles during the acute phase and that acute phase was defined as within 30 days of infection or a negative test. The post-acute cohort included participants enrolled during the chronic phase that is more than 30 days after the date of infection or a negative test. And as depicted in this figure, post-acute participants could enroll during any visit and enrollments ranged from visit month zero to visit month 12 or later. Both the acute and post-acute cohorts included infected participants as well as uninfected participants. And importantly, the uninfected participants were critical here as they served as contemporaneous comparator groups. The acute cohort made up about a quarter of the full cohort and overall there was information on about eight infected participants for every one uninfected participant in this study. Next slide.

So some important differences existed between the acute and post-acute cohorts, which are important to emphasize and are highlighted here as these differences were presented or were present, I should say by design and will help put some of the findings in context. So first of all, the post-acute cohort included participants who were infected both before and after the time that the Omicron variant became dominant in the United States. That is before and after December 1st, 2021. The acute cohort, on the other hand included almost exclusively participants who were infected after the Omicron variant became dominant. A second important feature to note is that RECOVER enrollment began after vaccines had become widely available. As a result, the acute cohort participants were largely fully vaccinated at the time of enrollment. The post-acute cohort, on the other hand included participants who were vaccinated at the time of infection as well as those who were not vaccinated at the time of their infection. In both cohorts, the large majority, approximately 90% of the participants who were first infected when the Omicron variant was dominant, were fully vaccinated at the time of this infection. Next slide please.

Ongoing data collection for the RECOVER cohort includes demographic data, self-reported symptoms as shown here in this slide, as well as social determinants of health, laboratory tests, clinical assessments and clinical histories including acute phase treatments and existing and new onset comorbidities. Select participants also receive additional tests and procedures including, for example, the six-minute walk test, chest CTs, renal ultrasounds, vision tests, and pulmonary function tests. The data used for this first analysis that were presenting today was limited to 44 self-reported symptoms spanning these multiple organ systems and associated severity

measures data on preexisting comorbidities and demographics at the time of enrollment or infection, including age, sex assigned at birth, race and ethnicity. Viral variant and vaccination status were also considered. Next slide.

Finally, in terms of the design, the initial analyses focused on a single time point per person that occurred at least six months after the initial infection. That means for acute cohort participants, symptoms reported at the six-month visit, which was the second follow-up visit were used in the analysis. But for participants in the post-acute cohort, the first visit at six months or later was used. So for example, if a participant enrolled at three months after infection, then their symptoms at the first follow-up were used. However, if a participant enrolled at 12 months after infection, then their enrollment symptoms were used. So that's an overview of the design and I'll hand it over now to my colleague Dr. Thaweethai who'll discuss the approach and findings.

Dr. Tanayott Thaweethai:

Thank you. Go to the next slide. Great. So I'm going to be talking about the approach for the analysis.

Next. Sorry, next slide. Thank you. So the goal of the analysis was to develop a definition for PASC or long COVID by pinpointing combinations of symptoms that can be used to identify people with long COVID. And our approach for doing so was to identify combinations of persisting symptoms which were present six months or more after an individual's index date, which is their infection date for infected individuals and a negative test date for uninfected individuals. And to figure out which symptoms are different between people with and without a history of SARS- CoV-2 infection. Next slide.

So we put together this figure to summarize the rationale for why comparing symptoms between infected and uninfected participants can help us define long COVID. So across the top we have types of participants starting with uninfected participants, then among infected participants fundamentally there are two types. There are those without long COVID and those with long COVID. So that's the PASC negative and the PASC positive and that's a thing that we're trying to define. So in our data, from the beginning, we don't actually know who develops long COVID and who doesn't. All we see is the column on the right, which is all infected participants together.

So the color gradient shows that symptoms with lower frequency are more yellow and symptoms with higher frequency are in dark blue or purple. So for symptom one, the frequency is relatively low in the uninfected group. Among infected participants who do not have long COVID, the PASC negative, we expect the frequency to be approximately the same as for uninfected participants since they don't have long COVID. But let's say that people with long COVID have higher rates of symptom one. So the frequency of symptom one is higher for PASC positive than PASC negative. And so what we see on average for all infected participants together is this kind of teal color, which is somewhere between yellow and dark blue. For symptom two, the frequency is a bit higher in uninfected participants compared to symptom one. So it's just generally more common amongst people whether or not they have a history of COVID.

But the story's the same. The symptom is more common in PASC positive compared to PASC negative infected individuals. And so we see that the rate is higher and infected overall compared to uninfected, and that's the dark blue color that we see on the right for symptom two. Now, consider symptom three. The frequency is the same in the uninfected, the infected PASC negative and the infected PASC positive. So the frequency in the infected overall group is going to be the same as the uninfected. And so this is a symptom that is not associated with long COVID. If we already knew who had PASC and who didn't, we would just compare the middle two columns. With this gold standard label, we would just assess which symptoms are associated with PASC. The problem is that we do not actually observe the middle two columns when we enroll people into the study.

And so what we have to do instead is compare the uninfected group with the infected overall group and any differences that we detect between those two groups are going to be indicative of differences between the infected PASC positive and the infected PASC negative and therefore will inform our definition of PASC. Next slide. So here's an overview of the analytic approach that we took. So there's 44 symptoms that we considered in the analysis. As Dr. Foulkes mentioned, 37 of these were present in at least 2.5% of the study population and were included in all subsequent analyses. And so given the large number of symptoms that we were considering simultaneously, not just the three that I showed in the prior slide, we used a statistical technique known as lasso to identify which symptoms were the best at differentiating infected from uninfected participants.

And so lasso gives us a set of symptoms with corresponding symptom scores, which are derived from the logistic regression coefficients from the lasso model. You divide them by 0.1 and then you ran them to the nearest

integer. So we end up with a set of symptoms and associated scores from the statistical model. And then an individual's overall PASC score is calculated by adding up the individual symptom scores for each symptom a participant has. So we calculated then the overall PASC score for all participants in the study, including uninfected participants and a score threshold. The optimal score threshold was identified for identifying participants with PASC. This was done in a way that is as inclusive as possible while limiting the number of uninfected participants who are going to be incorrectly labeled as PASC positive. Next slide.

So here I'm going to go over the results from the manuscript. Next slide. So there's a total of 9,764 participants who met the study criteria. This is the table one showing how the demographics differed between infected and uninfected participants. Overall in the study, 71% were female, 16% were Hispanic or Latino, and 15% were non-Hispanic Black. The median age of participants overall in the study was 47. When we look at the differences between infected and uninfected participants, infected participants were younger and a higher proportion were female. In this statistical approach that we took, balancing weights were used to make the distribution of age, sex and race ethnicity match between the infected and uninfected groups in all subsequent analyses. Next slide.

So when we looked at all the symptoms individually, all 37 symptoms with a frequency of 2.5% or greater were more common in infected than uninfected participants. This Table 2 here shows the 13 symptoms identified by lasso that were the best at differentiating infected from uninfected participants. The symptoms here are ordered by decreasing score. The very last symptom here, the score was rounded to zero. So essentially there were 12 symptoms that contributed to the overall PASC score. Some symptoms including brain fog, chest pain, and fatigue, required additional severity criteria. So participants who indicated that they had a given symptom had to answer an additional follow-up question as part of the symptom survey to indicate whether their symptom was of moderate severity or worse in order to have their symptom counted in the analysis.

So to calculate an individual's overall symptom score, this is done by adding up these scores for each symptom that a participant has. So for example, if a participant has loss of smell or taste and chronic cough and brain fog, and those are the three symptoms out of these 12 that a participant has. So they have none of the other symptoms, their score would be eight for smell taste, four for chronic cough, and then three for brain fog. So eight plus four plus three, which is 15. So that person's score overall would be 15. Next slide.

So we calculated the overall PASC score for all the participants in the study, and we validated these scores against their responses to three questions in the PROMIS Global 10 survey. When we looked at the questions related to general quality of life, general physical health and ability to carry out everyday physical activities. And what we found is that for participants who had higher PASC scores, so within each of these tables going from left to right were scores were associated or correlated with worse responses to these PROMIS questions. So generally having a higher PASC score corresponded to having worse quality of life, physical health and ability to carry out these activities. Next slide.

So using tenfold cross validation and optimal score threshold for PASC was selected as 12, meaning that participants who had an overall score of 12 or above were classified as PASC positive. All others were classified as PASC unspecified or PASC indeterminate, meaning that they do not meet the symptom-based criteria. But we don't want to rule out PASC, so that's why we're not calling it PASC negative. These participants may have subclinical disease or long COVID that has not yet manifested in severe enough symptoms to meet the scoring threshold. Importantly, I want to point out that someone doesn't need to have all 12 symptoms to meet the scoring threshold.

As I showed earlier, an individual who had loss of smell, taste, chronic cough and brain fog got a score of 15. So that person would meet the threshold even though they didn't have all 12 symptoms. There were also some other symptoms that we found to be highly correlated with the symptoms included in the PASC score. And these are listed here. The use of 12 symptoms for the score in no way is meant to minimize the importance of the many other symptoms people experience, and we don't intend to say that any of them are less real or debilitating or common or important or worthy of scientific research and medical attention. Next slide.

So this figure shows how frequent each of the 12 symptoms are among participants who were classified as PASC positive. So the symptom with the highest score, loss of or change in smell or taste was not the most frequent symptom that we observed. Some of these symptoms were quite rare, but are still important symptoms for defining PASC because they're strong differentiators of infection history in our study population. Next slide.

Could you go to the next slide? Thank you. So this table shows how many participants were classified as PASC positive or PASC indeterminate overall, and then within specific sub cohorts. So in the study population overall, 21% of infected participants were classified as PASC positive.

If we look only at infected participants who were in the acute Omicron cohort, meaning that they were recruited within 30 days of their first infection and that first infection occurred on or after December 1st, 2021, then 10% were classified as PASC positive. So that's the acute Omicron infected row in this table here. The rate of PASC positivity was higher among post-acute pre-Omicron and the Omicron groups, but that may just be due to self-referral into the study among post-acute participants. Next slide.

So the proportion of PASC positivity was lower among infected participants who were fully vaccinated prior to their infection compared to those who were not fully vaccinated in all of the different sub cohorts that we looked at. So that's the acute Omicron, post-acute pre Omicron and post-acute Omicron cohorts. So for example, in the acute Omicron cohort, the rate of PASC was 9.7% among fully vaccinated participants compared to 17% among those who were not vaccinated. In the Omicron cohorts, the proportion of PASC positivity was higher among participants who had a reinfection between their first infection and the study visit that was used in the analysis. So that's in the bottom half of this table here, which is all part of Table 3 in the manuscript. Next slide.

So in addition to developing this rule, we also performed clustering analyses among participants who were classified as PASC positive using a technique known as unsupervised learning. And this was based on the 12 symptoms that were identified using lasso. We identified four clusters each consisting of roughly one fourth of all PASC positive participants. So this is a dendrogram showing how the four clusters were identified. Next slide. So this heat map from the paper shows how frequent each symptom was in each cluster. So the four clusters are on the left and there's two groups on the right, which is all of the PASC positive participants and then all of the PASC unspecified participants. So in cluster 1, 100% of them had loss of or change in smell or taste. In cluster 2, 0% of these participants had brain fog and 3%. So very, very few had loss of or change in smell or taste, but 99% of them had post exertional malaise and 84% had fatigue.

In cluster 3, loss of or change in smell or taste was quite rare, but 100% of participants in this cluster had brain fog and almost all of them had post exertional malaise or fatigue. And in cluster 4, rates of all these symptoms that I've discussed were very high, and this cluster appeared to have the most severe symptomatic presentation of long COVID. And we also found that among PASC positive participants that those in the pre Omicron group were more likely to be in this cluster four than participants who were in the Omicron groups. Participants who were unvaccinated at the time of infection were also more likely to be in cluster 4 compared to those who were fully vaccinated and participants with infections were more likely to be in cluster 4. Next slide.

So finally some conclusions and then Dr. Foulkes will talk about next steps. Next slide. So to conclude, we reported early findings from a large prospective cohort study with ascertainment of patient-reported symptoms. It showed how we developed a straightforward data-driven scoring framework to classify PASC as a condition unique to COVID. Many of the symptoms identified here overlap with that of other conditions that many have discussed as being potentially associated with long COVID, including dysautonomia and myalgic encephalitis or chronic fatigue syndrome or ME/CFS. We also found that 98% of participants in the study who have ME/CFS also met our long COVID criteria. In addition, we identified four long COVID manifestations of PASC using clustering analyses. There was one cluster whose hallmark symptom appeared to be loss of or change in smell or taste with few other symptoms.

There was also a very severe cluster that was characterized by the presence of many different symptoms. This suggests that PASC might be a syndrome of syndromes rather than just one disease that manifests in one particular way for all participants. Additional manifestations of PASC may also be identified when biomarkers and other clinical findings are incorporated into the working definition as we refine this definition in the future. Finally, for risk factors we observed that being unvaccinated, being infected with a pre Omicron variant or being reinfected were all associated with being, with having long COVID and amongst people who did have long COVID with the more severe manifestation.

Importantly though, I want to point out that these findings are preliminary. They were unadjusted for confounding factors beyond the ones that were included in the balancing weights, and they're going to be the subject of upcoming manuscripts out of RECOVER that dive deeper into risk factors. Vaccination is also a very complex time varying factor. So in these analyses we didn't consider the time between the initial vaccination series

and infection or the potentially time varying effect of boosters. So I hand it over back to Dr. Foulkes to talk about some next steps.

Dr. Andrea Foulkes:

Thank you Dr. Thaweethai. Before moving to the panel discussion, I just want to highlight a few of the important attributes and the significance of this study as well as next steps. First, as was described, this is a prospective cohort study that followed many of the individuals from the time of their first infection. And in this subgroup of people who were following from the time of their first infection, which we're calling the acute cohort, there is less selection bias than studies that enroll individuals several months or even now years after their initial infection. Secondly, the RECOVER study included a contemporaneous comparator group of uninfected individuals because many of the symptoms of long COVID are experienced by individuals with and without a history of SARS-CoV-2 infection, it's important to include a comparative group to parse those symptoms that best distinguish those with and without a history of infection.

In RECOVER the survey instruments were designed by many different stakeholders, including patient and community representatives, clinical scientists, epidemiologists and biostatisticians. And as a result, the RECOVER study included symptom questions that did not appear in many earlier studies. And one notable such symptom identified was post exertional malaise. The RECOVER study was also based on self-reported symptoms, which is different from electronic health record data or EHR data. So EHR data can be helpful in identifying individuals who reported a symptom, but if a symptom is not recorded in the EHR, it's unclear to researchers whether an individual doesn't have that symptoms or did not have the opportunity to report it. So for this reason, self-reported symptoms are considered more accurate. In the RECOVER study as was described, one in 10 of the acute cohort participants with a first infection after Omicron became the dominant strain in the United States met the symptom threshold for long COVID.

However, the score cannot tell us if someone does not have long COVID. That is if someone doesn't meet the score threshold, they may still have long COVID. And further evaluation of clinical assessment and laboratory tests may reveal more participants who have long COVID. One of the more significant contributions of this work is that it provides a unifying framework for studying long COVID. That is the proposed definition of long COVID takes an important step beyond consideration of each symptom individually. Rather, the definition integrates information across multiple symptoms simultaneously taking into account if and how symptoms tend to occur together. By consolidating information on multiple symptoms, the approach we took in the JAMA paper described turns an important corner providing a framework for identifying people with long COVID.

And as such, it provides a critical launching point for investigations into the risk factors and mechanistic underpinnings of disease. In other words, by having a definition of long COVID, we can begin the pivotal next step of in-depth investigations into why some people get sick and experience the more severe manifestations of long COVID while others do not. And ultimately, what are the pathways to recovery? Next slide please. Next slide please. Thank you. In addition to further refining the definition of long COVID in adults, it is essential to independently consider pediatric populations and how long COVID manifests in children. At this stage, we do not know if long COVID is different in children and a rigorous analysis of data from the RECOVER pediatric cohort is of paramount importance to unravel this.

Finally, fully understanding long COVID will inevitably require careful consideration of the longitudinal trajectories of individuals over time. We recognize that symptoms may come and go over time. We saw that in the report that it was presented in JAMA and that over time individuals will be exposed to vaccinations, boosters, treatments, and repeat infections, not only to SARS-CoV-2, but other viruses as well. With this all in mind, further research we'll need to approach the complex interplay of all of these factors comprehensively. Next slide please. So before we move to the panel discussion, I just want to take a moment to thank all of the participants enrolled in the recovery initiative, the National Community Engagement Group, or NCEG, and all patient care caregiver and community representatives. So thank you.

Dr. Christine Bevc:

Thank you to our presenters, and I'd like to extend a special thanks to those of you who have submitted questions. We've got a very healthy list to get to. So with the time remaining, we want to make sure that we can get to as many as possible. But first, to help recap the findings because we've got 40 minutes of information here. I

want to ask the panel and have them go around the room to share what they see as the key takeaways from this analysis. Let's start with Dr. Singh and then go around the room.

Dr. Upinder Singh:

Yeah, thank you so much. So I think the work really nicely demonstrates that individuals who score greater than 12 points meet the criteria and definition for long COVID. But as Dr. Thaweethai said multiple times, and I think it's really important as a takeaway that people who have a score of less than 12 may still have long COVID. I'm going to just say that again. So people who have a score of less than 12 may still have long COVID, which is why the PASC indeterminate definition was used and not PASC negative. And I think that has been a question that many individuals have and that's something we want to make sure people take away.

Dr. Sairam Parthasarathy:

And if I may add, I think one of the other key takeaways is that this JAMA paper findings should not be the past core, specifically should not be used for clinical use or for designing disability ratings. It's a first step. It's the initial step for coming up with a working definition that needs to be further refined. And it's not time for application in the clinical or in the disability realm. But I think that's a very extremely important takeaway that we need to take. But goes along with what Upi just said.

Dr. Upinder Singh:

And I know that a lot of individuals are wondering about clinical trials, when will treatment options become available? We are really excited to see the emergence of important clinical trials through RECOVER and other mechanisms. But I think it's really important to recognize that the past or in our expert opinion should not be used for assessing eligibility for clinical trials. Instead, the eligibility should be based on the history of COVID infection. If somebody has proved COVID infection by seropositivity or a history of probable or definite infection and then symptom or organ dysfunction if there's a certain focus of the trial, but definitely not a PASC score cutoff.

Dr. Andrea Foulkes:

And I'll just jump in to add to that, the 12 symptoms that are identified or not necessarily the most common or the most troublesome or the most burdensome symptoms that patients experiencing. We found them to be the ones that most set apart, most discriminated in the RECOVER cohort between the infected and uninfected participants at this six month or later visit. And therefore serve as this important first step in studies, again to unravel the mechanistic underpinnings. But in addition to the 12 symptoms that contributed directly to the score, we also found 25 other symptoms that were more common in those with a history of SARS-CoV-2 infection than those without a history of infection. So the JAMA paper really does highlight the diversity of symptoms that individuals are experiencing beyond the 12.

Dr. Tanayott Thaweethai:

I would add, I think to that just in terms of, so one of the key findings I think has to do with the different manifestations of long COVID that we identified. I think they are a helpful starting point for understanding the different ways in which people are affected by long COVID. And we're really hopeful that this is going to help motivate mechanistic studies to understand some of the subclinical changes that are occurring in people who develop long COVID so we can understand why it is that people become sick, and then identify potential treatments that are specific to different manifestations of long COVID.

Dr. Upinder Singh:

I think I'll add another takeaway, which is that COVID vaccination did seem to be associated with reduced odds for long COVID. This I think provides a rationale for added benefits to primary and especially booster vaccination to protect against another variant. So as you saw in the presentation, vaccination seem to be protective, repeat infections seem to be more harmful. So I think that does provide all of us with ongoing public health recommendations for people to stay up to date on vaccinations and to avoid further COVID infections.

Dr. Sairam Parthasarathy:

Yeah, and another interesting finding I think is the demonstration of the data that Tanayott presented with regards to multiple infections and the more [inaudible 00:40:52] strains in the pre Omicron era such as Delta

strain, variant and such, were associated with the greater risk of neutrals having PASC, such as saying that it could be multiple hits on those organs and that's causing the organ dysfunction as the anti-pathogenic mechanism. But again, PASC is a syndrome or syndromes, there are other pathogenic mechanisms such as viral persistence and autoimmunity and immune dysregulation and even got dysbiosis. But what this says is that when the virus hits multiple times, that's more organ injury and the creative likelihood of PASC as evidence, but also a greater chance of having PASC in people with hospitalizations as opposed to without hospitalizations. So I thought that that was a very interesting point and a takeaway.

I would even go first to say it's not of a reason combined with the takeaway that Upi just talked about in terms of vaccination, it's important that people don't just resort to natural immunity, and this essentially underscores the importance of reducing repeat infections and the fact that vaccines confer protection. And this is why people should get the booster shots. Unfortunately, only 17% of the nation has taken the booster shots, although upwards of 70% odd have taken the primary series, our country is still exposed to another new variant that would emerge, which is rated at a 20% chance over the next two years.

Dr. Christine Bevc:

Thank you. We've lots of detail in here to unpack a little bit, and this is mentioned as a first step. How do these findings presented today compared to or expand on some of the prior research that's been done?

Dr. Upinder Singh:

Maybe I'll take that as a first thing. It's obviously been a heroic effort by the investigators, the participants and the entire scientific community. And as has been discussed, this is the largest prospective cohort study. It's very additive to data that's emerged from EHR, et cetera. And I think in many ways this is the first example, but I think a lot of the power of this work is going to be demonstrated over the next year as we see participants follow up to see how their symptoms progress, change or not, as we see participants participating in further studies, imaging tests or blood work. And as we see further analysis emerging from pathobiology studies, so a really, really important setting the framework, establishing the cohort, setting this national framework for research, and I think so much more important data will emerge. Dr. Parthasarathy, what do you think?

Dr. Sairam Parthasarathy:

Yeah, you said it. And I would say that what I would add is that this is a, like you said, a large adequately powered prospective study. And going to what Andrea mentioned is the fact that this was specifically designed for PASC with patient input, representative input, other stakeholder infected design questions for symptoms such as post exertional malaise that are specific to the SARS-CoV-2 infection. That was including a contemporaneous uninfected cohort so that it can make contemporaneous comparisons during the middle of the pandemic because we know even in uninfected individuals, their health deteriorated during the course of the pandemic, people gain weight, their blood pressure is not under adequate control. And as a consequence, there was even incident diabetes and cardiovascular disease during the pandemic, even in uninfected individuals. So I think one of the key strengths is the perspective observational nature with the contemporaneous uninfected controls.

And then to top it up is you have the Omicron, acute Omicron infected individuals so that you can actually see at least with the Omicron variant, what was the incident, PASC, and it comes up to about 10% or after just been for weight rated comparisons, it's about 9.8% or something, which is remarkably similar to the CDC household pulse survey for what happened during people who are infected during the Omicron era being infected and having symptoms of PASC or long COVID. So there's external validity to the findings of this perspective observation cohort. So I think that's why this actually sets the study apart. And the last thing that I want to say is that there's simultaneous settlement of multiple symptoms, every single symptom that we can lay our hands on. Yes, there are 44 symptoms, yes, we could have gone up to 200.

Some of that may refer to language as well, but in terms of how patients relate their symptomatologies, but because there are other studies, even if there are smaller or perspective, if they don't ascertain or if they don't measure a particular symptom, are they going to end up having skewed findings? Whereas I think a lot of thought went into making sure that we got all of the symptoms as well as the data analysis approach. It was essentially a data driven scoring framework that was developed. So the data spoke for itself and drove the scoring and the system as opposed to arbitrarily us choosing some symptoms saying, oh, this is more important. No, that's more important. So I think that it's the perspective observational contemporaneous controls, uninfected controls as well

as an acute Omicron cohort and methodology, statistical methodology that are sources of strengths for the study that sets it apart.

Dr. Christine Bevc:

Right. Thank you. So as a follow-up on related question, so next week National Academies is going to be hosting a workshop on examining the working definition of long COVID. We don't have any information on it at the moment, but it was brought to our attention by one of our attendees. How would you advise that those that are participating in that workshop to use this work? I mean this is part of the body of literature that's out there.

Dr. Sairam Parthasarathy:

Yeah, I mean that's a great question. I would say that I think the way it was espoused by my colleagues here in this panel as well as, gosh, over 200 odd authors, I don't know if I got the number and the investigators and the institutions acknowledging their contributions and thanking them for their hard work because we are just representing, merely representing a lot of work, a lot of people behind the scenes, including the National Institute of Health. What I wanted to say is that there's a lot of minds that ran into this and the key thing for them to consider is that this is a framework. This is not the final definition in no shape or form, this is a first step as clearly states also in the paper as was presented by Andrea, Tanayott and Upi. And further refinements need to occur with regards to the clinical diagnostic tests and imaging tests that are going to be available and brush in the future of biomarkers and of further analysis of extreme phenotypes.

So that's going to give us greater and greater resolution and clarity. I would liken it to a telescope before you go to the Hubble, before you go to the James Webb, so that you get a bit more and more better and better resolution of the images and of the definition. And this by no shape or form is meant to be the final definition and power to them for them to dissect this and take that. But the key thing is the framework because when you set the framework as Andrea said, now you can stop working within that framework to keep refining and refining it in an iterative manner. I think that is one of the valuable contributions and kicking that can essentially initiating the effort to define.

Dr. Christine Bevc:

Not an easy task here. I wanted to switch gears a little bit for a quick clarifying question. We've had a few questions that relate to the data itself and how it was cut. And so one of the questions that we had was, is RECOVER gathering the dates and number of vaccines and boosters administered over the trial period? And can you clarify, I think it's also important to clarify whether it's accurate to call this a trial period. So there's two parts to that question. I mean, that goes to-

Dr. Andrea Foulkes:

I can start with that. So yes, we are collecting information on vaccination and boosters over what we think of as the observation period. We're also collecting information on repeat infections that's been discussed. So we have a lot of what we think of as time varying exposures, so multiple vaccinations or boosters, multiple infections, infections with other viruses and other clinical outcomes that are measured over time. So we are collecting that information and again, this is really a first step where we wanted to get some results out as swiftly as possible.

Given the scope of this large study, there are many, many more questions that we will be probing and thinking about. They're very complex questions and require a lot of input sophisticated methodologies from our epidemiologists and biostatisticians, but also really critical input from clinicians, patients, patient representatives, as well as patients with long COVID. So we are beginning to embark on those additional questions that integrate all of these different sources of data and particularly as was mentioned, the information on vaccination and boosters over time.

Dr. Christine Bevc:

So to add to the complexity of the analysis that you guys have, we did have the question of how individuals who were COVID negative at the start of the observation period and have subsequent infections during the observation period, whether they're symptomatic or not, how is that treated in this analysis or later analysis?

Dr. Tanayott Thaweethai:

Yeah. Oh sorry.

Dr. Upinder Singh:

Go ahead.

Dr. Tanayott Thaweethai:

Just from a data perspective, individuals who enroll as uninfected but then develop infections crossover into the infected arm of the study and their questionnaires reflect this. So they have now an updated beginning of a new index date is getting in some of the technical details. So now we're able to study them as infected. It's also really nice in future analyses when we look at each person can now, those types of individuals can now serve as their own control in a sense. So it's a natural crossover design. So those are individuals that we can actually learn a lot from going forward in analyses. So that's part of how those individuals data would be incorporated into RECOVER aims. Upi, did you have... Sorry to cut you.

Dr. Upinder Singh:

Yeah, I was just going to add to what Dr. Thaweethai said. I think this is the power of a longitudinal observational study that we can see people who are not infected who then get COVID maybe once or twice and then follow them. So you have their symptoms and their general health before they got infected. Now you'll have their symptoms and general health during acute infection and then for several years after. So that really, those types of individuals will contribute data to different aspects of the analysis, but such a powerful way to follow people. And I think that really does highlight one of the great things about this study.

Dr. Christine Bevc:

So here's another just clarifying easy question and we've got some challenging questions coming up too, but how is infection defined here? Were participants required to have a positive PCR or an antigen test? Is it self-reported? Is a physician diagnosis accepted? How is that determined for this study?

Dr. Upinder Singh:

I can start and then hand it off to others. I think the goal of this study was to be as inclusive as possible and to be as scientifically rigorous as possible. So the idea here is to take people who have all a range of definitions of positive. So if somebody had a positive PCR, somebody had a positive antigens test, self-reported, you don't have to be physician reported, somebody had a evidence of antibodies before vaccination occurred and then people who had clinical syndrome consistent with COVID, but were not able to access testing. And I think that is so, so important both for people who may have been infected early in 2020 before tests were easily available and then people who were infected during some of the surges where you just didn't have enough access to healthcare or testing.

So again, in order to be as inclusive as possible, people are allowed to enroll with a variety of different definitions of positive. We do note when they're enrolled whether they had a positive antigen or PCR or self-reported or a clinical syndrome consistent with it because again, to be scientifically rigorous, we do want to follow those individuals and understand how they entered the study. But yeah, it's important question and I think it is again, one of the strengths of a study like this.

Dr. Christine Bevc:

Great, thank you. And so the follow-up... Oh yeah, go ahead Sai.

Dr. Sairam Parthasarathy:

Yeah, I just wanted to mention there's a health disparity angle to what would be mentioned as well because there are people who come from disadvantaged neighborhoods, so who don't have access to testing. And so we needed to be all-inclusive to make sure that people who were disadvantaged in such a manner were also included in the study. I just wanted to add the disparity.

Dr. Andrea Foulkes:

I would just add one more layer to that as well, that for our uninfected participants that we do do enrollment testing to see if there's an infection that they didn't know about, but we may not capture all of those. So one of the challenges that we face is that we don't have perfect classification particularly of our uninfected. So

we expect some of the individuals who we think are uninfected may actually have had a history of infection that was not reported that they didn't know about or wasn't included in the data capture.

Dr. Christine Bevc:

So this really does help to refine that uninfected category and how that's captured and assessed for this study. Great. Thank you. All right. So on the other end of the spectrum, so we've covered the asymptomatic. On the other end, the severity of the infected population stratified by the acuity of the illness that they've experienced, whether they were hospitalized or not, as it was highlighted, the symptoms could be confounded and compounded by pulmonary fibrosis or other and organ damage.

Dr. Tanayott Thaweethai:

I can speak briefly to what was mentioned in the paper about severity of illness and then, so which I wasn't able to have time to cover in the presentation, which is that in the results we reported that amongst all infected participants amongst those who were hospitalized for their first infection, 39% were classified as PASC positive compared to 22% who were classified as PASC positive for those who were not hospitalized during the acute infection phase. And so we were seeing that if you were to just stratify on hospitalization versus not, looking at infected participants overall the rate was higher. We're collecting information on other aspects of severity of illness, so types of treatments that were received, the level of care looking at ECMO, ICU admissions and things like that. But for the purposes of the first paper, we just focused on hospitalization.

Dr. Upinder Singh:

I do want to also just mention what Dr. Thaweethai said. Obviously, initial severity of illness did seem to be associated with worst disease. But again, to just set the stage, people who had mild infection never were hospitalized, maybe even had asymptomatic infection, but were diagnosed because a family member was positive can have PASC and can be quite symptomatic with their PASC. This is one of those illnesses where you almost can't predict who's going to get... And when we had acute COVID or have acute COVID, who's going to get really sick with acute, who's going to get hospitalized, who's going to do worse, who's going to do better? Unfortunately, those parameters seem to be carrying over. It's hard to predict necessarily individual by individual the initial severity of symptoms and associated PASC. Collectively, when we look at this large almost 10,000 participant population, there's definitely themes, but I don't want people to walk away thinking, people who had mild COVID get PASC. That's not true. People who have mild COVID or asymptomatic can't get it.

Dr. Sairam Parthasarathy:

And if I may, that's why PASC is technically scientifically the more accurate term than long COVID. In other words, someone who had never had symptomatic such condition called COVID, which is due to the SARS-CoV-2 infection, someone who's relatively asymptomatic or completely asymptomatic as if you said can go on and develop those symptoms. But to also add additional answers to the questionnaire is that in terms of underlying pulmonary fibrosis and other conditions, that's where the additional clinical diagnostic tests, including imaging becomes available and it's an ambidirectional study. In other words, we can actually go and get the information that they give us access to in their medical records and images from before that we can actually obtain not just through questionnaires, but also through the EMR information that's available so that we can see what was, did they really have pulmonary fibrosis before or is this new fibrosis? So a lot of rich data is going to come out of this and it's going to start answering a lot of those specific questions that this questionnaire had.

Dr. Christine Bevc:

All right, so we have a question and we saw it go into the chat and so other folks have seen it there. So let's go ahead and address that there. This has been one of the most highly read articles from JAMA recently. It's getting a lot of attention and it's been raised that there's serious concerns about having a limited number of symptoms and the paper has 12, the tables have 25, we go up to 45. Can you speak to the engagement with the patient community, the patient engagement, the community engagement, how this work is going to influence decisions moving forward from where we are now?

Dr. Upinder Singh:

I can address some of those and then hand it off to others. We've been involved with RECOVER since the very beginning when a group of investigators were selected by the NIH and asked to come together to discuss developing a protocol. And we've always had really strong patient and provider and community engagement representation. I think my answer may not always get to be as satisfactory, but science is a compilation of thoughts, opinions, observations that are iterative so that we always get better. Our understanding of cancer, lung cancer, breast cancer is different now than it was 50 years ago or even 20 years ago. Our definition of what it means, should women get hormone replacement therapy is different now than even 10 years ago. Science moves, science improves, science keeps taking new information. And I think this study more than almost any other study, or in fact more than any other study I've been involved in, has taken a global inclusive approach from the whole time.

I do think we've been very careful in the paper as well as in our conversations with media, et cetera, to say we understand there's hundreds of symptoms that people with long COVID can have. We're simply defining some that are the most different between those who appear to have long COVID and those who may or may not have long COVID, again PASC indeterminate. I think unfortunately what happens is that it's become a yes, no. And I think what we're saying is yes, maybe, and that black and white philosophy tends to be the soundbite that gets projected and that is absolutely not what we are saying. That's absolutely not what's in the paper. And we do want patient engagement, provider engagement to continue because again, people will help us iterate. So that's my perspective, but I don't know what others think.

Dr. Sairam Parthasarathy:

Yeah, what I would like to add is going back to what Upi said was her main first takeaway from these papers is that just because someone doesn't have their symptoms represented in those 12, which also Andrea underscored are not the most common or not the most bothersome, not the most troublesome or burdensome symptoms, they can still have PASC, they can still have some of those other 25 persons to make about 37 persons. And then it was acknowledged by this group in the paper, in the JAMA paper as well to speak to the fact that it's getting a lot of hits is that the reader should discern and be a discerning reader and see what the limitations are. And so there are limitations. There's limitations to the study that have United identified.

One of the limitations is that there are many patient groups, some of whom I do see here at this venue who have done their own collection of symptoms, which they have provided input early on, but also they have done independently work and there are about 200 symptoms that we did not incorporate. And so completely because some of them are overlapping symptoms and also the way the patient calls those symptoms. So we acknowledge that there are other symptoms that need to be looked at, and the fact that just because their symptom is not confront to anyone or all of these 12 distinguishing symptoms, that doesn't mean that they don't have PASC or long COVID, they should still seek medical attention. And that's why we don't want this to be used for clinical use or disability ratings for that exact reason.

Dr. Tanayott Thaweethai:

I would add to that. The symptoms that were part of the symptom survey were meant to, these had to be questions that could be answered by a patient regardless of their level, regardless of their prior diagnoses that they had received from other clinicians that they had seen in the past. We were trying to capture the symptoms that they were experiencing and make sure that it was in a format that was reasonable for them to complete alongside the other symptoms that we considered alongside the other forms that are part of each of the follow-up visits and of the initial visit that someone has in the study.

I think further the reason why, as I walked through in the presentation, we were trying to develop a framework for identifying people who met this symptom-based criteria for PASC and try to identify which symptoms, again, I'm reiterating the same points, but said that we're the best at differentiating people with infection history from those without. And that again, there are many other symptoms that were correlated with the ones that ended up in the scoring framework. The idea there being that we would, for the most part be able to capture and include individuals who had those other symptoms because they were highly correlated with the ones that were included in the score. So I think just speaking a little bit to the methodological approach about how we developed that scoring framework in the end.

Dr. Christine Bevc:

So I have a follow-up to that one to where you're talking about the symptoms and the correlation there. So one of our attendees noted that the symptoms of smell and taste, thirst, GI, things that add up to a PASC score of equal to 12, those would show up as minimal loss of function over on the promised 10 scale. So as you're looking forward into next steps, how do some of the analysis that you've done here relate to some of the other metrics and the other protocols and the other measures and models that are out there that contain similar symptoms?

Dr. Andrea Foulkes:

So I'll just begin by saying that we were actually somewhat heartened to see that there was a correlation between the PASC score and some of these existing metrics of overall quality of life and physical health. So in fact, in our investigation, we did see this association between the PASC score. That's not to say as I think has been reiterated many times that people who have a score less than 12 don't also have very severe symptoms. And that will be part of a next step to identify those individuals, to be sure to include them. So we are actually in fact seeing correlation with existing metrics and continue to integrate these different types of data into the analysis. I might also add a little bit to the prior discussion and a question that we see that came up among participants about what is the use of this definition, if not for clinical or diagnostic purposes.

And I want to really emphasize here first that people with a very high PASC score do appear to have poor quality of life, poor physical health, and this presents a scientific opportunity to understand better what's happening for these really sick people. And this approach of looking perhaps at more extreme phenotypes we see in lots of different research settings by understanding mechanistically what's happening with these more extreme phenotypes that we've identified, it will hopefully provide insight into the full spectrum of PASC. It won't necessarily, and we have a lot more work to do to find many more people than meet this symptom-based definition. But this definition gives us a way of saying these are people we fairly sure have long COVID. And then by, as Dr. Thaweethai presented, we have these different manifestations, some that have loss of smell and taste and others that have post exertional malaise, brain fog, fatigue, et cetera.

By looking at those different manifestations we can understand, are there different pathways, are there different ways in which people are getting, having these persistent symptoms? And that's so critical if we're going to start treating people. If we're going to be able to identify effective treatments, the first thing we need to do is understand, well, one of the major things I should say that we need to do is understand mechanistically what's going on. So again, by creating this definition of who has long COVID, who we feel certain meets this definition of long COVID, we can start to really begin to understand what's under the hood and what's making these people sick so that we can start the really and critical process of finding effective treatments.

Dr. Sairam Parthasarathy:

Yeah, I just wanted... I mean, Andrea said it well, I just wanted to give an exemplar for how it would help is that the ones that have a score greater than 12, that we are fairly positive they have a long COVID or PASC rather, you can do, the researchers can identify biomarkers that's associated with those extreme phenotypes and then take those biomarkers and apply it to the unspecified group. The people who did not make it up to 12 and sift through that population, find out who's more likely to have PASC got left out of that mix because they had a score less than 12. That's just one example besides understanding the mechanisms of disease as Andrea spoke about, so that way no one gets left behind. The key thing is not to leave anyone behind to identify everybody and do it in a scientific and rigorous manner.

Dr. Christine Bevc:

We have just a few minutes remaining and I have to help us move forward. There's a score, it's there, it's out there. Where do we go from here? How do we take that and continue to move forward and evolve the science, as Upi, as you highlighted, what are the next steps? Are there opportunities for access to some of the preliminary data sets to be able for those that are interested in conducting their own studies, the availability of this. So I wanted to close with that question of, what comes next and what does the score mean and what you're looking forward to?

Dr. Sairam Parthasarathy:

I'll take a first pass at it, but I'm sure all of my colleagues here will want to add to that and give their angle as well. But this is just the first step as we said. So we talked about the clinical tests, the imaging, diagnostic tests that are been done. That's going to further refine this definition. Then you have participants that are still in the study that didn't get caught by this net of the six-month requirement. So there are more participants involved. And then there's biological samples that's been obtained from them. There are these research tests which these diagnostic tests, which are called tier two or tier three, depending upon the level of invasiveness and how intrusive they are to someone in terms of undergoing the testing as part of the study. And so all of that is going to allow us to further and further better define, but also longitudinally follow these people out to see what are some of the consequences that we don't know of.

For example, are they more likely to develop diabetes? There are some reports out there in smaller studies, more likelihood of developing diabetes or cardiovascular disease. Is that really true? And then as Tanayott mentioned, people who move from one category to another category also so as their own controls. And it gives data clarity as to us better understanding so that then we can figure out what is the underlying mechanisms based on these biomarkers are not just to identify people but also identify which one of those four or five disease processes that we talked about earlier are playing a role here. And then to do precision medicine for them. If it's a gut dysbiosis versus vascular injury versus organ injury versus autoimmunity or immune dysfunction dysregulation, then we can do appropriate treatments for the appropriate patients. So there's rich opportunities for identifying it as well as most importantly I think social determinants of health because we are seeing what's happening to people losing their jobs and not being able to work and how is that affecting their lives.

And because that's something that, as you mentioned, the National Academy of Sciences needs to pay attention to because we need to swiftly address that, not let that happen while we observe to bring other resources in to address them, some changes in their life situation such as joblessness and things of that nature that needs to be addressed because those are all important factors and there's a group that's working on it. So there are multiple groups working on that though those are all the next steps and the foundations have been laid and some of the various steps of evolution. So I'll pass it on to my colleagues.

Dr. Andrea Foulkes:

That was so well put, Sai, that I'm not sure how much to add, but I do want to mention that the data that went into the initial study are currently available for investigators within RECOVER and plans for making the data more widely available to the public are underway. And we do anticipate in the coming months that the data will be available more broadly and we really do encourage groups to use the data and hope that collectively we're going to be able to continue to improve on the definition of long COVID and more importantly the mechanisms of disease and how we can find pathways to recovery.

Dr. Upinder Singh:

And I guess I would just say that COVID and long COVID has seen this attraction of so many different scientific realms. Dr. Parthasarathy is a sleep physician, I'm an infectious disease physician within RECOVER as well as other site were seeing people in pulmonary with lung disease or people with expertise in neurology. So it really does have the attention of a very broad and deep group of scientists. And so I do think we're going to obviously learn a lot about long COVID. I'm also really excited to see what else we're going to learn about illnesses that's mimic long COVID, ME/CFS or others. And to me, the way I always describe things to my kids is one experiment leads to one answer, but often leads to more questions and more things to do. And I think a well-designed experiment, which I think the study has been opens a lot more doors actually than it closes.

And so that's what I would encourage people to think about is it's opening all these doors for different questions that we can answer and help answer. It hasn't closed the door on anything. It hasn't said you don't have long COVID, but what it's doing is iteratively now going to lay the framework for us to answer so many more questions. I think if we talk in a year or in, there'll be a lot more information that's going to have emerged including things that I bet surprise all of us. So I think that's the cool stuff about science is that you don't always have, you have a preconceived notion and sometimes you're right and sometimes you're not. And I think we do want to go into all of this with a really open mind.

Dr. Tanayott Thaweethai:

I totally agree with everything the other panelists have said. I think to answer just very simply from a very specific research perspective, we have a score. Now, what makes it so much easier to do other types of studies that rather than looking at, oh, we have this, oh, you're looking at a clinical test and you're seeing is this associated with long COVID? Rather than administering a survey that consists of dozens and dozens of questions where, and you're looking at whether some exposure is associated with each individual symptom or each specific comorbidity. There is now as was stated, unified framework for thinking about is something associated with long COVID. So we're really hopeful that others will use this research tool that we've conceived in future research to again answer all the new questions that have arisen as Dr. Singh mentioned for future research.

Dr. Upinder Singh:

I do want to make one comment, which is, I know we thanked all the participants and the physicians and the people at the different sites, but I think it's so important to recognize that the four of us are just privileged here to present this work. But this is the work of hundreds, probably thousands of people including research coordinators and nurses and social workers at the different sites including community engagement and others.

And it really wouldn't happen without participants continuing to come in and give of their time, their blood and other samples. And we're just really so grateful and the success of ongoing work will be dependent on all the stakeholders continuing to be engaged. And it's been a lot of work, a lot of hard work, but just so gratifying to see. So I hope that community and patients and everybody recognizes that really this is a collective success for all of us.

Dr. Christine Bevc:

Thank you Dr. Singh. And thank you to our audience for being with us today to being able to share your thoughts, your feedback on this. We are sharing, there's a little more information about that National Academy's workshop that was mentioned that's being shared out. So Kate just shared that out as well. Thank you to our attendee for providing that information to us. And the FAQ for all of the questions that we've received is going to be posted along with the recording of this webinar on recovercovid.org. The FAQ is going to include answers to those questions that are relevant to today's webinar, including those that were submitted in advance or during the session that we didn't get a chance to address. Questions on other scientific topics are also, we've got upcoming series coming that are and also an existing FAQ that answers some of the broader questions that RECOVER is going to be answering.

And those are available in the general FAQ section as well, along with past recordings of our R3 webinars. And so if you're interested in some of the work we've shared on the mechanistic pathways and viral persistence, we encourage you to check out those recordings as well. Also, you're always welcome. We invite you back to come back and attend our future R3 webinars. We're going to continue to dive deeper into some of these topics that were discussed. And as a reminder, please sign up for those future announcements so you have, can hear first about what's coming up. And then lastly, if there are topics and discussion items that you want to learn more about or that you are interested in being a part of or have research that you're doing over in your space, please be sure to enter those into the survey. Shane is going to put that up on the screen for folks, for you to complete at the end here. And thank you, Shane for putting up our July 11th seminar.

We're going to dive into those disparities and environmental risk factors in PASC and that's going to leverage some of our environmental, the electronic health record data that we have. So today was our cohort, observational cohort, and then next month we'll be looking, taking a step back to our electronic health record data. That R3 seminar survey is on your screen now. Please, we appreciate the feedback, how we can improve future seminars, what topics you'd like to see and any other feedback that you'd like to have. At this time, thank you to our presenters and our audience for joining us today. And this concludes today's R3 webinar. Thank you.