Transcript

Melissa McPheeters

Hi, I'm Melissa McPheeters for the RECOVER Administrative Coordinating Center. And I'm the moderator for today's webinar. Welcome to the RECOVER Research Review or R3 seminar. The goal of this whole webinar series is to catalyze the shared understanding of the research of the scientific stakeholder community across the RECOVER consortium. We have a really fascinating topic today. Today's presentation is focused on COVID 19 in the pediatric population, including MIS-C or multi-inflammatory syndrome in children. It's important to note that this seminar series is focused on scientific research, it's not intended to provide any kind of clinical guidance. I want to start by thanking everyone who submitted questions in advance of our seminar, but if you have questions during the seminar, please feel free to put them in the Q and A. After the presentation, we'll answer as many questions as we can that are focused on today's seminar and on today's presentations, but some questions may get answered in the Q and A, if there's simple things we can respond to there.

We're also going to be producing an FAQ document for the seminar, and that will be posted with the recording of the seminar on our website, which is recovercovid.org. It'll include answers for questions relevant to the seminar that were submitted in advance. In addition to those that were submitted today. Questions about other scientific topics are likely to be addressed in future webinars, so we'd encourage you to look at the other topics that are coming up and continue to join us on these webinars. Answers to broader questions about RECOVER are available on the FAQs, but also on our website, recovercovid.org.

Today's speakers are going to discuss what is known about COVID-19 in children and MIS-C, the gaps in our knowledge, and how the RECOVER initiative will contribute to filling those gaps.

So, without further ado, I'm very excited to introduce to you our speakers today. Dr. Tellen Bennett is a pediatric intensivist and informaticist whose research focuses on critical care decision making, high dimensional predictive modeling, electronic health record data, and clinical decision support tool implementation. He leads the section of informatics and data science at the University of Colorado Department of Pediatrics, where he's also the informatics director of the CTSA hub. He is one of the five NPIs for the N3C RECOVER EHR Cohort project. And he's going to talk to us a little bit about that today. Dr. Ravi Jhaveri is Division Head for Pediatric Infectious Diseases at the Ann and Robert H. Lurie Children's Hospital in Chicago and a professor of pediatrics at the Northwestern University Feinberg School of Medicine. He's a fellow of the Infectious Diseases Society of America and he currently serves as the chair of the IDSA Standards and Practice Guidelines Committee. He's an expert in leveraging electronic health record data to answer big questions about infectious disease and that's what he's talk to about

today.

Dr Ericka Fink is an associate professor of critical care medicine and pediatrics at the University of Pittsburgh school of medicine. She's an attending physician in the pediatric intensive care unit at the UPMC Children's Hospital of Pittsburgh. She's the principal investigator of the NIH funded multicenter personalizing outcomes after pediatric cardiac arrest study and co-PI of the multinational GCs Neuro COVID Consortium. And she'll be sharing information about that study with us today. We also have two discussants with us today, and we're very excited to introduce them as well. Dr. Josh Fessel is the senior clinical advisor in NCATs division of clinical innovation. Before joining NCATs in December 2021, he was a medical officer at the NHLBI Institute, where he oversaw a large portfolio of projects in pulmonary vascular disease.

Luckily for us, he took on additional roles in response to the COVID 19 pandemic, including participating in the active public private partnership and helping lead several efforts all across NIH to address post COVID 19 conditions. He's board certified as a pulmonologist and intensivist. Dr. Gail Pearson is a pediatric cardiologist who serves as the associate director of the Division of Cardiovascular Sciences at the NHLBI. And she's the director of NHLBI's Office of Clinical Research. As the multisystem inflammatory syndrome in children emerged in this current pandemic, she really stepped up and took a strong leadership role across the Institute, pushing forward the science in this area. So we're very fortunate to have both her and Dr. Fessel with us today. So without further ado, let's turn it over to our first speaker, Shane.

Tellen D. Bennett

All right. Well, my name is Tellen Bennett, thank you so much for that kind introduction. It's really a pleasure to speak with you today, I really appreciate the opportunity. I'm going to talk about pediatric COVID 19 and MIS-C in the National COVID Cohort Collaborative or N3C. Next slide please. As mentioned, there are five principal investigators of the N3C EHR project that is part of the RECOVER initiative. Melissa Haendel is the contact PI here at the University of Colorado. Emily Pfaff at the University of North Carolina Chapel Hill. Chris Chute at Johns Hopkins and Richard Moffitt at Stony Brook University, as well as about 15 additional sites. And we work closely with the other EHR cohorts, as well as the Clinical Science Center to work to achieve the RECOVER objectives. Next slide please.

So, the N3C enclave is the largest public HIPAA limited dataset in US history. And I'm showing data from the April 14th, 2022 data release. Data releases are about weekly, and it includes information from 72 sites, not quite five million COVID positive cases, as well as nearly 13 million individuals in the US. So nearly 15 billion rows of data, and

these are EHR data. So these are typical laboratory results, medication records, vital signs, procedures, encounters, things like that.

And the link at the bottom shows the dashboard where this information is readily available and dynamically updated. Next slide please. So in a nutshell, data comes into N3C from those 72 sites. In one of the four most commonly used data models from the sites themselves. We harmonize it. We generate a lot of mappings to increase value in the information, and then we release the data for use to investigators. You can see the types of real level data available there on the slide. We have information about all types of encounters, inpatient, emergency department, outpatient, and we have information for patients in N3C back to January 1st, 2018. Next slide please.

So the first point that I wanted y'all to take home is that contrary to early reports, children in fact have been heavily impacted by COVID. In addition to the social emotional impacts, which I won't talk about today, but the medical impacts. Next slide please. So this is from a manuscript that we published in JAMA Network Open a few months ago. These are data that were through late September of 2021. And at that time more than a quarter million children had positive tests in N3C from 58 sites. We had data about nearly 230 deaths, as well as nearly 16,000 hospitalizations. And you can see the geographic distribution in the top right corner of the slide of pediatric COVID 19 and MIS-C patients within the enclave, more or less representing the population centers in the US. Next slide please.

Okay. In this cohort, the demographics were representative of the United States. The mean age in this case was 10 and a half years, 49 and a half percent female. Importantly, 20.6% Hispanic and 16,5% black or African American as these communities were heavily impacted by the pandemic. And this information was representative. Next slide please. So I will just share the URL with you of a pediatrics dashboard that our team built in response to the pandemic and this dashboard shows information about severity distributions for children, and as well as some comparison adult severity information, age distributions over time, information about viral coinfection, and geographic distributions. And you can see I've pointed out, with the red arrows, some links to the tabs that you need to use to navigate the dashboard. We've had to move platforms in the last couple of months. So the information available there today is from February if you go check it out, but we'll have it updated by next week. Next slide please. So the next point that I wanted you to take home today was that Omicron, in particular, severely affected children. Next slide please.

So I have a few slides with this construction, and so I'll take a minute just to orient you. The X axis here is time and each vertical bar is a month. On the left side, March 2020. On the right side, all the way to March 2022, the left Y

axis is the percent of each vertical bar and the right Y axis is the number of patients. And so the line kind of tracking from left to right is that number of patients that's the count in each month. And then the bars are broken down by age groups, where the darkest ages at the bottom are kids under a year of age. Next one up, one to five. Next one up, five to 12, 12 to 19, and then 19 to 25. So a couple of take home points from this slide.

First of all, if you just look at the line tracking from left to right, you can see the alpha and other early variant coverage of that first winter, but 2020 to 2021, you can see another little bump during Delta and then a huge spike during Omicron. So first take home point, Omicron really affected kids substantially. And then next slide, please. You can also see that the age distribution got younger as the pandemic progressed, and especially with the Omicron wave. There're probably a couple of things going on here. Older kids potentially had been vaccinated, but there also were some sensitivities of younger kids, particularly to the Omicron variant. Next slide please.

And so we published this paper just over a week ago about the phenomenon of so-called Omicron croup. And it turned out the Omicron variant actually reproduced, the virus itself reproduced a little bit better in upper airways than in lower airways, as in earlier variants of SARS-CoV-2. And it is young kids who are more vulnerable, because their airways are small, to infections in the upper airway. And so we showed that there was a really demonstrable increase in croup and tracheitis and other upper airway infections as the Omicron variant became the dominant one here in the US. Next slide please.

So next take home point is that MIS-C is a uniquely pediatric form of PASC or postacute sequelae of COVID. PASC is really what RECOVER is all about. IMISA or in adults does exist, but it's rare. And it makes up a much smaller proportion of the impact of SARS-CoV-2 on adults than MIS-C does on kids. Next slide please. So the CDC case definition of MIS-C includes a few things that I'll specify in a second. But in a nutshell, MIS-C is a post-infectious complication of SARS-CoV-2, a form of PASC. It's a hyperinflamatory disorder. It can have involvement over a number of different body systems, including the cardiovascular, respiratory, neurologic, gastrointestinal, and mucocutaneous systems. As of a few days ago, nearly 8,000 cases had been reported to the CDC and something like a half of those require ICU care and something like a third of those, at least early on, required treatment for shock. Advance, please.

Next slide. Thanks. And so the CDC case definition includes that they are children less than 21, that they have a presentation consistent with MIS-C including fever, laboratory evidence of inflammation, at least two organ systems involved, and then a severe illness requiring hospitalization. Also, no alternative plausible diagnoses with the exception of something else called Kawasaki disease, and then recent recurrence SARS-CoV-2 infection or exposure. Now, that's a lot of information. I will say that it's the cardiovascular impacts that people are most

worried about because of the risk for coronary artery inflammation of the walls that can lead to dilation and then risk of clots in those and heart attacks either acutely or later in life. Next slide, please. And then there are a couple pictures here of the potential for changes in the tongue and lips, as well as rashes on the skin that can go along with this condition.

Next slide please. So that's in contrast, the other major form of SARS-CoV-2 impact on kids is acute COVID 19, and this looks much more like it's adult counterpart. So-called acute COVID, it can cause pneumonia, often bilateral. It can cause hypoxemic respiratory failure, which we take care of here in the ICU all the time. It can cause clots. It can cause heart and kidney dysfunction, and it can also have hyper inflammation going along with it. Next slide please. And so here are just a couple of chest x-rays that were published from an early report of acute pediatric COVID 19. Next slide please. So there are a couple of really landmark MIS-C studies that are still ongoing. First on the left side, the overcoming COVID 19 group led by Adrian Randolph as a number of really high impact publications.

This was one of the first ones, the first kind of comprehensives report of MIS-C in the US. And I'd encourage you to check out their other papers. As well as the study mentioned on the right, the COVID music study led by Jane Newberger and Ann Troung, and the URL there is available for you if you want to check it out. This is a prospective more long-term outcome study that is part of the RECOVER consortium. Next slide please. So we've been able to develop a computable phenotype for MIS-C in the N3C enclave. And here I'm going to show you some information of data that we have analyzed using that computable phenotype. And so this image is just like the earlier figure that I showed you, but it's just the kids with MIS-C, the earlier one was both acute COVID and MIS-C.

And so we have more than 3,700 patients with MIS-C in the N3C enclave as of the April 14th data release. And this is in contrast to nearly 400,000 SARS-CoV-2 positive kids who don't have MIS-C. Now, importantly, N3C is not a population sample, so that 1% or so is not indicative of the sort of population risk of MIS-C. In reports from Denmark, where they do have a population sample it's on the order of one in 2000 or 0.05%. Another take home point from this slide is that that school age band, the five to twelves is the largest age group for MIS-C. Next slide, please.

So these figures have the same construction. Time is on the X axis. Percent on the left Y axis. Number of patients on the right Y axis, but the bars are divided instead of by age, they're divided by peak severity, sort of how severe was the most severe encounter that that child had for MIS-C. And so I'll show you just a couple of features of this figure. The red at the bottom, those are encounters where the most severe encounter involved things like invasive ventilation or ECMO, or unfortunately the child died or was discharged to hospice. The yellow ones are inpatient hospitalizations without the severe features. The dark green are emergency department visits, and the light green

are outpatient visits or clinic visits. And so you can see a couple of things. First, you can see that there was an MIS-C spike after the first COVID wave in the US.

So that was around may of 2020. Next slide, please. You can see that the MIS-C case count and severity both were highest during that first winter 2020 to 2021. Next slide, please. And then there was a sustained MIS-C wave during Delta and kind of early Omicron that also had pretty substantial severity. Next slide, please. So this figure shows the time from COVID positive event to MIS-C for those kids where we have both events in N3C. And you can see a couple of things. First, the overall median, where the length of time or the length of all those individual bars. The overall median is about 21 days, so three weeks. And we usually think about that clinically kind of two to six weeks is the timeframe when if a kid comes in, that's where we think of MIS-C if they have a presentation that's consistent. And then you can also see that there's that steep drop off where the largest number of MIS-C cases occurred during winter 2020 to 2021. Next slide, please.

Now, we also have been able to determine several MIS-C severity phenotypes. And so the most common severe phenotype is that children who receive or require an inotrope, or vasopressor, a medication often for heart function or blood pressure. But did not in fact need support for ventilation. And then the curves down at the lower end of the figure are those kids who also need ventilation or needed ventilation, but not blood pressure support or who happened to be on ECMO. Next slide, please. Now, importantly, there are differences in biomarkers and in physiology for kids who have MIS-C versus those who have acute COVID 19. And this is from a paper that we published a couple of months ago. Basically you can see that the teal bars tend to be substantially wider than the purple bars. And so all of these inflammatory markers and indicators of systemic inflammatory response are more substantial in MIS-C. Next slide. And keep going. Now, and this is also corresponds to a higher increase severity with MIS-C then with acute COVID. Next slide.

Now, there are a couple of demographic risk factors for MIS-C versus acute COVID. I mentioned that five to 12 age group already, boys are a little bit higher risk of MIS-C versus acute COVID. And in that sample from September, through September of 2021, children who were black or African American had higher risk as well. Next slide, please.

Now, interestingly, kids who have other comorbidities were a little higher risk of having acute COVID 19, but obesity was the only comorbidity that appeared to be associated with MIS-C in our sample. Next slide please. And one more. So overall they have fewer comorbidities. Next slide, please. Now, I just want to mention that N3C pediatric data have also been used to support a pediatric challenge. So a computational challenge or sort of hackathon that was run by BARDA, the Biomedical Advanced Research and Development Authority. You can see

the link there. The winners were announced just a few weeks ago, and the two challenges were intended to produce deployable models that could be used to predict hospitalization among those who tested positive as outpatients. And then a second model intended to predict severity, including things like cardiovascular support among those who were hospitalized. Next slide, please.

So I'll just mention very briefly that there are other N3C RECOVER products that will be extended to children in the future. Next slide, please. Including a project led by Emily Pfaff, a machine learning based long COVID predictor that we are now applying to the entire N3C on cliff. That manuscript is in press at Lancet Digital Health. Next slide, please. Now, it works quite well in discriminating those who will and will not ultimately develop long COVID. Next slide, please. And the features in the machine learning model make clinical sense. And so difficulty breathing is associated with higher risk of PASC. And there's been a lot of speculations on vaccination being associated with lower risk of PASC. And we found that as well. Next slide please.

So I really want to recognize, and thank the team that worked hard on these pediatric analyses. Peter DeWitt and Seth Russell are data scientists here at the University of Colorado. Blake Martin is one of my pediatric ICU colleagues, a junior faculty member here. Richard Moffitt at Stony Brook. As well as the N3C leads, Melissa, Chris and Ken Gersing at NCATs. Next slide. Also want to thank our funders for all of their support. NICHD for support for the dashboard. NCATs for their support for N3C and NHLBI for their support for RECOVER. Thank you very much. And I'll be happy to take any questions when we get to that phase of the meeting.

Ravi Jhaveri

Hello everybody. So my name is Ravi Jhaveri. I am at, as mentioned, at the Ann and Robert H. Lurie Children's Hospital in Chicago. And I'm speaking today on behalf of the whole PEDSnet EHR cohort team. And we're going to talk a little bit about the PEDSnet system, and then leveraging that infrastructure to inform our understanding of PASC and MIS-C. Have some disclosures as well. Nothing that really impacts the content of this talk. So we're going to briefly review our PEDSnet structure and the goals of PEDSnet. Highlight some of our prior COVID 19 studies in children. Discuss some of the plans for ongoing MIS-C analysis and answer your questions. And I do apologize for needing to leave before the end of the discussion. So that's not intentional, just unfortunate. And I think I would start by saying, I think many of the observations that I'm going to share are very much in line and consistent with what you've already heard from Dr. Bennett.

So first, just a little bit about what is PEDSnet. So really PEDSnet is designed to leverage the HR network from many of the largest children's hospitals across the country. The idea is that these institutions have what's called a common data model, so the data all looks the same, that's essentially in the same language. And so it allows the

data to be combined very easily into these larger cohorts. And so just for some broader context, one of the biggest challenges with pediatric research and healthcare in general is that because of the smaller numbers of patients, in general, with conditions, pediatric studies often take longer to do, or are much more difficult to really come to front conclusions about. And so studies need to be much larger and include many other sites, which makes it quite expensive and logistically difficult to do these kinds of studies. And so that's part of the design of PEDSnet is to overcome many of those challenges.

This is an overview of the PEDSnet institutions. And I appreciate Chris Forrest, our PI for PEDSnet sharing some of these slides. This is a little bit about the geographic distribution of PEDSnet centers, and it's sort of coupled or overlaid on a geographic density map. Just to give you a sense of the scope collectively each year, these institutions care for almost two and a half million of the nation's children. And so we also have the ability to connect with sites in the broader national PCORnet EHR network. And so the reach can go beyond just the children's hospitals within PEDSnet, and we are hoped to weave together larger cohorts that encompass even a broader population groups across the country.

All right, so what have we done as part of the RECOVER pediatric EHR network? So I want to discuss the first paper that we published as a group. This was a summary of the acute COVID 19 data, really from the start of the pandemic in March 2020 until December 2021, this summarized data for over 82,000 children within the PEDSnet data set who had positive testing for SARS-CoV-2. I think this mirrors what you've already seen, that when you look at all comers, less than 10% of kids with COVID 19 had moderate to severe symptoms based on those classifications that the CDC and others have put together for acute COVID 19. We did not see a notable difference in severity with Delta compared to earlier variants. There was sort of a summer spike or early summer spike with Alpha in May to July of 2021, but we didn't see the same thing quite with Delta.

We have a second paper that is describing the syndromic and systemic PASC manifestations in children. This is looking from March to 2020 to December 2021. This summarized data for almost 60,000 kids with positive SARS-CoV-2 testing. We included symptoms, conditions, and medications from days 28 to 179 after initial testing. And the scope of the search evaluated 669 potential task features. When you look at the overall rates of PASC and all comers, the rate was about 4%. And we recognize that this is a much lower estimate than many early reports. I think there's a couple of reasons for that. One, obviously we're using a pretty large geographic cohort with a very large denominator, and so our denominator was quite high. The other thing that I think was very interesting was there was a very high level of background complaints. So people who did not have a positive test still had a component of many symptoms.

Now, people could argue is that the background of living in a pandemic, whether you've been infected or not, and the stress and burdens of regular life? Is it just that our current life comes with a lot of maybe mental health and other complaints? It's hard to know, but the 4% is sort of a differential estimate that comes with trying to account for all of those things. When looking at the syndromic features of PASC, I think looking at the pediatric data, it's quite similar to what has been reported in adults with the loss of taste and smell being very prominent and then complaints of pain, whether it's chest pain or generalized pain, and then fatigue as part of that as well.

When we look at systemic highlights, so certainly affirming the idea that MIS-C was one of the most common systemic manifestations. Others that are expected, things like myocarditis, which is an intense inflammation of the heart, a variety of mental health issues and mental health treatment. Thrombo phlebitis and embolism or clotting. So we've known that COVID 19 infection has been associated with an increased risk of clotting disorders or severe manifestations of clots. And so, again, it's reassuring to us to know that we're able to pull the signal out from our patients. And then speaking to the impact on younger patients, especially the idea of bronchiolitis, as we looked at this bronchiolitis, we know is inflammation of the smaller and medium airways that we typically see in infants and toddlers with other respiratory viral infections. And so the idea that as we saw more and more younger kids being infected, particularly with Delta and Omicron, that we were seeing more and more cases of bronchiolitis.

So I want to highlight a little bit about our plans for digging into the MIS-C data. I'm referring to this a little bit as the deep dive, so our current work aims to design a computable phenotype for MIS-C. The idea that we... MIS-C right now is a diagnosis that is made with a collection of clinical criteria. And so it takes a lot of work to look at how patients, each individual patient compares to those clinical and lab criteria. And so that strict analysis is really hard to do over a broad number of patients. And so if you're able to come up with what we would call computable phenotype, a list of the key critical features that is highly associated with MIS-C, you're able to sort through large data sets and able to do that in an efficient way. And so it would allow for a rapid case identification and allow for us to expand into some of the other groups that I've already mentioned.

So, as we look at our search parameters, we'll start at the outset of pandemic and go through our most recent data set, which ends March 31st, 2022 for a total of 25 months. We'll look at the date of first evidence of MIS-C or other criteria supporting MIS-C or a possible case definition, plus some other criteria that is affirming for MIS-C. And we'll look to allow ourselves the possibility that a patient may have been tested in some way before they actually entered our cohort. We'll look from 42 days before to 42 days after, just to make sure that we don't miss any patients. The things that we're looking to try to do is to look for MIS-C diagnosis terms using any of the EHR sort of key search parameters that we'll use. Over the course of a hospitalization are two or more of the same terms in

the outpatient setting. We'll also look for people who match the first criteria, plus another positive COVID 19 test plus minus that 42 days.

And then we have a lab based criteria that I think, again, align well with what Dr. Bennett highlighted. The N3C group found. They're slightly different parameters, but many of the same lab tests that we've done. And then we wanted to refine it a little bit, looking at some of the other lab tests depending on which institutions use which test and what the threshold will be. We also wanted to look at a little bit about timing, explore the initial association or description of a Kawasaki like phenotype. Just to remind everyone Kawasaki disease is an inflammatory disorder that results, in severe cases, in dilation of the coronary arteries. When MIS-C was first reported, it was described as sort of Kawasaki like, and further investigation has showed that it's really a distinct entity from Kawasaki. And so we wanted to make sure we could sort of separate the two reliably in our data set. And then some of the other adjustments looking at serologic criteria, plus other lab abnormalities, again, to make sure that we've captured as many of the patients as we can from our data set.

So one of the challenges as I mentioned is because these diagnosis is used with clinical criteria, there's no, what we would call goal standard test for the diagnosis of MIS-C. No one can just send an MIS-C test and make the diagnosis. And so how will we evaluate our computable phenotype? And so what we're trying to do is we're going to leverage work that's already been done by each of our institutions. Individuals at each institution has already reviewed and reported cases to either the CDC or to state public health departments. And so we have the ability to obtain those lists and then anonymize them, remove the individual patient identifiers, and then take those that list and combine it across institutions. And now we've got a gold standard list that's been confirmed against CDC criteria, and we can look at how our algorithms perform against this gold standard list, so I think this is really important. This is key to the success of being able to generate this computable phenotype and knowing how well it works.

So I have a sneak peek with a couple of preliminary data from our MIS-C. I think, again, as you've heard already from Dr. Bennett, our initial results show that the MIS-C cases tend to skew younger than SARS-CoV-2 alone. There is a slight male predominance. We did not see the same racial ethnic skewing. That just may be a representation of our geographic distribution. What I think is very interesting is we have a cohort of MIS-C patients who were never admitted, and that's very different than what's described in other studies, which are obviously very focused on inpatient studies. So we think we have the ability to really perhaps broaden the definition of MIS-C. Again, we have to make sure that these patients do still meet criteria for MIS-C, and if they don't, what is sort of the copycat for MIS-C. And so we plan to study this in much more detail as we move forward.

And then I think the time trends, again, Dr. Bennett covered this a little bit, but I think this graph really shows nicely the offset peak from the peak in infectious cases, which is the red line or COVID positive cases, I should say. And then the MIS-C cases. And so you'll see that it's offset by about four weeks, which is pretty much the average offset. And so I think that it certainly validates some of our initial search methods compared to other studies on MIS-C. And then to highlight again, we saw that initial sort of severe peak in late 2020, early 2021, a spike in cases around the time of alpha circulation and then a seemingly lower percentage with Delta. And I don't have any data with Omicron yet to share. We're going to dive deeper on that.

And then looking at lab testing. Again, the patients who had lab abnormalities that were most frequent very much supports the observations of the N3C team that you've already heard from Dr. Bennett. And so we're using a combination of these labs as we build our computable phenotype. So just future queries on MIS-C. One of the things we'd really like to cover is looking at treatment options, trying to see if we can discern any differences between the variety of therapies that have been used, whether it's intravenous, immunoglobulin, corticosteroids, anti-TNF agents, or perhaps some of the other less common immunomodulatory agents, explore this cohort of outpatient MIS-C patients, and try to figure out exactly what that phenotype looks like.

The additional validation of our computable phenotype in collaboration with the N3C group, as well as some other PCORnet partners, and then looking at some other practice patterns for treating MIS-C in relation to some existing protocols for Kawasaki disease. We think that many of the institutional protocols have been derived from prior experience. And so we are really interested to see if there's a big difference, or if there's been an expanded pattern for that. So, again, just to summarize our PEDSnet data offers the ability to interrogate large numbers of pediatric patients with a variety of conditions. We think the queries we're going to do on MIS-C will really advance our current care models and achieve greater efficiency into the future.

All right, so I'd like to thank all of you for your attention. I'm going to stop sharing my slides here. I do just want to comment briefly on a question that's come up over the last couple of weeks in relation to the reports of the severe hepatitis that we're seeing in kids that seem to be related to adenovirus. And the question that comes to everyone's mind is what impact does COVID 19, the pandemic have on our observations about this. I'm going to... The spoiler alert is that no one's really sure right now. And I can't give you a definitive answer. I can talk a little bit about the fact that with the pandemic and with the changes in our behavior, as a result of the pandemic, we have seen significant changes in the way many common viruses circulate in our population and particularly amongst children.

And I think many of you are familiar with the fact that we've seen other non-COVID respiratory viruses circulate at very high levels outside of their normal seasons because of the changes in when and how we get together, who's in school, who's unmasked. And so it is very likely that the observations that we're seeing now are related to changes in our behavior as we start to normalize things. The other thing to consider is that the pandemic really impacted who is exposed to viruses on a day to day level and who is susceptible. And so many of us might have coincident infections that sort of boost our local immunity or immunize us in quotations with these natural infections against future, perhaps more severe ones. And it may be that these severe manifestations reflect a lack of infection with other organisms that might protect us from these severe manifestations. So these are all the possibilities, but very much to be determined. So, again, thank you very much for allowing me to speak, and I look forward to questions later on.

Ericka L. Fink

Hi, I'm Erica Fink and I'm again from Children's Hospital at Pittsburgh. Thank you so much for having me to speak a little bit about our work in the GCS NeuroCOVID Consortium, and present at your webinar series. The only related disclosure is some of this work is funded by an INCLINE grant from Neurocritical Care Society. And I was lucky to be invited to participate in the NIH Common Data Elements Working Group for COVID 19 in children. And families provided any consent for any pictures you'll see. Going to give you an overview on this topic, because it's a little different than the prior wonderful speakers. This is going to be focused on the neurologic manifestations in children with COVID or MIS-C and in the future in PASC and a little bit about our work so far and some future directions.

So through April of 2022, globally there's been over 500 million cases of COVID in adults and children, and 6.2 million patient deaths, 10.8 billion vaccine doses given, but we really don't know what the impact either in the short or long term is in terms of new impairment. Trying to find global data, which is always interesting to me to look inside our country and also outside. I think UNICEF probably has the best compilation of data to see what's happening in children and of 105 countries reporting their data to UNICEF, that includes age, children and adolescents under the age of 20 account for 33% of the global population and 20%, or nearly 100 million of the cases. That's an estimated 100 million children are infected. But on the right, looking at deaths, among the 91 countries that report COVID deaths by age, only 0.4% are occurring in children and adolescents under 20. And you can see they're slightly more than half are occurring in ages, children ages 10 to 19, versus 42%, ages zero to nine.

And then for a recent talk they gave, we were really interested in how this is mapped across low income, middle income, and high income countries. You could see that most cases are reported in children and high income

countries, but there's a tenfold increase in deaths that are reported to be associated with COVID in lower income countries, which is important.

And so keeping in mind those 100 million children who are infected with the virus, let's talk about the general ways that viruses can manifest neurologically, because there are many. So first children can experience neurologic symptoms just like us, like headaches and fatigue. As noted in the prior talks, they can directly invade the CNS or revoke para-infectious responses, leading to things like ADEM or Gullain-Barre. They can also exacerbate preexisting neurologic diseases in patients with epilepsy or muscular sclerosis. Children especially admitted to the hospital and even more so the ICU are at increased risk of post intensive care syndrome, secondary to exposures like hypoxia, hypotension, stillness, inflammation, delirium, and they can come out with all sorts of new impairments in emotional cognitive health and physical health. Notably, nearly all of these except direct CNS viral invasion have been consistently reported in children with SARS-CoV-2 infection. The landmark paper, looking at neurologic manifestations.

And the first one came out with Kerri LaRovere up in Boston, in JAMA Neurology, and they studied 61 centers, 1700 children and 61 centers in the US and found that 22% of their cohort, which included both acute COVID and children with MIS-C, 22% of them had some sort of neurologic manifestation. And the most common ones were fatigue and weakness in 35 to 60%, which was more of those complaints occurring in older children versus younger. Altered awareness or confusion in about 40% and followed by headache. All of these children survived notably.

However, children that had life threatening manifestations, encompassed 12% of their cohort. And those were children that had encephalopathy, stroke, notable CNS infectious, or post-infectious complications, Guillain-Barre or Fullen and cerebral edema. And 40% of those survivors had health sequelae and 26% of them died. So neurologic manifestations appear to be an important towards morbidity and mortality in SARS-CoV infection in children. Some of the imaging from their study is depicted here, displaying a wide variety of neurologic manifestations. And just to mention a few of them briefly here, we have a child that has encephalomyelitis with gray and white matter disease and hemorrhagic lesions right here. And then this children had focal spinal cord lesions. This child presented with classic signs of hemispheric stroke.

Thrombotic infarct in the left MCA. And on the right was a child who had hemorrhagic stroke while on ECMO treating MIS-C. Last is a child with acute Fullen cerebral edema who presented with encephalopathy, seizure, and shock. And the team on the right shows a spinal MRI showing classic signs of Guillain-Barre with enhancing Coquina. Looking at summarizing what's known about PASC prior to the big data studies coming online. First one I

saw was in 2020, and it was a report in Sweden of five children. All were outpatients, all had reported these issues as late as six to eight months post infection. Their infections were diagnosed clinically. This is before Sweden had testing available, and you could see the litany of symptoms and signs that they had with over half of them being neurologically related. Like those mentioned before fatigue, headaches, and then even more so like difficulty concentrating, memory loss, sleep issues, continued anosmia. None of these children fully returned to school by the time of publication. Only one was admitted late with peri-myocarditis.

And then last year there was a paper published from Italy and 129 children. Most of these children were outpatients, but a few of them were inpatients. 2% wound up in the ICU. Only 2% of them were clinically diagnosed with MIS-C and four to six months after discharge, their parents reported one or two symptoms that were ongoing or new in about a third of the cases. And in about a quarter of the cases, children had three or more symptoms. And you could see the symptoms most commonly reported were insomnia, respiratory issues, congestion, fatigue, concentration, again, comes up just like brain fog in adults and joint pain. This is a newer report that's EHR based. Recently published in JAMA Network Open. Aggregated over 330,000 adult and child patients. And they looked 31 to 150 days post SARS-CoV-2 testing upon hospital admission, so these children were all admitted. When looking at what kind of symptoms were more common in children that tested positive versus those that tested negative later on, they found that only shortness of was different. There were more children with shortness of breath who had tested positive several months after discharge.

When looking at preexisting diseases, they only found that type two diabetes, mellitus had a higher frequency in children that tested positive and had symptoms reported. But the prevalence overall is low of that condition. So that's a little bit of background for looking at neurologic manifestations. A little bit about our story. So up there with Michelle Schubert from Utah and Courtney Robertson in Hopkins. These ladies are all NIH funded, pediatric intensivists, and focused on neurocritical care and involved in the pediatric neurocritical care research group. We also got in touch with one another wanting to do something to help. We joined up with one of my partners here in the adult critical care world who's now at Northwestern, Dr. Sherry Cho and Molly McNet who's in their scientist, their Ohio state.

They had started this consortium and we formed the pediatric arm. And our collective mission was really to understand the frequency of neurologic manifestations and their post discharge consequences. And perhaps even if we can then take that information to look forward into pathophysiology of neurologic manifestations with the long term goal of forming some sort of platform for making it more feasible to do future neuro pandemic study, to really help in public health.

You could see our pediatric partners. We formed this network rather quickly and had over 100 site PIs sign up to want to participate from all around the globe. Not everyone was able to participate. And this was an unfunded initiative. People were very, very passionate about being involved, but not everyone had the resources to continue, but we're grateful for everyone. So this is our first publication in pediatric neurology. And we labeled it a preliminary dataset looking from the very beginning of the pandemic through April of 2021. Most centers that reported patients in this round were from the US. And obviously most of the almost 1500 patients as well. 86% of these patients who are all were hospitalized and under the age of 18 had acute SARS-CoV-2 infection. And 14% had been diagnosed with MIS-C. We looked at neurologic manifestation type and timing of their initiation.

And when they stopped and by looking at charts, we looked at hospital disposition and lengths of stay in this paper as our primary outcomes, so there's a lot of tables, a lot of data, but to summarize some of the patient characteristics, 44% of children had any neurologic manifestation in our list. So you can see here in the orange there, this column. And the middle or six month up here, July to December of 2020, saw the most patients overall reported. All of which were prior to Delta and Omicron. You could see that children with neurologic manifestations were slightly older with a median age of 12 versus five years. They were more like to have a preexisting condition, 65% versus 53. Those are high numbers. And 20% of those were either pulmonary or neurology related conditions. There were no differences by sex, race, or Hispanic ethnicity. But in children who had neurologic manifestations versus did not. The table on the right was comparing children with characteristics between acute infection and MIS-C. Children with MIS-C in our cohort were slightly older, less likely to have preexisting condition.

And there were more children with acute infection that were of Hispanic ethnicity versus MIS-C. So slightly different mix than the other two you heard, although I'm sure there's some overlap in patients. So the most common neurologic manifestations were for the acute group were headache, acute encephalopathy, and seizures. You could see the frequency here reported, and this is extracted again from the medical chart, so it had to be recorded so less likely you're going to know if a headache occurred in an infant. But you'll know what a seizure is. So those are some of the limitations of doing this kind of research. You could see that the same mix and most common symptoms in MIS-C were the same. However, there was higher frequency of headache, almost half the patients, more children presented with acute encephalopathy. However, there were more seizures reported in children with acute disease and far less common where things like stroke reported in only 13 patients, but 12 of them had the acute infection versus one with MIS-C in this cohort.

And as we asked patients... Sorry, we asked for write-ins for other neurologic conditions, because when we launched our study, we didn't really know the full scope of what to look for. It made me wish I had written acute psychosis into the case report form. You could see that was reported as a write-in by many people, as well as

photophobia, co-acute neurologic condition. And 12% of patients had more than one neurologic manifestation, especially those with acute infection. Next, the Initial Glasglow Coma scale scores were normal in 98% of children, whether they were on the ward or the ICU. And while 12% of kids that had neurologic manifestations had or are presenting Glasglow Coma Scale score of less than 12. So that led to more than double or half the patients with neurologic manifestations being admitted to the ICU for at least observation, if not treatment. Versus 22%, going to the ward. Children with neurologic manifestations had longer ICU and hospital lengths of stay.

You can see here, 15 total children died. 14 of them who died had neurologic manifestations similar to Dr. Rivera's study. More children without neurologic manifestations went home after hospital discharged. Comparing acute COVID versus MIS-C patients, more than twice as many MIS-C patients were admitted to the ICU with double the length of stay. And most deaths occurred in the acutely infected group. As I mentioned, 11 versus four patients with MIS-C. So sorry, I went a little bit of out of order. In our multi, very logistic regression in the overall group. This highlights that older age, MIS-C status, neurologic, and metabolic preexisting conditions and throat and abdominal pain were associated with neurologic manifestations.

Okay. This figure displays different types of manifestations in the Y axis and days to onset with day zero being hospital admission day. So the minuses are the days leading up to hospitalization. Overall group, the combined group is in blue, MIS-C in the green triangle, and acute infections in the red circles. You can see in the overall and acute groups, the earliest pre-hospitalization, neurological symptoms included headache, aguesia, anosmia. All occurring median three days prior to hospitalization. Encephalopathy seemed those patients. Obviously, they mostly had presentation on the day of hospitalization. In the MIS-C group in particular, the earliest pre-hospital neurologic symptoms were syncope, which was very early. Ataxia at six days and headache at four days, which is very interesting and could be a way to herald onset of this issue. Non-neurologic manifestations almost all occurred prior to hospitalization.

Now, the tier one final data set goes through July of 2021. We have, I should say, over 2,500 patients, at least. We're still finalizing and cleaning our data at 43 sites. And our objectives are to now look at hospital based treatments, testing results. We have a neurological outcomes using the Pediatric Cerebral Performance Category score at baseline and hospital discharge. And we'll look at all these different groups as well like we did in the preliminary work. Tier two is launched at 13 of 15 centers. So far, it's an observational study. Single assessment of post discharge outcomes.

And we took a subset of patients from US sites that wanted to participate from tier one. Our primary outcome is looking at health related quality of life by neuro manifestation status. And this is what's funded by the

Neurocritical Care Society. Our questions include how is the child functioning? These are a parent report. Their pediatric PCPC, their health related quality of life. Also, the family impact module of PedsQL. We're going to ask about ongoing or new symptoms, healthcare utilization like readmissions, are they back in school? Are they vaccinated? Ask the parent how they're doing globally. And a coronavirus impact scale.

So that work has launched. And we have, I think, 32 patients in our dataset so far. Aiming for much higher, but we're on our way. Another ancillary project that got on the way is trying to collate and examine existing brain and spinal cord MRIs, looking for syndromes and feature based signal changes. There's a whole case report form that's been developed for this with Peter Ferizano in Wisconsin and Matthew Kirsten at CHOC that's launching now. And we hope to have 100 to 200 scans uploaded for this analysis very quickly. And so I will just sort of summarize in the next couple slides, what are the critical knowledge gaps for thinking about neurologic manifestations? I think we're getting to what their prevalence is. It seems quite prevalent and we're likely underestimating it. Who's at risk for these neuro manifestations and why? Perhaps we can head sort of understand the phenotype and apply the correct treatments and monitoring in a timely fashion. What are the effects of variance in neurologic manifestations? Perhaps the two prior speakers will be able to get to this question as well if I can convince them to look.

What are the mechanisms of neurologic manifestations? So we can best target treatments to patients. We don't know what these types of outcomes are, so I'm really thrilled that the NIH is all of these programs ongoing, that you're participating in to find out. I mentioned, we don't know what the optimal monitoring and treatment regimens are or the impact of vaccines. And I will add another question is who should best treat these patients that have PASC and neurologic problems? We really don't know.

So some of these studies in addition to the ones already talked about will fill in some of these blanks. These are the ones on clinicaltrials.gov that I had seen a little bit ago in addition to RECOVER. This is my last slide, a vision slide. While I'm glad we're able to develop this consortium to serve the COVID pandemic. We were limited in terms of resources to really act quickly and efficiently to best serve our patients. So wouldn't it be really valuable and a silver lining if we can try to invest in infrastructure to have an at the ready collaborative platform to serve future pediatric pandemics and neuro pandemics with simplified case report forms, data and sample coordination to facilitate rapid and equity minded research response towards saving children's lives and normal development. I think so. I want to thank everybody for their time today and welcoming us to present our work. I'm really thrilled to acknowledge all the incredible people that are part of this. These are just some of them and our funding agencies. Thank you very much.

Melissa McPheeters

Thank you so much, Dr. Fink. And to all of our presenters that was fantastic. We're going to turn now to our discussants who will share some thoughts with us, and I just want to encourage everyone, if you have questions or thoughts to put them in the Q and A. We are monitoring the Q and A, and so we'll get to those questions as we move forward, so please do so. To our discussants, Dr. Fessel and Pearson.

Josh Fessel

Wonderful. Thank you. So, first, thanks so much to the presenters. This was an incredible tour de force of some really impactful research in the pediatric population for COVID and long COVID. And so this is really great. I can't say thanks enough and thanks so much to all of our attendees. So, gosh, so many things that we could talk about, but I think I'll start us off with a question that kind of bubbled up for me really in the first two talks from Tellen and Ravi, and unfortunately Ravi has had to drop off. And that I kind of had in mind as you were talking Erica, but I want to hear from both of you, from all of you, and it has to do with the question of what do you compare to when you do these studies?

So anytime you do a clinical study, the question has to be asked, what group are you comparing to? And I think that's been kind of a tricky question as we think about long COVID or PASC. Are you comparing to people who never had COVID and who feel totally healthy or to people who had COVID, but don't have any residual symptoms? How does vaccination factor into that? How do variance factor into that? And I think it's are you looking at people who have similar symptoms, but didn't have COVID? And I know that, I realize I may be asking a big thorny complex question, but I'd be really curious to hear you say a little bit about how you think about choosing the right comparator groups. How you've gone about that and where you think thinking needs to go on that.

Tellen D. Bennett

Yeah, I can try to start. It's a terrific question, Josh. And I mean, I think the summary version is all of the above and tailored to the question and the purpose. In the sense that if you are trying to develop a clinical decision support tool to identify kids who are going to need something, then your control group might be the kids who did not ultimately end up needing whatever that was. If you were trying to develop predictors to allow discrimination between MIS-C and acute COVID, there's a natural comparator group there. I think you raise really important questions as we think about sort of the prospective arms of RECOVER. And I know they have multiple types of controls and we have on the N3C side built in multiple types of controls for our risk factor analyses that are in process as well. Including those who are COVID positive, but we don't have any sense really that they have long

COVID as well as a spectrum of sort of probability of long COVID so that we are enriching kind of both ends, but I'd love to hear Ericka's thoughts as well.

Ericka L. Fink

Yes, I think that's a really great question. And sometimes if you start too early in a pandemic, you really don't know if you're choosing the right items for us. It was children that were all hospitalized, so we chose to look primarily at children that had neurologic manifestations versus not. That's our primary comparison groups for both the tier one, looking at symptoms and hospital outcomes. And tier two, where we're looking at post hospital outcomes. But however, as Tell mentioned, I think there are other natural groups in there and I showed you some of them, which was the acute COVID versus MIS-C. And then also ward versus ICU is sort of highest level of care because children that go to the ICU are certainly a different cohort at the end of a bell curve. It's tricky though with COVID in the beginning because some of the children were diagnosed clinically because there were no tests, so there's a lot of caveats. And then there's children that come in later that test positive, but are asymptomatic. So is that another natural control group for a hospitalized cohort to look at? These are great questions.

Gail D. Pearson

I wanted to first echo Josh's thanks because I think these are wonderful talks and there's a unique opportunity, I think, in children to learn things more broadly, especially with the difference with MIS-C, which seems to be a unique or nearly unique pediatric disease. And you both, as well as Ravi, have harnessed the power of big data, which isn't always brought to bear in pediatrics to try to answer some of these questions and generate some hypotheses. It's certainly understandable that people who are experiencing long COVID are looking for treatments. And so I wonder if you both could talk about how the data you've gathered and the platforms you've established could be turned to identifying potential treatments and maybe even executing trials.

Tellen D. Bennett

Yeah, I can start. And so N3C is in its current form observational data, so we can only see what current providers are doing in the real world. It is a great environment for so-called comparative effectiveness analyses, which as you say, can both hypothesis generate and give some early sense of potential for causal effect and potentially help to plan and power trials. And we are engaged in that type of analysis on the adult side right now, actually. And I think in pediatrics specifically, we've definitely seen variation in therapy for MIS-C in the observational data. And so I'm very intrigued about whether we can get to some sense of comparative effectiveness. At my institution, for example, we've used a lot of TNF inhibitors. In other institutions it's been more IVIG and corticosteroids. And so I'm really curious to see those groups get compared.

Gail D. Pearson

And maybe their long term outcomes as well.

Tellen D. Bennett

Yeah, absolutely.

Gail D. Pearson

Not just immediate, but yeah. Thank you. Ericka, what are your thoughts?

Ericka L. Fink

Yeah, I agree with what Tell said and he's going to be able to get more at dosing and timing using big data. We didn't want to totally over bear people, digging data out of the charts, so we have what medications children received and starting on what day compared to hospitalized day and for how long. But I think it's not going to give enough information really to say what's the best treatment. And like Tell said, maybe we did something similar among sites or among attendings, but before there were really good data, I think, there's probably a big variety of approach. And then when it comes to a child that has neurologic complications or more severe presentations, they're certainly going to probably get more of the aggressive approach reaching for tools that we're not sure of. I wonder, Tell, if you're able to get at severity of illness using your dataset because obviously that'll be important.

Tellen D. Bennett

Yeah. I mean our severity of illness data, we can certainly get to laboratory results as their components of severity scores and things. And we can certainly get to utilization of a variety of technologies and therapies as they are components of severity scores. But your chart review may be able to get to all of the components, we usually are missing a few.

Gail D. Pearson

So thank you both very much. And again, congratulations on your work. There are a few questions in the Q and A, and I'll start and then hand it back over to Josh. Was there any data on recovery of the lung conditions and fatigue? So I guess the lung conditions would be to Tell, fatigue could be both of you.

Tellen D. Bennett

So we have information about sort of hospital disposition, which is pretty course. And so we are limited in our capture of those long term outcomes, so it'll be studies like Ericka's, like music and like others that are able to get to the recovery after kids and adults go home who develop these conditions.

Gail D. Pearson

Thank you. Ericka, anything to add?

Ericka L. Fink

Not just yet in our study anyway, but I think fatigue is going to be a big issue. That big data study I presented said it was all about the lung, so I'm interested in to see more.

Gail D. Pearson

Thank you.

Josh Fessel

Excellent. Thank you. Yeah, we have several good questions here in the Q and A, so I'll take them in order. The next one relates to the neurocognitive effects of long COVID. Could you both say a little bit more about where your thinking is and where your thinking is going as far as the research on neurocognitive effects. Particularly if you have thoughts on interventions and treatments. And Ericka, maybe we can start with you and then kick it to Tell.

Ericka L. Fink

Thank you. Yes. I don't think there are any studies out there that have reported detailed neuro cognitive outcomes just yet. But I think that is really important to see those types of studies. I think it's just like what was discussed earlier, it's going to be a little hard to tease out the general effects of the pandemic, missing school, or missing your friends, parents who are no longer there, or lost their job. And if you're looking at things like school outcomes, or emotional health outcomes, perhaps the ability to pay attention.

I don't know how you're going to tease out the general effects of the pandemic, unless you have a good control group, like you were mentioning earlier. But I think regardless, we're going to learn a lot about what children are going through during this pandemic. So, yeah. In our study, we don't have those types of detailed neurocognitive outcomes. But I did mention, we're going to look at some gross multidimensional categories of function, and your

health impact on quality of life and how the family's functioning. So we hope to get at some of these answers, but I think that the types of studies that the person asking the question is really important.

Tellen D. Bennett

Yeah. I agree 100% that those are among the most meaningful outcomes. And I think that they will be best elucidated in sort of linkage between prospectively collected kind of gold standard outcomes. And perhaps the rich EHR data about the encounter experience when they were more ill. And so I think teaming up on those two data sources would provide the best information to those studies. And I know that RECOVER has plans along those lines.

Gail D. Pearson

Yes. Good point about RECOVER, so some of these data, there's a lot of neurocognitive testing that will go on in the RECOVER cohorts. And I agree that pairing those data up with the EHR records is a great idea. The next question is addressed to Erica. Was there a prevalence of any specific preexisting condition among children and an increased risk of neurologic manifestations of MIS-C?

Ericka L. Fink

Thank you for the question. I was bringing up our paper. What we reported was that 61% of children with acute COVID had preexisting conditions versus 37% of the children with MIS-C. The most common preexisting conditions were respiratory and neurologic at 13 and 9%. However, I don't have it readily available exactly what preexisting conditions were present in children with MIS-C and neurologic problems in our multivariate, which I did not show. I should say that only children with respiratory preexisting conditions was associated with having a neurologic manifestation of any kind. So, that was respiratory, GI, preexisting diseases were protective for some reason. So I think a lot of these results are really hypothesis generating. Thanks for your question.

Gail D. Pearson

Great. Thank you.

Josh Fessel

Excellent. Thank you all so much. Well, we've had some great questions trickling in. I wish we had tons more time to keep talking about this. We're nearing the end of our time, and I want to make sure that we have plenty of time for our wrap up and to make sure everybody has the information on events yet to come. So I'm going to, once

again, thank you both and thank Ravi in his absence, and thank you, Gail, and to the whole team that made this happen. This has been a great discussion and, Melissa, I'm going to let you bring us home. Thanks.

Gail D. Pearson

And I'd like to thank everybody as well.

Melissa McPheeters

It was amazing. Shane, I think we have another slide to share. I want to thank everyone for joining us today, particularly want to thank our presenters. What an amazing opportunity to hear from them about this exciting work that's going on. This is one in a whole series of seminars. So just want to let everyone know these are the topics that are in this series at this point. Lots more to come. Lots of great information, fantastic research that's happening out there. And we want to make sure we keep people apprised of where things stand with that. All of this information is on our website. So recovercovid.org. I know I've said that a few times and I'll keep saying it. Please go to our website and this information is there, but also the webinar itself will be posted there so you can watch it again. You can share it.

The FAQ document, answering questions that came in before and during the webinar itself will also be posted there. And lots of other information about the RECOVER initiative as a whole. So please do visit the website. Thank you once again for joining us today. This has really been a terrific honor to moderate this session. Thank you very much.

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