

Transcript

Christine Bevc:

Welcome to the RECOVER Research Review or R3 Seminar. My name's Christine Bevc, and I'm a Translational Health Scientist with the RECOVER Administrative Coordinating Center, and I'll be your moderator for today's seminar.

The goal of the seminar series is to catalyze a shared understanding of the research within the RECOVER consortium, and I want to start by thanking everyone who submitted questions in advance. You can submit any questions today using the Q&A feature in the Zoom menu. And after today's panel, our speakers will answer as many questions as possible. A Q&A document will be posted with the recording of the seminar on recovercovid.org. The document will include answers for submitted questions relevant to today's presentations. Questions about other scientific topics will be addressed in future seminars, and answers to broader questions about RECOVER will be available in the FAQ found on recovercovid.org. As a reminder, we can not answer individual questions about clinical care.

Our presenters today are Dr. Suchitra Rao, Dr. Abigail Case, Dr. Melissa Stockwell, and our representative discussant will be Ms. Rebecca Letts.

Dr. Suchitra Rao is an Associate Professor of Pediatrics and an Infectious Diseases Physician and Hospitalist. She's spent the last 16 years studying respiratory viral pathogens in children, with a more recent focus on influenza and COVID-19. She's one of the principal investigators for RECOVER's Pediatric EHR Cohort Initiative and also serves as the Site Principal Investigator for PEDSnet, a large data network and learning health system spanning multiple sites across the country.

Dr. Abigail Case is a Pediatric Rehabilitation Physician and Program Director of the Pediatric Rehabilitation Medicine Fellowship at the Children's Hospital of Philadelphia. She also serves as CHOP's Quality and Patient Safety Champion of the Division of Rehabilitation. She's also an Assistant Professor of Clinical Pediatrics at the University of Pennsylvania. Her clinical interests include treating traumatic and acquired brain injury, inpatient rehabilitation medicine and pediatric cardiac rehabilitation. Her expertise and functional assessment and management for pediatric patients has driven her involvement in the RECOVER Initiative and ongoing scientific efforts towards understanding PASC in children.

Dr. Melissa Stockwell is the Chief of the Division of Child and Adolescent Health and the Felice K. Shea Professor of Pediatrics at Columbia University's College of Physicians and Surgeons. She's also Professor of Population and Health in the Department of Population and Family Health at the Mailman School of Public Health. She's a Pediatrician in a New York Presbyterian Hospital Community Clinic and is Associate Director of the American Academy of Pediatrics Pediatric Research in Office Settings practice-based research network. Dr. Stockwell serves as the Contact PI for RECOVER's hub site at Columbia University. And she currently serves as the Chair of the Recover Pediatric Cohort Coordinating Committee.

Ms. Rebecca Letts has been a pediatric long COVID caregiver and long COVID patient since March 2020. Her youngest child brought home COVID from school and neither recovered afterward. As an early longhailer, Rebecca's become involved in multiple infection associated chronic condition and illness advocacy organizations, chiefly engaging with the COVID-19 Longhailer Advocacy Project. She joined RECOVER in June of 2021 as one of the first pediatric representatives and she currently serves as a member of the NCEG Representative Engagement Subcommittee. She's an active contributor in multiple manuscript writing groups.

The topic of today's seminar is PASC in Children: State of the Science and Future Directions. Today's speakers will discuss our current knowledge of long COVID in children, including the epidemiology and risk factors underlying mechanisms that cause symptoms and functional outcomes.

And with that, I will hand things over to our first presenter, Dr. Rao.

Dr. Suchitra Rao:

Thank you so much, Christine, and really wonderful to be here today. Welcome to everybody who is joining live on the webinar, as well as those who are going to be joining at a later stage.

As you'd heard, we really are going to be taking the time today to be talking about long COVID as it pertains to children. And if we go to the next slide, I just wanted to disclose that I am one of the main Principal Investigators for the Pediatric EHR Cohort that is doing research into long COVID through the RECOVER Initiative. Next slide.

What I really wanted to cover in my portion of today's talk is to really go into the state of the science with regards to long COVID in children. We'll talk about some of the epidemiology and risk factors of long COVID or PASC in children and cover some of the presentations that we're seeing commonly in children and relate how that might be different to what we've been seeing in adults. And we really are starting to learn more about some of the underlying mechanisms of long COVID and its different manifestations. We'll relay that back to what we know about long COVID in children as well. Can we go to the next slide?

Really just to set the stage for what we're about to be talking about today, really soon after the emergence of SARS-CoV-2 back in a few years ago, we really, a few months later, started to see that some patients were recovering from the COVID infection, whereas other people were having more persistent symptoms. And these symptoms were lasting anywhere from a few weeks, to a few months, to even a few years after the initial infection.

There was a lot of research and understanding of what was happening with long COVID in adults, but there was still a paucity of information about what was happening with children. So many of us in the pediatric community were seeing these types of symptoms and manifestations in our pediatric populations. And the scientific community, the medical community and the general community that knew more about this really urgently wanted the NIH and other scientists across the world to do more work into exploring long COVID and how it presents in the pediatric population.

Really in response to that need, there is a pediatric branch of the RECOVER Initiative, funded by the NIH, that is solely focused on understanding PASC or long COVID in children. And the research that's being done by this group spans large retrospective studies using EHR cohorts, as well as large prospective studies following people over time. If we'd go to the next slide.

And before I launch into what we're seeing in the pediatric space, I just wanted to cover some of the definitions that you may be seeing or hearing about, just to make sure that we're all thinking about things the same way. When we talk about PASC, we're talking about the post-acute sequelae of SARS-CoV-2. And this refers to the ongoing, relapsing or new symptoms or other health effects that are occurring after the acute phase of SARS-CoV-2 infection that is present for four or more weeks after the acute infection. And this is a term that the NIH and the RECOVER Initiative uses a lot in their studies. Next slide.

The CDC uses the term post-COVID-condition, and the way that it's defined by the CDC is, "The continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation."

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Now, the World Health Organization has also used a definition of post-COVID-condition which is a little bit different from what the CDC has been using. And more recently they convened a group of experts to come up with a pediatric specific post-COVID-condition definition. And that is here for you, "At least one physical symptom persisting for a minimum of 12 weeks after initial confirmed infection

that may continue or develop after COVID-19 infection. Can not be explained by an alternative diagnosis and has an impact on everyday functioning and may fluctuate or relapse over time." I do appreciate the pediatric focused definition used by WHO.

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The way that I like to think about the post-acute-sequelae of SARS-CoV-2 is really represented in this sort of conceptual framework here. Some of these symptoms and conditions may reflect those persistent symptoms that were occurring from acute infection. These might be things like cough, like headaches, like fatigue, that occur with the onset of the viral infection. But these might also be symptoms that are arising de novo, completely separate from the acute infection. And these might include some autoimmune phenomena, dizziness, for example, multi-system inflammatory syndrome in children would be considered one of these de novo type conditions. But then we also have to remember that it could also represent some of these exacerbations of underlying conditions that may have been preceding the acute SARS-CoV-2 infection. And we'll explore each of these different manifestations.

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How common is SARS-CoV-2, the post-acute-sequelae of SARS-CoV-2, in children? There has been a lot of work trying to answer this question with very sort of varied results. What I'm sharing with you now is a meta analysis and systematic review of a number of different pediatric studies looking to explore how frequently we're observing long COVID in children. And you can see there's a vast range of numbers starting at 1% and going all the way through to 70%. And this wide range that you're seeing in the literature really relates to the differences of how long COVID is being defined, differences in terms of the study design from one group to another, the setting in which patients might be enrolled in studies, the population of those children and adolescents, the followup period, as well as some of the ascertainment methods of how they're determining what those symptoms are.

If we focus just on some of those larger prospective studies that incorporate a control that are well-designed, those estimates from those studies are looking at more of the 10 to 20% range within that first six months of infection.

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Now, just to talk a little bit about some of the natural history and other aspects of the epidemiology, really less is known about the trajectory of PASC in children. Very few studies right now have examined outcomes beyond that 12 month period. And many studies with RECOVER are going to be exploring that period and beyond. There was one study that was showing that about 30% of kids that were experiencing long COVID continue to have symptoms even at that 12 month mark.

We know that people can have flares of long COVID. With every subsequent COVID infection, you're at risk of having a flare of your long COVID symptoms. And we also know that the overall prevalence appears to be decreasing over time. There were earlier reports of long COVID in kids during that early phase of the pandemic, and now in the Omicron and beyond, we're starting to see less reporting of it. But I do want to emphasize that for those people who are still experiencing symptoms, these can be going into years after their initial infection.

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We're also starting to learn more about the risk factors for long COVID. And I tried to pick ones that were relevant for the pediatric population. We know that older adolescents are more likely to have long COVID than younger children. If you're female, you're at a slightly higher risk than if you're male. If you have a history of allergic disease, some studies have shown an increased risk of long COVID or PASC. As well as having a lot of medical complexities, having a number of medical comorbidities. The severity of your acute COVID is also a risk factor. If you were hospitalized or in the ICU, you're at higher risk of having long COVID symptomatology. And as I mentioned, the pre-Omicron period is a greater risk of having those symptoms.

It appears too that the number of organ systems that were involved during the acute infection is a risk factor for long COVID development. As well as increased weight status. And I as I mentioned, you can have flares our bouts of long COVID. The more repeat infections you had, the more at risk you are. And there are number of studies that talk about the social influences or social drivers of health, that one's environment and vulnerability could also put someone at risk of having more prominent symptoms. And we can talk a little bit more about the vaccination story, but we do know that vaccination is a protective factor. If you're unvaccinated, you do appear to have a higher risk.

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And we know that long COVID can really virtually affect any organ system in the body. And so here is just a summary of some of the conditions and the symptoms that have been described in children by different organ systems. And as you can see, it can really range from everything from respiratory manifestations to things affecting your hematologic system, skin rashes, GI manifestations, a lot of constitutional systems and sort of neurodevelopmental, neurocognitive symptoms as well.

We're going to talk about some of these common symptoms that we're seeing in children over the next 45 minutes or so. In terms of if, if we go to the next slide... If we want to think about how some of these symptoms are manifesting differently in children compared with adults, I just wanted to share with you a study that was sort of an example of looking at these differences.

This was published in Scientific Reports earlier this year and it was looking at a population of children as well as adults with long COVID and looking at differences in their presentations. The two boxes on the top are showing you the top symptoms that were experienced in adults on the left, and then on the right in children.

And so if you just focus on the right top box for now, some of the top symptoms that were being reported included cough, fatigue, headache, sleep disorders, as well as difficulty concentrating. And then if you look at the box just on the left then, a lot of those symptoms were also being exhibited by the adults, but just in sort of different reported frequencies. In summary, a lot of the symptoms that have been reported in adults are also being seen in children and that there's definitely some sort of different variations of long COVID in kids.

Some of these other studies that have looked at some of the differences do report that the recover appears to be sooner or faster in children compared with adults. Just kind of talking sort of generally. And that there appears to be some features that appear to be more frequently seen in kids, and rash would be a good example of that, dermatologic manifestations, as well as some of the GI manifestations.

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We also did a study trying to explore some of the more frequent manifestations of PASC in children. These are just some results of a study that we published a couple of years ago. This was looking at a cohort of close to 660,000 children who were tested for SARS-CoV-2. This was across 11 to 12 different pediatric hospitals around the nation and included hospitalized patients as well as outpatient children. And we looked at the frequency of certain conditions and symptoms in the tests positive group and compared relative frequency to the tests negative group.

The graph that is shown on the left here is looking at some of the different symptoms and you can see that some of the common ones being reported were other changes of smell and taste, hair loss, chest pain, abnormal live enzymes and generalized pain. And then the panel that you see on the right is referring to some of the health conditions that were associated in our cohort. And so we see here myocarditis, acute respiratory distress, myositis and the need for mental health treatment. There's clearly some differences that we've been seeing in terms of what's being reported in children compared with what's being reported in adults.

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We are really starting to understand a little more about the underlying mechanisms of long COVID in adults as well as children. There's a number of different proposed mechanisms. We know that there is definitely going to be overlap with what we've been seeing in adults studies compared to pediatric studies. But we definitely need more pediatric studies really reviewing the mechanisms since there may be quite important differences in just how children are sort of manifesting with their pathophysiology.

I just wanted to share a few of the underlying mechanisms that have been sort of proposed to date. One of them talks about immune dysregulation where you have your immune system that is supposed to be targeting the virus ends up having this sort of dysregulated response or an exaggerated response or one particular arm might be sort of upregulated than another. And that dysregulation can lead to inflammation and innocent bystander organ systems can get infected.

The second is a microbiota dysbiosis theory where if you have viral persistence, it can stimulate disordered microbiota and that can put you at risk of GI and potentially systemic manifestations.

The next a molecular mimicry theory where you have antibodies that should be targeting the virus but end up going on to attack cells in the body and cause destruction locally or more generally.

And then we know that SARS-CoV-2 is a prothrombotic state, so that can lead to blood clotting and endothelial abnormalities that can also affect certain organ systems.

And then finally, there's also a theory about dysfunctional neurological signaling where that can then impact some of those neurological and as well as systemic manifestations.

There are other theories that have been proposed and have been studied, one including the latency of viruses that are already being in the body being restimulated. And the mast cell activation syndrome theory as well.

If we go to the next slide, what I wanted to do next was just go over some of the more common manifestations that we have been seeing in children. And I wanted to just provide a couple of examples of what we know about some of the pathophysiology to help explain some of these symptoms. In kids, some of the more common symptoms that we've been seeing have been including things like fatigue, malaise, post-exertional malaise, chronic fatigue syndrome or ME-CFS, post-COVID fatigue, aches of the muscles as well as the bones, cognitive difficulties, brain fog, persistent headaches or migraines, as well as dizziness.

And in terms of some of the pathophysiology that has been reported, there is a concept of neuroinvasion leading to neuroinflammation that can then go on to cause tissue damage of the nerves that can also then result in impaired clearance. Usually you have these microglia that will help to clear debris, and that impaired clearance is also contributing to some of these symptoms.

And there's also a theory about micro-clots that might be causing some sort of microvascular changes in the brain that may also be contributing. Studies have looked at different neurotransmitters and also found decreased levels of serotonin amongst many of the patients that have been experiencing some of these cognitive difficulties and brain fog.

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I also mentioned that the respiratory manifestations are very commonly seen in children. And these can be manifesting as persistent, more chronic cough, as chest tightness, as shortness of breath at rest and with exercise, chest pain as well as exertional fatigue with functional limitations.

And again, what we're seeing here is when the virus comes along and binds to the ACE-2 receptors in the upper and lower respiratory epithelium, you end up with this excessive inflammatory response. That can then lead to irreversible lung fibrosis and local damage to the parenchyma, as well as lung vascular damage in the micro-vessels and the micro-thrombi that may be preventing that appropriate exchange of gases across the alveolar membrane. And that can then lead to compromised respiratory function.

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Now, I want to talk a little bit about some of the cardiac manifestations of PASC or long COVID in children. And again, these are relating to things like myochorditis, to multi-system inflammatory syndrome in children, to conduction abnormalities and arrhythmias, as well as postural orthostatic hypotension and tachycardia syndromes.

What more research into POTS has been revealing, that the acute infection triggering of the immune system is leading to antibody production. And so some of the antibodies are binding to the aganglionic, adrenergic, muscarinic acetylcholine receptors. And that might be then promoting dysautonomia that then relates to POTS. More research is being done into that pathophysiology and seeing if there are ways to overcome that.

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I wanted to also talk about some of the GI manifestations. As I mentioned, we're seeing a little bit more of this frequently seen in children. And so these are manifesting as things like chronic abdominal pain, vomiting, having loss of appetite, diarrhea and weight loss.

And there's some interesting work that's being done in both pediatrics as well as adults looking at what is happening at the mucosal level within the gut. And there have been a number of reports showing the persistence of SARS-CoV-2 virus in the GI mucosa that can then lead to dysregulation of the ACE-2 receptor mediated functions. That persistence is leading to a lot of mucosal micro-inflammation and that can lead to translocation. Microbes that really need to be hanging out in the lumen of the gut are now translocating and getting into underneath the mucosa and then into the blood vessels and getting in systemically. And that can then cause dysregulation of the intestinal barrier and you get this distorted microbiota which then can lead on to having GI manifestations.

And there are some interesting studies underway looking at whether there's a relationship to what we're seeing with the gut microbiome as well as what might be happening more systemically as well.

And then I just wanted to also show the next slide here, which is just to touch upon the fact that we can also be seeing exasperation of underlying conditions. These might be manifesting as children with asthma having a lot of asthma exasperations, of having acute pain states upon people who have fibromyalgia or connective tissue diseases, it can lead to worsening hypoglycemia, for example, amongst people who have type one and type two diabetes, as well as the exasperation of things like sickle cell disease.

And if we go to the next slide, I also wanted to touch upon some of the new conditions that have been associated with development after COVID-19 infections. These would be considered those de novo ones, separate from any of the acute symptomatology.

You might be familiar that there have been studies that have demonstrated an increased incidence of both type one and type two diabetes during the pandemic after SARS-CoV-2 infection. There have also been a number of reports of autoimmunity arising after SARS-CoV-2 infection, including idiopathic thrombocytopenic purpura, Grave's disease, lupus, antiphospholipid antibody syndrome, vasculitis, myocarditis, Sjogren's syndrome, with findings of autoantibodies after the acute infection.

And then as an infection diseases physician, I've been consulted many times on some of these post-inflammatory neurologic conditions such as meningoencephalitis, optic neuritis, anti NMDA receptor encephalitis and GBS. And so, again, I think more of an understanding of what is happening to promote these new conditions is really going to be an active area of research.

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There's still a lot that we need to know about the manifestations and prognosis for children and adolescents with long COVID. We need to do more focused study of underlying mechanisms in pediatric populations, with the hopes that we might be able to come up with some sort of biomarker for PASC

that can help with the diagnosis or identifying those that might be at higher risk. We need to do more studies into the natural history of PASC in children, following these children really over long periods of time. And then also to think about what treatments are effective to prevent or treat PASC using really rigorous methodology, really good evidence-based directions on how to manage patients or prevent their manifestations.

I just wanted to finish my portion just by acknowledging, if we go to the next slide, just wanted to acknowledge the team of people that I work with on the RECOVER Initiative, including folks from PEDSnet and PCORnet and the folks that are involved in the RECOVER Initiative. I also wanted to acknowledge the co-authors on a recent manuscript that we published in pediatrics, which was a collaboration between the EHR group as well as the prospective cohorts as well as some of our parent and family and patient partners. Thank you so much and I'll hand it over to our next speaker. Thank you.

Dr. Abigail Case:

Hi, good afternoon. I am so pleased to be here today to talk a little bit more about functional outcomes in children and adolescents with long COVID.

The objectives of this portion of the talk are to describe the importance of rehabilitation and tracking functional outcomes in long COVID in children, to go over what's known about functional outcomes with patients that have long COVID, and to consider the next steps in advancing knowledge and functional outcomes in children. Next slide.

Just as a bit of a background for those that aren't as familiar with rehabilitation medicine, we focus on function in all domains and across many different settings. Early on in the pandemic, it became quite clear that rehabilitation was going to be really important to a lot of patients that were suffering from acute SARS-CoV-2. And later on, as patients continued to have persistent symptoms, that they may also benefit from rehabilitation in the outpatient setting as well. Several studies show that early and continual rehabilitation, evaluation and treatment was beneficial to those recovering from infection. And as a way to really disseminate information quickly, a lot of organizations got together, Living Guidance or Rapid Living Systematic Reviews, trying to disseminate what expert opinion, although there weren't large prospective high-powered studies, but to try to get information out there to meet this demand of a growing body of patients that had functional impairment.

The World Health Organization had a Living Guidance statement, Cochrane Rehabilitation had a Living Systematic Review that was updated quarterly. And the AAPM&R had multidisciplinary consensus guidelines on the most common post-COVID conditions. And while it was great that this information was out there, it was incomplete because it is only in smaller, single site studies and expert opinion. Next slide.

Before we talk about what the ideal outcome measures might be, it's important to talk a little bit more about what we mean by function. And so thinking about having a common language set to talk about disability and impairment. And in 2001, the World Health Organization came out with the International Classification System for Function or ICF. And in 2007, it was expanded to children and youth, the ICFCY. And these are a way to structure and organize language talking about function. And when we say function, we mean the complex interaction between any given health condition, the body structures and the way they function, activity and participation, as well contextual factors or environmental factors.

And so when we think about obtaining outcome measures to track a patient's function, it'll be important to have clinician based assessments, so potentially more objective information using validated tools and instruments, and patient and parent reported outcomes measures to really capture the patient and family's experience as well. Next slide.

And so the importance of functional outcomes can't be understated for the RECOVER Initiative, which as we mentioned before, is seeking to characterize but also to inform future treatment and prevention efforts. Tracking functional outcomes can allow us to determine a baseline status, potentially have clinical trial endpoints, monitor treatment effectiveness, assess changes in function, and hopefully predict prognosis more accurately. Next slide.

As a rehabilitation medicine physician, we think about the different domains of function. On the shorter term or acute, we think about mental status, sensory function, communication, motor function, feeding ability and respiratory status. And then we have longer term domains which are more sub-acute or chronic, and that's cognition, school or work performance, ability to perform daily routines and maintain relationships, getting good quality sleep and mood. Next slide.

Now, just to talk a little bit about what is known about functional outcomes, so I can say, early on, there was an explosion of information being released, lots of single site studies talking about the acute outcomes and mortality of SARS-CoV-2, and since then, there have been some looking at the more sub-acute or longer term but not many. And there aren't many studies that are looking primarily at these functional outcomes as their primary outcome measure.

The clinical manifestations of PASC or long COVID continue to be well recognized and further defined, but there are a few studies that have shown decline in function in adults following SARS-CoV-2. And not only that, but they've shown reduced health quality of life. Looking at parent or patient reported outcomes, reduced occupational performance and then in one multi-center prospective study, which does tend to be more nationally representative of the population it showed, 11% of survivors not returning to work due to poor health. Next slide.

Despite the growing body of literature on long COVID in children, there are few if any studies looking at how these persistent symptoms impact daily function and quality of life. Further, there's no tool or validated instrument to help clinicians track or measure these outcomes. In the adult population, there has been a tool developed, which is called the Post-COVID-19 Functional Status Scale, which is an ordinal scale, which is not a new concept. Ordinal scales are helpful because they're simple tools that can be applied quickly and to heterogeneous populations. But these tools have not been developed or validated for the use in adolescent or children. Next slide.

Developing an outcome measurement in pediatrics is kind of a tricky or a balancing act. It's been a challenge to develop, and this is in general for pediatric populations for any disease, but especially in long COVID, because it has to span all of the developmental stages from infancy to adolescent. It has to be well-defined and sufficiently rapid yet reliable, minimally rely on subjective assessments and applicable to as full as possible age spectrum. This is a difficult act to ask, and in some situation you may have to sacrifice potentially how rapid it can be done to apply to a larger population. But again, trying to really encapsulate all of the factors that go into measuring how long COVID's affecting children. Next slide.

As I said, few studies looking specifically at functional outcomes, some of the studies that we've seen have had secondary measures or descriptive information that can extract functional outcomes. In this retrospective cohort study, looking at pediatric patients that had MIS-C or multi system inflammatory syndrome in children. There was little organ specific sequelae, meaning that all of the lab work and further studies like chest X-ray were negative, but patients had physical, mobility and mental health support needs. And so this really highlights that despite gaining information about patients, these functional deficits or impairments are there and perhaps we didn't have a sensitive enough way to measure it. And so that was important to note. Next slide.

And again, looking at a descriptive study of patients that had PASC, so these were patients in a single site study at a large academic institution where patients with already diagnosed long COVID were presenting to a pulmonary clinic. And they had many reports of persistent dyspnea and cough, but their

pulmonary function, chest X-rays, echocardiograms were all normal, but they did have an impaired six-minute walk test, which is a validated measure often done by physical therapists, looking at how far patients can walk in six minutes and tracking different symptoms that may pop up during that test. This all, again, suggests that there are functional limitations that are persistent but not necessarily being able to be picked up on. Next slide.

The next steps from how I view this is how can we try to encapsulate or capture the functional impairments that we're seeing? And I think it's going to be utilizing different tools and asking different questions. An important part would be to utilize PROMIS or Patient-Reported Outcome Measure Information System instruments. These are validated tools that can measure different areas like pain, fatigue, function, depression, anxiety and social function, and these have been used for different disease processes in both adult and adolescent and children, that could be applied to potentially long COVID. Next slide.

In addition, there are several validated pediatric outcome instruments that are commonly used in different disease process that might be important to take a look at. Just of note, these are used in different settings and in different age ranges. An example, the functional status scale or the FSS is typically used in an intensive or acute care setting, has been applied to track some of those acute domain function that we were looking at in ICUs for things like sepsis. And then in the outpatient setting, you can use things like the Bayley Scales Of Infant and Toddler Development for younger children that you may be concerned. All the way from Functional Independence Measure or FIM, which we use in inpatient rehab as well as in outpatient to track and monitor functional independence, which uses domains of communication, ADLs or activity of daily living, functional, as well as cognitive. Next slide.

These are also cognitive screening tools that are from the NIH Toolbox but should be potentially used to capture any cognitive impairment that may be happening validated for different ages. I like the idea of a toolbox because there may not be one measure that is going to capture everything for the wide or heterogeneous disease of long COVID. But the other thing to note are these battery of testing take varied lengths of time and some require materials and some are looking at more executive function versus memory processing. And so really, depending on what the symptoms are, the age of the patient and the tools at hand, you may choose to use a different tool. Next slide.

I spoke about these earlier, the short term domains. These are, if we can just hit next slide, these are some of the questions that may come up if you were trying to assess this in real time. Thinking about if a patient's having a change or difficulty expressing themselves, for motor, difficulty walking, more previously able to do activities that they aren't now, feeding ability, respiratory status. These are questions that we should be asking when we're examining or taking the history of patients that have potential long COVID.

And if we hit next slide one more time... These are the ways it might manifest in terms of a patient's function. It could show up increased reports of behavior concerns or school absences or increased referrals to specialists. Next slide.

That's in the acute setting, and then in the longer term, we really focus on some of the translation of... like earlier Dr. Rao was talking about some of the specific symptoms and the potential pathologic or mechanisms of how they are affecting patients, and these are the end product, how they might look and what questions we should maybe be asking. Next slide.

Thinking about memory concerns or forgetfulness, has a patient's grades dropped, are they requiring new or updated support, 504 or IEP, how are they participating in school, in their extracurriculars, maintaining friendships, relationships with family, their sleep and mood disturbances? That can all be affecting and may, again, present or be seen as, next slide...

Increased referrals or behavior reports, need for more specialists, increase in school absences.
Next slide.

Now, just a bit of practical information here, thinking about how can a pediatric rehabilitation specialist be helpful. If you think a patient or you yourself have a contact that might have long COVID, I think this was easier for clinicians for identify at the early stages of the pandemic and there were more severe presentations. Patients having really significant and severe functional changes, it became clear that rehabilitation was needed. And I think it's been more difficult in the outpatient setting for a number of reasons, partly due to the limited guidance, due to the low quality of research and anecdotal reporting. There's such a wide spectrum of illness and throughout all of this some patients are recovering so they may have symptoms of long COVID are passed that then recover before they're ever even diagnosed. And there's overlapping psychosocial concerns.

But reasons I can think to refer to a rehabilitation specialist are if a patient had a complex medical history, in the past they've had existing functional impairments and you're noticing that they've worsened, patients that may have required physical therapy or occupational therapy, speech therapy in the past. If they've had a significant functional status change, they've gone from being able to be a high level athlete to now just barely being able to get out of bed, move around. That would be a significant function change. And especially if you're in a limited resource area, you may want to consider trying to partner with local rehabilitation teams, including neuropsychology, for additional resources.

And so that was the bulk of, next slide, what I wanted to talk about with functional outcomes. In summary, I think we need to be tracking using a variety of tools and measures that can get more objective information and larger prospective studies to really capture how this is affecting children on a day to day basis. Thanks.

Dr. Melissa Stockwell:

Thank you so much to the both of you. This is really an amazing review of what we know so far about long COVID in children, adolescents and young adults and really how profoundly long COVID can affect them in their daily lives. And also illustrates how much we still have to learn. There's a lot of unanswered questions, and I think that really helps illustrates so well the importance of the RECOVER Initiative overall but I'm going to focus on the pediatric cohort since that's what we're all involved in.

And some of the really key questions that we are trying to tackle and discover and uncover in the pediatric cohort is why do some children get long COVID and others don't? What causes long COVID to happen? What are some of the symptoms that children feel? How long do children feel sick for? What do we know about relapse and recovery? And then how does long COVID affect not only both the current physical health, mental health and development in children, as Dr. Case mentioned, but also what about the later? How are kids going to change as they develop and as they grow older? What's going to be the impact of long COVID?

And just to reassure everybody, we are using a number of the PROMIS measures and the NIH Toolbox, both of which Dr. Case mentioned. We really do hope to, particularly for the functional outcomes, it's a really big focus of ours in the pediatric cohort.

I wanted just to open up the questions. I have a few questions first before we open up to the greater audience and I want to focus first on talking to Becky. Becky, thank you so much for being here today and really you have given so much to the RECOVER Initiative. This is just one of the very, very many things that you are doing as part of the initiative, so thank you so much for all of that.

My first question for you is can you talk a little bit about what are the reasons that you had for joining RECOVER in the first place?

Rebecca Letts:

When I joined RECOVER, I actually already had long COVID for about 15 months. And at that point, it felt like a lifetime. And we were, I say we because the long COVID community became a community early on because we had to. There was kind of a lack of help and we had to figure things out on our own. And so I was recruited when RECOVER was in the planning stages to be part of the pediatric cohort and I had many reasons but before I got sick was used to doing things and helping. And it seemed, and my other longhaulers agreed, that the best way to help in that circumstances was be part of the change. We really agreed with the idea of...

Wow. I am a longhauler myself.

Dr. Melissa Stockwell:

Yeah. Take your time.

Rebecca Letts:

Maybe I should back up a little bit.

Dr. Melissa Stockwell:

Yeah.

Rebecca Letts:

Maybe I should back up a little bit.

I have long COVID and I've had it since March 2020 and my youngest son of three also has it. And we've had to really kind of dive into the science because no one was doing it for us at the beginning. And so we, as in long COVID patients, are going to be part of the process step-by-step. And I've always wanted to be doing things. And when you stop being able to physically do things, you want to do as much as possible. And so I was happy to be there.

Also, the kids with long COVID desperately need someone to be there speaking for them. What my son had gone through already at that point was something a child should never have to go through. And honestly, he had it easier than the adults, but to be a child, it wasn't okay.

I think some of the adults with long COVID and chronic illnesses in general seem to break pretty frequently and have to pick ourselves up and put ourselves back together. And to see that in a child is tragic. And I wanted to speak for the children so that that wouldn't be forgotten and the experiences of both my child and all the other children in the communities that I was part of, thousands of other families just like mine, could be represented as well.

Dr. Melissa Stockwell:

It resonates so much. Those are so many of the same reasons why there's so many pediatricians that got involved with RECOVER. You talked about being the voice of children, I really think that we are the voice of children as well and you and all the other patient and parent representatives are such an important part of RECOVER overall and the pediatric cohort specifically because you are the voice, helping us to be the voices of these children.

What do you think are some of the primary concerns that parents and children, at least or older children who are old enough to voice their own concerns, have about pediatric long COVID?

Rebecca Letts:

I think the biggest concerns are first of all be listened to and heard. And then we're concerned about the future outcomes. What is going to happen in the future with these children? Many patients and many long COVID families are reading the studies, are actually paying attention to what's happened in the past with other infections.

I want to make it clear that what is going on in my family is not unusual. What I found out in this whole journey that I don't wish on anyone is that this is not abnormal. I have complex chronic illness and I should have known before. Long COVID actually set it up for me to figure out that I should have had completely different treatment my whole life. And so many other people should have too, thousands and thousands of other people, because not only did the medical system not have... it wasn't prepared for chronic illness and infection associated chronic conditions with COVID and it wasn't prepared before.

The vast majority of the medical providers that the long COVID community ran into at the very beginning of the pandemic, it's much different now, I would like to say, the very beginning, did not expect the virus at all to make people sick and not get better. And that's the experience the patients had. It's not an accusation, it's just our experience.

And so we need the system to be different in the future for our children. For my children, I'm doing something different. What I did is I kind of went on a journey, kind of going backwards, discovering that COVID made all of these things much, much worse in both my son and my other children too, who would be diagnosed with long COVID in the strictest sense, but compared to my other son and me, they're fine. What can you do? We have hypermobility, you have Ehler-Danlos syndrome in our family. That hypermobility is now a risk factor for long COVID, and that's published, but three and half years ago, the long COVID community was saying the same thing.

Yeah, sorry.

Dr. Melissa Stockwell:

No, you're doing great.

I know that you have talked a lot about, you talked about it now and you talked about it before, about obviously being a patient yourself and that you're really here for all your children. And I know that, as you said, your children are affected differently. I think we had a slide I think we're hoping we'll get put up.

Rebecca Letts:

Yeah. Oh, yeah.

Dr. Melissa Stockwell:

Yeah, I think we've got a slide.

Oh, there we go, perfect. Oh, wait, go back one. Yeah. Yeah.

Rebecca Letts:

My long COVID child, Alex, he was actually the first one sick of all of us. He came home from the last day of in-person school ill but we didn't know he was ill. It was over the next week. And his symptoms were not on any COVID list at that time. The children really do have COVID differently. And it's important I think that physicians don't write off anyone's illness because it doesn't present the way they think it's going to.

In the first months of the pandemic when longhaulers were first getting sick, adults were very sick, we still were talking about our children, and all of them had symptoms that lasted, not all of them,

but a fair number of them had symptoms that lasted a while. And there were a great number of rashes and fevers and GI symptoms definitely. But we didn't hear anything about this in the news except that children were not affected by COVID. And we had a different experience, but of course, our kids didn't have tests or anything because we didn't have tests.

And so we wished that we could give that information somehow to wherever it could be useful, but at that point, nobody was asking for information about children, data about children. And if they were, they would want a positive test. Yeah.

Dr. Melissa Stockwell:

There's so much that we have learned about how COVID acutely looks different.

Rebecca Letts:

Yeah.

Dr. Melissa Stockwell:

In children and then overall.

Rebecca Letts:

Yeah. Yeah. My son and I, our immune system became dysfunctional. We did get many reinfections after that, especially me. But with each of the reinfections, we got new chronic symptoms or conditions and one of them was the absolute worst for my son. He got PANS on his second reinfection. That's Post Acute... Oh, shoot. What does that stand for? I have that written down.

Dr. Melissa Stockwell:

An autoimmune, neurological...

Rebecca Letts:

Yeah. Let me see what I...My brain doesn't want to remember anything. It's Pediatric Acute-onset Neuropsychiatric Syndrome. So much easier to say PANS. But that is absolutely worst. It's worse than long COVID in general for him because he had managed to be able to go back to school with long COVID with a 504 plan at school. He was missing a day or two each week of school, which was bad, but he was slowly getting better. And then with the second reinfection, he got PANS and he had to go out on home hospital education and he became a different person with flares. And his brain inflammation that will cause rage and suicidal ideation... I can't say the word.

Dr. Melissa Stockwell:

Ideation.

Rebecca Letts:

I need someone on here to just, ideation, to help me with words.

Dr. Melissa Stockwell:

Yeah, no, you're doing... yeah, yeah.

Rebecca Letts:

My kids help me with charades.

And he couldn't talk or really communicate for at least six weeks, and then it was not great after that for a long while. That was over two years ago when it first started. It was because he already had long COVID, because I was in all the long COVID communities, including the pediatric ones, and that he had all these specialists that he managed to get diagnosed and helped within a couple of months. Because the day the PANS was triggered, I looked at it and I thought, "This could be PANS." And we contacted his pediatrician, had a virtual appointment that day and made appointments with his doctors at UCLA. He's in the POTS pediatric clinic. And none of them would have suggested PANS, but I suggested it, and they're like, "Could be. Maybe. I don't know." Which is fine, but they agreed to refer him to a PANS specialist.

Dr. Melissa Stockwell:

I think that's [inaudible 01:03:23]. Yeah.

Rebecca Letts:

When he got there, he got diagnosed. All of these chronic illnesses, the normal average time to get diagnosed is seven years, but what it looks like when it doesn't get diagnosed is kind of scary because the kids look like they've lost their minds. Yeah.

Dr. Melissa Stockwell:

Yeah. I think... yeah.

Rebecca Letts:

It's a lot of psychological diagnoses.

Dr. Melissa Stockwell:

Yeah. And I think that that's why it's so important the pediatric RECOVER cohort is really... we're really trying to look at all of these angles. And I think that your... Whenever you share a story, it's always so hard for me because I just get to think of how you and your children have suffered so much. And I think the hope is that doing this kind of research will, one, will answer questions, we'll get more children and families help. And I think your story really outlines so much of the different symptoms, the functional outcomes, all of those things. And thank you so much for being here and sharing. I know it's not easy on many levels. As I said in the beginning, I think the amount of time and input and everything you've given to RECOVER is really amazing. Really, really amazing. And thank you for all of that.

Rebecca Letts:

I hope people understand the lack of executive function that I have.

Dr. Melissa Stockwell:

Yeah, no, it's hard. I fortunately don't have long COVID, I have had COVID and I know what that feels for a very, very short period of time and I can't imagine. I can't imagine what it's like for you and thank you again so much for sharing.

I want to leave time for some questions from the audience. I'm going to ask two super quick questions to Rao and Dr. Case.

Dr. Rao, I know you touched about being unvaccinated is a risk factor potentially for long COVID. Could you tell us just a little bit more about that? I know you have a whole other paper on that and you're going to get to touch on it, but anything else you want to share about that?

Dr. Suchitra Rao:

Yeah, yeah, definitely. I think a very important topic that has been coming up with all of this is what is the role of vaccination in long COVID. Can it prevent symptoms from occurring or the development?

There was a study that we did and published very recently in Pediatrics and there was actually an R3 webinar series on it that was done by Hanieh Razzaghi who was one of the first authors on that paper. For folks more interested in that in depth, highly recommend watching that webinar. But we looked at our data from multiple different health centers across the country, over a million children, and looked to see whether vaccines could prevent development of long COVID.

And we looked at different definitions of long COVID. There was one that was sort of a more stricter, stringent definition. And so when you looked at that, we did find that there was a protective effect of vaccines against the development of long COVID. And so it was around 42% for that more stringent definition, and it was even more protective, so closer to 60%, if you looked at sort of adolescents within that first six months after receiving a vaccine. We did see that that effect did wane over time. It was just, again, I think just promoting the benefits of getting those booster doses or the recommended schedule of those vaccines. But it did appear to have a protective effect, yes.

Dr. Melissa Stockwell:

Thank you. As a vaccine researcher in my other life, it's always good to know.

Dr. Case, I know that some parents aren't familiar with rehab medicine specialists and thank you actually for talking about it and kind of what you do. And I know that a lot of rehab medical doctors take care of children with many different kinds of conditions, but do you have any suggestions for parents if they're referred to a doctor, a rehab doctor, who might know a little bit less about long COVID? What do you think are some of the important highlights that they should share?

Dr. Abigail Case:

Yes, thanks. That's a great question. We are a small field so in terms of working with a rehabilitation specialist, we really operate under diagnoses of impairment. We work with children that have cerebral palsy or muscular dystrophy and they may have muscle weakness, but we're treating the muscle weakness, not necessarily the diagnosis of cerebral palsy. I think about that for families or patients and parents that are coming to talk about long COVID. While it would be really important to highlight the context of the functional change, potentially, "We all had an infection. We tested positive for SARS-CoV-2. Six to eight weeks later, X, Y and Z happened," but then really highlighting what it is that the patient was able to do before and what they want to get back to.

It may be crossing different spans or domains. It may have some cognitive pieces as well as physical. But if you can highlight what you want to work on, then a rehabilitative specialist can troubleshoot different techniques, referrals to different specialists like neuropsychology or psychology to work on memory retraining, or maybe it's partnering. One of the things I've done commonly as a rehabilitation specialist is partnering with schools as to what exactly a patient needs in an IEP to be successful. And so just really having them help walk with you in this impairment and try to return to optimal function. Thanks.

Dr. Melissa Stockwell:

Thank you. Thank you so much.

I'm going to turn it over to Christine who I think is going to be moderating the questions that are pouring in.

Christine Bevc:

Yes, thank you, Dr. Stockwell. Yes, we'd like to turn to some of the questions that have been submitted both in advance and during today's presentations. The first question we want to ask to both Dr. Rao and Dr. Case is around the, actually, this one's to Dr. Rao, around the evidence of flares of long COVID in persons with long COVID and after other subsequent non-COVID infections and if you can speak to that?

Dr. Suchitra Rao:

Yeah, that's a great question. We have certainly seen anecdotally these reports of people having another viral illness and then having flares of their long COVID symptoms. It's not something that's reported a lot in the literature. I think it's a very important topic area. But it is something that we see with our patients that we're following over time, that this can happen, not just with SARS-CoV-2 positive infections but we've seen it occurring with others potentially as well.

Christine Bevc:

All right. Thank you. And along a similar line around immune response, I believe you mentioned the allergies that put children at higher risk of developing long COVID. Is that any kind of allergy or can you expand and provide a little bit more detail around that?

Dr. Suchitra Rao:

Yeah. There was a report that came out of Nature that was looking at, again, risk factors for long COVID. This was a study that was done in adults but some other studies in kids have shown this association as well. If you have a history of allergies, and they looked at any kind, it was seasonal as well as some food related allergies, that if you had that predisposition, that that was considered a risk factor, which is an interesting thing to see being reported in different types of studies.

Those types of studies as well as other ones looking at pathophysiology wondered about a mast cell activation syndrome as being a proposed mechanism for some of the features of long COVID. The tachycardia, the flushing, some of the POTS manifestations, even some of the neurocognitive things. And so there have been some folks that have looked at whether we can do anything to minimize that histamine release and will that impact treatment? Still work that needs to be done in this area, but it was just a risk factor that was picked up, a theory that makes a lot of sense, and then now studies that need to get done to explore that association more.

Christine Bevc:

Thank you, Dr. Rao. Dr. Case, around related to rehabilitation, have you found that any treatments or medications that are working differently in children than they are in for adults in PASC?

Dr. Abigail Case:

That's a great question. I can't say that there's a lot of medication that we're seeing in rehabilitation at this point, although maybe in the future. But right now, some of the treatments that we have found to be more, and this is, again, anecdotally or in clinical experience, to be affective are some

of the brain retraining and cognitive behavioral therapy. In general, it's thought that the pediatric brains have more neuroplasticity, but again, this is all still very new in terms of tracking outcomes and potential.

Christine Bevc:

And Dr. Stockwell or Dr. Rao, feel free to, on any of these questions, if you'd like to also come off of mute and share your responses to add to the discussion as well.

Scrolling through. We've had some really great response to today's panel and the discussions. And the followup question is related to the providers and what would you suggest to providers and other practitioners in terms of being able to help recommend for primary care physicians and pediatricians that may not know about long COVID, that this may affect the outcome of the treatment and the care that they're provided, that could determine the health status, are there any short term trainings that providers could undertake or feel better equipped to provide care for long COVID patients? And at least to do the right referral.

Dr. Melissa Stockwell:

I think I can jump on this one quickly. There is actually the American Academy of Pediatrics, on their website, actually has a really great outline for pediatricians about long COVID and does walk through a lot of the domains in the similar way that Dr. Rao did. And actually talks about each and when you might want to refer. That's often where I'd point pediatricians to if they want to learn about long COVID. We definitely hear in RECOVER from a lot of the families in the study that their pediatricians don't really know about long COVID and they are finding that they do have to educate the educator. And I think similar to Becky's experience and I can see sometimes the questions that are coming in that really having to feel, which is unfortunate that they have to be educating the pediatrician about it as opposed to the pediatrician already knowing about it.

I think one of the reasons why we did publish the paper in Pediatrics that Dr. Rao mentioned was really to try and get out information about long COVID very broadly to pediatricians. RECOVER did also have a really nice tip sheet actually that talks about how to talk about long COVID to your pediatrician if your pediatrician doesn't really know a lot about long COVID. That's something that came out of the RECOVER pediatric cohort as we were hearing from families that they really needed to have a way to help talk to their pediatrician about it.

We have a long way to go, but hopefully we're starting to make some changes.

I don't know if, Dr. Rao, you had anything else? Or Dr. Case?

Dr. Suchitra Rao:

Yeah, I was actually going to say all the exact same things that you mentioned and I really like the AAP website. I know the CDC has put out some materials as well. When I talk to providers about these types of things, I think it's obviously important for us to learn more about the conditions. It is important for us to think about that biosocial model of just thinking about ways that we can support and help the child and the adolescent really be at their best capacity and their best potential. And I think just as important is to really take the time to listen to the child, to the families, to the parents, to their stories and what they're experiencing.

There's still some disbelief out there about just the extent of these symptoms and conditions. And so I think really one of the most important things is just to take that time to hear what's happening. It is an evolving field. We are learning more and more by the month. And I just wish that we could proceed in a faster pace and try and come up with answers and treatments and make this all sort of go

away. I think that validation of just, "This is not in your head. This is real. We believe you. We'll help you through this," can really go a long way.

Christine Bevc:

All right, we've gotten several questions also around autoimmunity and virus reactivation. And so the question is what's being done to look for the possibility of a new autoimmune disease occurring because of long COVID or COVID infection? Do you think long COVID will increase the risk of a future autoimmune disease?

Dr. Suchitra Rao:

Yeah, that's such a great question and such an intriguing area of research. As you've heard me mention with my talk, there's been associations with autoantibodies in people after having acute COVID infection. For example, there was a study that looked at adults who were hospitalized with COVID. They found that 50% of them ended up having some sort of autoantibody in blood work compared with only 15% of controls.

We've been seeing that there are some antibodies that are directed at specific organ systems versus other ones that might be more general. And again, we're trying to learn the association between finding them and relating that to what symptoms and conditions people are experiencing. We know that this is true of other autoimmune conditions. We know that when people get a virus or some sort of infection, that even after that virus clears, the autoantibodies can continue and then can cause chronic disease. We've been accruing more data on what some of those conditions look like, trying to figure out is there a way we can look for them. They're going to be outside of what we can do clinically a lot of the time in terms of the panels that we currently have available, but definitely a very active area of research.

And I think we also need to know that this risk may not just be in that short term within a few weeks after infection. That's why we're doing a lot of these longer term studies, enrolling people over longer periods of time to see if something might develop even years after the initial viral infection.

Christine Bevc:

Thank you. There've been talks in the presentations talking about microvascular inflammation or the angina type pains for kids with long COVID chest pains. What are some of the tests or scans to confirm this, and then combining this with another question that we also received around the micro-clots and research being conducted around that and treatments and whether there's any additional information around this topic?

Dr. Suchitra Rao:

Yeah, yeah. All great questions. In terms of some of the cardiac manifestations, we talked about how some of these can be presenting as chest pain in individuals. Some of it might be respiratory related, more cough and respiratory system that's involved, but some of it could be related to that cardiac presentation too.

If people are exhibiting chest pain, we really want them to be referred to the cardiologists and to undergo a cardiac evaluation. That usually looks like getting an EKG, looking at the heart rhythm, and then potentially going on to getting an echocardiogram to look at the structure and the function of the heart. And then the next steps is ruling out other potential reasons to have chest pains. Is it respiratory, is it related to the GI system?

What we're seeing in kids is not the same chest pain as what we might be seeing in older individuals where there might be ischemia or parts of the heart that are damaged because of clots in the

larger coronary arteries. We're seeing different kinds of manifestations that might be more global inflammation of the heart, myocarditis was something that we talked about, or completely normal echos, completely normal EKGs, but still there's ongoing symptoms that we can't necessarily pick up on our clinical testing.

For some of these folks, we need to be very careful in terms of their returning to playing sports. We want to make sure that we're not going to exacerbate things in any way. For that reason, we talk about referrals to cardiology. They can help with some of those return to play pieces, make sure that there's nothing structural going on and can talk about whether there's any other steps that need to be taken treatment wise.

That's a little bit different then from talking about the micro-clots and the changes that we see within the vessels. Again, we call this micro vessel damage. It can be you have a predisposition to clotting and then it can cause some sort of distortion or changes to the lining of the vessels. And that has been shown to be associated with some of these local symptoms and conditions.

In terms of what can be done about them, we know that with acute COVID, we will often give people preventative measures to stop them from having clotting problems. And sometimes they need to go on to get specific treatment if they do have a clot. It's still unclear what we need to be doing with certain conditions that are associated with the micro-clots. Does anticoagulation, the same way that you would do with a large clot, is that beneficial for these patients? Because obviously there's going to be risks with any procedure that hasn't been studied well.

I think more to come in this space. We'll see if there's any directed treatments to help any of those symptoms down the road.

Dr. Melissa Stockwell:

I think the only thing to add is that there have been some interesting recent studies that have looked for micro-clots in the muscles. Not only in the vasculature but whether that might be part of the link between long COVID and then post viral conditions and post exertional malaise. As Dr. Rao said, must research still needs to be done as we're trying to piece this all together.

Christine Bevc:

And on that note, we've got time for maybe one or two more questions here. And this is one that's very forward-thinking in terms of whether there's any proposed studies that use whole genome sequencing to search for genetic variations which may predict PASC in kids given the quest for a unique diagnostic protein biomarker will really be futile given the plethora of symptoms involved. I think this might be a question to Dr. Stockwell.

Dr. Melissa Stockwell:

It is actually a wonderful question. It is something that is part of RECOVER is we are collecting many different types of samples, but including doing some whole genome sequencing as well because I just think when we're looking for potential risk factors, not only for long COVID itself but also for recovery, which is really important for all of us. We want to make sure we're looking in that multiple level. There's the social, the biological, as well as the genetic.

Christine Bevc:

And then just to close us out, Dr. Case, can you speak to a little bit about how long COVID in pediatrics is evolving in this post-Omicron and just wrap us up with that today?

Dr. Abigail Case:

Yeah. I think the way that we're thinking about post COVID or long COVID conditions really stems from the fact that we don't have a great baseline or information to start from. It's a little bit of learning as we go, and that's been a big challenge. But I think one of the things I wanted to mention is the MIS-C or multi system inflammatory syndrome in children was something that I saw as a consultant in the ICUs for a fair amount in the beginning and even during the Omnicron wave and then that kind of trickled out. I think knowing that that is one of the phenotypes of PASC, it's shown me that things have definitely shifted and evolved and potentially there are subclinical or more mild MIS-C but it's not to that degree where they're requiring ICU care. And so I wonder if everything has just shifted a bit.

And alternatively, or I guess in addition, we've also still seen a couple cases of MIS-C, but it's been in children under two. And so I wonder if this has been their first exposure to a SARS-CoV-2 infection, whereas maybe one of the larger takeaways is that a large portion of the population has been exposed or vaccinated.

Anyway, that's a great question. It has evolved. And I don't necessarily take it to mean that the outcomes are more mild, but it haven't seen as much as a consultant in the ICU type arena.

Christine Bevc:

Thank you, Dr. Case. And thank you so much to our presenters and our audience for attending today's seminar and really engaging with the question and answer period here. As a reminder, a recording of today's seminar is going to be available on recovercovid.org in the next few weeks. We'll also be posting a Q and A document that has responses to the questions that we received today, including those that we did not have time to address.

We hope that you will return and join us for our next session on May 14th when we discuss SARS-CoV-2 infection during pregnancy and the development of long COVID. Please take a moment to visit the R3 page on recovercovid.org to register and receive more information on upcoming sessions. And additionally, before you leave, you'll see a short survey come up on your screen. And this will ask for feedback on the seminar. And it just popped up on mine, so you should see that as well. It popped over my script. There we go. If you could take a moment there to fill out that brief survey, that will help our planning for future seminars as well.

Thank you and have a great day.