Transcript

Dr. Sarah Hatcher

Good afternoon and welcome to the RECOVER Research Review or R3 Seminar. My name is Sarah Hatcher and I am a Research Epidemiologist with the RECOVER Administrative Coordinating Center at RTI International and the moderator of today's seminar. The goal of this seminar series is to catalyze a shared understanding of the research within the RECOVER consortium. Next slide. I want to start by thanking everyone who submitted questions in advance. The chat feature is disabled, so please submit any questions that arise during today's presentation using the Q&A feature in Zoom. After the presentation, we will answer as many questions as possible. Some questions may also be answered within the Q&A feature on Zoom. An FAQ document will be posted with the recording of the seminar on recovercovid.org. It will include answers for many of the questions we received today, including those we did not have time to address, questions about other scientific topics will be addressed in future seminars, and answers to broader questions about RECOVER will be available in the FAQ's at recovercovid.org.

Next slide. Our presenters today are Dr. Melissa Haendel, Dr. Christopher Chute, Dr. Thomas Carton, and Dr. Rainu Kaushal. Dr. Melissa Haendel is the Chief Research Informatics Officer and Marsico Chair in Data Science at the University of Colorado Anschutz Medical Campus and Director of the Center for Data to Health. Her research has focused on integration of genotype and phenotype data to improve rare disease diagnosis and mechanism discovery. Dr. Haendel's vision is to weave together healthcare systems, basic science research, and patient generated data through development of data integration technologies and innovative data capture strategies. Dr. Christopher Chute completed his undergraduate and medical training at Brown University, internal medicine residency at Dartmouth, and doctoral training in Epidemiology at Harvard. He is board certified in internal medicine and clinical informatics and a fellow of the American College of Physicians, the American College of Epidemiology, and the American College of Medical Informatics.

Dr. Chute's current research focuses on translating basic science information to clinical practice and on how we classify dysfunctional phenotypes or disease. Dr. Thomas Carton is the Chief Data Officer for the Louisiana Public Health Institute, Principal Investigator of the Research Action for Health Network and Executive Director of the Greater New Orleans Health Information Exchange. He has held multiple leadership positions within the National Patient-Centered Clinical Research Network or PCORnet, including chair of the PCORnet Steering Committee. Dr. Carton's research projects leverage electronic health record, health information, health insurance claims, and community level and patient report data across subject matter, including COVID-19, adult congenital heart disease, cardiovascular health, pregnancy health, and healthy aging.

Dr. Rainu Kaushal is the Senior Associate Dean for Clinical Research, chair of the Department of Population Health Sciences, Nanette Laitman Distinguished Professor at Weill Cornell Medicine, and the physician-in-chief of Population Health Sciences at New York-Presbyterian Hospital Weill Cornell Medical Center. Dr. Kaushal

leads Weill Cornell Medicine's clinical research enterprise bridging cutting edge science with patient care, including ongoing scientific studies surrounding COVID-19. Dr. Kaushal has authored over 200 scientific publications and is an elected member of the National Academy of Medicine. Dr. Josh Fessel and Dr. Rachel Hess will serve as our discussants today. Dr. Josh Fessel is the Senior Clinical Advisor in the National Center for Advancing Translational Sciences or NCATS Division of Clinical Innovation, where he serves as a liaison between basic and clinical scientists, and helps build bridges between multiple stakeholders to ensure that the most innovative clinical science moves forward. Before joining NCATS in December 2021, he was a medical officer at the National Heart, Lung, and Blood Institute.

And Dr. Fessel took on additional roles in response to the COVID-19 pandemic, including participating in the ACTIV public-private partnership and helping lead several efforts across NIH to address Post-Acute Sequelae of SARS-CoV-2 infection. Dr. Rachel Hess is a professor of Population Health Sciences and Internal Medicine, the founding chief of the Division of Health System Innovation and Research, and the Associate Dean for Clinical and Translational Science at the University of Utah schools of the Health Sciences. She serves as the contact PI of the Utah Center for Clinical & Translational Science and is the University of Utah lead for the Greater Plains Collaborative in the PCORnet Clinical Research Networks. Dr. Hess's research aims to improve patient centered outcomes in clinical care. And her implementation work uses health information technology to engage patients in their care.

Next slide. The topic of today's seminar is Leveraging Electronic Health Records and Real World Data to understand Post-Acute Sequelae of SARS-CoV-2 infection or PASC. With that, I will hand it over to Dr. Fessel.

Dr. Josh Fessel

Thank you so much, Dr. Hatcher. I'm going to keep this introduction very pithy and short. We could have a lot more time to do prelude if we weren't graced with such impressive people to hear from today, and you didn't sign up to hear from me, you signed up to hear from them. Just to give you a little bit of context for why there is an electronic health record and real world data component to the RECOVER initiative. In the first place we knew when we were conceiving of what RECOVER might look like and what it needed to do. And this was really, even before we knew it was going to be called RECOVER, but in thinking about how to address PASC or long COVID, it was really clear from the earliest time points that this was something that was really being understood as an outgrowth of what people were experiencing as they survived Acute COVID-19, and then went on to recognize and report that things were not back to normal yet.

And we understood pretty early on that this was going to be a wide spectrum of issues that all needed to be thought about together, as much as possible to understand what's going on. Why are people experiencing this? Who is at risk to experience this? How do we help better? And one of the places where those pieces of information, all kind of come together is in electronic health records and in real world data where people are

seeking out care from their trusted healthcare teams. And we're lucky enough to know or to come to recognize that there were several teams already in motion that had at their disposal, not only secure private data assets that protected people's health information, but still allowed conclusions to be drawn, but they also had the multidisciplinary teams already around the right, at the time virtual tables to really think about this from lots of different angles and to get moving as quickly as they could.

And I think that's probably enough preamble for why we have an electronic health record component to RECOVER. And I think the excitement is going to come from hearing from those teams and that's what we're here to do today. And so I want to thank all of them for being here. Thank everyone who's signed on to the seminar today. And with that, I will turn it over to our first presenters, which I believe are our PCORnet presenters to talk about clinical phenotypes and sub-phenotypes and we'll roll on from there, so the floor is yours.

Dr. Rainu Kaushal

Thank you, Josh. This is Rainu Kaushal, thank you for your kind introduction. And I will be presenting the first half of this, and then my close colleague and multi-PI Tom Carton will be presenting the second half. Next slide. Both Tom and I are founding PIs of an entity called PCORnet. The Patient-Centered Outcomes Research Network, it was funded and established by PCORI in 2014. It currently consists of over 65 sites with about 80 million lives. And within PCORnet, there are 41 sites that are enriching their data for RECOVER. You will note that there are a number of pediatric sites in here, and we are really happy and that the pediatric consortium was also funded to help drive important discoveries in that population, they presented at the last seminar series. Across these sites, we have over 15 billion rows of data. This includes structured EHR information.

We're in the midst of collecting unstructured EHR information. We have links to public payor data, links to exposome data, including race/ethnicity, socio-economic, environmental, and so on. We have about 145 different exposome variables that we're linking to. And links to vaccine data, which I think will become increasingly important as even this hour unfolds. Next slide. The arc of the three data grantees is to detect, predict, treat, and prevent, to drive EHR based discoveries in detection, prediction, treatment, and prevention of PASC over this first 12 months. We have primarily focused on phenotypic development in order to enable characterization of PASC, to iteratively quantify incidents and prevalence to start exploring temporal trends. And in addition, we've done important work in the epidemiology of PASC as already described, but also in terms of disparities, both racial and ethnic disparities, as well as socio-economic disparities. I will be presenting mainly on our machine learning and artificial intelligence work.

This work has been led by Fei Wang at Weill Cornell Medicine. Tom Carton will be primarily presenting on the epidemiology and health services research and adding in a discussion of queries. Just a brief aside about queries, queries are our opportunity on behalf of the entire recovery network to query, to do a simple analytical look at our overall data set. And queries are important because they allow us to understand trends, and they allow

us to help with hypothesis generation, including understanding a potential pool of participants, in a cohort of participants, in a clinical trial, and so on. Next slide. With that, I am going to dive pretty deeply for the next 10 minutes into the development of computable phenotypes. And I think what I should start with is that PASC is, it has been clear to us from the outset, particularly because many of us are clinicians that PASC is a very varied disease, right?

Like it sort of affects many different systems, there are obviously different types of clusters that are occurring of symptoms and conditions. And so what we hope to do was to harness the power of machine learning and AI to really help us first, to robustly understand computable phenotypes, and then to start sub-phenotyping through something that's often called patient similarity analytics, where we start looking at cohorts of patients that are quite similar. Next slide. For our computable phenotyping we used a data-driven high-throughput analysis. This manuscript, the preprint has been published on medRxiv and its under review. And what we did in this piece is we characterized PASC through increased burden of new EHR diagnoses and medications in SARS-CoV-2 patients compared with controls. And let me break out a couple of those things, because I think that understanding the methodological approach is I think very, very important.

The first is that we looked at SARS-CoV-2 patients who had either PCR or antigen laboratory test positivity. That felt important to us to do it in that way, even though it decreased our sample size, because we knew that with some certainty that those patients had an Acute SARS-CoV-2 infection. The second thing is that the way we chose to do this was we looked at incident diagnoses in medications in the Post-Acute COVID period, so we looked at the 31 to 180 days post COVID. And we looked at conditions that were brand new, so for example, if a patient had existing asthma and they had an asthma code in the Post-Acute phase, they would not be included in this. We did this again to be as pure as possible, we wanted to really understand what were likely conditions to be associated with COVID. And then we compared these incident diagnoses and medications in our SARS-CoV-2 patients compared with controls. We studied over 57,000 SARS-CoV-2 patients, 500,000 controls.

Our data set was derived from 14 million people in the greater New York City area and 17 million people in Florida, the fact that we did two geographical areas becomes important in a second. And the way in which we identified punitive past diagnoses and medications was based on literature review and expert clinical consultation, so there's been about a hundred studies published on PASC. We reviewed every single one of them to derive diagnosis lists and medications that have been used to treat PASC. And then as I mentioned, we have about 40 or so clinicians representing a multitude of different specialties. And so we relied very heavily on expert clinical consultation to come up with this 137 punitive diagnoses and a 459 punitive medications. We ended up identifying significantly higher incidence of conditions in 10 systems, they're listed here. I don't think they'll be surprising to anyone respiratory, circulatory, musculoskeletal and connective tissue, neurologic disorders, such as brain fog, psychiatric disorders, particularly anxiety, gastrointestinal disorders.

This becomes very interesting when we get into our sub-phenotypes, there was a very nice piece published in Cell Medicine sometime this week. It may have been yesterday, which demonstrated that patients with Acute COVID infections continue to shed virus in fecal matter for up to four months, endocrine, metabolic, blood, genitourinary. What was very interesting and I won't dive deep into this because I want to cover too much in my allotted time, but happy at a later point to describe this in more detail, was that there was higher burden of PASC in New York City compared with Florida. We think that geographic variation is likely tied to the fact that in New York City, we had the original variant, we were the epicenter of the pandemic worldwide, but also very much so in the US. And the treatment modalities weren't yet sophisticated, like even the use of steroids to treat Acute COVID disease was not well established until after that original onslaught here in New York City. And we think that there is some links to variance. Next slide.

These are incident hazard ratios, the salmon colored are New York City risk of these conditions. The purple ones are OneFlorida's. And as you can see, there are several different organ systems represented as I mentioned in my first slide. And that there's a higher burden in the New York City market compared to the OneFlorida market. Next slide. This slide, we looked at cumulative incidents and we broke out our outpatients versus inpatients for their acute illness, we broke out patients in terms of age, and we broke out patient patients in terms of gender, the graph on the right shows from zero to a hundred in terms of incidents, rate, density of disease. And what you see here is that people who were hospitalized for their initial COVID infection, older patients and males had higher burden of Post-Acute incident symptomatology and conditions. Next slide.

Now I'm going to go into sub-phenotyping, so here again, we relied on advanced machine learning and AI methodological approaches. Fei actually holds the first patent in healthcare for patient similarity analytics, and the way in which he approached this work is by using what is called topic modeling. And so what we did is we took the 137 newly incident diagnoses that we found through our phenotyping work. And we categorized them into 10 topics based on co-recurrence patterns across over 34,000 patients. We then analyze the clustering of the topics in these patients to demonstrate four sub-phenotypes. These sub-phenotypes become really, really important because for clinicians and for researchers, if you can understand how patients cluster, you can help them both in terms of defining treatment, but also in terms of prognostication, so the four sub-phenotypes were characterized first by cardiac and renal disorders, these were older patients, this had the greatest proportion of males, and had the highest severity in the Acute phase. The second phenotype was respiratory conditions, including sleep disorders, and anxiety. These were the youngest patients, the highest rate of females, and the lowest rates of initial hospitalization.

The third was musculoskeletal and nervous system conditions, here in the middle for age and gender distribution. And the last very consistent with what we're starting to see in the literature was digestive system accompanied by some respiratory conditions. The next four slides are circus plots. You can keep going. What this plot shows on the left is the relative incidents of each of the conditions and the past conditions in the first sub-

phenotype cardiac that stirs me as heart failure, renal failure, things that we see associated with renal failures, such as electrolyte disorders and anemia, malaise, fatigue, and sleep disorders. Next slide. Sub-phenotype two was the mildest of the four characterized by breathing abnormalities or pain, non-specific chest pain, anxiety disorders, and headaches. I say the mildest, because it seems like even in the time period that we are observing these patients, that their symptoms are starting to resolve. Next slide. Sub-phenotype three, musculoskeletal pain, connective tissue disease, osteoarthritis, brain fog. What is very interesting is that patients in this sub-phenotype have the highest incidents of co-morbidities that are related to musculoskeletal and nervous system issues. Next slide.

And then this is the digestive system one, a lot of different types of gastrointestinal disorders, some pelvic disorders as well, and accompanying respiratory issues, a little bit of chest pain or cardiac dysrhythmias. Next slide. I'm going to end here. I have just two main points. The first is PASC is very clinically diverse, there is so much for us to still learn about this set of symptoms and conditions. I think that the electronic health record is very rich, particularly in terms of symptoms and will be a good source to enable us to continue to characterize this, ideally with patient input through surveys and other modalities. I already mentioned the geographic variation. And then I would end with the fact that our work is indicating that there's four sub-phenotypes. They vary based on demographic characteristics, severity of initial disease, and pre-existing co-morbidities, particularly for the musculoskeletal type. But for example, for cardiac and renal, these patients had existing heart failure and renal dysfunction, sorry for that typo with dysfunction and for respiratory system, pre-existing breathing abnormalities, and so on. Let me end there and turn it over to my colleague, Melissa.

Dr. Melissa Haendel

It's great to be here today to present on behalf of the National COVID Cohort Collaborative or N3C's participation in the RECOVER program. I wanted to just give a quick overview of what we've been doing in the N3C. The N3C was launched at the beginning of the pandemic in order to collate the nation's electronic health record to better understand the new disease that is COVID, and now PASC. We now have 73 different institutions who have contributed data, with 13.5 million patient records in our secure enclave. The cohort is representative of the United States in terms of race, ethnicity, gender, geography, socio-economic status, and health background. And one of the really special things about the N3C as it's really the first publicly available national harmonized limited data set in which we can really overcome the source data heterogeneity.

And you can see on the lower half of this slide, that we collect data from multiple different common data models such as OMOP, ACT, TriNetX, and PCORnet, as well as other data models. And our pipeline harmonizes all of these different data from different institutions into one patient level repository, where we can perform some of the kinds of analytics that are not possible in a distributed context, which is really important in the face of this new disease. We now have 455 organizations participating in the use of these data with over almost 4,000 users. And

so it's quite the exercise in team science and also in making real world data fundamentally rigorous, computable, and interoperable at a scale that's unprecedented. I wanted to talk a little bit about work that's been led by Dr. Emily Pfaff and Andrew Girvin.

And this is the development of a machine learning approach to phenotyping for PASC patients, essentially coming up with, in the face of not having a clinical gold standard for defining PASC, coming up with a variety of different approaches in order to define who may actually have PASC in the absence of a code for U09.9, which is the new code that has been made available in October of last year. And so what this method leveraged was essentially, we coded patients that had been seen at a long COVID clinic and based on a variety of different sort of inclusion and exclusion criteria in terms of the temporality of those patients were able to develop a machine learning approach that would identify those patients based upon a training set from those long COVID clinics or from patients with the U09.9 code. As we have advanced since the launch of that UO9.9 code, we have been refining this computable phenotype to identify long COVID patients.

And the more that the U09.9 code is utilized, the more we can actually try a number of different approaches for validation. Basically what the method does is it learns patterns of the clinical features of PASC, such as dyspnea, fatigue, not having a vaccination, a new albuterol prescription, many outpatient visits, new corticosteroid prescriptions. And this allows the machine learning PASC phenotype to identify previously unknown cases using these learned patterns. The algorithm can be used today to identify cohorts for study recruitment and treatment considerations nationwide using your electronic health record data well beyond the National COVID Cohort Collaborative. And so we believe in the absence of a clinical build standard, that it is critically important to have a mechanism to identify potential long COVID patients for these purposes. And I'd also like to point out that this work was the first RECOVER manuscript and has recently finally released in Lancet Digital Health, and the link is there at the bottom.

What did we learn from this definition? This machine learning phenotype allows for sensitivity analyses to determine which factors are most important in predicting when someone has PASC. And so you can see that we looked at both qualifying non-hospitalized patients as well as hospitalized patients, and then we have a model that leverages all patients together. Outpatient utilization is a key factor in defining whether or not somebody may have PASC. And then we also saw that vaccination is associated with a lower risk of being identified as potentially having PASC. And you can see a variety of other features such as sex, drugs, a variety of different diagnoses for metabolic diseases and Vitamin D deficiencies that are all predictive when we trained the model in order to identify those patients. Using this method, we were able to identify 138,000 adult long COVID patients in the N3C, which is approximately 8% of all of our COVID patients with high confidence that would be eligible for the RECOVER research studies.

I wanted to talk a little bit more about the U09.9 code and its use in our phenotyping algorithm to identify PASC patients. There is another code B94.8, which is basically other specified infectious and parasitic diseases,

which is used often as a proxy before the U09.9 code was made available. What's really interesting though, is we've been looking across our 73 sites that are in our release data set and only 36 at this time, after six months are actually utilizing the U09.9 code, which really speaks to this sort of slow adoption of new codes, so there was a question from the audience in advance about the adoption of this code and how could we get codes faster? And I guess one point here is just that even when we do have codes, it doesn't mean that they're in common use. And then we've also been doing a fair amount of work to characterize their adoption at each individual site, which is actually quite variable.

And you can see on a summary of those results over there on the right where we see the adoption of the code U09.9 long COVID code in blue, and the more generalized B94.8 code in orange. And what's interesting is that even though the use of the U09.9 code has had significant uptake, that people are still using the B94.8 code, even in some patients that may have both codes. And then also you'll notice that there's U09.9 codes applied before they were actually released in October. And so these are retrospective codings where institutions have gone back and entered those codes after the fact. And so these are all things that need to be taken into account in the context of our evaluations. The other thing I wanted to mention briefly as it was another question that was brought up in advance. Was how do we address biases given the fact that not everyone is using U09.9, not everyone has a COVID positive test or a COVID diagnosis. How are we ensuring that we are including long COVID patients that may not have any of these things in our analyses?

And so I just wanted to reassure our patient community that we are doing everything we can in working with the patient led research consortium to define strategies and methods that help us include long COVID patients that may not have those original diagnoses. And this includes comparing hospitalized and non-hospitalized patients, not requiring those positive tests for some of our analyses, but making sure that we take that information into account. And then just in general, making sure that we include patients in all of our work, in directing and evaluating our analytics. I wanted to move on to how do we, now that we have this effective computable phenotype using this machine learning algorithm, we can identify those punitive PASC patients. We can now actually perform a variety of different clustering approaches to identify PASC subtypes. And just shown on the right here are just some of the subtypes that we've seen in a variety of different methods. And I'm going to present two of the methods that we've been using today. There's a neurological category, a metabolic or obesity related category, and a cardiopulmonary category.

And I want to impress upon everyone that these are not extraordinarily distinct categories and I'll show an example of that, but are in fact a mechanism by which we may wish to consider these subtypes in the context of who gets different types of workups within our RECOVER recruitment and study protocols, as well as our understanding of underlying mechanisms for the outcomes that we see in these different categories, so fundamentally we need to figure out how similar are two patients, as a precursor for understanding what subtypes of PASC may exist. This is just an example, our target data model is the OMOP data model, so the OMOP concepts

are things like respiratory finding. I mean, we want to understand is if a patient has a code for respiratory finding or acute kidney injury, how similar is that to another patient that may have a code for cough or transient renal failure? Whereas other types of features may be an identical match such as chilblains shown at the bottom.

And addressing this type of clustering approach is led by Justin Reese, Peter Robinson, and Charisse Madlock-Brown. And this is a pretty novel approach, so I wanted to give a quick overview. Here we have a sub graph of the human phenotype ontology, which is a OWL based computational resource that we use a lot in the clinical genetics context, where we can robustly describe phenotypic features represented in a graph, representing those features as a graph rather than as a simpler taxonomy, as you might see in ICD. Provisions, additional algorithms that we can use for understanding that patient similarity that I showed on the prior slide. This shows two sets of patients, two patients that are similar to each other, and two that are not, just to kind of show you what that looks like. And so we take all of that OMOP data that we have from our harmonized electronic health record data in the N3C enclave.

And we transform it to the human phenotype ontology based upon a robustly provident set of mappings, that's been led by Tiffany Callahan. And in this case, you can see on the left, there are two patients that have very similar features. Some of them are identical, such as headache and depression. Some of them are similar, such as visual hallucinations and auditory hallucinations. And using that graph structure, the parent term hallucinations, we can know that those two terms are quite similar. On the right, we see two patients who are not so similar, so we may have things like dyspnea and hypoxemia that are abnormalities of the respiratory system physiology, but also related. We also have an exact match to dyspnea. And so you can kind of see how the graph works here. Similarly, we have things like brachycardia, which is similar to tachycardia and palpitations with the kind of super class arrhythmia from the human phenotype ontology. But then we also have terms like dermatographic uticaria, which has no match to patient number three.

And so this would be a set of patients that have less similarity. Basically, what we did for this particular experiment that I'm about to show you next. We took all of the patients with their human phenotype ontology codes and made a giant patient by patient similarity metric, and then applied some clustering algorithms using the graph matching algorithm to understand what clusters may exist. And this is the result of that work. After optimizing that clustering algorithm came up with six clusters, they are overlapping in some of their features, and you can kind of see some of that overlap in the colors represented here. And as I mentioned earlier, that's not to say that they still aren't potentially good targets for sub-phenotypes used for subclinical workups in the interventional trials or other mechanistic characterization. Cluster 1 is sort of our severe category and is varied and has phenotypic features in pretty much all categories.

Cluster number 2 has a lot of pain and pulmonary features. Cluster number 3 has a lot of pain in neuropsychiatric features. Cluster number 4 has a lot of enteric features and actually looks quite different. Cluster number 5 also has pain, but has cardiovascular features. And then cluster number 6 is also quite severe in a lot of

the categories. And so this just gives you a sense of what the outcome is, and we've done a lot more characterization of each of these in a manuscript that was just submitted for pre-print today. I wanted to move on to a different approach. This is a topic modeling approach. And what topic modeling does is it looks at the labels of the various kinds of observations, diagnoses, and treatments to look to see sort of, what is enriched in different groupings of patients. And so just shown here is a snippet of approximately 60 different topic categories, and this is work that's been led by Shawn O'Neil.

And in this case, you can kind of just see some examples, like you here in the middle we have disorders of the digestive system, disorder of the intestine, gallstones, things that are sort of gastrointestinal. In this context, we can visualize these topics of relevance that based upon their probability of a patient being in one of those topics, the larger of the text, the higher the probability that a patient is in that category. And then we can look to see how do patients fit into these different categories across all of our different sites. And so shown on the left is a set of pre-COVID primary topics and Post-Acute topics. And we're really interested in understanding the longitudinal trajectories of these patients as they move from one topic prior to COVID during the Acute phase and in multiple phases post-COVID. And so this diagram just kind of shows how patients have a tendency to move from one topic category to another. And so what we're really trying to do is build a foundation on which we can do longitudinal subtyping.

And this is again an example of how we're approaching that from a longitudinal perspective. On the right, we see patients kind of usage of each topic category. Again, approximately 60 categories were identified, although the exact number is not particularly important, and you can see how pre-COVID patients usage changes in the different, if you go top to bottom from pre-COVID through the different Post-Acute phases, Post-Acute and then during the Acute phase. And so, again, we're just trying to garner an understanding of how patients are characterized in terms of their topics as they move through the progression. Important to this work is to understand site level, data heterogeneity, and quality assurance, and understanding sort of where some of the outliers are. And you can see on the left, we have pretty good systematic use across our data partners on the bottom, but we do see some outliers. And so those are things to either look at in terms of the clustering or in terms of the way in which the sites are coding their data. And I will stop there, and I think it's time for our discussion.

Dr. Rachel Hess

Okay, I think I am up next. I just want to thank both Dr. Kaushal and Dr. Haendel for really wonderful overviews of the work that both PCORnet and N3C are doing in this space. I just briefly want to note that I'm one of the PIs of one of the hubs of the RECOVER cohort study, as well as participating in the RECOVER EHR study. And I came to this as a women's health physician who has really seen these types of related diagnoses being not well understood in many, many of my female patients. And I'm excited to be seeing the attention paid to these post infectious

syndromes now. I think that both presentations did a really great job, really trying to describe how our electronic health record data can help regarding under-diagnosis and misdiagnosis and specifically the inappropriate attribution of symptoms.

As Dr. Haendel noted, we're able within the electronic health record data to see clusters of symptoms that are identified within people diagnosed with the long COVID codes, and then see whether or not similar clusters of symptoms are seen within patients who have had COVID, but may not have had that code applied to them. And that kind of surveillance allows us to understand within these large EHR data sets, whether we are seeing a systematic under-diagnosing or mis-diagnosing or mis-attribution of problems for these symptom clusters to other conditions, whether they be psychiatric, psychosomatic, or other areas. But the wealth of the data in the EHRs makes those patterns of symptoms possible.

The large data also really allows more rapid identification of phenotypes, which then can be further explored in more detail in other studies. These data can really be hypothesis generating, they can help us ask the right questions within our cohorts, they can help us ask the right questions within our intervention studies to help us understand how to begin to answer and disentangle the basis of PASC. Why do some people go from COVID to this long COVID phenotype? And how can we begin to understand how to treat this so that we do not have this number of people suffering for years, decades, et cetera.

They do have some limitations however, and I think that these were touched on briefly. They're limited to people who do and are able to seek healthcare specifically at participating institutions. Those institutions may have more sophisticated electronic health record data, they also have enough staff to be able to package and send their electronic health record data in ways that are digestible by these formats. That may exacerbate some of our health inequities, both teams work very hard and diligently to have broad representation of different types of patients across the entire country, being seen in different health systems. But we are still limited to those systems that have capacity to participate and have excess capacity one might say, within their infrastructures to be able to do this. And while these groups are not linked to specific insurers, there are differences in how frequently and where differently insured patients are seen.

We may have seen that a little bit within our Florida versus New York data. We may have also seen that a little bit in the data that Dr. Kaushal was presenting regarding the different levels of symptoms seen in those areas. There's also limitations regarding the documentation of a COVID diagnosis, while these codes are not limited to people who have a documented history of COVID, as testing moves from home, excuse me, moves to the home and away from medical centers. Do we miss more people who have a history of COVID, but do not have PASC? Those who got over their COVID pretty quickly and pretty easily, and may have done a rapid at home, or I've been to New York may have just tested on the streets of New York. And we may not know all of those individuals, so are we seeing some bias there?

I think that these data are huge, they're hugely important. I know that I'm running out of time, but contextually, I like to think of the EHR data as our rapid monitoring and our broad strokes. If you're thinking about how we monitor COVID activity within a community, we can think about waste water surveillance as sort of understanding where things are in a general population, and our EHR data help us with that. They help us understand where to target, what to target, how to target. We then can move to more specific testing in people or our cohort studies like the RECOVER cohort initiative, so the RECOVER EHR data very much takes us in a big picture. The RECOVER cohort initiatives allow us to dive a little bit deeper into the specifics of a single patient.

And then our clinical evaluations, which do feed into our EHR data really are akin in some ways to our hopefully emerging quickly, randomized controlled trials to be thinking about the treatment. And that bundle together becomes the RECOVER initiative that we are really trying to understand the broad population of PASC, the details of why PASC, and then the house of treating PASC. With that, I'm turning it over to Q&A. Sarah, you're muted.

Dr. Sarah Hatcher

Happens once a day, so I'll start us off with a question we received in advance of the seminar. What does the EHR data indicate is being used to treat long COVID most frequently? And are these good candidates for randomized control trials?

Dr. Christopher Chute

I have a slide in the epidemiology section that will partly address that and we'll do so at that time.

Dr. Melissa Haendel

Yeah, I think that question might be good to wait until we've, because I know both groups have content on that question in their second set presentations.

Dr. Rainu Kaushal

We actually don't have that content in our second presentation, but do have it in our preprint that's on medRxiv and happy to dive deeper into any of this with any of the clinical cohorts.

Dr. Sarah Hatcher

Great, thank you all. If that question is not addressed in the next session, we'll bring it up during that Q&A. I think a follow on to the discussion about limitations. We have a question about how well RECOVER and

other EHR based studies cover PASC outcomes in underserved and poorly surveilled communities like rural areas?

Dr. Rainu Kaushal

Yeah, I think that's an excellent question. And I think Rachel was touching upon this as well. I'll speak on behalf of PCORnet, but I suspect that Melissa will say similar things for N3C, which is that PCORnet has made an intentional effort to include networks and consortia that treat underserved communities. In addition, in PCORnet, we are actively linking to public payor data, including Medicaid Data. But I think that part of why we see, for example, the higher burden of disease in New York City compared to Florida, the higher burden of PASC in New York City compared to Florida, in addition to the severity of the initial infection and so on is an access issue. And I think it's something we have to be very, very cognizant of, and to dive deeply into, and to try to characterize in certain communities. Tom, you're part of the Louisiana Public Health Institute, I don't know if you want to expand on my answer?

Dr. Thomas Carton

I'll add briefly. We have some that we'll present in the Epi section and I'll draw a little bit on Rachel's comment about various types of insured populations presence in the PCORnet common data model. While we have a lot of academic medical centers that are the backbone of PCORnet there are a good number of community based hospital systems as well. I can think of [inaudible 00:53:27] and Baylor Scott & White as a couple of examples, so we do have those patient populations represented. And then to Rachel's point about the size of the data and the ability of things that you can do with the size is be able to do subgroup analyses, both regionally, and by socio-economic, and race, and ethnic disparities and some of which we'll show soon.

Dr. Rachel Hess

And if I can just add something, I know I'm in Utah, which we like to call a rural and frontier state and both the University of Utah and Intermountain Healthcare, which between the two of them provide care to about 80 to 90% of all Utahns. And cover our entire state, including rural and frontier populations in those data are included within University of Utah within N3C. And both University of Utah and Intermountain within PCORnet, so for those of our states that do serve more broadly, we move into our Idaho, Montana, and rural South Dakota communities as well. I think that there are pockets, but again, I think as Tom is noting, the data is so large that those differences are able to be seen, but we do have better coverage, I think as the questioner was alluding to within larger cities and larger population centers.

Dr. Sarah Hatcher

Thanks everyone.

Dr. Melissa Haendel

I'd just like to add one additional comment, so I agree with Dr. Hess, we've really worked very, very hard to include rural organizations, and safety net hospitals, and public institutions that serve underserved communities, so it's actually, and we've done quite a lot of analysis to look at the representation of the various kinds of demographics to ensure that it is as representative as possible. The other thing I will say though, is that one of the biggest challenges and that I think is something that we all need to think more carefully about in the RECOVER program is the way in which we code that information in the electronic health record, so that we can actually do a better job of understanding the influences of environmental health, of social determinants of health in the context of the clinical outcomes.

And so we've been working very closely with a number of sites to try to do that better, and also performing analytics to kind of understand how do we actually improve some of that coding. And so, things like rocket codes and other measures of access have been integrated into the N3C so that we can do that kind of multimodal analytics with those kinds of data assets at the same time in combination with the clinical data.

Dr. Sarah Hatcher

Thanks everyone. In the interest of time, we're going to move on to the next session of the presentation.

Dr. Thomas Carton

I'm going to continue the presentation that Rainu started. Focus on the epidemiology, health services research, to answer vital population health questions of PASC. Then make a quick final overview of queries and connections with the clinical cohorts. Next slide, please. I'll begin by discussing two recent publications. The first on prevalence of new PASC symptoms and conditions among adults and children in the 30 to 150 days after a positive SARS-CoV-2 test, and the second assessing cardiac complications among patients following a SARS-CoV-2 infection versus an mRNA vaccine. These represent collaborative work across the PCORnet EHR and CDC PCORnet COVID response teams. Next slide. For PASC symptoms and conditions the objective was to compare prevalence of new and select symptoms and conditions after 31 to 150 days among persons testing a positive versus negative for SARS-CoV-2. We conducted this within 40 health systems across the PCORnet network.

We looked at roughly 170,000 COVID positive adults between March and December of 2020. We required that patients had a medical encounter, both in the pre-index period, seven days to 18 months before the COVID infection and 31 to 150 days after the index. We excluded patients with record of symptom or condition in the

baseline pre-index period, similar to what Rainu described earlier, so we're capturing incident conditions and symptoms. We split the patients into age based cohorts, divided them into COVID positive and negative groups with a corresponding, a PCR, or antigen test. We calculated prevalence ratios of SARS-CoV-2 positive versus SARS-CoV-2 negative patients. And we found that patients hospitalized after a positive SARS-CoV-2 test had higher rates of diagnosis of certain symptoms and conditions compared to negative patients. Next slide, please.

This slide displays the prevalence ratios of COVID positive versus COVID negative adults, age 18 and over further segmented by severity, non hospitalized, hospitalized, and hospitalized with mechanical ventilation. For symptoms, fatigue, and shortness of breath were most prevalent amongst hospitalized and mechanical vented patients. Heart rate abnormalities, cognitive dysfunction, and sleep disorders were more prevalent amongst hospitalized patients only. For conditions myoneural disorders, type 2 diabetes, ataxia, and peripheral nerve disorders were more prevalent amongst mechanical vented patients. While myoneural disorders and type two diabetes were more prevalent amongst hospitalized patients as well. Next slide, please. For cardiac complications, the objective was to calculate incidents of cardiac outcomes, three of them. Myocarditis alone, myocarditis or pericarditis, and a combo of myocarditis pericarditis, or MIS-C after SARS-CoV-2 infection and vaccination. We assessed myocarditis, and myocarditis or pericarditis after SARS-CoV-2 infection and vaccination.

We further assessed these diagnosis with MIS-C after infection only. We calculated 7, 21, and 42 day incident risk ratios complications compared of infection compared to vaccination. We looked at one, two, or unspecified, or any dose of vaccine. And we calculated the incidence of myocarditis after infection divided by the incidence of myocarditis after vaccination with an mRNA vaccine. We did the same for myocarditis and pericarditis, the second outcome. And for the third and last comparison for myocarditis, pericarditis and MIS-C after infection, we divided by the incidents of pericarditis or myocarditis after vaccination. We found that the risk for cardiac complications was significantly higher after infection than vaccination for both males and females in all age groups. Next slide, please.

This slide displays the risk ratios for cardiac complications after infection versus vaccination among males aged 12 to 17, and 18 to 29, to varying magnitudes across all conditions, follow up periods, and age groups. The risk for cardiac complications is higher among patients with the SARS-CoV-2 infection versus vaccination. Next slide, please. I'll now pivot to discussing two publications currently under review, both investigating PASC disparities amongst hospitalized and non-hospitalized adult patients in New York City. These analyses were conducted within the insight network as the Vanguard site for the PCORnet adult EHR cohort, and will be replicated across all PCORnet RECOVER sites. Next slide, please.

Across both studies our objective was to understand if the risk of incident PASC conditions differ by patient race, ethnicity, and socio-economic status among SARS-CoV-2 positive patients. Similar to what Rainu described, we developed a list of 137 possible PASC diagnostic categories. And then we identified the top 10 conditions with the largest difference in incidents between COVID positive and negative patients. We performed

adjusted logistic regression comparing for baseline demographics, co-morbidities, year-month of positive test or diagnosis. We defined positive and negative patients by a PCR or antigen test, or by a COVID-19 diagnosis between March of 2020, October of 2021. Patients were grouped by non-Hispanic white, non-Hispanic black and Hispanic. We used a patient's zip code tabulation area as a proxy for socio-economic status categorized into five quintiles based on income, so it's area, level, socio-economic status, and we made comparisons between the highest and the lowest quintiles.

The next two slides display the results. Next slide, please. This slide displays racial and ethnic disparities, comparing black and Hispanic patients versus white patients, racial and ethnic disparities existed in both hospitalized and non-hospitalized patients, and in certain PASC conditions. Disparities in respiratory signs and symptoms, chest pain, and headache existed amongst both hospitalized and non-hospitalized groups. Next slide, please. This slide displays socio-economic disparities comparing low income quintiles versus the highest income quintile. Income based disparities were not evident amongst hospitalized patients, but present overall and for specific conditions amongst non-hospitalized patients like chest pain, musculoskeletal pain, lower respiratory disease, and headache, migraine.

Next slide. I'll now transition to juxtapose the study results just presented with the concept of queries, a less sophisticated, but valuable method of inquiry and hypothesis generation. Queries account for patients in a database who meet certain specified characteristics. They often stratify patients by demographics and other clinical parameters, so that trends in patients with different characteristics can be observed. And they're designed to provide data driven evidence to support hypothesis generation for specific studies. They are different than an analysis in that a analysis is the output of a more sophisticated set of queries. For example, exploring the differences in outcomes due to baseline characteristics in two groups. What we presented previously was the results of more sophisticated analyses, but as an example of queries that the EHR based cohorts can support. Next slide, please. What is PASC? How many people have PASC? How many people have the PASC sub-phenotype? What is the mortality rate of people who have PASC? Are patients with certain conditions more susceptible to certain types of PASC? Next slide, please.

I'm going to conclude by summarizing the arc of work and offering ways in which the EHR cohorts can be of assistance to the clinical cohorts. First we're generating important evidence to detect, predict, treat, and prevent PASC. We're utilizing two different scientific approaches, machine learning and health services research. Queries are an important tool to allow us to determine trends and generate hypothesis. And we stand ready to support the clinical cohorts to run queries, dive deeper into research results of studies beyond published results, develop and implement and evolve computable phenotypes, and support the execution of clinical trials. Thanks.

Dr. Christopher Chute

Thank you. I'll now share my screen or try, thank you. Thank you, so I'm Chris Chute, I'm one of the co-leads of the N3C and happy to share this with you today. This is just to remind you of what Emily's work earlier that was described by Melissa on identifying COVID patients using a machine learning approach that was published last week. That was the basis for some of these slides. This is if you will, a geographic characterization of PASC, at least in the N3C consortium. Where you can see a magnitude of counts for those participating sites. These are not full population denominators, we understand that. But they do give a sense of the distribution of the disease across the country. And of course, then the relative fraction of patients within the contributing sites by intensity across the country. And we have a few sites for whom we don't have enough qualifying patients to make that determination.

This was a slide that presented earlier last month by Tellen Bennett showing if you will, the incidents of the percent of patients with PASC in our cohort that have been hospitalized. And you can see there's actually a modest spike associated with Delta compared to those patients who were outpatient, not inpatient, but a smaller incidence rate. But nevertheless, also with that corresponding spike. Among children, we see that over time from early July to January, these are the proportion of children by age group that the children with PASC are getting younger, that these younger age groups are having increasing frequency. And then the absolute count, this is the scale on the right, was showing a bump in the Delta and a very large bump in the Omicron space, more recently. These are markers of post-infection trajectories, this happens to be Serum Creatinine.

We're comparing PASC and non-PASC. They're actually statistically significant because there are so many patients, but they're obviously significantly overlapping. And this contrast not-hospitalized with hospitalized, where it's actually less significant. Again, Ferritin measures appear to show in PASC patients in red, a bit of a higher shoulder, and then a lag among non-hospitalized patients and perhaps an even higher shoulder and a longer lag among hospitalized patients with more clear distinction of these overlaps and their range of value. For lymphopenia, we're seeing a much stronger signal of greater lymphopenia among non-hospitalized PASC patients and a less strong, but nevertheless, notable pattern of lymphopenia among PASC patients who have been hospitalized. This is the survival question of hospitalized versus non-hospitalized patients who have PASC. And you can see not surprisingly that not-hospitalized patients have a longer survival than hospitalized patients, a greater mortality associated with patients who endured hospitalization and subsequently had PASC.

However, there is a paradox in this data. This is something Richard Moffitt has pointed out that for many of the persons we lose to follow up and that is we cannot make a prediction. And those persons appear to have less mortality partly and due to their being lost to follow up and not being able to know the outcomes. And then at the other extreme for hospitalized patients, we actually lose patients to death where they die and therefore have a greater, so we are not able to make a prediction whether they have PASC or not, because they die before we can do so and have enough data on that question. And this otherwise represents the patients with PASC and not-PASC.

We did look at risk factors for PASC in these data. One of the queries we were asked, we were asked to look explicitly at apnea, sclerosis, diabetes melitus, and obesity.

You can see there's strong univariate, well, reasonably strong risks of these conditions associated with that subsequently develop a PASC and after adjustment, they still remain in the 50 to 60% increased risk range. Persons with apnea, having a 60% increased risk of generating or experiencing PASC. For diabetes, less compelling and obesity, not as strong either. Obviously the key question is around vaccination and we are in the process of rigorously exploring what impact does vaccination have on PASC? We used historically what we called a historical control, looking at patients before any vaccinations were available and then the post vaccination period. And we're using, again, in our current analytics, the more detailed information associated with state registries. These are the vaccination profiles of the sites that contribute data, the 73 sites that contribute data to N3C. And you can see we have what appears to be fairly complete coverage of vaccination.

And we know that many of these sites are linked to their state registries. And we have other sites which not surprisingly have lower reported vaccination, this is probably a mis-classification of their vaccination status, so before we pursue this aggressively, we are seeking to increase the number of linkages we have with state registries for these sites, so that we have a more complete ascertainment of vaccination status permanently that we can with confidence, say that a patient has not had a vaccination. That's an important statement to understand. Overall, we have the characterization of PASC with trends over time, geographic distributions, biomarkers, mortality rates, co-morbidities, and vaccination. There were a few questions that came up before the environment. I have three minutes left, so I should be able to at least address some of them. One of them was what treatments are being used for patients with PASC?

And this looks at common medications. You can see that there's a larger percentage of respiratory drug systems, that's not terribly surprising. Anti-infectives as well. And arguably cardiovascular and nervous system drug categories are perhaps overrepresented compared to some of these other agents that are used. Not definitive, but it's suggesting at least patterns of treatment for persons with PASC in this case, defined with the U09.9 characterization of PASC, rather than our inferenced PASC characterizations. Now the other question or another mode of understanding what happens to these patients are procedures that they experience, obviously they're diagnostic procedures and imaging procedures, that's not terribly surprising. But again, consistent with cardiovascular findings that have been previously reported by both groups. We see a sizable incidence of at least diagnostic tests associated with ECG and Echo that is out of proportion to some other tests that are used.

Pulmonary tests of course are not terribly surprising, in this particular context. One of the questions was around metabolism and whether weight or diabetes has a question with this. And this again is from a manuscript in review where it was demonstrated that for the control patients, all patients with diabetes and the COVID-19 patients, there was really no significant difference in hemoglobin A1c or weights after contracting COVID, so in terms of having a metabolic profile that would contribute to this does not, at least at a surface level appear to be a

high risk element. And with that, I do want to make the point that N3C as I think all of these communities are, are really a village. And that the communities that have contributed to this have been extraordinary, not only in terms of data provisioning, but the communities that have come together for analytics and optimization of the efforts that we are sharing. And with that, I will stop and we can begin questions.

Dr. Josh Fessel

Thank you all so much. This is, it sparks a thousand thoughts and a thousand ideas every time I hear you all present this work, so thank you. You've done a great job of addressing some of the questions that have come in both beforehand and during, and I really appreciate that. In thinking, there are always a few things that come up for me and I'll lead off just to make sure we have enough time for this, with a question that is partly question, partly public service announcement. And it has to do with how we think about big data, particularly electronic health record and real world data contributions to a bigger scientific effort like the RECOVER initiative, or like any other initiative that incorporates a component like this. The kind of science that you all are doing, I think has some really unique aspects to it. And I think both groups have done a really fine job of highlighting some of those.

Speaking from my own sort of learning about all of this, I know that I sometimes find myself challenged to remember, to remind myself that some of these unique aspects, I have to keep them at the front of my mind. And I'm thinking about things like, these data assets that you all are building on and interrogating to discover key things about PASC or long COVID, they change all the time, they grow on a weekly basis. And so what we know today may and probably will evolve over some period of time. And I think a lot of us have seen that, that period of time can be compressed with regard to the pandemic. And that's not just true for Acute COVID. I think that's true for long COVID as well, or for PASC as well. Learning that computable phenotypes and machine learning models probably do need to change over time and to be updated with new knowledge as we acquire it.

And so I think what I've learned is that's a strength of the kind of science that you all do. I've come to think of that as not a limitation, but a strength. The question slash public service announcement here is for anybody else who might be challenged to keep these things at the front of mind, to remember that there's not like an answer and we're done and moving on. Do you all have some tips, pointers, tricks, hints, to help the person receiving this knowledge that you're generating to stay aware of and oriented to what are truly unique strengths?

Dr. Christopher Chute

Well, you're really talking about the intrinsic nature of observational data, as opposed to prospective cohort data, and both are hugely complimentary. We experienced early in the N3C environment. I'm sure PCORnet had the same experiences where the darn codes just didn't exist for a lot of things we wanted to capture like vaccinations, specific mRNA vaccinations that we had to invent codes and use them on a temporary basis. That begs the question. Well, are there things that are occurring that are not yet coded that we're not even aware of?

And how do we capture those and how do we retroactively capture those? The other major challenge is we are always really fraught with this problem of missing information. I think the vaccination data that I showed is a poster child example of that. We know we have missing information in those, for some sites on vaccination status, so we have profound mis-classification.

And let's admit it, for some of those sites. As that data improves, then the picture becomes more and more clear, more and more compelling, more and more robust. Again with observational data, it still may be biased, it doesn't mean it's absolutely right. And then we have the challenge of looking for undiscovered or unrecognized biases so that we can, to the extent practical, account for them and adjust for them. And it's an ongoing continuous process, but I think we still have robust findings that have stood the test of time so far. Thomas?

Dr. Rainu Kaushal

[inaudible 01:21:41].

Dr. Thomas Carton

Yeah, thanks Chris.

Dr. Rainu Kaushal

Go, go ahead, Tom.

Dr. Thomas Carton

I'll kick it over to you in a second Rainu. Just respond to Josh's question, and a couple of things from Chris. Agree on, on the arc, and the connection, and the role, and contribution of observational research into the arc of knowledge generation. What we're seeing is science in real time, as codes come into play, as data evolves, vaccine registries become linked, computable phenotypes are developed and validated on charts at sites. One thing that came up earlier that Chris alluded to is this, and Rachel brought it up first is this concept of testing trajectory and COVID positivity, and how we're defining COVID positive patients just in general, right? At first it was only a diagnostic code, then the lab results that Chris mentioned were mapped, and were queryable, and were usable, then testing went into the home.

And we're now back to considering diagnostic codes as part of our case definition, where we made that decision not to include the diagnostic codes at certain periods of the pandemic previously, so it goes through sort of the arc of decision making, the way that these decisions change and evolve over time. And Josh, I think you alluded to an important point as to how do we message that to a scientific community or community writ large,

that this is just the arc of the work. And these discoveries are happening and definitions are changing regularly. Rainu?

Dr. Rainu Kaushal

Yeah, I think it's a fabulous question, Josh. And I certainly would echo both what Tom and Chris have shared. And I think I would add one more thing, which is, I think of data science at scale, which this certainly is with millions and millions of patients being studied across both initiatives, as a very powerful tool to understand what is happening at a population level. Whereas clinical trials and our clinical cohorts for RECOVER are able to derive more evidence at the individual level. And I think that that's also helpful because I see our work as helping to start to characterize this diverse set of conditions, start to lay out the large scale epidemiology, start to develop punitive risk factors, punitive treatment modalities, and very much in partnerships with our clinical cohorts that can then take some of these early findings and dive very, very deep.

Dr. Josh Fessel

Excellent. I think that's really helpful. And yeah, I think that complimentary nature is really important. We probably have time for one more question and I'm going to pull one up from the Q&A. Oh, Nope. I'm getting the message actually, that we need to go ahead and wrap up, so we capture everything in the Q&A, we could probably carry this conversation and this discussion on for another hour, if we had it. And I think that speaks to the impact that you all are having and the importance of the work that you're doing, so thank you so much. I am going to go ahead and wrap this up, turn it over to Dr. Hatcher to take us home. And once again, say thank you to everyone who participated today.

Dr. Sarah Hatcher

All right. Thank you, Dr. Fessel. Thank you to all of our speakers for the wonderful presentations and very interesting discussion. Just to wrap things up, I want to also thank our audience for attending and engaging with the Q&A. As a reminder, a recording of today's webinar will be available on recovercovid.org within a few weeks. We will also be posting a Q&A document that will have responses to many of the questions we've received today, including those we did not have time to address. Now, this slide lists the topics for future sessions and our three seminars are held on the second and fourth, Tuesday of the month from 12:00 to 13:30 PM Eastern Time. We have some exciting topics coming up and we hope to see you at future sessions. Thank you and have a great day.

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