Responses to Participants' Questions

The overarching goal of the R3 Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses* to questions raised by webinar participants related to the following presentations at the R3 Seminar ***RECOVER in Action: Characterization of PASC Among Adults, EHR Insights*** held on March 14, 2023:

- **Presentations from PCORnet and N3C**
  Talk 1: Thomas Carton, PhD, MS
  Talk 2: Emily Pfaff, PhD, MS
  Talk 3: Melissa Haendel, PhD
  Talk 4: Fei Wang, PhD
- **Discussant: Megan Fitzgerald, PhD**

  * Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. How did you pick up the critical signs or symptoms of post-exertional malaise (PEM) since it doesn't fall within a specific organ system or have a ubiquitously accepted medical term? Did you use natural language processing (NLP) to find it?

Response:

Dr. Pfaff: NLP would certainly be an option for picking up PEM in this period before a diagnosis code is available. And we hope there will be a code in the not-too-distant future. Although we did not use NLP in our analysis here, it is absolutely an option for future work in this space.

Q. I'm confused why dysautonomia/postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and their comorbidities are not mentioned at all as phenotypes or part of a phenotype.

Response:

Dr. Pfaff: ME/CFS does appear across all age groups in our U09.9 clusters, which are categorized as part of the neurological clusters. I would also expect POTS to be there; however, the diagnosis code for POTS only became available in late 2022 and consequently was not in use when we performed this analysis. It will likely take some time for the new code to get enough uptake among clinicians to appear in analyses like this, but having a code now is a step in the right direction. MCAS does have an ICD-10 code; however, it may not be used with enough frequency to display in our visualizations, which only show the top 30 co-occurrences. The code may also not be used frequently, even if patients are diagnosed with MCAS. Sometimes coding practices don't line up perfectly with actual patient health, which is an unfortunate limitation.

Q. Many clinicians have divided PASC into 2 main categories: a disease, with organ damage; and a syndrome, with no known organ damage, biomarkers, etc. It's the latter group, those with no organ disease, that forms a majority of the patients in Long COVID clinics and parallels chronic, poorly understood illnesses, such as ME/CFS and fibromyalgia.

Response:

Dr. Haendel: While I don't disagree with the split you're proposing, we also want to understand "hypomorphic" responses to the viral infection and aim to treat it more as a continuum on which we can layer a variety of subclassifications, including the one you mention. Hopefully, this will help us better reveal underlying mechanisms and classifications that might be responsive to different treatments no matter the degree of severity.

Q. Does post-exertional malaise (PEM) have a diagnostic code?

Responses:

Dr. Pfaff: To the best of my knowledge, unfortunately PEM does not have a diagnostic code. I believe the Patient-Led Research Collaborative (PLRC) is advocating for a new code to cover PEM and perhaps Dr. Fitzgerald can speak to that.

Dr. Fitzgerald: Lisa McCorkell presented in support of a PEM diagnostic code at the CDC's ICD-10-CM meeting last week. It's under consideration for an expedited implementation for October 2023. It's very important to have a diagnostic code for this key symptom of Long COVID.

Dr. Haendel: I had the honor of being there for Lisa's presentation to the WHO/CDC and it was received very well. I couldn't agree more about the importance of having the code.

Q. Is the white female skew more a reflection of them being the patient population that visits doctors and therefore get diagnosed with Long COVID as compared with male and nonwhite patients?

Response:

Dr. Pfaff: We believe that there are several factors behind this skew, including the factors you suggest. Patients with U09.9 diagnoses also are more likely to live in more affluent areas, with higher average education. We don't believe this is representative of the true Long COVID population, but rather is likely a result of some people having more access to health care, including specialty health care, than others. This is a disparity that should be addressed.

Q. Can any of the presenters speak to how they defined "co-occurring COVID positivity"? Was there a time interval used in regard to occurrence of PASC symptoms/diagnoses?

Responses:

Dr. Pfaff: For this particular analysis we looked at U09.9 occurrences at any time, regardless of whether we had any record of the patient's acute COVID infection; that is, we didn't require a positive test to "count" the U09.9. We then looked 60 days out from the date the U09.9 was entered in the patient's record and collected any other diagnoses that occurred during that period. We then used an algorithm to perform the clustering you saw to show which diagnoses tended to co-occur most frequently with each other.

Dr. Carton: For our computable phenotyping and machine learning approaches, we identified the COVID index date based on COVID testing. For people that tested positive, we took the first positive test as index. For people that never tested positive, we took the first negative COVID test as index. We used 30 to 180 days post index—positive or negative COVID test—as the PASC period.

Q. Why aren't myocarditis and pericarditis included in the cardio cluster?

Response:

Dr. Pfaff: To ensure the visualization is readable, we were limited to the top 30 conditions for each age group. It's certainly possible that these conditions are on the list but just further down.

Q. Did you differentiate PASC patients who were hospitalized with COVID-19 pneumonia from patients who were never hospitalized; for example, severe as compared with mild acute COVID-19 disease?

Response:

Dr. Carton: Yes, across our work and teams, we differentiate COVID severity by looking at both hospitalized and nonhospitalized patients.

Q. Were the differences between COVID-positive and COVID-negative groups statistically significant after controlling for potentially confounding covariates; for example, underlying risk factors for congenital heart defects (CHD) or chronic obstructive pulmonary disease

(COPD) incidence/exacerbation? Might increases in surveillance—such as more frequent clinical encounters/health care utilization after diagnosis of COVID-19—have contributed to increased likelihood of uncovering incident and/or worsening CHD or COPD?

Response:

Dr. Carton: The results shown here are crude incidence and exacerbation; consequently, not controlling for confounding covariates. Our health services research team takes developed computable phenotypes and conducts analyses that control for these factors. An example is an analysis of exacerbation of type 2 diabetes, which is near complete and will be disseminated. Regarding increased surveillance, we require all patients to have at least one pre-index encounter and at least one post-index encounter. This doesn't completely control for this difference in time under surveillance; but again, these are crude numbers and other teams take these validated computable phenotypes for more sophisticated analyses.

Q. As various therapeutics are clinically trialed, is there a way for that data gathering to be fed into your broader data gathering and analysis?

Response:

Dr. Haendel: Absolutely! Within the N3C we're able to examine outcomes of early drug usage—as we did for Paxlovid for the White House—and to help support trial design by emulating trials with different subpopulations.

Q. Is a "COVID positive" designation based on (lab) testing only? There are PASC sufferers who never had a confirmed positive COVID test, but a diagnosis based on a clear clinical picture. Also, I wonder if the profile of people who have no record of a positive test is somehow different than people with a positive test on record; for example, demographically, clinically, or otherwise.

Response:

Dr. Carton: We define "COVID positive" by positive lab or Paxlovid prescription if there's no COVID-positive lab. We understand, especially in the era of home testing, this is a challenge—which is why we recently introduced Paxlovid as entry into COVID positive. The challenge with just using a diagnostic code is that we can't be sure of date of diagnosis to determine the PASC period.

Q. Would it be fair to say that most of these data depend on clinicians using the relevant codes; that is, deciding at the visit that the patient's problems are related to COVID? And does that make it difficult to truly identify controls?

Response:

Dr. Haendel: Our work does depend on the coding, whether by clinicians or expert coders. However, when you have a lot of data from a lot of sites, you can correct for differences in coding practices. We know, for example, that we have patients with likely Long COVID, but who have never had a diagnosis. These are the kinds of patients we try to remove from the control groups; again, having a lot of data helps. We also look at features that are explicitly related to the COVID diagnosis; though again, that's not always done and we also have to take that into account.

Q. Is there a way for private studies and studies in other nations to also feed in and be analyzed?

Response:

Dr. Haendel: The way the N3C Enclave is set up, we can only consume data from US organizations. However, they can be from any organization willing to be signatory to the NIH Data Transfer Agreement. That said, because we are using the Observational Medical Outcomes Partnership (OMOP), one could also analyze international data along some of the same lines using the Observational Health Data Sciences and Informatics (OHDSI) international network, although that's a distributed network rather than a centralized network like N3C.

Q. How do you justify or standardize removing people with "likely Long COVID" from the controls?

Response:

Dr. Pfaff: One thing I can say while we're talking about EHR caveats is that the control group can be complicated because what we work with in EHR is the absence of information. If my EHR, my personal one, does not say I have diabetes, we have to assume that I don't have diabetes but that may not be the case. I may have diabetes and it may just not be recorded in my EHR. Consequently, in my example, I might end up in a control group, and that might be inappropriate. For the purposes of most research, we do have to make the assumption that the absence of information means that the patient does not have the condition. However, that's potentially problematic with Long COVID in particular because, as Dr. Haendel was saying, that U09.9 code or other ways of getting potential Long COVID in the EHR is not as well used as for diabetes, which has been around for a long time and is generally well coded in EHRs.

It can be potentially problematic to assume that if a patient doesn't have Long COVID in their records that they do not in fact have Long COVID. So the only thing I can say as far as that goes is that the different methods that all of the presenters talked about today for trying to identify patients, if we take the union set of all of the patients identified by those methods and try to use as many different techniques as possible for identifying potential Long COVID patients, we'll do the best job in making sure that patients who have the potential to have Long COVID or likely have Long COVID don't accidentally end up in a control group. Are we going to get every single person? Are

we going to get it right a hundred percent of the time? No, we're not. But if we can do our best and use different techniques to identify patients, then we'll do better than, for example, just using U09.9.

Q. Is there a way that we as patients can know if we have a U09.9 diagnostic code in our charts?

Response:

Dr. Pfaff: If you have access to a patient portal (like MyChart, or another equivalent), you may be able to see if that code appears in your "Problem List" or after-visit summaries. If it's still unclear, you could certainly ask your provider. In preparation for this meeting, I logged into my own patient portal, which many of you may have access to for yourself, like a MyChart or the equivalent. I wanted to see if I could see what codes were on my record from various health care encounters. I wasn't able to see U09.9 or whatever the code was, but I was able to see what codes, at least in English language translation, that my physician had applied at each one of my visits. I might suggest that patients who are interested log into their patient portal and see what you see in your after-visit summaries or on your problem list, and you may find a PASC description if that code is on your record.

Q. Can we as participants receive all our test results with an explanation of results from someone at the RECOVER study?

Response:

Dr. Haendel: Because of the regulatory approvals, we in the N3C are not allowed to reidentify any patients, so we cannot do that. However, in the context of RECOVER, there is an effort to create that data linkage. So, it's possible that through RECOVER, through future processes that are currently being finalized, that we may be able to provide not only information about what's in your record, but also how you might fit into some of these classification structures or other kinds of outcomes. It would be great to hear from the patient community about what would be useful but not overwhelming.

Webinar Slides

To request a copy of the R3 Seminar slides, please email RECOVER_ACC@rti.org.

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- **Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs**
- **CDC information: Information for the general public and for health care providers about Post-COVID Conditions: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/**
- **For medical/scientific terminology: https://medlineplus.gov/healthtopics.html**