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 seminar participants related to the following presentations at the R3 Seminar ***Advancing Long COVID Research by Fostering Collaboration between RECOVER and the All of Us Research Program*** held on October 8, 2024:

- ***Advancing Long COVID Research by Fostering Collaboration between RECOVER and All of Us Research***
  Chris Lunt
  Emily Pfaff, PhD, MS
  Hiral Master, PT, PhD, MPH

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. What were the biggest barriers to collaboration? What were the things that you had the hardest time getting done while working across these different programs?

Responses:

Dr. Pfaff: There are several things that come to mind, but it touches on what you were just saying about how difficult it is to move healthcare data around. That applied to this collaboration as well, where there are so many really good reasons for the restrictions that we have in place, both in the All of Us program and in N3C, and in any other system that contains healthcare data. It is imperative to protect patient data since it is extremely sensitive data. People entrust us with those data, and we owe it to those participants to take care of their data as best we can. However, there is also this other side of that coin, where it can make working together across healthcare data repositories really challenging.

And so, one thing that I felt really great about during this collaboration was the fact that we were able to work around those barriers. It took longer than it probably would have if there were no restrictions. In fact, I know it did take longer because of that. There were certainly moments of, I'll call it frustration, where I felt like, "If only I could get my hands on the data that Dr. Master is using, we could fix this problem a lot faster." But we were able to get it

done. With collaborations like this, maybe if everyone approaches it with their expectations a little bit lower in terms of time to get things finished, I think that those kinds of barriers are surmountable.

Dr. Master: Yeah. I agree with the barriers that Dr. Pfaff and Mr. Lunt mentioned. I would like to highlight that we had the best brains working together. We focused on advancing cross-platform interoperability to simplify processes for researchers, reducing the effort needed to manage platform differences. The team worked collaboratively to facilitate programming language translation (e.g., from N3C's PySpark and Spark SQL to All of Us's Python (pandas) and Google BigQuery), ensuring that the algorithm could be consistently replicated across systems. This required adapting the code and maintaining algorithm stability on these cloud-based platforms. Overcoming these challenges through teamwork allowed us to make the work accessible and replicable for users in a short time frame (~12 weeks).

And the second thing was also about the data types. We had electronic health record (EHR) data. And again, our EHR data is structured Observational Medical Outcomes Partnership (OMOP) data, and they were concerned. "Oh, what if we have clinical notes here? Can we expand this? Can we validate more?" There were some challenges on that, but again, that's for future research and how we can expand this model further.

Q. There's the domain of research and the domain of care, and there are a lot of barriers that are put up very deliberately between those two. I know it's been a challenge for a lot of programs to understand how we take the work that we're doing and make sure that it's delivering improved values for people. In working on this project, did you see any ways that you thought you could do that? Did you see a way to be able to translate the work that you were doing into improvements in care?

Responses:

Dr. Pfaff: I think the best opportunity for us to be able to translate this particular work for Long COVID is the idea of simulating or emulating clinical trials. That is a great opportunity because it takes data-driven work beyond a lot of the descriptive work that we've been doing for a long time, which is really interesting and important, but doesn't often feel to patients as if it's as actionable or translatable to their situation.

Whereas I think being able to simulate a target trial using data, and then potentially handing off the results of that target trial to folks who actually have the capacity and expertise to start a real randomized clinical trial—which, of course, is the gold standard—is a very translatable, impactful thing that I think we should be doing more of in the EHR space. But in order to be able to do those target trial emulations, the first step is doing this modeling work that we both talked about. It is literally impossible to do that more translatable work until we can correctly identify the population under study. In the case of Long COVID, that is particularly tricky in data, which is why we've spent so much time and energy talking through that. But that's really where I see the direction going now.

Dr. Master: I agree. The clinical trials would be great. I would also encourage people to utilize the Researcher Workbench. The user can use the code and generate the Long COVID probability based on N3C ML algorithm on the All of Us Researcher Workbench. Additionally, All of Us has other data types such as genomics, wearables, and survey. If there are other ways that they want to explore, and if they have a research question, where they feel that Long COVID is critical in their research study design, we have this work done. They can try to incorporate that work into their work and see how it can further enhance their study.

Q. How do you take the work that you've done and promote it in a way that gets into something that becomes a common conversation?

Response:

Dr. Pfaff: I try to promote this work and talk about it in a way that doesn't suggest that we have the right answer. I'd like to think that we have a right answer. But I think that, particularly with the new National Academies Long COVID definition that has been making the rounds lately, we've looked at that very carefully, and there's a lot to like about that definition. It was very carefully constructed, with a lot of input from really important stakeholders. It looks pretty different from our definition, right? And we've started the work, although it's very much underway and not finished.

I'm trying to construct a Venn diagram to show which patients meet our machine learning definition that I talked about today, which patients meet the National Academies definition, and which patients are in common between both. What we're seeing is that there are a lot of patients that are caught by both definitions, but there're also plenty of patients that are only caught by one or the other. That's not to say that those are the only two out there. PCORnet has a definition that is also a right answer, and WHO has a definition that is a right answer.

I don't think that we have enough information right now to be able to decide who wins, if that's even an appropriate question to ask. But I think that it's the union of all of those definitions... as long as they are evidence-based and well-reasoned and are explainable. And by explainable, I mean that, for example, if it's a machine learning model, that the features that the model is using to make its decisions are not bizarre. They need to sound like a clinically reasonable definition. As long as those things are in place, then I think we can use a best-of-breed approach to come up with a suite of different possible definitions to use in this kind of work.

Q. Have you started to see distinct subgroups of Long COVID patients?

Response:

Dr. Pfaff: There has been work done by all of the RECOVER EHR cohorts along those lines. We refer to that as sub-phenotyping studies, where we attempt to put people into a category that best fits them. As you can imagine, that's not necessarily easy because Long COVID affects so many different body systems that it's not necessarily

mutually exclusive, right? So, if we have a cardiopulmonary category, that doesn't mean that somebody's not also experiencing neurological symptoms.

Some researchers—and I would be happy to follow up with some citations of work that's been done in this space—have tried their best to pick the most winning category for different groups of participants, and have found different patterns, such as cardiopulmonary clusters of patients within Long COVID, patients experiencing neurological symptoms that have Long COVID. There's even a gastrointestinal cluster. So, yes, there are absolutely sub-phenotypes that can be explored further and may need different treatments and different preventatives.

Here is some of the previous sub-phenotype work that has been completed:

- https://pmc.ncbi.nlm.nih.gov/articles/PMC9460974/
- https://pubmed.ncbi.nlm.nih.gov/36563487/
- https://www.nature.com/articles/s41591-022-02116-3

Q. Can this work inform other post-viral syndromes?

Response:

Dr. Pfaff: There is an ICD-10 code, B94.8, which is a catchall code for post-viral sequelae, and that's been around for a really long time. When we started doing this work on Long COVID, we actually wanted to look at what the usage of that was like, even in the pre-COVID period, and the numbers were very, very small.

Once Long COVID really came to the forefront, and before there was a specific diagnosis code available for Long COVID, all of a sudden, we saw usage of that B94.8 code ticking up and up and up, showing that there was, at least, increasing recognition of this idea of post-viral illness.

What I think would be very interesting to do as future work is looking farther back in time. We have records that go back quite a ways into the end of the '90s and actually try to apply some of these models that are identifying Long COVID patients to see if we can identify patterns in post-viral illness patients in the “earlier” times. I think that would be really interesting work and would maybe bring to the forefront some of this post-viral illness prevalence that really hasn't been talked about enough in the past.

Q. Do the ICD codes impact the ability of insurance companies to cover Long COVID care?

Response:

Dr. Pfaff: I have to admit that I am not a health economics person, so I don't want to speak out of turn. What I will say is that we did see that pattern of slow uptake of the new code when it became available, that U09.9 code. And I think I saw someone else in the Q&A reference the fact that there may not be enough provider education to tell providers that, "Hey, there's this code for this, and you can enter it into the chart," as well as that there may just

not be enough promulgation of the guidance from CDC that shows how to use that code and when it's appropriate to use that code.

While I admit that I do not have an answer to that, and I don't know what the implications are for reimbursement insurance, I will say that we have seen that gap between the guidance for using this code and actual use of the code. And I certainly think it is fair for patients to bring up with providers that, "There is a code for Long COVID, and is it appropriate to be on my record?"

Q. Is All of Us still admitting participants? Are participants outside of the US eligible?

Response:

Mr. Lunt: Yes, All of Us is still letting in participants. We are going through a platform change this December, so there will be a week when we're not available. But it is for US residents and people living in the US only.

Q. Will All of Us include participants under the age of 18?

Response:

Mr. Lunt: All of Us started pediatric enrollment for people ages 0 to 6 this year, but on a small scale. And our interest is to expand that to go to a larger group of children, and that's dependent on our budget, and that's dependent on what Congress does since we're under a continuing resolution at the moment, and Congress has to decide by December 20th what the next steps are for funding government programs.

Q. Can non-researchers join All of Us to be able to view some of this ongoing research that's happening?

Response:

Mr. Lunt: Yes. If you're not a researcher, but you're interested in what's going on, there is a research highlights newsletter that we put out regularly, it’s available at researchallofus.org.

Q. Can you speak to how this program is working to improve the lives of Long COVID patients?

Responses:

Mr. Lunt: I think we touched on this a little bit, the problem of translation. We're a research program, so we don't directly engage with care organizations. We don't directly try to create changes in standards of care. We're not funded to do so, or empowered to do so, but we've been in conversations with the National Center for the Advancement of Translational Sciences, or NCATS, which is an NIH group that is responsible for doing that, to talk

about how we can accelerate the process of, if we discover something, how do we get that to show up in terms of improvements in care.

That process, in my mind, takes way too long right now, and it is something I'm very interested in seeing what we can do to accelerate. We're on that front end of discovery, and we're trying to see what we can do to more quickly do that. As Dr. Pfaff talked about, too, I think this is where clinical trials and the capacity to accelerate the integration with clinical trials will be important. This is one of the NIH director's big priorities as well.

I think one thing that we can do to help is specifically to look for ways to reduce the cost of diagnosis. And so, finding new biomarkers is an example of a really important way to really help accelerate things like this. If there's a very easy way to test for something that you know is treatable, that's helpful.

This is an area, too, where ARPA-H, which is a new government agency responsible for trying out bigger ideas that can change healthcare, is doing work on trying to develop new biomarkers. So programs like ours can help support that by showing how people's health is measurable in a way that makes it easier to identify when somebody has a specific treatable condition.

Dr. Pfaff: My response to that question would be that I want to see us in the data space doing more that directly impacts patients. To Mr. Lunt's point, that can be difficult. Obviously, I'm not a provider, and nor are most of my colleagues in the data science world, but that doesn't mean that we don't want to have an impact on patient lives. Sometimes, the discoveries that we make in data feel important scientifically but are not things that patients can reach out and touch and feel like are making positive changes in their health. And not to continue to repeat myself, but I do think that our future involvement in clinical trials is probably our best way, as data scientists, to contribute to findings and discoveries that actually will feel impactful to patients in a way that maybe some of the other data-driven work has not.

Dr. Master: I would just like to add one thing, echoing Mr. Lunt's and Dr. Pfaff's comments, is use these resources, the big program resources, to basically generate your hypothesis. And again, translate that to your lab or start a small clinical trial, see if you can get data, and try to test your hypothesis. It's going to take time. But I think, though we don't immediately affect quality of life, this work provides substantial evidence, which helps in generating the hypotheses, allowing researchers and scientists to take the next step and try doing small exploratory work.

Q. Are the data in N3C representative for urban/rural residence as well or just sociodemographics such as age, gender, race/ethnicity, and socioeconomic status?

Response:

Dr. Pfaff: There are many geographic variables available in N3C, and I believe those include rural-urban community area (RUCA) codes to identify urban/rural areas. If the RUCA codes themselves are not available in the platform, the ZIP codes that are available would still allow a researcher to translate to RUCA codes on their own.

Q. There is one element of diversity that may add complexity to recruitment and compliance but is still an important one to include: participants under age 18. Will there be an effort to incorporate this population into future iterations of the program?

Response:

Mr. Lunt: All of Us started pediatric enrollment this year for children ages 0–6. Our ability to expand that work depends on our 2025 budget (still unknown—Congress's current deadline is December 20, 2024). N3C collects pediatric data, but the model they created does not work for pediatric participants, only adults.

Q. Is there a medical outreach or education platform to recruit medical staff into using appropriate coding for Long COVID and related conditions? I am still running into doctors who have never heard of or refuse to treat people with Long COVID. Mandatory (or at least medical professional-focused) education in some form that patients could refer medical staff to would be very helpful.

Response:

Mr. Lunt: Both All of Us and RECOVER are research programs, and don't have the mandate or budget to push for improvements in the standard of care. That "translation" is an important part of the process, and we have been in discussions with the National Center for Advancing Translational Sciences (NCATS), which is the part of NIH charged with helping improve care faster.

Q. Are you concerned that having healthcare utilization in the model introduces bias related to healthcare access?

Response:

Dr. Pfaff: Yes, this is absolutely a concern. We have run the model without this variable and were not satisfied with the performance. However, this is something that we always cite as an unfortunate limitation of this methodology—patients with less care access, or who have stopped seeking care out of frustration/other reasons, are not as well represented.

Q. Are you able to access a patient's EHR from providers who are in private practice and do not use high-end EHR software, like the type that is part of a larger healthcare organization?

Response:

Dr. Pfaff: Most of the EHRs in N3C are not from private practices—they are more likely to be from larger healthcare systems. This is absolutely a limitation of this kind of work!

Q. Are the false positive pre-2020 Long COVID predictions actually picking up other infection-associated chronic condition (IACCs)?

Response:

Dr. Pfaff: Yes, we think it is very likely that some of those "false positive" patients may indeed have other post-viral illnesses, ME/CFS, or other conditions with overlapping signs/symptoms to Long COVID.

Q. Can non-researchers join All of Us to view ongoing research?

Response:

Mr. Lunt: You can sign up for research updates here: https://cdn.forms-content.sg-form.com/e793377f-2e71-11ef-a9aa-c6289830c400

Q. Given the close relationship between Long COVID and syndromes like Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), I wonder if some of the historical "false alarms" might not be false alarms at all. COVID might just be one of the routes to this common post-viral syndrome.

Response:

Dr. Pfaff: Yes, we think it is very likely that some of those "false positive" patients may indeed have other post-viral illnesses, ME/CFS, or other conditions with overlapping signs/symptoms to Long COVID.

Q. Can someone explain the difference of All of Us vs. RECOVER EHR (Biodata Catalyst)? For example, it seems like I can onboard to All of US as a registered user with training to access low-risk data. But Biodata Catalyst RECOVER data is restricted purely to senior investigators. Are these similar datasets in terms of RECOVER EHRs?

Response:

Mr. Lunt: All of Us and RECOVER are completely independent data sets and programs. All of Us uses recruiting of consented participants, whereas RECOVER uses data that was given by health provider organizations under the permission provided by the COVID crisis, without the express permission of the audience. Both programs use standard formats for EHR data, so research on one is translatable to the other, as Dr. Master is describing. All of Us does not select its audience for any specific disease or condition. Neither program's cohort is representative of the US population (All of Us deliberately oversamples from underrepresented populations).

Q. Why hasn't Post Exertional Malaise (PEM) been assigned its own diagnosis code yet, not only because it is a huge factor in Long COVID but also because it has been a hallmark of ME/CFS for years?

Response:

Dr. Pfaff: I may not have the latest updates, but I am aware that the Patient Led Research Collaborative led an effort to request a new ICD-10 code be added to capture PEM. Their proposal is here: https://patientresearchcovid19.com/storage/2022/10/Post-exertional-malaise-ICD-10-Proposal.pdf

Q. Can you please share the GitHub link?

Response:

Dr. Master: https://github.com/NCTraCSIDSci/n3c-longcovid/tree/Srushti_PythonUpdates

Q. Who is working on subcodes for ICD-10 U09.9 that would classify conditions believed to be caused by Long COVID—for example, POTS, ME/CFS, PEM, etc.?

Response:

Dr. Pfaff: The Patient Led Research Collaborative is one group that I know is doing work in this space!

Q. How is All of Us different from My Data Helps?

Response:

Mr. Lunt: My Data Helps is the work of a private company (CareEvolution), All of Us is a public effort to collect and make data available to researchers. CareEvolution is a vendor that provides some services to All of Us, but data is not shared between My Data Helps and All of Us.

Q. How will participation be "advertised," for lack of a better word, to Long COVID patients so they can be aware that joining All of Us or other programs will contribute to Long COVID research? Often providers are not aware of these studies, and it is up to the Long COVID patient to seek out these types of studies.

Response:

Mr. Lunt: All of Us works with community engagement partners to help build awareness of our program. In the early years of the program, we did not work with disease advocacy groups out of concern that it would overly bias the early data set, but now that the program has a large existing audience, we've started to engage with those groups. We encourage you to introduce any advocacy group you are involved with to us.

Q. What is your definition of Covid positive?

Response:

Dr. Hiral: It is based on "condition" and "laboratory" results in EHR data. To be included in the analytical cohort, the participant needs to have a COVID-19 diagnosis code (U07.1) or a positive SARS-CoV-2 PCR or antigen test for which at least 145 days have passed since COVID-19 index date, and at least one healthcare encounter between 45 and 300 days from their COVID-19 index date.
Sharing the manuscript that was published to learn more about how the algorithm was implemented in All of Us: https://pmc.ncbi.nlm.nih.gov/articles/PMC10280348/

Q. Could the model be improved to 97%? What are your thoughts on the need to improve accuracy and the way to get there?

Response:

Dr. Hiral: When we initially ran the N3 ML models in the All of Us Research Program, the pandemic era in the data was relatively short, as it included participants enrolled from May 2017 to January 2022. As more data becomes available, we can re-test the model's accuracy, and this could potentially lead to improvements. However, it's important to assess whether such a significant increase in accuracy is necessary, considering the trade-offs, such as overfitting or diminishing returns.
In future work, we plan to expand on this by re-running the ML models with refreshed data on the Workbench. Our team is exploring how integrating additional data types, such as genomics, COPE surveys, and wearables, can improve model robustness and predictive power. Here's the preprint of the work that is ongoing: https://pmc.ncbi.nlm.nih.gov/articles/PMC10775401/

Q. Is All of Us still enrolling participants?

Response:

Dr. Hiral: Yes, All of Us is still enrolling! Here's the link to learn how to join All of Us: https://www.joinallofus.org/

Q. There is a devastating gap in both research and clinical care options for pediatric cases of Long COVID. For adolescents, this is particularly glaring as they are in a critically formative part of their social development that is effectively paused by this isolating disorder. When will more focus be placed on expanding research to help this population?

Response:

Mr. Lunt: All of Us hopes to expand its pediatric enrollment in 2025 if Congress restores our budget.

Q. Are pregnant individuals represented in the data?

Response:

Dr. Pfaff: Yes, pregnant patients are definitely included in the model, N3C in general, and All of Us. The RECOVER EHR cohorts have done some work specific to the risk of PASC in pregnant patients.

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

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- Information about RECOVER research and to volunteer for studies: https://recovercovid.org/research
- Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs
- CDC information: Information for the general public and for healthcare providers about Post-COVID Conditions: https://www.cdc.gov/covid/long-term-effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/
- For medical/scientific terminology: https://medlineplus.gov/healthtopics.html