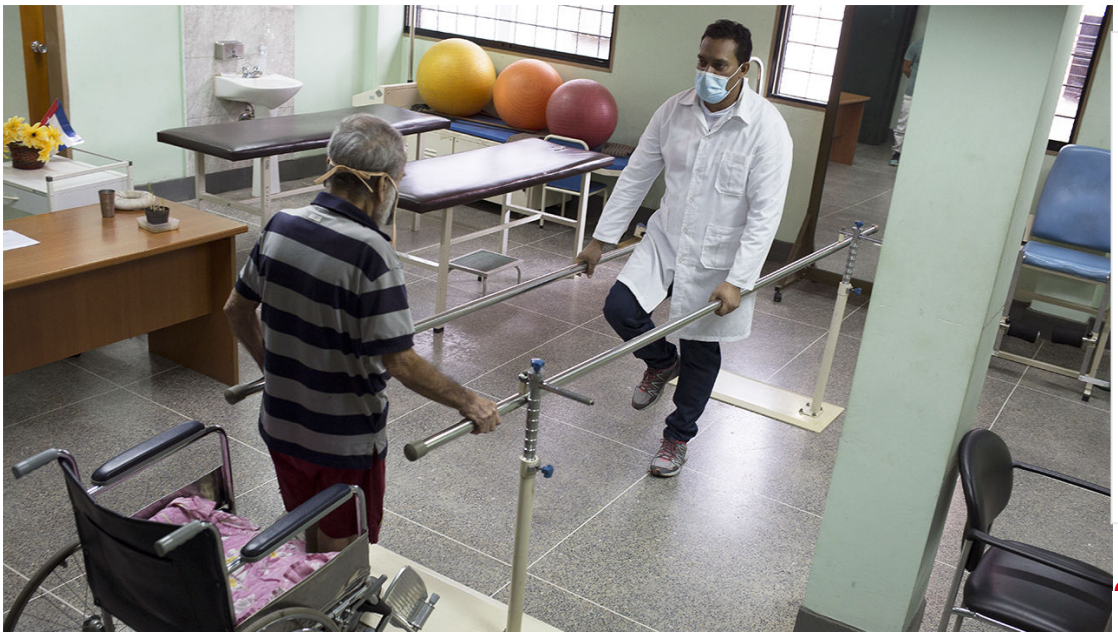

A COVID-19 survivor in Caracas, Venezuela, exercises at a rehabilitation center for patients like him. PEDRO RANCES MATTEY/PICTURE-ALLIANCE/DPA/AP IMAGES

How scientists are teasing apart the biology of Long COVID

By **Jennifer Couzin-Frankel** | Apr. 13, 2021 , 12:50 PM

***Science*'s COVID-19 reporting is supported by the Heising-Simons Foundation.**

After the first surge of COVID-19 cases in spring 2020, a new worry emerged: **Some people didn't get better**. For those with so-called Long COVID, lingering symptoms ranged from brain fog and intense fatigue to shortness of breath and loss of smell and taste. So far, there's little clarity about what causes or how to treat this constellation of symptoms. Some surveys suggest between 10% and 30% of people infected with the pandemic coronavirus may struggle to recover, but these data are preliminary.

Emilia Liana Falcone, an infectious disease specialist at the Montreal Clinical Research Institute, and Michael Sneller, an infectious disease specialist at the National Institute of Allergy and Infectious Diseases (NIAID), are each leading a large Long COVID clinical trial. They are recruiting volunteers who've had COVID-19—some with ongoing symptoms and some without—along with a control group of people who never caught the virus. Volunteers come in regularly for medical tests, and scientists probe their blood for immune abnormalities. The goal: a biological explanation of chronic symptoms after COVID-19. The pair spoke with *Science* about their work, their thoughts on Long COVID, and their efforts to let the data guide them. This conversation has been edited for brevity and clarity.

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Q: We've known for a long time that many infections—not just COVID-19—can cause enduring and disabling symptoms, like crushing fatigue and brain fog, in some people. Is Long COVID just another example of this?

Michael Sneller: Maybe it's new, maybe it's not. There are precedents for this kind of postinfectious, noncritical illness, such as posttreatment Lyme disease. And there are people with chronic fatigue syndrome, some of whom pinpoint the onset of their symptoms to a viral infection. During polio outbreaks in the 1950s, there was another syndrome that developed in people: fatigue, concentration difficulties, aches and pains. I thought early on that given tens of millions of people who were likely going to get infected with COVID, that we would be seeing this.

Emilia Liana Falcone: In terms of fatigue, some of the neurological complications, brain fog, lack of concentration, is common for sure after other infections. That being said, I think there are certain features that are not quite as common that we're seeing now—the loss of smell and taste I've seen in the clinic at least 6 months out. There's also this new onset of some endocrinopathies, such as thyroid problems. Maybe this happens in the context of other viral infections and we're not looking for it. But it might be something more distinctive of COVID.

Q: How did you get interested in Long COVID?

E.L.F.: I spent almost 9 years at the National Institutes of Health, where I was looking at long-term inflammatory complications in patients with inborn errors of immunity. It seemed to me highly plausible that given the intense inflammatory processes in the acute phase of COVID-19, there would be long-term effects.

M.S.: About 6 years ago, I was asked to help lead a study of Ebola survivors in West Africa. In the 2014 outbreak, it infected hundreds of thousands of people. **Of those who survived**, there emerged persistent symptoms such as headaches and joint pain. We enrolled approximately 1000 Ebola survivors and about 2300 Ebola-negative people in Liberia—it was an NIAID-Liberia collaboration. I knew we needed to have a control group, in order to really determine whether any of the things we were seeing were related to Ebola per se, or just life in Africa, which can be hard. I learned a lot that I was able to apply to studying post-COVID syndrome.

Q: Why don't we yet have a clear definition of Long COVID?

M.S.: A year ago, this didn't exist. So that's why.

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E.L.F.: A lot of the first studies were based on questionnaires and chart reviews, especially in hospitalized patients. There's been a lot of describing symptoms. There's a lack of mechanistic data.

Q: How is your study set up to dig into the biology?

M.S.: We have a COVID group, at least 6 weeks out from the onset of symptoms, of 18 years and older. We've enrolled about 150 survivors, and about 55% have no post-COVID symptoms. As was the case with the Ebola study, we knew it was important to have a control group. We ask participants to identify people that they had contact with who didn't get COVID, and we ask them to join the study. We try to match them for age, and if you do that, you get pretty good matching for other comorbidities, including hypertension, diabetes, obesity, and so forth. We've got just about 100 controls now enrolled.

Both groups undergo basically the same evaluations, which include lung function, exercise testing, and heart MRIs. Cortisol and thyroid functions are measured to work out reasons for various things like fatigue. We have an extensive mental health evaluation with neurocognitive testing, psychiatric interviews. And then we have a whole laboratory component, looking at aspects of the immune response, evidence of persistent virus, persistent inflammation. It's a longitudinal study for 3 years. We see people every 6 months, sometimes sooner.

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E.L.F.: This is very similar to our study. We also begin with a slew of questionnaires that include information on diet, well-being, etc. There's neuropsychiatric or neuropsychological testing by a separate team. We look at every organ system. And then there's collection and analysis of blood and tissue samples—we have laboratories right upstairs. We also have a team of specialists that we refer to for deeper workups of anyone with an actual organ dysfunction.

Q: You both include control groups of people who have not had COVID-19. Why is that important?

E.L.F.: You need to control for the background noise. We're in a pandemic, and that is creating anxiety, stress, insomnia, depression. We have to include people who are living that to be able to tease out what is really related to the infection.

M.S.: With the Ebola study, by having a control group, we showed that a lot of symptoms that were thought to be post–Ebola syndrome symptoms actually occurred at the same frequency in the control group.

I can give you two examples from our current study. There are published reports about tinnitus being a post-COVID problem. About 12% of our COVID group complains of tinnitus, and about 14% of the control group has tinnitus. It's the same thing with finding a mild abnormality in a lung test that measures how well lungs transfer oxygen to the bloodstream. About 50% or 60% of the COVID group has that, with a median age of 50. Had I not had a control group, I'd say, "This is from COVID." Well, exactly the same percentage of the age-matched, comorbidity-matched control group have the defect. You need a control group to really attribute any abnormality to the viral infection. Without a control group, that's difficult, if not impossible.

E.L.F.: Exactly.

Q: Might your findings help explain who is susceptible to Long COVID?

M.S.: Potentially. It might give some clues to what might be causing these symptoms. If you had detailed biospecimens from the acute illness phase from the same patients, that would be ideal, but that's very hard to do. In my cohort, 90% rode COVID-19 out at home. So they've got no biospecimens.

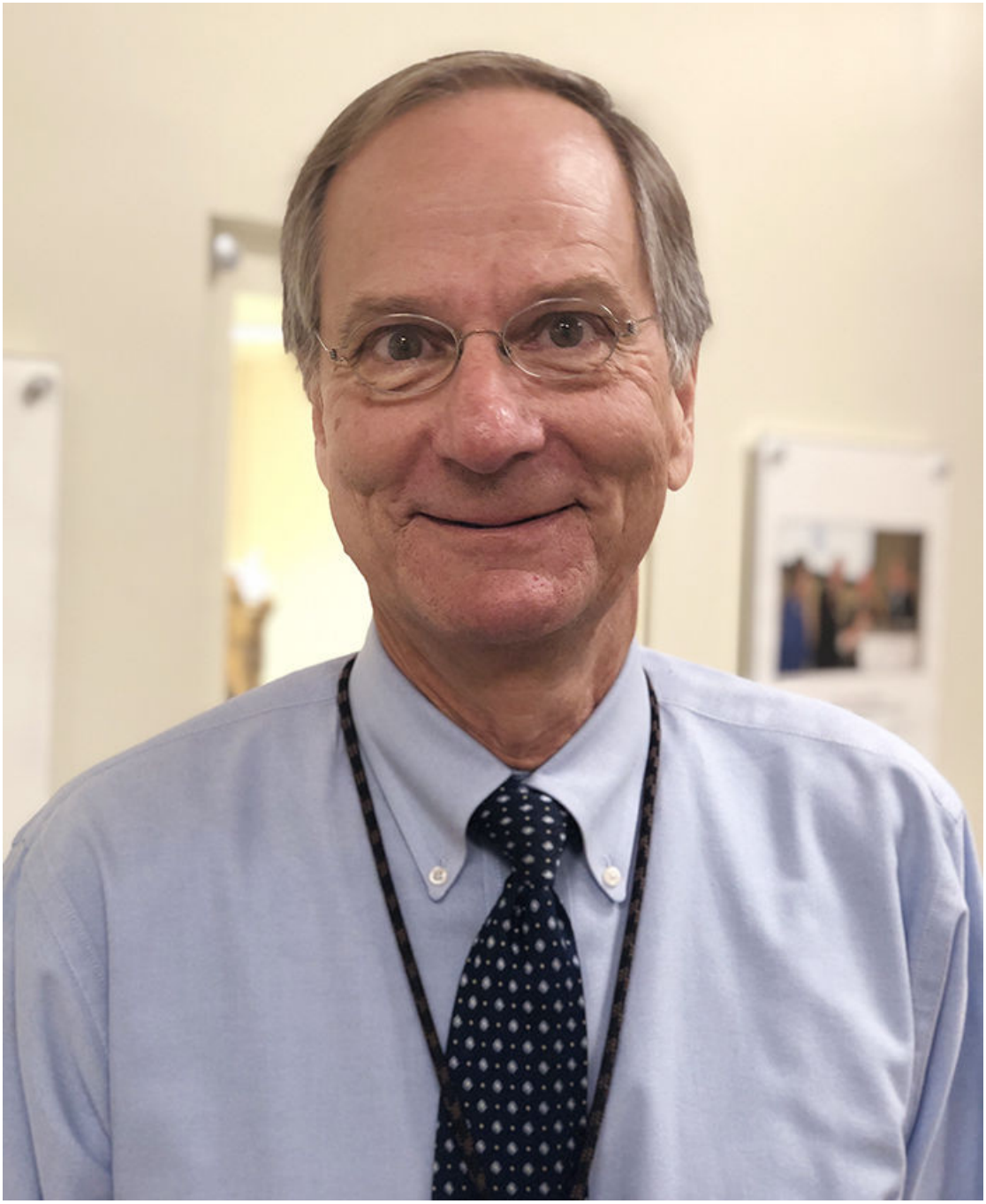
E.L.F.: Developing predictive models is very attractive, and people have been interested in that. But the issue is with those patients who are not hospitalized, you just don't have any samples from before or during the illness to compare to the present.

Q: It's going to take time for your studies and others to tease this out. Are there ways to help people with Long COVID right now?

E.L.F.: There isn't a clear treatment pathway. You can treat the obvious reversible issues—someone who's anemic, someone who's vitamin D deficient. A lot revolves around rehabilitation, depending on the patient.

Q: What does rehabilitation involve?

E.L.F.: If it's pulmonary, there are exercises you can do to improve shortness of breath, some of which are related to the exercises opera singers do. We've been approached by the Opera House of Montreal to develop a rehab program for patients, because a lot of these exercises work on improving lung function.



Michael Sneller TAE-WOOK CHU

M.S.: I find in talking to patients, they're afraid to exercise because they think they have heart damage or lung damage. I tell them that we're doing a lot of testing. If we don't find any evidence of serious damage in the lungs, I encourage them to start gradual exercise. There are a lot of mental health issues, and in the control group, too. There is a lot of room for better mental health evaluation in the community, and treatment.

E.L.F.: The only thing I would add is if you think that the patient has chronic fatigue syndrome, then it's more of a conservational approach in terms of their energy, rather than forcing an exercise progression.

Q: Do you think that some of these cases are chronic fatigue syndrome?

E.L.F.: I think there's a subgroup of post-COVID patients where maybe they will fall into that category, but there might be others that have something else.

Q: There have been anecdotal reports about people with Long COVID getting better after vaccination. What do you think of this?

E.L.F.: It's very provocative; it's intriguing. With the control group, you have to take a careful look. It could just be patients' natural rate of healing.

M.S.: We asked people to let us know when they are getting vaccine. On a subset, we're trying to draw blood at certain time points to study B cell and antibody response in both groups after vaccination.

E.L.F.: We, too, are sampling patients after the first dose and the second dose, although here in Quebec, if they've had COVID, they only get one dose.

M.S.: As far as symptoms go, the majority of people in my protocol who got vaccinated haven't said one thing or the other. We'll just see what happens.

Q: Long COVID is in the news constantly. What do you think about how it's being described to the general public?

M.S.: There's a lot of misinformation out there that does not give context. There will be a headline saying psychosis is a new symptom of Long COVID, and it turns out the story is about just one person. My patients, some of them tell me they spend 6, 8 hours a day on social media pages related to Long COVID. I think that's not always a good thing.

Q: But they might be doing that because they're not getting the support they need from the health system, right?

M.S.: That's true.

E.L.F.: You're right, there are people who feel like it's not being recognized. The reports started with infectious disease doctors in the U.K. who were like, "Hey, at several months out, I'm not performing like a normal doctor." That for me struck a chord. It's important that we listen, that we acknowledge that there's something going on. But, like Mike said, there's misinformation. That's where research projects play a role. We get to have some concrete, objective data to put it all in perspective.

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doi:10.1126/science.abi9904

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