Attempting to define Long COVID: The NIH-funded RECOVER initiative trial

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Postacute sequelae of COVID-19 (PASC), often referred to as Long COVID, has had a substantial and growing impact on the global population. Recent prevalence studies from the United States and the United Kingdom found that the complication has affected, on average, around 45 percent of survivors, regardless of hospitalization status.

No accurate tally of the number of people affected and its real global impact has yet been made, but conservative estimates of several hundred million and trillions in economic devastation would hardly be an exaggeration. Even in China, after the lifting of the Zero COVID policy late last fall and the tsunami of infections that followed, social media threads are now widespread with people complaining of chronic debilitating fatigue, heart palpitations and brain fog.

Yet, more than three years into the "forever" COVID pandemic, with Long COVID producing more than 200 symptoms, impacting nearly every organ system and causing such vast health problems for a significant population across the globe, it remains undefined and somewhat arbitrary in the clinical diagnosis. Additionally, the assurances given to study potential therapeutic agents have remained unfulfilled.

In this regard, a new Long COVID observational study called the "RECOVER [researching COVID to enhance recovery] initiative," was published last week in the *Journal of the American Medical Association*, with almost 10,000 participants across the US. Funded by the National Institutes of Health (NIH), it attempts to provide a working definition for Long COVID (PASC).

While the study represents an advance from the standpoint of assessing the impact of Long COVID, and has been celebrated in media coverage, it must be viewed with several reservations and caveats. It is exclusively focused on describing the disease, rather than supporting efforts to alleviate its impact, let alone find a cure. And its definition, however preliminary, could well be misused by insurance companies and other profit-driven entities in the healthcare system to restrict diagnosis and care.

Comments by Dr. Leora Horwitz, one of the study authors and director of the Center for Healthcare Innovation and Delivery Science at New York University, give some sense of the misgivings felt by serious scientists. Horwitz stated, "This study is an important step toward defining Long COVID beyond any one individual symptom. This definition—which may evolve over time—will serve as a critical foundation for scientific discovery and treatment design."

Certainly, a working definition that medical communities can agree on is critical. But after three years and nearly all the $1.2 billion given to the NIH already spent, one must ask how much another observational study contributes to answering pressing questions affecting patients that have not already been addressed in more than 13,000 previous reports, as tallied by the *LitCOVID* search engine?

Why have there been so many delays in conducting clinical trials studying potential treatments and preventative strategies in the acute phase of infection that could reduce or eliminate the post-acute sequelae? Where is the urgency at the NIH and in the Biden administration to expand funding and initiate an all-out drive to develop treatments for Long COVID like the $12.4 billion spent on the COVID vaccines?

Scoring post-acute symptoms

The findings in the recent study, published on May 25, 2023, in *JAMA*, titled, "Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection," are somewhat limited and problematic in their current formulation. The authors have identified 12 primary symptoms that distinguish COVID survivors with Long COVID from those without those aftereffects. These include loss of smell or taste (8 points), post-exertional malaise (7 points), chronic cough (4 points), brain fog (3 points), thirst, (3 points), heart palpitations (2 points), chest pain (2 points), fatigue (1 point), dizziness (1 point), gastrointestinal symptoms (1 point), issues with sexual desire or capacity (1 point), and abnormal movements (1 point).

Assigning points to each of the 12 symptoms and adding them up gives a cumulative total for each patient. Anyone scoring 12 or higher would be diagnosed as afflicted with PASC, accounting for 23 percent of the total. In general, the higher the score, the greater the disability in performing daily activities.

The researchers also noted that certain symptom combinations occurred at higher rates in certain groups, leading to identifying four clusters of Long COVID based on symptomology patterns, ranging from least severe to most severe in terms of impact on quality of life. Why such clusters were seen remains uncertain.

Some symptoms were more common than others, and this did not correspond to the severity of the symptoms as measured approximately by the points. Symptoms of post-exertional malaise (87 percent), brain fog (64 percent), palpitations (57 percent), fatigue (85 percent), dizziness (62 percent), and gastrointestinal disturbances (59 percent) were most common.

The study's lead author, Tanayott Thaweethai from Massachusetts General Hospital and Harvard Medical School, explained, "This offers a unifying framework for thinking about Long COVID, and it gives us a quantitative score we can use to understand whether people get better or worse over time."

Andrea Foulkes, the corresponding author and principal investigator of the RECOVER Data Resource Core and professor at Harvard Medical School, said, "Now that we're able to identify people with Long COVID, we can begin doing more in-depth studies to understand the mechanisms at play. These findings set the stage for identifying effective treatment strategies for people with Long COVID—understanding the biological underpinnings is going to be critical to that endeavor."

The currently evolving definition could have significant implications, and not just medically. For instance, if people suffer only brain fog and post-exertional malaise and score less than 12 on their symptomology, they would not be construed as having PASC. Under such a construct, the definition could be used by employers and health insurers to deny compensation or treatment by telling people they don't have a recognized Long COVID complication. Additionally, it is not clear how long these symptoms have to be present before the diagnosis is accepted.

Lisa McCorkell, one of the authors of the study, explained on her social media account, "If people didn't meet the scoring threshold for PASC+, that doesn't mean they don't have PASC! It means they are unspecified. Unspecified includes people with Long COVID. Future iterations of the model will aim to refine this—that will include doing analysis using the updated RECOVER symptoms survey, adding in tests/clinical features and ultimately biomarkers. That is also why this isn't meant to be an official prevalence study. The sample is not fully representative, but also, we know that there are people in the unspecified groups that have PASC."

She continued, "It is very clear throughout the paper that in order for this to be actionable at all, iterative refinement is needed. In presenting this to NIH leadership, they are fully aware of that. But the press is not fully understanding the paper which could have dangerous downstream effects. Since the beginning of working on this paper I've done everything I could to ensure the model presented in this paper is not used clinically."

Unfortunately, in the world of capitalism, such things take on a life of their own. The definitions will influence how health systems will choose to view these patients and demand their clinicians abide by prescribed diagnostic codes. This has the potential to dismiss millions with Long COVID symptoms and deny them access to potential treatments if and when they materialize.

The concerns of Elisa Perego

Dr. Elisa Perego, who suffers from Long COVID and coined the term, offered the following important observations.

In response to the publication, she wrote, "Presenting a salad of 12 symptoms, (many of which many patients might not even experience) as the most significant in #LongCOVID is also detrimental to new patients, who might be joining the community now, and might not recognize themselves in the symptom list."

She added, "We are also in 2023. There are thousands and thousands of publications from across the world that discuss imaging, tests, clinical signs (=objective measurements), biomarkers, etc. related to acute and #LongCOVID. We have many insights into the pathophysiology already. The #LongCOVID and chronic illness community deserve more. Other diseases, including diseases linked to infections, have sadly been reduced to a checklist of symptoms in the past. This has made research, recognition, and a quest for treatment much more difficult."

There are additional findings in the report worth underscoring as they provide a glimpse into the ever-growing crisis caused by forcing the world's population to "live with the virus."

Hannah Davis, a Long COVID advocate and researcher, with Dr. Eric Topol, Lisa McCorkell, and Julia Moore Vogel, wrote an important review on Long COVID in March, which was published in *Nature*. She said of the RECOVER study, "The overall prevalence of #LongCOVID is ten percent at six months. The prevalence for those who got Omicron (or later) AND were vaccinated is also ten percent … [However] reinfections had significantly higher levels of #LongCOVID. Even in those who had Omicron (or later) as their first infection, 9.7 percent with those infected once, but 20 percent of those who were reinfected had Long COVID at six months after infection."

Furthermore, she said, "Reinfections also increased the severity of #LongCOVID. Twenty-seven percent of first infections were in cluster four (worst) versus 31 percent of reinfections." These facts have considerable implications.

Immunologist and COVID advocate Dr. Anthony Leonardi wrote on these findings, "If Omicron reinfections average six months [based on current global patterns of infection], and Long COVID rates for reinfection remain 10 to 20 percent, the rate of long COVID in the USA per lifetime will be over 99.9 percent. In fact, the average person would have different manifestations of Long COVID at different times many times over. Some things reverse—like anosmia [loss of smell]. Others, like [lung] fibrosis don't reverse so well."

The work done by these authors deserves credit and support. Every effort to bring answers to these critical questions is vital. The criticism to be made is not directed at the researchers who work diligently putting in overtime to see the research is conducted with the utmost care and obligation it merits. Rather, it should be directed at the very institutions that have adopted "living with the virus" as a positive good for of public health.

The Biden administration neglects Long COVID

In a recent scathing critique of the Biden administration and the NIH by *STAT News*, Rachel Cohrs and Betsy Ladyzhets place the issue front and center. In their opening remarks, they write, "The federal government has burned through more than $1 billion to study Long COVID, an effort to help the millions of Americans who experience brain fog, fatigue, and other symptoms after recovering from a coronavirus infection. There's basically nothing to show for it."

They continue, "The NIH hasn't signed up a single patient to test any potential treatments—despite a clear mandate from Congress to study them. And the few trials it is planning have already drawn a firestorm of criticism, especially one intervention that experts and advocates say may actually make some patients' Long COVID symptoms worse." This is in reference to a planned study where Long COVID patients would be asked to exercise as much as possible, when it has clearly been shown that such activities have exacerbated the symptoms of Long COVID patients.

As the report in *STAT News* explains, there has been a complete lack of accountability in how the NIH funds were used. Much of the work to run the RECOVER trial has been outsourced to major universities.

Michael Sieverts, a member of the Long COVID Patient-led Research Collaborative with expertise in federal budgeting for scientific research, told *STAT*, "Many of the research projects associated with RECOVER have been funded through these organizations rather than directly from the NIH. This process makes it hard to track how decisions are made or how money is spent through public databases."

In April the Biden administration announced they were launching "Project Next Gen," which is like the Trump-era COVID vaccine "Warp Speed Operation." It has promised $5 billion to fund the development of the next iteration of vaccines through partnership with private-sector companies, monies freed up from prior coronavirus aid packages. Incredibly, it has left Long COVID out of the plan.

Indeed, this diverting of money back into the hands of the pharmaceuticals and selling it as the Biden administration's continued proactive response to the ongoing pandemic, while divesting all interest in preventing or curing Long COVID, is on par with every effort the administration has made to peddle the myth that "the pandemic

is *really* over." Long COVID is one of the central elements of the worst public health threat in a century, in a pandemic that is far from ended.