August 20, 2021

To: Dr. Francis S. Collins, Director, National Institutes of Health
Dr. Anthony S. Fauci, Director, National Institute of Allergy and Infectious Diseases
Dr. Gary H. Gibbons, Director, National Heart, Lung, and Blood Institute
Dr. Walter J. Koroshetz, Director, National Institute of Neurological Disorders and Stroke
CC: Dr. Amy Patterson, Deputy Director, National Heart, Lung, and Blood Institute

Subject: ME/CFS and Research on Long COVID

Dear Drs. Francis S. Collins, Anthony S. Fauci, Gary H. Gibbons, Walter J. Koroshetz:

We appreciate your timely investment in the RECOVER Initiative. This effort will help identify the frequency, severity and pathobiology of what will likely be *multiple* different post-acute sequelae of SARS-CoV-2 infection (PASC), including "Long COVID" (or post-acute COVID-19 syndrome). We also appreciate your statements to the effect that Long COVID has features that are similar to other post-infectious fatigue syndromes and to myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), and that the study of Long COVID also may shed light on other post-infectious fatigue syndromes and ME/CFS, and vice versa.

The first phase of the RECOVER Initiative involves assembling a large cohort of people who have been infected with SARS-CoV-2 and building the necessary research support infrastructure to study the above questions, as well as to conduct randomized, placebo-controlled clinical trials.

We write to discuss the subsequent phases of the RECOVER Initiative and any other initiatives investigating PASC and Long COVID. In contrast to investigator-initiated research, the Research Opportunity Announcements that fund these initiatives allow NIH to determine the research questions and methodologies that will be funded following the first phase. In so doing, we would deeply appreciate it if you would consider the following:

1. Inclusion of symptom data collection instruments sufficient to determine if the post-COVID patients meet either the National Academy of Medicine criteria or the Canadian Consensus Criteria for ME/CFS. To do this, we recommend the use of the DePaul Symptom Questionnaire along with other NINDS Common Data Elements instruments. It is particularly important to determine the presence of post-exertional malaise, a key symptom of ME/CFS that has also been reported by many Long COVID patients.
2. Inclusion of the following control groups:
    a. People with ME/CFS without evidence of past SARS-CoV-2 infection;
    b. Uninfected healthy control subjects, matched for age, gender and socioeconomic status;
    c. Matched post-COVID patients who return to full health;
    d. People with two other common infectious illnesses that can lead to post-infectious fatigue syndromes—those with acute infectious mononucleosis, and those with acute Lyme disease, who are without evidence of past SARS-CoV-2 infection;

e. People with other chronic illnesses characterized by fatigue: e.g., multiple sclerosis, systemic lupus erythematosus, Sjogren's syndrome, major depression, cancer, and post-intensive care unit fatigue syndrome, who are without evidence of past SARS-CoV-2 infection.

3. Creation of a formal ME/CFS advisory group consisting of representatives from NIH, CDC and DOD; from government-funded and privately-funded ME/CFS research centers; and from major ME/CFS patient, professional, and research funding organizations. This advisory group could provide input on ways to integrate what has been learned from ME/CFS research into the strategy for studying Long COVID, and vice versa.
4. Inclusion in the PASC research agenda of areas that are proving fruitful in the study of ME/CFS: metabolomics (particularly, energy metabolism), redox imbalance, systemic immune dysfunction, autoimmunity, neuroinflammation, autonomic dysfunction, ion channelopathies, and abnormalities of the gut microbiota;
5. Inclusion in the PASC research agenda of treatment trials that are based on the pathophysiological pathways identified in ME/CFS.
6. Expansion of support for studies of ME/CFS: this can inform studies of Long COVID, and vice versa.

We hope you will consider these suggestions. The research agenda for PASC can not only expedite progress on Long COVID but also achieve a better understanding of ME/CFS and post-infectious fatigue syndromes more broadly.

We look forward to your response to these recommendations.

Respectfully,

DEPARTMENT OF HEALTH & HUMAN SERVICES **National Institutes of Health**
National Institute of Neurological Disorders and Stroke

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Date: September 10, 2021

To: [redacted]

Subject: ME/CFS and Research on Long COVID

Dear [redacted]

I am responding to your letter addressed to me as well as to Dr. Francis S. Collins, Director of the National Institutes of Health (NIH); Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases; and Dr. Gary H. Gibbons, Director of the National Heart, Lung, and Blood Institute (NHLBI).

Thank you for your detailed recommendations concerning subsequent phases of the RECOVER Initiative and any future research efforts relating to post-acute sequelae of SARS-CoV-2 infection (PASC), including Long COVID. You explained that your suggestions can lead to a better understanding not only of Long COVID but also of ME/CFS and other post-infectious fatigue syndromes. We appreciate your thoughtful consideration of approaches to benefit research on these diseases.

We expect to release new information about the RECOVER Initiative soon. Updates will be posted on the RECOVER website (https://recovercovid.org/). In the meantime, please be assured that the NIH is committed to supporting critical research on both PASC and ME/CFS, as well as other post-infectious syndromes with symptoms that include fatigue.

Sincerely,

Walter J. Koroshetz MD

Walter J. Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke
Chair, Trans-NIH ME/CFS Research Working Group