February 25, 2021

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892

Larry A. Tabak, D.D.S., Ph.D.
Principal Deputy Director, NIH
9000 Rockville Pike
Bethesda, Maryland 20892

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH
9000 Rockville Pike
Bethesda, Maryland 20892

Michael S. Lauer, M.D.
Deputy Director for Extramural Research, NIH
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Director Collins, Principal Deputy Director Tabak, and Deputy Directors Gottesman and Lauer:

As you and your colleagues continue the crucial work of mobilizing resources to combat the pandemic, we, the undersigned public health, health advocacy, research, and disease organizations, are writing to share our collective knowledge, recommendations, and urgency regarding post-acute COVID-19 syndromes, sequelae, and related illnesses. The $1.15 billion recently provided by Congress for long-term studies of COVID-19 will form the backbone of the American scientific response to the next phase of the pandemic, addressing the "25 to 35% or more [who] have lingering symptoms," according to Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases.[i]

These "lingering symptoms," also known as "post-acute COVID-19 syndrome (PACS)," post-acute sequelae of SARS-CoV-2 infection (PASC)," or the patient-preferred term "Long COVID," have already impacted the lives of an estimated 3.2 million Americans, and counting.[ii] [iii] Some Long COVID patients are being diagnosed with other chronic, disabling, and potentially life-long illnesses, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), other forms of dysautonomia, Ehlers-Danlos syndrome (EDS), hypermobility spectrum disorder (HSD) and mast cell activation syndrome (MCAS). These chronic illnesses, many of which are known to be associated with viral triggers, *are more likely to occur in women*[iv] and impact people of every race, age group, gender, and socio-economic class in every part of America.

This growing patient population represents a secondary wave of chronic illness, slow healing COVID-19 survivors, and long-term disability, which may disproportionately impact women. With this knowledge driving us, we summarize below key recommendations from Long COVID and related disease patients, doctors, and leading scientists. We strongly urge you to incorporate these recommendations into the PASC Initiative as well as any existing and future NIH initiatives.

1. **Prioritize Patient Engagement and Inclusion.** Patient engagement and inclusion is increasingly seen as critical to public health program efficacy. It is essential to include patients voices at all stages of the research process. The success of Long COVID patient-scientists[v] [vi]further illustrates their vital importance to the PACS research process. We encourage NIH to create and maintain an inclusive dialogue with Long COVID patients, related disease patients, researchers, clinicians, and interagency partners. We also recommend that NIH formalize this dialogue in the form of a

task force that facilitates and promotes inclusion and equity, patient identified priorities, and transparency.

2. **Capitalize on Existing Infrastructure and Expertise from Related Diseases.** As the undersigned organizations demonstrate, public-private partnerships, NIH projects, and stakeholder investments have created a core foundation composed of neuroimmune clinical experts, chronic illness scientific knowledge-base, and related research infrastructure. We strongly urge NIH to invest in, utilize, and expand this existing infrastructure into a *clinical trials network linked by data management centers*. When creating this multi-site project, it is important that NIH prioritize collaboration with existing disease experts and stakeholder groups. These resources can be leveraged in a multitude of ways, including diagnostics, treatments, comparison group data, patient engagement, and organizational structure. With the right investments, these existing tools will fast-track real outcomes and improvements for patients.

3. **Invest in Data Harmonization and Data Tracking.** The use of high-throughput technologies, "big-data" analysis, and "omics" (for example genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, etc.) is effective only when the data is harmonized across platforms, patient cohorts, and projects for collaboration and comparison. We strongly encourage NIH to prioritize and invest in data harmonization, data infrastructure, and data sharing, as these are the keys to accelerating collaborative results. We support your stated intentions to do so in the recently-released Notice of Intent to Publish ROAs (OTA-21-015) for the (PASC) Initiative. We especially want to highlight the success of the National Database for Autism Research (NDAR) as a model for data infrastructure investment. These cost-effective and proven systems can meet the need for robust datasets and ***longitudinal*** patient tracking, especially in regards to medical history, comorbidities, and demographic and socio-economic factors (e.g. age, race, ethnicity, sexual orientation, gender identity, and geography[vii]). These datasets will prove key to identifying potential disparities, tracking and comparing patient outcomes over time, identifying risk/resiliency in diverse populations, and accelerating treatments to patients.

4. **Utilize an Interdisciplinary, Upstream/Downstream Approach.** Long COVID is a broad, multisystem, and complex illness which includes, but is not limited to, dysregulation of immune and neurological function. Accelerating "bench to bedside" results will take a simultaneous and multi-pronged approach. Longitudinal studies should also be of sufficient duration to understand the full natural history of Long COVID cohorts and to test strategies that treat symptoms and prevent chronic disease among Long COVID patients. We commend the multidisciplinary, exploratory, and collaborative approaches NIH articulated in the "Notice of Intent to Publish" OTA-21-015[viii] released earlier this month and recommend that NIH invest in elements of research that are traditionally "upstream" and "downstream" simultaneously, prioritizing: 1) basic science 2) natural history of long COVID and related illnesses, 3) Long COVID prevalence and epidemiology, 4) diagnostics and comorbidities, with multiple disease models 5)

Long COVID risk and resiliency, 6) whole genomic sequencing, 7) exploratory clinical trials, and 8) existing treatment models.

5. **Diversify Long COVID and Control Group Criteria. "***Who*" is studied is just as important a question as "*what"* is studied. For key time periods and in many communities, testing for SARS-CoV-2 was extremely limited and many patients experiencing obvious symptoms of COVID-19 never received a positive diagnostic or antibody test. Instead, some patients were able to received a clinical diagnosis of COVID-19 during or after the acute phase of their illness. It is vital that these Long COVID patients (who received a clinical diagnosis without a test) and *non-hospitalized COVID-19 patients* are included in research and study parameters should be designed to facilitate their participation. Additionally, there is a potential wealth of scientific discovery to be had in comparing Long COVID patients with other post-infectious syndromes or similar chronic illnesses. We strongly encourage NIH to prioritize Long COVID studies that utilize ME/CFS, POTS, MCAS or EDS patients control groups in addition to healthy controls and recovered COVID-19 patients. We call on NIH to continue and expand efforts relating to diversity and inclusion of traditionally under-represented patients in upcoming Long COVID projects and funding announcements.

6. **Incentivize Public/Private Partnership.** Many doctors and scientists specializing in Long COVID related illnesses have already developed promising findings and research outcomes related to post-infection and viral-triggered long-term illnesses that could be applied to Long COVID scientific and medical efforts. Please also take time to review the attached list (Appendix A) of research initiatives that highlights ongoing and planned projects with direct application to Long COVID. In light of the current state of the literature and data on Long COVID, we also recommended NIH prioritize the promising areas of research below:

- Origins of Post-Infection Autonomic Dysfunctions and related symptoms, like POTS, post-exertional malaise and other biological mechanisms behind relapses
- Longitudinal studies of new Long-COVID patients that include other chronic illness patients as controls, specifically targeting immune cell exhaustion, NK cell count and function, and neutrophil behavior
- Comprehensive, longitudinal comparisons between post-infectious immune and neurological dysfunction caused by COVID-19 compared to other infections
- Treatment opportunities through Immunotherapy and Immune modulation
- Small Fiber Neuropathy /Ganglititis (autonomic ganglia), specifically developing collaborative centers and infrastructure for conducting baseline research and clinical care
- Energy production and metabolism at cellular level
- Nutrient absorption and related gastrointestinal inflammation

- Endothelial dysfunction or vascular impacts of infection and the role it plays in post-infectious sequelae
- Hypometabolism found in the brains of post-infectious patients
- The role of connective tissue disorders in post-infectious sequelae
- Genetic research, including whole genome sequencing and gene expression
- Long-term impact of COVID-19 on microbiome and virome composition
- Development of better imaging and diagnostic tools for post-infectious neurological symptoms
- Development better antivirals, especially that target latent and non-lytic viruses

We appreciate your leadership as NIH continues to guide our nation's scientific and medical response to Long COVID. We fervently hope that you will implement and fully resource these recommendations in the upcoming trans-NIH Long COVID planning.

Thank you for your attention to our request.

Sincerely,

LONG COVID ALLIANCE

Your organization's logo here!

CC: Anthony S. Fauci, M.D., Director of National Institute of Allergy and Infectious Diseases (NIAID)
Walter J. Koroshetz, M.D., Director of National Institute of Neurological Disorders and Stroke (NINDS)
Nina Schor, M.D., Ph.D., Deputy Director, NINDS
Steven M. Holland, M.D., Director, Division of Intramural Research NIAID
Avindra Nath, M.D., Clinical Director, Division of Intramural Research NINDS
Matthew J. Fenton, Ph.D. Director, Division of Extramural Activities NIAID
Vicky Whittemore, Ph.D. Program Director NINDS
Joseph J. Breen, Ph.D., Section Chief NIAID

[i] Strazewski, Len. *Dr. Fauci Offers 2021 Forecast on COVID-19 Vaccines, Treatments*, American Medical Association, 9 Nov. 2020, www.ama-assn.org/delivering-care/public-health/dr-fauci-offers-2021-forecast-covid-19-vaccines-treatments.

[ii] Neufeld K.J, et al. Fatigue Symptoms during the first year after ARDS. Chest. (2020) S0012- 3692(20)30686-3. https://journal.chestnet.org/article/S0012-3692(20)30686-3/pdf

[iii] Solve ME/CFS Initiative. (2020, December 4). *Long-Covid-Research-Congressional-Letter-Final.pdf*. Solve M.E. https://solvecfs.org/wp-content/uploads/2020/12/Long-COVID-Research-Congressional-Letter-Final.pdf

[iv] Youn, Soo. *Way more women are reporting 'long-haul' covid symptoms. Doctors aren't sure why.* The Lily, 5 Feb. 2021, https://www.thelily.com/way-more-women-are-reporting-long-haul-covid-symptoms-doctors-arent-sure-why/

[v] Collins, F. (2021, January 19). *Trying to Make Sense of Long COVID Syndrome*. NIH Director's Blog. https://directorsblog.nih.gov/2021/01/19/trying-to-make-sense-of-long-covid-syndrome/

[vi] Davis, Hannah E.; Assaf, Gina S. et al. *Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact*, 27 Dec. 2020, https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2

[vii] Division of AIDS Cross-Network Transgender Working Group. Guidance on the Use of Gender-Inclusive HIV Research Practices: Protocol Design, Data Collection, and Data Reporting, March 2020, https://www.hanc.info/legacy/Documents/Guidance%20on%20the%20Use%20of%20Gender-Inclusive%20HIV%20Research%20Practices%20March%202020.pdf

[viii] "Notice of Intent to Publish Research Opportunity Announcements (OTA-21-015) for the Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative." *Open Funding Opportunities*, National Institutes of Health, Feb. 2021, https://covid19.nih.gov/sites/default/files/2021-02/PASC-Pre-Notice.pdf