February 25, 2021

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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

www.LongCOVIDalliance.org

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)
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Appendix A: Research Initiatives of Importance, Priority, and Quality Compiled by the Long COVID Alliance

You + M.E. Registry Long COVID Study

Sadie Whittaker, PhD. Chief Scientific Officer. Solve ME/CFS Initiative, Los Angeles, CA.

Using the You + ME Registry and Biobank to collect data and biological samples from individuals with and without persistent Long COVID symptoms. We will also compare these data to information from people with myalgic encephalomyelitis (also known as chronic fatigue syndrome or ME/CFS), to characterize similarities and differences between the two groups.

DecodeME: International ME/CFS Biomedical Partnership

Professor Chris Ponting, Chair of Medical Bioinformatics, University of Edinburgh

DecodeME is a Patient-Public-Involvement Co-Production study of 20,000 people with ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) in the UK enlisted via social media and digital marketing. The project will build a phenotype-genotype Bioresource that will facilitate future research studies into ME/CFS globally. It will also undertake a genome-wide association study to identify genetic factors contributing to ME/CFS risk.

You + ME Symptom Tracking App: **Capturing a Moving Picture of Symptoms**

Sadie Whittaker,PhD. Chief Scientific Officer. Solve ME/CFS Initiative, Los Angeles, CA.

To facilitate ongoing, longitudinal, symptom tracking, Solve M.E. created the You + ME Symptom Tracking App. Here, participants are able to track their experience of a set of symptoms core to You + ME, including level of fatigue. Beyond these core symptoms, participants can also add other symptoms to customize their list for tracking.

DecodeLongCOVID: International Long COVID Biomedical Partnership

Professor Chris Ponting, Chair of Medical Bioinformatics, University of Edinburgh & Dr. Mike Morgan, University of Cambridge

Decode Long COVID is a Patient-Public-Involvement Co-Production study of 20,000 Long Covid cases enlisted directly from the UK community via social media and digital marketing. The project is building a phenotype-genotype Bioresource that will enable researchers globally to generate and test biomedical hypotheses. Its vision is to reveal the biomedical causes of Long Covid and to catalyse reproducible and robust biomedical research and assessment tools that improve outcomes for people living with Long Covid.

Global Long Covid Data Coalition: Big Data Dream

Allison Ramiller, MPH. Director of Research Programs. Solve ME/CFS Initiative, Los Angeles, CA.

Solve M.E. seeks to establish partnerships with others who are collecting data on individuals who've had COVID-19, centered around the concept of data harmonization. By agreeing to capture similar information on these individuals, we can later collate our data and amass enough information to see a

clearer picture of the causes of these long-term effects. We are also offering our registry infrastructure and access to our symptom tracking app to anyone who is interested in using it as a mechanism to easily collect longitudinal data.

The pandemic offers an opportunity to understand susceptibility or resilience to these long-term effects, and we may well also shed light on ME/CFS and post-infectious fatigue syndromes following infections other than COVID-19.

Genetics Of Mortality In Critical Care (GenOMICC)

Professor Chris Ponting, Chair of Medical Bioinformatics, University of Edinburgh

GenOMICC is an open, collaborative, global community of doctors and scientists trying to understand and treat critical illness. It recently reported the results of a genome-wide association study in 2,244 critically ill Covid-19 patients from 208 UK intensive care units. It is planning whole genome sequencing of over 1,000 people with Long Covid.

Early blood and brain imaging biomarkers of immune dysregulation associated with Post-COVID-19 ME/CFS

Maheen M. Adamson, PhD, Rehabilitation Service, VA Palo Alto/Neurosurgery, Stanford School of Medicine & Elisabeth A. Wilde, PhD, Neurology & PM&R, University of Utah

This proposal leverages the collaborative power of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) COVID-19 Working Group with added ME/CFS expertise to examine neuroimaging, blood and cognitive biomarkers in participants across four geographically diverse sites at various time-points. The overall hypothesis is that a dysregulation of immunological and inflammatory responses in Long COVID patients with ME/CFS can be predicted by several specific biomarkers, including neuroimaging. These patients may also show greater cognitive and psychosocial (CPS) dysfunction and lower quality of life. Therefore, we propose to identify and evaluate the validated biomarkers of ME/CFS to determine if they can help with early detection of ME/CFS in patients with Long COVID. Further, as COVID-19 has disproportionately impacted underrepresented groups, we will also assess the biomarkers that are associated with development of ME/CFS in women and under-represented minorities.

The development of an instrument to assess post-exertional malaise in patients with myalgic encephalomyelitis and chronic fatigue syndrome

Leonard Jason, PhD. Director of Center for Community Research, DePaul College of Science and Health, Chicago IL.

Post-exertional malaise, or a variation of this term, is a key symptom of myalgic encephalomyelitis and chronic fatigue syndrome, as this symptom is mentioned in almost all myalgic encephalomyelitis and chronic fatigue syndrome case definitions. Until now there has not been a comprehensive questionnaire to assess post-exertional malaise. To rectify this situation, in this article we describe the development of a new questionnaire, called the DePaul Post-Exertional Malaise Questionnaire, which was based on input from hundreds of patients. Preliminary validation was provided by the findings of

significant and predictable relationships between different domains of this post-exertional malaise questionnaire and physical functioning.

In-Depth Analysis of the Plasma Proteome in ME/CFS Exposes Disrupted Ephrin-Eph and Immune System Signaling

Arnaud Germain, PhD. Center for Enervating NeuroImmune Disease, Cornell University, Ithaca, NY

To gain insights into the molecular disruptions in ME/CFS, we utilized an aptamer-based technology that quantified 4790 unique human proteins, allowing us to obtain the largest proteomics dataset yet available for this disease, detecting highly abundant proteins as well as rare proteins over a nine-log dynamic range. We report a pilot study of 20 ME/CFS patients and 20 controls, all females. Our results illustrate the promise of plasma proteomics for diagnosing and deciphering the molecular basis of ME/CFS.

Numeric Rating Scales Show Prolonged Post-exertional Symptoms After Orthostatic Testing of Adults With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

C. Linda van Campen & Peter C Rowe, M.D. Professor of Pediatrics Johns Hopkins Baltimore, MD

Muscle pain, fatigue, and concentration problems are common among individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). These symptoms are commonly increased as part of the phenomenon of postexertional malaise (PEM). An increase in the severity of these symptoms is described following physical or mental exercise in ME/CFS patients. Another important symptom of ME/CFS is orthostatic intolerance, which can be detected by head-up tilt testing (HUT). The effect of HUT on PEM has not been studied extensively. For this purpose, we assessed numeric rating scales (NRS) for pain, fatigue, and concentration pre- and post-HUT. As pain is a core symptom in fibromyalgia (FM), we subgrouped ME/CFS patients by the presence or absence of FM. NRS for pain, fatigue, and concentration were significantly increased up to 7 days after orthostatic stress testing in ME/CFS patients. NRS for pain in patients with FM were all significantly higher than in patients without FM. Our data show that an orthostatic stressor is an important determinant of PEM.

Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning

Bruce K Patterson, M.D. CEO & Founder IncellDx, Inc. San Carlos, CA

Individuals with systemic symptoms long after COVID-19 has cleared represent approximately ~10% of all COVID-19 infected individuals. Here we present a bioinformatics approach to predict and model the phases of COVID so that effective treatment strategies can be devised and monitored. We investigated 144 individuals including normal individuals and patients spanning the COVID-19 disease continuum. We collected plasma and isolated PBMCs from 29 normal individuals, 26 individuals with mild-moderate COVID-19, 25 individuals with severe COVID-19, and 64 individuals with Chronic COVID-19 symptoms. Severe cases are characterized by excessive inflammation and dysregulated T cell activation, recruitment, and counteracting activities. While chronic patients are characterized by a profile able to induce the activation of effector T cells with pro-inflammatory properties and the capacity of generating an effective immune response to eliminate the virus but without the proper recruitment signals to attract activated T cells.

Symptom Cluster Characterization in Complex Chronic Disease

Jaime Seltzer, & Mady Hornig, MA, MD Associate Professor Epidemiology Columbia University Medical Center

Symptom Cluster Characterization in Complex Chronic Disease is a survey-based study to determine symptoms experienced by people with ME, long COVID, POTS, hEDS and MCAS. Symptoms were derived not only from diagnostic criteria but through personalized interviews with people who have each of the diagnoses in question. Our goal is to determine each disease's most distinguishing symptoms and which symptoms are common in early vs late disease in post-infectious disease. This is a year-long project that will lean on our robust relationship with the patient community.

Long COVID, GWI, and ME/CFS Phenotyping Study

Nancy Klimas, MD. Institute for Neuro-Immune Medicine, Nova Southeastern University, Ft Lauderdale, FL.

This project will expand and add collaborators to ongoing phenotyping initiatives funded by the Centers for Disease Control. This study includes home visits for blood draw sampling, and cognitive measures. In addition to direct study analysis, physical samples will be stored into a biorepository for future analysis to facilitate collaboration with other teams and data harmonization.

Integrative Medicine Practices for Long COVID and ME/CFS Utilizing Longitudinal Registry

Irina Rozenfeld, DNP, MSHS, APRN, ANP-BC Assistant Prof., Nova Southeastern University, Ft Lauderdale, FL.

This project will create an integrative medicine set of practices while enrolling patients in a longitudinal registry. This team will evaluate interventions, function, domains, and patient and clinicians perceptions of response. The team would especially like to target restoring antioxidant levels, other algorithmic multiple modalities, and document the effectiveness of integrative approaches that combine neuroinflammation, oxidative stress , and other areas of interventions using the leading post-infectious models in the field.

Bateman Horne Center of Excellence ME/CFS, Fibromyalgia and Long COVID

Lucinda Bateman, MD Medical Director and Suzanne Vernon, PhD Research Director, Salt Lake City, Utah.

Enrolling a subset of up to 100 local long COVID patients in clinic for treatment and care management alongside ongoing clinical work with ME/CFS and FM patients. Data from both groups to be collected and evaluated. Will establish groundwork for future research projects as well as educational offerings and possible publication for the provider community.

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