August 22, 2024

Monica M. Bertagnolli, M.D.
Director
National Institutes of Health
U.S. Department of Health and Human Services
9000 Rockville Pike
Bethesda, MD 20892

Dear Director Bertagnolli:

As basic and clinical researchers with extensive expertise in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), we are writing to express our appreciation for your recent comments on the need to expand the NIH's efforts in studying ME/CFS. We are also providing recommendations on key steps the NIH can take to implement language in the Fiscal Year 2025 (FY25) Labor, Health and Human Services, and Education (Labor-HHS) appropriations report, that directs NIH to incorporate ME/CFS into the RECOVER Initiative.

For the purposes of this letter, we are defining "ME/CFS" as the illness that arose well before the emergence of SARS- CoV-2. As a result of multiple outbreaks of ME/CFS that occurred in the 1980s, along with many sporadic cases since, tens of millions of people worldwide have been ill for decades, with no FDA-approved drug to ameliorate their debilitating condition.

As you recently stated to the NIH Advisory Committee to the Director (ACD), "Another lesson learned from ME/CFS is that we really need to do better for people with these chronic post-infectious syndromes… Now that we have this opportunity, we don't want to waste the opportunity to include them, and make sure that we understand how to solve this for that entire community." Moreover, we were particularly heartened by your recent interview with *The Sick Times*, where you announced that an upcoming September 23–25 conference on the RECOVER Initiative will include consideration of ME/CFS research in future clinical trials. The planned solicitation of new clinical trial proposals and your commitment to involving the ME/CFS community directly in this process are crucial steps forward. We strongly support your efforts to ensure that ME/CFS is fully integrated into the evolving research landscape.

The Senate Labor-HHS appropriations report for FY25 recognizes the impact of Long COVID, notes that it "resembles other post-acute infection syndromes" (PAISs) and directs the NIH to broaden its approach within the RECOVER Initiative to include ME/CFS. This is encouraging for the 3 million Americans with ME/CFS who have suffered for decades. ME/CFS patients have few champions and federal investments have been inadequate. As evidence of this, we note that the NIH centers focused on ME/CFS were recently refunded for a second five-year award of $1.2M each in annual direct costs — the same level of support allocated to these centers in 2017. Inflation since 2017 has been 28%; thus, the NIH has in fact considerably reduced its investment in ME/CFS. Furthermore, as only two centers were funded rather than the three that were funded in the first cycle, the investment is lower still.

We appreciate that the physical and financial toll of Long COVID is daunting. There is no question that research into the pathobiology of Long COVID and the development of strategies to prevent and mitigate this complex disorder are high priority. Some of our colleagues believe that Long COVID research is sufficient to address ME/CFS. We disagree. While there can be similarities in the clinical presentation of Long COVID and ME/CFS, the underlying pathophysiology may not be the same. What we do know is that

the pathogen(s) that induced pre-2020 cases of ME/CFS were not variants of SARS-CoV-2, and that this has implications for the design of intervention trials. An obvious example is that the rationale for trials of CoV antivirals in Long COVID does not apply in ME/CFS. We also want to emphasize that there have been no rigorous studies using the same instruments and assays in both patient groups. The RECOVER Initiative can address these gaps by deliberately including not only healthy control subjects but also ME/CFS cases with onset prior to 2020. Such studies have the potential to reveal similarities and differences that have implications for understanding the pathogenesis of these disorders and to provide insights into strategies for intervention. We also note, that as in oncology, where one size does not fit all, parsing these post-infectious disorders will likely have implications for management.

To realize the vision described in your recent discussion of Long COVID and ME/CFS and the Senate's recommendations we ask that you consider the following:

- **Enhanced Focus on Clinical Trials:** The Senate report points out the necessity for a broader evaluation of treatments across the symptom spectra of Long COVID and ME/CFS. It is imperative that NIH champions this cause by actively supporting and prioritizing the development of clinical trials focused on comprehensive symptom profiles. Trials should be designed to test both existing and novel therapies that show promise in addressing the complex nature of ME/CFS and related conditions. To enhance the impact of existing RECOVER Initiative trials, we recommend including ME/CFS with onset of disease prior to 2020 as a comparison group. This will facilitate direct comparisons between Long COVID and ME/CFS and ensure that therapies developed for one condition are evaluated for their potential benefits in the other.

- **Subject Selection:** We recommend a deliberate expansion in the RECOVER Initiative's research criteria to comprehensively cover the diverse and overlapping symptoms associated with ME/CFS. The 2024 NASEM definition emphasizes the importance of recognizing a broad array of symptoms, including, but not limited to, cognitive impairment, persistent fatigue, post-exertional malaise, autonomic dysfunction, and various forms of pain. Approximately 45% of Long COVID patients meet the case definition for ME/CFS. This overlap underscores the necessity of studying both conditions in tandem. One cannot effectively study Long COVID without also assessing each Long COVID patient for the symptoms that define ME/CFS and using instruments employed in studies of people with ME/CFS.

- **Test Selection:** A literature review of more than 10,000 publications has documented and replicated underlying and similar abnormalities involving the central and autonomic nervous system, the immune system, energy metabolism, endothelial dysfunction, and the gut microbiome in both Long COVID and ME/CFS (1). Unfortunately, two studies from the NIH on laboratory abnormalities in Long COVID (2,3) have included only the standard battery of hematologic and chemistry tests used by clinicians to evaluate patients with common illnesses. Multiple past publications have found these tests uninformative in Long COVID and ME/CFS. Furthermore, the two NIH studies published have included virtually none of the studies that have been shown repeatedly to be abnormal in both people with Long COVID and ME/CFS. In its further studies, we urge NIH to expand the tests used to include those tests that other studies have already proved to be informative.

- **Utilization of Existing Research Networks:** The two NIH ME/CFS centers and other centers with expertise in ME/CFS are eager to assist in this effort. We have worked together in formal and informal collaborations for decades, sharing samples, data, and other resources. Together we have

independently and collaboratively tested the validity of immunologic, metabolomic, proteomic, transcriptomic, and microbiome findings. We have found ourselves in agreement in most instances, including debunking prominent articles in *Science* and *PNAS*, respectively, wherein XMRV and pMLV were implicated in ME/CFS. We are confident that our work has yielded mechanistic insights that may be helpful in identifying targets for intervention. It is essential that the RECOVER Initiative leverage past insights and avoid duplicative efforts. This integration is crucial to accelerate the research timeline and to enhance rigor and reproducibility.

- **Integration of Patient and Expertise-Driven Insights:** To truly align the RECOVER Initiative's research objectives with the needs of those affected, we recommend the establishment of an advisory panel comprising patients, caregivers, and scientific experts with experience in ME/CFS. This panel would serve a critical role in advising on research priorities, study design, and patient engagement strategies, ensuring that the initiative remains responsive to the community it aims to serve.

Thank you for your leadership and dedication to this cause. We look forward to a fruitful collaboration and are excited about the future this initiative promises for patients with Long COVID, the ME/CFS community, and beyond.

Sincerely,

W. Ian Lipkin, M.D.
Columbia University and
Center for Solutions for ME/CFS

Anthony L. Komaroff, M.D.
Harvard Medical School and
Center for Solutions for ME/CFS

Susan Levine, M.D.
Private Practice and
Center for Solutions for ME/CFS

Jose Montoya, M.D.
Palo Alto Medical Foundation

Nancy Klimas, M.D.
Nova Southeastern University and
Institute for Neuro-Immune Medicine

Lucinda Bateman, M.D.
Bateman Horne Center

Derya Unutmaz, M.D.
The Jackson Laboratory

Daniel L. Peterson, M.D.
Sierra Internal Medicine

Maureen Hanson, Ph.D.
Cornell University and
the Center for Enervating Immune Disease

References

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