ME/CFS Research Recommendations for the Long COVID National Research Action Plan

Numerous studies have demonstrated that myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) is one of the significant sequelae of acute COVID-19. Many people with Long COVID have symptoms consistent with ME/CFS and are going on to acquire an ME/CFS diagnosis.[1]

ME/CFS is a debilitating, chronic, complex disease that most often follows an infection and is associated with neurological, autonomic, immunological, and metabolic abnormalities. Patients experience a substantial impairment in functioning as the result of symptoms such as sleep dysfunction, cognitive impairment, orthostatic intolerance, pain, flu-like symptoms, fatigue, sensory sensitivities, and the hallmark symptom, post-exertional malaise (PEM). PEM is an exacerbation of symptoms (and/or appearance of new symptoms) and a further reduction in functioning following even small amounts of previously tolerated physical or cognitive activity.

The National Academy of Medicine estimated in 2015 that 836,000 to 2.5 million Americans of all ages, genders, races and ethnicities have ME/CFS, with a greater prevalence in females, adults and possibly people who are Black or Latinx. There are no validated biomarkers nor FDA-approved treatments, and patients can struggle to access adequate clinical care. Recovery is rare and patients can remain ill for decades, with an estimated 25% homebound or bedbound and 75% unable to work.

ME/CFS has also been reported after infection with SARS, MERS, West Nile Virus, and EBV with rates ranging from 5-27%.

The integration of knowledge gained from ME/CFS and other post-infectious illnesses into the Long COVID research strategy will help expedite progress for people with Long COVID and also improve our understanding of ME/CFS onset, natural history, and pathology. This is a singular opportunity to validate previous post-infectious illness research findings on ME/CFS, and achieve meaningful outcomes (e.g., biomarkers, treatments), for all patients impacted by post-infectious chronic illness.

Research into Long COVID should:

1. accurately characterize ME/CFS as a meaningful, distinct, and replicable Long COVID phenotypic subgroup and elucidate its natural history;

[1] A review of Long COVID and ME/CFS studies reports a significant overlap of symptoms between the two conditions (Wong and Weitzer 2021). Two studies involving cohorts between 40-50 COVID long-haulers have reported roughly 45% satisfying ME/CFS criteria (Kedor et al. 2021, Mancini et. al 2021), while two studies of several hundred Long COVID patients applied a validated PEM scale used in ME/CFS research and found that roughly 60% experienced PEM, the hallmark symptom of ME/CFS (Twomey et. al 2022, Jason et. al 2021). Another study found 74% to 89% of housebound and bedbound COVID long-haulers satisfying the ME/CFS criteria (Jason and Islam 2022).

2. identify associations between ME/CFS phenotypes and observed biological changes in Long COVID research cohorts that could be amenable to therapeutic intervention;
3. enable enrollment of homogenous subgroups of Long COVID-ME/CFS cohorts in clinical treatment trials and clinical studies to demonstrate disability; and
4. ensure Long COVID research findings are generalizable and applicable to future studies of post-infectious ME/CFS patients without a prior SARS-CoV-2 infection

Long COVID represents a natural experiment that is currently underway and cannot be replicated. This calls for swift and decisive action. Early in the disease is not only a critical time for data and biosample collection, it is also the best opportunity to begin interventions that may change and/or prevent long-term outcomes for patients. We recommend ME/CFS be integrated into Long COVID research in the following ways:

1. Standardize how ME/CFS is identified and tracked across all studies to ensure data can be effectively harmonized. To accurately identify ME/CFS cases in Long COVID cohorts, use either the National Academy of Medicine Criteria or the Canadian Consensus Criteria along with the DePaul Symptom Questionnaire, plus other ME/CFS Common Data Elements (CDEs) as needed. It is particularly important to determine the presence of PEM, as this is a key symptom of ME/CFS in all modern definitions and is reported by a significant portion of Long COVID patients. Use of research criteria that require PEM will ensure the best translation to US clinical care, where PEM is required for a diagnosis. Older sets of criteria that do not require PEM (such as Fukuda) should not be used to identify ME/CFS patients, as they capture a very different cohort.

    a. Use the standardized definition of PEM and assessment method recommended by the NIH ME/CFS CDE Initiative for all studies assessing ME/CFS.

    b. Prioritize research designs that incorporate PEM assessment by collecting biosamples and physiological and subjective symptom measurements before, during, and up to 24-48 hours after a provocation requiring minor mental or physical exertion.

2. Include patients with ME/CFS and other post-viral illnesses as comparator groups in Long COVID studies. Include ME/CFS patients with both short- and long-duration illness and no evidence of SARS-CoV-2 infection.[2]

3. Include in the Long COVID research strategy those areas of ME/CFS research that are proving fruitful, including metabolic abnormalities; mitochondrial dysfunction; redox imbalance; systemic immune dysfunction; viral reactivation and potential pathogen

[2] Other comparator groups could also include: 1) People with two other common infectious illnesses that can lead to post-infectious fatigue syndromes—acute infectious mononucleosis and acute Lyme disease – who are without evidence of past SARS-CoV-2 infection; 2) 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.

persistence; autoimmunity; neuroinflammation; neuropathies including small fiber neuropathy; autonomic nervous system dysfunction; vascular dysfunction including endothelial dysfunction and hypoperfusion in the brain; ion channelopathies; gut microbiota abnormalities; and hypothalamic-pituitary-adrenal axis abnormalities.

4. Leverage ME/CFS clinical learnings and pathophysiological findings to accelerate selected clinical treatment trials for Long COVID. Such trials can be designed to advance understanding of disease mechanisms (e.g., neuroinflammation, viral reactivation) using drugs with known pharmacological mechanisms that target such pathophysiology, in parallel with establishing evidence for treatments that reduce patients' symptom burden (e.g., orthostatic intolerance, sleep, cognitive function, pain) and improve their function and quality of life using existing FDA-approved interventions.

5. Assess patients for the emergence of ME/CFS and other post-infectious illnesses/conditions [e.g., dysautonomia including postural orthostatic tachycardia syndrome, mast cell activation syndrome] at multiple time points (from time of infection through 2 years post-infection) in Long COVID prospective longitudinal studies. Follow those who develop ME/CFS and other Long COVID-associated conditions for an extended duration beyond 2 years to elucidate the natural history of ME/CFS and other post-infectious illnesses.

6. Undertake large-scale whole genome sequencing/genome-wide association studies to identify predisposing and symptom-associated risk variants that may indicate causal pathways, with cluster analysis for major subgroup identification, including ME/CFS cases.

7. Evaluate available tools and make recommendations for new tools to assess the functional impairment seen in ME/CFS. Tools being used in ME/CFS research today include cardio-pulmonary exercise tests, the 10-minute NASA lean test, tests for cerebral hypoperfusion, activity meters, and neuropsychological testing for assessment of cognitive function. Tools from other fields may be useful. People with ME/CFS have struggled immensely to access social services, disability benefits, school and work accommodations, and other needed services, and they are often met with denial due to lack of objective measures of functional impairment. Clinical studies to demonstrate disability and functional impairment are an urgent need that should be addressed in parallel with other initiatives outlined here.

8. Create a formal ME/CFS advisory group to provide input on all federal Long COVID initiatives and strategic plans, including NIH's RECOVER and CDC's INSPIRE studies, as well as other federally-funded Long COVID studies. This group would consist of representatives of federal agencies; federal, commercial, and private funders; and ME/CFS stakeholders including researchers, clinicians, patients, caregivers, and patient advocacy organizations. It would provide input on ways to integrate what has been learned from ME/CFS research into the strategy for studying Long COVID, and vice versa.

9. Develop surveillance and epidemiological studies on Long COVID-ME/CFS and other common Long COVID phenotypes in adults and children. Identify symptoms, prevalence, incidence, risk factors, impact of vaccination status and reinfection, natural history, and other epidemiological factors of disease, disaggregated by demographic characteristics, such as race, ethnicity, age, sex, gender, and socioeconomic status.

10. Improve understanding of the health and socioeconomic burdens on people with Long COVID-ME/CFS phenotypes through collection of comprehensive data on how many people have reduced working capacity, are no longer working or going to school, have applied for disability, and/or have lost or reduced health insurance, because of Long COVID-ME/CFS and other debilitating post-acute COVID chronic conditions. Valid and reliable estimates on annual income loss, medical costs, national economic burden, and disease burden, disaggregated by race, ethnicity, and socioeconomic group must be pursued.

This above information and recommendations are based upon:

- ME/CFS Research Priorities *(Community Advisory Committee for the NIH ME/CFS Collaborative Research Centers)*
- Joint letter to NIH on ME/CFS and Research on Long COVID *(#MEAction, Open Medicine Foundation, Solve M.E.)*
- Letter to NIH on Identifying and tracking ME/CFS cases in Long COVID Research (#MEAction)