Towards a Patient-Driven National Research Action Plan: Recommendations for the National Research Action Plan on Long COVID

This document lists high-level recommendations for research priorities, design, and oversight to be included in the National Research Action Plan for Long COVID. These recommendations were compiled by members of the Long COVID and associated conditions patient community and have been endorsed by Patient-Led Research Collaborative, Strategies for High Impact, #MEAction, and Marked by COVID. The list is not exhaustive but is intended to give a broad overview of some of the key issues that are of importance to the community but may not have been explicitly discussed in listening sessions. For questions or more information on any of these recommendations, please contact the corresponding author, Lisa McCorkell, at lisa@patientledresearch.com.

Research Priorities

Biomedical

- Accelerate research that has been prioritized by the patient community and by post-viral illness experts (see Appendix for example research questions), including as part of the RECOVER Initiative.
- Integrate into Long COVID research the study of associated post-infectious illnesses/conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), dysautonomia including postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS), which will help expedite progress for people with Long COVID. Specific steps to ensure ME/CFS is appropriately and effectively included in Long COVID research include standardizing how post-COVID ME/CFS onset is identified and tracked and including patients with ME/CFS and other post-viral illnesses (not triggered by COVID-19) as comparator groups. For a complete list of ways to integrate ME/CFS into the National Research Action Plan see these additional research recommendations.
- Accelerate research into Long COVID in children, accounting for the difficulties in ensuring a proper control group due to children being less likely to have positive PCR and antibody tests compared to adults.
- Accelerate one-year clinical trials for treatments that have shown promise in the Long COVID and associated conditions patient community (e.g., anticoagulation, BC007, Low Dose Naltrexone, Ampligen, Low Dose Abilify).
- Require future trials of COVID vaccinations and acute COVID treatments to consider impacts on Long COVID.
- Accelerate research into those experiencing Long COVID-like symptoms post-vaccination.

- Identify the imaging or diagnostic tools that are sensitive enough to capture persisting neurological symptoms and abnormalities, particularly in patients with normal MRIs and X-rays.
- Work with the pharmaceutical industry to identify and address barriers to rapid development and testing of novel Long COVID therapeutics (e.g., lack of validated endpoints).

Policy and Communication

- Conduct a needs assessment for people with Long COVID identifying needs for care, treatment, and support, particularly those in the key populations and settings identified by the Presidential COVID-19 Health Equity Task Force**.**
- Evaluate the role of structural enablers/barriers to Long COVID treatment, care, and support, particularly in marginalized communities.
- Conduct communication science research to develop a well-informed approach to health communications and public education on Long COVID across different cultural and linguistic communities.
- Collect comprehensive data on how many people have reduced working capacity and/or are no longer working because of Long COVID by incorporating new questions into Bureau of Labor Statistics and Census Bureau surveys.
- Track the number of SSI and SSDI applications, approvals, and denials for Long COVID and associated conditions.

Prevalence

- Launch multi-year surveillance and epidemiological studies on Long COVID, results of which are posted regularly on a publicly accessible dashboard, that studies:
    - Disparities of prevalence of Long COVID, disaggregated by demographic characteristics, such as race, ethnicity, age, sex, gender, and socioeconomic status (validating and expanding on Household Pulse Survey data)
    - The probability of Long COVID onset after:
        - reinfections if one did not develop Long COVID from their first infection
        - infection with different SARS-CoV-2 variants
        - vaccination

Research Design

- Ensure all federally-funded Long COVID studies meet best practices for Long COVID study design:
    - Definition of Long COVID for purposes of study design should align with the World Health Organization's definition, which includes suspected cases. Positive PCR, antigen, or antibody tests should not be required due to inherent biases these tests introduce.
    - Symptoms tracked should be as comprehensive as possible, as patient research has documented over 200 symptoms of Long COVID. Included among these should be the inclusion of post-exertional malaise (PEM) - a cardinal symptom of ME/CFS, cognitive symptoms, and menstrual symptoms.

    - Due to the high prevalence of PEM in people who have Long COVID, each study should use the standardized definition of PEM and assessment method recommended by the NIH ME/CFS Common Data Elements (CDE) Initiative.
        - 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.
    - Require meaningful patient engagement in studies, which includes ensuring patients have decision-making power in every step of the research process (from ROA to publication, and as part of executive and steering committees), compensating patients for their engagement, and ensuring patient representatives are accountable to their community. In addition to requiring this of forthcoming studies, ongoing studies like RECOVER and INSPIRE should improve their patient engagement practices by adhering to these standards.
    - Require post-viral illness researchers to be consulted and/or be part of executive and steering committees of forthcoming and ongoing research studies.
    - Ensure careful interpretation of Electronic Health Records (EHR) analyses, as EHR data are heavily biased towards:
        - Certain types of patients:
            - More severe / hospitalized patients
            - Patients with respiratory / non-neurological symptoms
            - Patients who have positive PCR and/or antibody tests
            - Patients who have healthcare access
        - Certain diagnoses:
            - POTS and fatiguing illnesses are often initially misdiagnosed as anxiety and/or depression
- Ensure all federally-funded Long COVID studies meet recommended demographic targets for recruitment [for race/ethnicity, age, gender (including transgender and non-binary people), sex, multiple co-morbidities, disability, etc.], which may require oversampling certain populations, compensating BIPOC and LGBTQ+ patients, and conducting outreach through community health workers and organizations.
- Require the RECOVER Initiative to accept the RECOVER Study Design Committee's recommendation to increase enrollment of participants with Long COVID, as opposed to its current focus on recruiting people with acute COVID. The recommendation would not compromise incidence/prevalence estimates and would assist in a better study of the pathophysiology of Long COVID.

Research Oversight

- Establish an Office of Complex Chronic Conditions Research (OCCCR) in the NIH Director's Office, modeled on the Office of AIDS Research. The office should be authorized to:
    - Establish research priorities for Long COVID and all complex chronic conditions (e.g., ME/CFS, fibromyalgia, chronic / post-treatment Lyme disease, MCAS, Ehlers-Danlos syndrome, dysautonomia), working across the

NIH and with the scientific and affected communities to establish scientific research priorities for the global fight against these conditions.
    - Develop the strategic plan for research on Long COVID and other complex chronic conditions, identifying research priorities for NIH-funded intramural and extramural research.
    - Ensure funds are invested in areas of highest scientific priority in the NIH-wide research portfolio, based on the strategic plan, identifying opportunities, and addressing gaps to guide the research agenda.
    - Address emerging needs by convening stakeholders, encouraging collaboration, and catalyzing innovation to address emerging scientific and public health challenges in complex chronic conditions.
    - Oversee, coordinate, and manage all NIH research related to complex chronic conditions, including the scientific, budgetary, legislative, and policy components of NIH research.
    - Charter the Office of Complex Chronic Condition Research Advisory Council (OCCCRAC) as a Federal Advisory Committee to advise the OCCCR Director on the planning, coordination, and evaluation of research and other activities conducted or supported by the NIH. The OCCCRAC, which must include representatives who are living with complex chronic conditions, should advise the Secretary of Health and Human Services, the Assistant Secretary for Health, the Director of NIH, and the Director of OCCCR on all relevant research programs and the development and annual review of the comprehensive strategic plan.
    - Hire people exclusively dedicated to fulfill the mission of the OCCCR
- Ensure that forthcoming ARPA-H prioritizes projects on Long COVID and associated conditions including repurposing already approved drugs for applications in associated conditions such as ME/CFS and POTS, etc.

APPENDIX

Key Research Questions:

- Is there SARS-CoV-2 viral persistence (including RNA, protein fragments, or full virus particles still able to replicate) in places like the gut, other tissue, or elsewhere?
- What is the role of the SARS-CoV-2 spike protein after infection or vaccination?
- What is the role of reactivation of other viruses (e.g., EBV, HHV-6, HHV-7) in Long COVID? Do reactivations impact mitochondrial fragmentation and poor antiviral defense as they do in ME/CFS?
- What are the mechanisms underlying post-exertional malaise?
- What are the mechanisms underlying relapses?
- What is the overlap between collagen/connective tissue/possible EDS? What is the role of connective tissue degeneration? What is the role of fibroblast dysfunction?
- What is the role of spinal degeneration and/or ossification? What is the role of the cervical spine?
- How do subsequent infections or viruses affect Long COVID & ME/CFS? What is the impact of multiple reinfections on Long COVID? Does ME/CFS develop only after a certain number of assaults to the immune system and/or nervous system? How does having ME/CFS or an autoimmune disorder prior to getting COVID alter risk for developing Long COVID?
- What is the role of craniocervical obstructions?
- What is the role of dysfunctional cribriform/glymphatic drainage?
- What is the role of mitochondrial fragmentation or other forms of mitochondrial dysfunction? What is the role of metabolic abnormalities and redox imbalance?
- What is the impact of sex/gonadal hormones on Long COVID development, symptoms, and relapses?
- How is Long COVID affecting people who menstruate and their menstrual cycles?
- What is the role of hypothalamic-pituitary-adrenal (HPA) axis dysfunction?
- Are those with Long COVID more likely to serorevert, serorevert earlier, or never seroconvert?
- How is the immune response in Long COVID patients different among those who had asymptomatic vs. mild vs. moderate acute COVID and were not hospitalized early on, and those who had severe acute COVID and were hospitalized early on?
- What does the course of Long COVID look like over the first five years? What changes - including cytokine profiles, lipid profiles, and reactivations - are seen?
- What components of the immune system (innate, adaptive) are dysfunctional prior to COVID and/or during acute COVID or become dysfunctional post-acute COVID that make one more susceptible to developing Long COVID?
- What components of the nervous system are dysfunctional prior to COVID and/or during acute COVID or become dysfunctional post-acute COVID that make one more susceptible to developing Long COVID?
- What is the role of autoimmunity and neuroinflammation? What changes in brain chemistry, circuitry, and structure are occurring?

- What is the role of neuropathies, including small fiber neuropathy? What is the role of autonomic nervous system dysfunction, sensory nervous system dysfunction, motor nervous system dysfunction, and altered proprioception?
- What is the role of vascular dysfunction, including endothelial dysfunction, and hypoperfusion in the brain? What is the role of platelet dysfunction and microclots? What is the role of red blood cell dysfunction and deformation?
- What is the role of gut microbiota abnormalities (dysbiosis), leaky gut, and dysfunctional gut-immune-brain axis?
- What is the role of low levels of vitamins and minerals, like vitamins B and D?

For more research priorities, please see Long COVID Citizen Scientists: Developing a Needs-Based Research Agenda by Persons Affected by Long COVID and ME/CFS Research Priorities.