Gaps and Opportunities to Inform Long COVID Research

The following list highlights the current and emerging research opportunities, gaps, and challenges in Long COVID research. This list was informed in part by the discussions from the recent "RECOVER Notice of Special Interest/Research Opportunity Announcement (NOSI/ROA) Awardee and Pathobiology Committee Virtual 2-Day Retreat" (May 2025) and the "2025 International Long COVID Pathogenesis Workshop" (May 2025). It will be updated periodically to reflect changes based on ongoing research progress. Areas highlighted below are meant not to limit research ideas, but to emphasize current research opportunities. The National Institutes of Health (NIH) encourages compelling research proposals that aim to accelerate and improve prevention, treatment, and management of Long COVID and will consider all innovative research ideas.

Emerging Research Opportunities, Gaps, and Challenges:

- Comparative studies of Long COVID with other postviral and postinfectious syndromes.
- Studies of vascular injury, thrombosis, and other related potential mechanisms of Long COVID across variants (e.g., complement pathway dysfunction).
- Advanced imaging analysis (e.g., artificial intelligence/machine learning [AI/ML]), to define the long-term impact of COVID on organ structure and function and to characterize Long COVID phenotypes.
- Linking of autopsy findings with pathobiological mechanisms of Long COVID to guide targeted interventions.
- Effects of reinfection, emerging variants, or both on the risk for Long COVID.
- Intersectionality of (1) social determinants of health; (2) built environments, including but not limited to studying aspects of how urban areas impact health such as access to green spaces, parks, and distances from public transportation; (3) preexisting conditions prior to acute infection; and (4) the risk for development or severity of Long COVID.
- Remaining gaps in tissue-specific manifestations of Long COVID, including molecular mechanisms such as dysregulation or disruption of normal physiologic pathways (reduction in serotonin; mitochondrial or bioenergetic cellular functions), correlating abnormal magnetic resonance imaging (MRI) findings in the brain, heart, and lung to pathologic mechanisms associated with symptomology in Long COVID (shortness of breath, cognitive dysfunction, etc.).
- Studies that propose to validate existing published studies on potential mechanisms of Long COVID, within the framework of the data and biospecimens collected from participants during RECOVER observational studies.
- Advancing the development and validation of bioassays, which are critically needed to inform future clinical studies.
- What are the causes of Long COVID?
- How can we better understand the baseline phenotypes of Long COVID?
- How can we differentiate between causation and association in Long COVID?
- What pathophysiological changes are specific to Long COVID?
- How do viruses persist in Long COVID patients, and what are reliable markers for viral persistence?

- What are the determinants of Long COVID in those with viral persistence, given that some people with viral persistence do not develop Long COVID?
- How can investigations of tissue immunity (e.g., mucosal sites, endothelial tissues, sites in brain, other specific organs, etc.) inform immune dysfunction stages?
- How do repeated infections affect host response, disease manifestations, and pathology?
- Do repeated SARS-CoV-2 exposures or vaccinations reduce Long COVID risk?
- What are the risk factors for Long COVID?
- What confounding factors, like allergies, inflammation, and other infections, affect Long COVID progression?
- How can we biologically link heterogeneous pathophysiological mechanisms?
- How can we assess the long-term trajectories of Long COVID—including biomarker specificity and sensitivity—and disease progression? What causes coagulation and endothelial cell activation in Long COVID patients?
- How does viral-mediated senescence lead to Long COVID in the elderly?
- How can we distinguish irreversible injury from ongoing processes in Long COVID?
- What are the critical factors that drive Long COVID outcomes in patients who transition from uninfected to infected states or who experience reinfections?
- How can we address the phenotypic heterogeneity of Long COVID?
- How can we leverage the positive impacts of collaboration and coordination among individual complementary research studies and System Biology studies to enhance our understanding of Long COVID? Options might include sharing biospecimens, data, and technologies; integrating and harmonizing data; cross-validating findings and measuring additional parameters and sample sets; using appropriate controls and standardizing assays; improving sensitivity of assay and quality of biospecimens and data; adding longitudinal assessments (e.g., for long-term follow-up studies); or collecting additional tissue samples.
- How can we revisit and validate data generated outside of RECOVER that might inform pathobiology studies?
- How does Long COVID affect susceptibility to other chronic conditions like Alzheimer's disease and diabetes mellitus?
- Are there different mechanisms for Long COVID in children compared to adults?
- How does Long COVID in pregnant women affect newborn health and development?
- How can findings be used to recommend new therapeutic targets or repurpose existing drugs for RECOVER-Treating Long COVID (RECOVER-TLC)? How can samples collected during RECOVER-TLC clinical trials be used to analyze drug efficacy?
- How can a consensus animal model or alternative models of Long COVID be established (as appropriate) for testing drugs or combination therapies?
- How can AI/ML models and analytical tools be developed for patient stratification, diagnosis, prognosis, and treatment selection?