

Gaps and Opportunities to Inform Long COVID Research

Given the variability in the maturity of the evidence, the NIH encourages research proposals with innovative research ideas that address the following priority focus areas. NIH will consider a stratified selection of proposed studies across these ten (10) topics to define the scope of research.

Research topics that will generate substantial evidence and findings with translational readiness, including:

1. Rigorous definition of phenotypes and endotypes linked to objective measures and/or prognostic measures.
 - Phenotype and endotype definitions linked to objective measures and longitudinal trajectories, including baseline phenotypes of Long COVID.
 - Integration of imaging, cellular, molecular, immunologic, metabolic, physiological, and clinical profiles, along with functional testing, to define clinically meaningful Long COVID subtypes.
 - Studies defining neurocognitive, cardiovascular, pulmonary, and other common disease phenotypes and trajectories using objective testing and imaging.
 - Longitudinal studies to understand presentation, progression, developmental impacts, and recovery patterns of pediatric Long COVID
2. Reproducible validation of biomarkers across clinical subtypes.
 - Development and validation of robust quantitative physiologic measurements, biomarkers, and objective severity metrics for Long COVID.
 - Validation-focused biomarker studies using human observational and longitudinal as well as clinical trial study cohorts rather than discovery-only approaches that only utilize a single cohort.
 - Identification of biomarkers and prognostic predictors for onset, recovery, disease severity, and long-term progression.
3. Mechanistic studies driven by biospecimen and tissue-based evidence.
 - Studies leveraging autopsy biospecimens and patient-derived samples as well as organ functional tests to link tissue injury with pathogenesis and therapeutic targets.
 - Research distinguishing irreversible organ injury from ongoing active processes, including mechanisms underlying spontaneous recovery.
 - Studies identifying and validating therapeutic targets directly anchored to human mechanistic evidence.
4. Focused studies of vascular, endothelial, and coagulation mechanistic pathways, leveraging defined phenotypes.
 - Investigations of tissue immunity, endothelial dysfunction, vascular injury, thrombosis, coagulation abnormalities, and complement activation tied to specific phenotypes.

Research topics that seek to improve understanding and clarity of evidence related to relevant topics, including:

5. Focused studies to strengthen the evidence for viral persistence and improve understanding of its impact.

- Evidence, effects, mechanisms and biomarkers of viral persistence.
 - Studies evaluating interindividual differences in viral persistence, immune dysfunction, senescence, and recovery.
 - Effects of SARS-CoV-2 variants, reinfections, vaccination, and viral reactivation on Long COVID risk, severity, and outcome.
 - Studies of dysbiosis, extracellular vesicles, and tissue-specific immune responses in Long COVID.
6. Definition of endotypic variation in organ-specific dysfunction, emphasizing cardiovascular, pulmonary, neurocognitive, gastrointestinal, and other clinically important sequelae.
 - Organ-specific dysfunction including lung fibrosis, autonomic dysfunction, mitochondrial dysfunction, and persistent cardiopulmonary abnormalities.
 7. Cross-cutting studies that embed and address risk and protective factors.
 - Pediatric-adult differences, sex differences, population-level differences, prior health status, comorbidities in Long COVID pathogenesis, progression, and recovery trajectories.

Research topics aiming to clarify and link mechanistic studies with clinically relevant phenotypes, including:

8. Establishing linkages between model-based system studies and clinically relevant phenotypes.
 - Use of cellular, organoid, and animal models to investigate targets and pathways identified from human studies and evaluate candidate therapeutics.
 - Development of precision medicine frameworks for individualized Long COVID stratification and therapeutic selection.
 - Studies seeking to understand treatment-response heterogeneity observed in Long COVID clinical trials.
9. Applications of predefined causal models and rigorous control selection to specify factors of progression.
 - Broad mechanistic studies of inflammation, allergies, co-infections, autoimmunity, and senescence affecting Long COVID progression.
10. Demonstrating testable mechanistic models to better understand the impact of Long COVID on quality of life and the risk of developing other chronic conditions.
 - Research assessing susceptibility to later chronic conditions such as neurodegeneration, diabetes, asthma exacerbation, and stroke.
 - Studies examining inter-organ communication mechanisms in persistent disease.
 - Research assessing the persistence or reoccurrence of Long COVID clinical syndromes.