Gaps and Opportunities to Inform Long COVID Research

Given the variability in the maturity of the evidence, RECOVER encourages research proposals with innovative approaches that address the following priority focus areas. These priorities are intended to support studies that generate substantial evidence, strengthen mechanistic understanding, advance translational readiness, and leverage existing RECOVER data, biospecimens, systems biology findings, and collaborative research infrastructure.

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

Rigorous definition of phenotypes and endotypes linked to objective measures and prognostic indicators

- Studies defining Long COVID phenotypes and endotypes using objective clinical, physiologic, imaging, cellular, molecular, immunologic, metabolic, and functional measures.
- Studies linking phenotype and endotype definitions to longitudinal trajectories, including onset, persistence, progression, recovery, recurrence, and response to treatment.
- Integration of imaging, cellular, molecular, immunologic, metabolic, physiologic, clinical, and systems biology data to define clinically meaningful Long COVID subtypes.
- Studies defining neurocognitive, cardiovascular, pulmonary, autonomic, gastrointestinal, and other common Long COVID phenotypes using objective testing and imaging.
- Studies examining pediatric and adult differences in disease presentation, progression, developmental effects, recovery, and long-term outcomes.

Reproducible validation of biomarkers and objective severity measures

- Development and validation of robust quantitative physiologic measures, biomarkers, and objective severity metrics for Long COVID.
- Validation-focused studies using multiple human observational, longitudinal, and clinical trial cohorts rather than discovery-only studies based on a single cohort.
- Identification and validation of biomarkers and prognostic predictors for disease onset, recovery, severity, progression, recurrence, and treatment response.
- Studies assessing the reproducibility, external validity, and clinical utility of candidate biomarkers across populations, clinical subtypes, and disease trajectories.
- Studies developing biomarkers suitable for use in clinical trials, including pharmacodynamic, prognostic, predictive, and patient-selection biomarkers.

Mechanistic studies driven by human biospecimen and tissue-based evidence

- Studies using autopsy biospecimens, patient-derived samples, vascular tissues, organ-specific specimens, and functional organ assays to link tissue injury with disease pathogenesis and therapeutic targets.

- Studies distinguishing irreversible organ injury from ongoing active processes and identifying mechanisms underlying spontaneous recovery.
- Studies identifying and validating therapeutic targets directly anchored to human mechanistic evidence.
- Focused studies of vascular, endothelial, coagulation, complement, and thrombotic pathways using well-defined clinical phenotypes.
- Investigations of tissue immunity, endothelial dysfunction, vascular injury, thrombosis, coagulation abnormalities, and complement activation tied to specific Long COVID phenotypes.

Systems Biology and multi-omics studies

- Studies that extend, validate, and integrate RECOVER Systems Biology findings with clinical phenotypes, longitudinal trajectories, imaging, physiologic measures, cellular phenotyping, functional testing, and organ-specific outcomes.
- Studies validating candidate molecular and cellular pathways identified through RECOVER Systems Biology analyses.
- Studies testing Systems Biology findings across additional clinical phenotypes, disease subtypes, organ systems, demographic groups, and longitudinal time points.
- Studies integrating proteomic, metabolomic, genomic, transcriptomic, epigenetic, immunologic, metagenomic, cellular, clinical, and longitudinal data to identify mechanisms driving Long COVID.
- Studies extending Systems Biology analyses to additional biospecimens, including stool, respiratory specimens, saliva, urine, cerebrospinal fluid, tissue, and other specimens not fully represented in existing analyses, when supported by strong scientific rationale and demonstrated feasibility.
- Studies addressing cross-platform integration, assay reproducibility, batch effects, quality control, and harmonization across laboratories.
- Studies that use standardized or harmonized sample processing, sequencing, assay, analytic, and quality-control approaches to facilitate comparison with existing RECOVER Systems Biology datasets.
- Studies developing shared reference datasets, analytic tools, standardized protocols, and other community resources that can support multiple RECOVER investigations.
- Studies that preserve limited RECOVER biospecimens and minimize unnecessary depletion, duplication, or competing use of overlapping sample sets.

Mechanistic studies of viral persistence and immune dysregulation

- Studies examining the evidence, effects, mechanisms, and biomarkers of SARS-CoV-2 viral persistence.
- Studies evaluating interindividual differences in viral persistence, immune dysfunction, senescence, autoimmunity, inflammation, and recovery.
- Studies examining the effects of SARS-CoV-2 variants, reinfections, vaccination, and viral reactivation on Long COVID risk, severity, persistence, and outcomes.

- Studies evaluating the role of dysbiosis, extracellular vesicles, tissue-specific immune responses, and altered host–microbe interactions in Long COVID.
- Studies investigating broad mechanistic pathways involving inflammation, allergies, co-infections, autoimmunity, senescence, metabolic dysfunction, and mitochondrial dysfunction.

Organ-specific dysfunction and inter-organ communication

- Studies defining endotypic variation in organ-specific dysfunction, with emphasis on cardiovascular, pulmonary, neurocognitive, gastrointestinal, autonomic, and other clinically important sequelae.
- Studies examining lung fibrosis, autonomic dysfunction, mitochondrial dysfunction, persistent cardiopulmonary abnormalities, and other organ-specific processes.
- Studies examining mechanisms of inter-organ communication in persistent disease.
- Studies assessing the persistence, recurrence, and re-emergence of Long COVID clinical syndromes.
- Studies evaluating susceptibility to later chronic conditions, including neurodegeneration, diabetes, asthma exacerbation, stroke, and other chronic diseases.

Mechanistic clinical trial readiness and therapeutic development

- Studies identifying and validating therapeutic targets for future mechanistic clinical trials.
- Studies developing biologically defined phenotypes and endotypes to support trial enrollment, stratification, and interpretation.
- Studies developing and validating assays, outcome measures, and biomarkers suitable for clinical trial use.
- Studies seeking to understand treatment-response heterogeneity observed in Long COVID clinical trials.
- Studies integrating molecular, cellular, physiologic, and clinical findings to inform therapeutic selection and precision medicine approaches.
- Studies using cellular, organoid, animal, and other appropriate models to investigate targets and pathways identified through human studies and evaluate candidate therapeutics.
- Studies using in vitro assays, organoid cultures, organs-on-a-chip systems, siRNA, CRISPR-Cas9 approaches, and genetically modified animal models when appropriate and supported by human evidence.

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

Cross-cutting risk and protective factors

- Studies examining pediatric and adult differences, sex differences, population-level differences, prior health status, comorbidities, vaccination, reinfection, viral variant history, and other factors influencing Long COVID pathogenesis, progression, and recovery.

- Studies identifying risk and protective factors associated with disease onset, persistence, severity, recovery, recurrence, and treatment response.
- Studies examining disparities in Long COVID diagnosis, access to care, disease burden, research participation, and outcomes.
- Studies evaluating how social, environmental, behavioral, and health-system factors influence Long COVID trajectories and quality of life.

Clinically relevant phenotypes and trajectories

- Studies linking mechanistic findings to clinically meaningful symptoms, functional limitations, quality of life, and objective outcomes.
- Studies establishing longitudinal trajectories of disease presentation, progression, recovery, and recurrence.
- Studies using rigorous control groups and predefined causal models to identify factors associated with disease progression and recovery.
- Studies examining the relationship between Long COVID and the development or worsening of other chronic conditions.

Integration with RECOVER data and resources

- Studies that confirm, validate, and extend RECOVER Systems Biology findings using additional RECOVER data, biospecimens, clinical measures, imaging, physiologic testing, and longitudinal outcomes.
- Collaborative studies integrating Systems Biology findings with clinical phenotypes, organ-specific outcomes, functional testing, and disease trajectories to identify risk factors and support disease staging and prognosis.
- Studies that coordinate across RECOVER scientific programs to reduce redundancy, increase comparability, and promote integration across scientific domains and clinical manifestations.
- Studies that develop shared analytic approaches, harmonized datasets, and collaborative resources for use by the broader RECOVER research community.
- Studies that clearly define how their proposed work complements existing RECOVER activities and adds value beyond ongoing projects.

Research topics that leverage model-based and systems approaches, including:

- Studies establishing linkages between computational, cellular, organoid, animal, and other model-based systems and clinically relevant Long COVID phenotypes.
- Studies using mechanistic models to identify causal pathways, therapeutic targets, and prognostic indicators.
- Studies integrating multi-omics, clinical, imaging, physiologic, and longitudinal data to identify mechanisms driving persistent disease.
- Studies using predefined causal models and rigorous control selection to specify factors associated with disease onset, progression, recovery, and treatment response.
- Studies developing precision medicine frameworks for individualized Long COVID stratification and therapeutic selection.

- Studies demonstrating testable mechanistic models that explain the impact of Long COVID on quality of life and the risk of developing other chronic conditions.

Research topics supporting coordinated community resources, including:

- Comprehensive and reproducible profiling of defined RECOVER biospecimen collections using consistent methods.
- Coordinated metagenomic, multi-omic, cellular, molecular, and functional analyses that generate broadly useful community resources.
- Studies that use common protocols, assay methods, quality-control procedures, and analytic pipelines when necessary to support comparison across samples and projects.
- Studies that address the preservation and efficient use of limited biospecimens, including appropriate prioritization of overlapping or competing sample requests.
- Studies that create datasets, protocols, analytic tools, reference materials, or other resources that can support multiple RECOVER investigations.
- Studies that establish clear processes for documenting, depositing, and returning generated data and analytic outputs to RECOVER for broader scientific use.

Coordination, harmonization, and data sharing

Applicants should describe how the proposed work will be coordinated with relevant RECOVER programs, including Pathobiology, Systems Biology, Observational, TLC, and other appropriate scientific committees or working groups.

Applications should address:

- Potential overlap with existing RECOVER projects and approaches for reducing redundancy.
- Coordination of sample selection, assay methods, analytic plans, milestones, and deliverables across related projects.
- Compatibility with RECOVER data standards, biospecimen access procedures, quality-control expectations, and governance requirements.
- Plans for appropriate data, metadata, protocols, analytic code, and results sharing with RECOVER.
- Submission of resulting data and relevant project outputs to the RECOVER Data Gateway or another RECOVER-designated repository.
- Return of validation results and other findings to RECOVER at the completion of the project.
- Protection of participant privacy and compliance with applicable consent, IRB, data-use, and biospecimen-use requirements.

Projects may be coordinated as a portfolio when multiple applications address related scientific questions. In such cases, investigators may be asked to harmonize methods, sample selection, quality-control procedures, data structures, and reporting requirements to maximize scientific value and comparability.