

Systems Biology Committee TOPMed Multiomics Proposal Synopsis

Overall Specific Aim: To characterize the molecular underpinnings of PASC and its subtypes via multi-omic data generation in 12,000 individuals at two timepoints across the RECOVER cohort that: **1) identify the mechanisms of disease development and progression**; **2) discover and characterize molecular disease subtypes**; **3) enable accurate prediction of the disease course**; and **4) lead to novel diagnostic and/or prognostic biomarkers and potential therapeutic interventions** to improve the clinical course of PASC.

Study Design (Adult Cohort): We propose a 1:1 case-cohort design including 4,500 cases and controls, totaling ~9,000 participants with multi-omic generation.

Study Design (Pediatric Cohort): We propose including all available pediatric post-acute Tier 2 (6-month visit) biospecimens (~3,000 individuals), as well as all follow up (12-month) biospecimens that are available in ~50% of these individuals.

Tier Options – The multi-omics proposal lists 3 potential tiers of funding, with each tier incorporating the same omics and sample size but variations in longitudinal assessments. High level details for each tier are described below and in Table 1. Additional considerations include whole genome sequencing data for research among all consented individuals in the observational cohorts.

- The **Gold Tier option** proposes the following omics profiling in 12,000 participants across the RECOVER cohorts: WGS and DNAm at one timepoint; RNAseq, proteomics, and metabolomics at two timepoints - via TOPMed.
- The **Silver Tier option** proposes the following omics profiling in 12,000 participants across the RECOVER cohorts: WGS, DNAm, and proteomics at one timepoint; RNAseq and metabolomics at two timepoints.
- We propose the following **two Bronze Tier options** that provide different cost points (**Bronze A, Bronze B**). We propose the following: WGS, DNAm, proteomics, metabolomics at one timepoint, and RNAseq at either two (**Bronze A**) or one (**Bronze B**) timepoint(s).

Table 1: Number of timepoints proposed across tiers.

TOPMed Omic	Number of Timepoints			
	Gold	Silver	Bronze A	Bronze B
Genomics	1	1	1	1
Epigenetics	1	1	1	1
Proteomics	2	1	1	1
Metabolomics	2	2	1	1
RNAseq	2	2	2	1

Impacted sample types: Plasma, buffy coat, Paxgene tubes.