

The RECOVER Study of the Post-Acute Sequelae of SARS-CoV2 (PASC)

Elizabeth W. Karlson, MD MS

Professor of Medicine, Harvard Medical School

Scientific Director, Mass General Brigham Personalized Medicine

Principal Investigator, PASC Data Resource Core

May 12, 2023



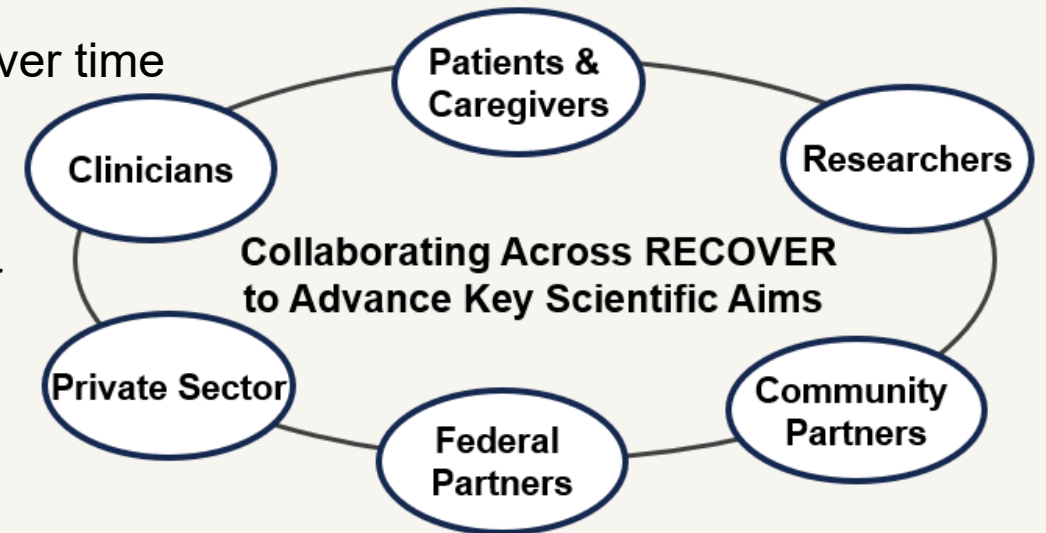
NIH RECOVER Initiative

Goal

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** PASC

Key Scientific Aims

- 1 Understand clinical spectrum/biology underlying recovery over time
- 2 Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
- 3 Study pathogenesis over time and possible relation to other organ dysfunction/disorders
- 4 Identify interventions to treat and prevent PASC



Guiding Principles



Patient-centered,
participants as partners
recoverCOVID.org



**National Scale with
Inclusive, diverse**
participation & community
engagement



Platform protocols,
standardized
methodologies, and
common data elements



Adaptive approaches
based on emerging
science

NIH RECOVER Initiative: Research Components

RECOVER Cores

Clinical Science Core

Data Resource Core

Biorepository Core

Research Studies



**RECOVER
Longitudinal
Cohort studies**



**EHR/ Health
Systems
Studies**



**Pathobiology
Studies**



**Tissue
Pathology
Studies**



**Clinical
Trials**

~40,000 participants

60 million+ records;
~7 million+ COVID cases

**Mechanistic studies of
pathogenesis**

50+ tissue types
Neuro-imaging

**Adaptive Platform
Multi-therapeutic domains**

Data Resources

Clinical

Imaging

Mobile and Digital
Health

EHR / Other Real-
World Data

Pathology

RECOVER Patient-Centered Approach

► Patient perspectives are a critical element of the RECOVER Initiative and **patient engagement is integral** to every element of the program

Examples of Patient Involvement

860+ Attendees at Discussions
of Patient Experiences

1,000+ Patients Participated
in Common Protocol
Design, Trial Application
Review, and/or
Symptom Survey

Participant Portal
22,000+ participants

Social Media Outreach



National Community
Engagement Group and
Representation Across Entire
Governance Structure

Mobile Health Platform for
Patient Reported Outcomes

14,000+ Direct Email Inquiries

14,743+ Email, Seminar Series,
Monthly Newsletter Subscribers

RECOVER PASC Consortium Main Protocol Aims

- **Aim 1:** What symptoms after a SARS-CoV-2 infection are most helpful to identify PASC? Are there different types of PASC with distinct groups of symptoms?
- **Aim 2:** How do PASC symptoms change over time, and how long do the symptoms last? Are there certain risk factors for severity of PASC over time after SARS-CoV-2 infection?
- **Aim 3:** What are the underlying biological causes of PASC? Is there overlap with other post-viral syndromes like ME/CFS? Does PASC lead to increased risk of other chronic diseases or impact child development?



Who can take part in RECOVER?

Up to 40,000 people of all ages and races and ethnicities, with and without history of COVID-19



Adults

Over 13,000
ages 18 years and up,
who are not pregnant



Babies, children,
and teens

Over 19,000



Pregnant people
and their babies

Over 2,000

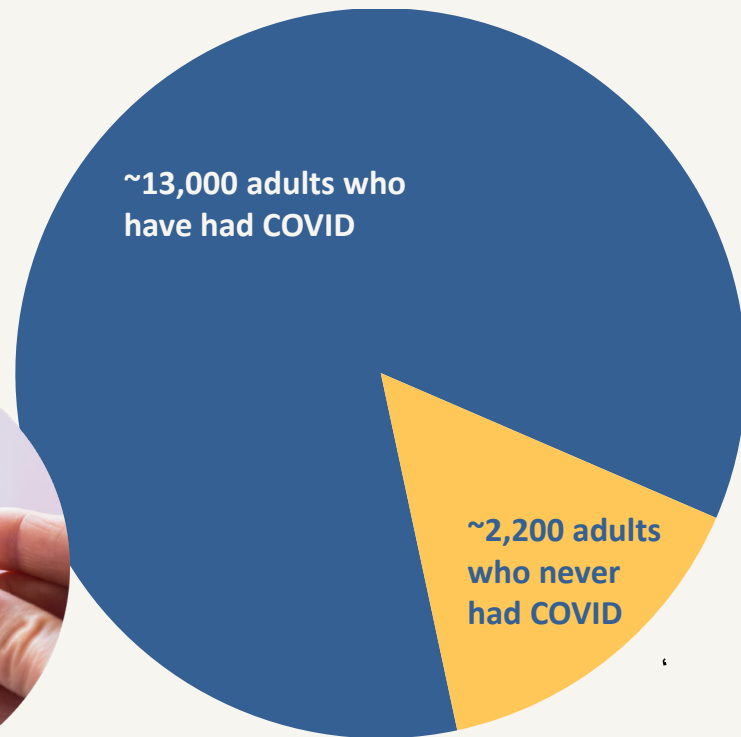


Adults can take part whether they've had COVID or not

~15,000 adults will take part to characterize the long-term effects of infection and trajectory of recovery over time

~13,000 adults who have had COVID:

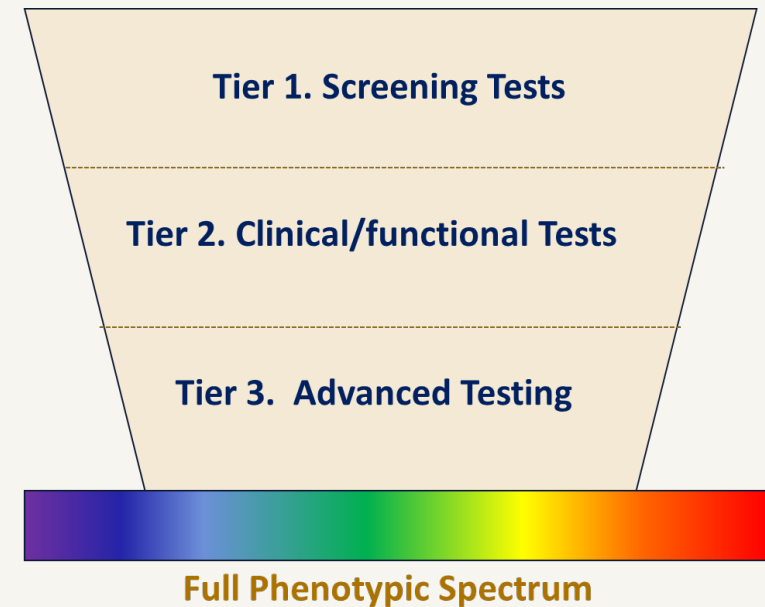
adults with a positive test showing they had COVID or had COVID symptoms



~2,200 adults who never had COVID:

people who never had a positive test for COVID and never had COVID symptoms

Prospective and Retrospective data capture with tiered phenotyping



RECOVER Adult Cohort Study Design

- Four groups
 - **Acute infected cohort** (within 5-30 days since infection date/index date)
 - **Uninfected cohort** with recent negative test (≤ 30 days since negative test/index date)
 - **Post-acute infected cohort** (> 30 days since infection date/index date)
 - **Uninfected cohort** with negative test (> 30 days since negative test/index),





Adult Study Overview: Tiered Phenotyping

Diverse population with and without COVID-19



Tier 1 Surveys, labs, biospecimens, minimal exam
(Target ~15,000 participants)



Tier 2 Low-risk clinical tests
(Target ~5,300 participants per test)



Tier 3 Advanced Testing
(Target ~3,500 participants per test)



RECOVER Adult Symptom Survey

Category ^(a)	#	Symptom short name	Symptom as it appears in the RECOVER questionnaire	Additional severity criteria ⁽ⁱ⁾
General	1	Fatigue ^{(c)(d)}	Fatigue (being very tired)	PROMIS Fatigue Score (moderate or worse)
	2	Fever/sweats/chills	Fever, chills, sweats or flushing	
	3	P-E Malaise ^(c)	Post-exertional malaise (Symptoms worse after even minor physical or mental effort)	
	4	Swelling of legs	Swelling of your legs	
	5	Unspecified pain ^(e)	Unspecified pain	PROMIS Pain Score (>3)
Cardiac	6	Chest pain ^(e)	Chest pain (including chest tightness, pressure)	SAQ-7 (<75)
	7	Palpitations ^(d)	Palpitations, racing heart, arrhythmia, skipped beats	
Dermatologic	8	Hair loss	Hair loss	
	9	Skin color changes ^(d)	Color changes in your skin, such as red, white or purple	
	10	Skin pain ^(e)	Skin pain	PROMIS Pain Score (>3)
	11	Skin rash	Skin rash	
Ear	12	Hearing	Problems with hearing (hearing loss, ringing in ears)	
Eye	13	Vision ^(d)	Vision problems (blurry, light sensitivity, difficulty reading or focusing, floaters, flashing lights, "snow")	VFQ-25 (composite<75)
Gastrointestinal	14	Abdominal pain ^{(d)(e)}	Abdomen (belly) pain	PROMIS Pain Score (>3)
	15	Dry mouth ^(d)	Excessively dry mouth	
	16	GI ^{(c)(d)}	Gastrointestinal (belly) symptoms (feeling full or vomiting after eating, diarrhea, constipation)	
	17	Mouth pain ^(e)	Mouth pain	PROMIS Pain Score (>3)
	18	Teeth	Problems with teeth	
Metabolic	19	Thirst ^(d)	Excessive thirst	
Musculoskeletal	20	Back pain ^(e)	Back/spine pain	PROMIS Pain Score (>3)
	21	Foot pain ^(e)	Foot pain	PROMIS Pain Score (>3)
	22	Joint pain ^{(c)(e)}	Joint pain	PROMIS Pain Score (>3)
	23	Muscle pain ^{(c)(e)}	Muscle pain	PROMIS Pain Score (>3)
	24	Weakness ^{(c)(d)}	Weakness in arms or legs	PROMIS Physical Function Short Form 4a (T<=40) or Neuro-QoL Upper

				Extremity Function (T<=40)
Neurologic	25	Abnormal movements ^(f)	Abnormal movements	
	26	Brain fog ^{(c)(d)}	Problems thinking or concentrating ("brain fog")	Neuro-QoL Cognition Score (<=40)
	27	Dizziness ^(d)	Feeling faint, dizzy, "goofy"; difficulty thinking soon after standing up from a sitting or lying position	
	28	Headache ^{(c)(e)}	Head pain/headache	HIT-6 (substantial or worse)
	29	Numbness/tingling ^(f)	Numbness, tingling, burning	Michigan Neuropathy Score (>6)
	30	Paralysis ^(f)	Inability to move part of body	
	31	Seizures ^(f)	Seizures	
	32	Smell/taste	Loss of or change in smell or taste	
	33	Tremor ^(f)	Tremor	
	34	Unspecified nerve problem ^(f)	Unspecified	
Psychiatric	35	Anxiety ^(g)	N/A	Anxiety (GAD-7>9)
	36	Depression ^(g)	N/A	Depression (PHQ-8>9)
	37	Sexual desire/capacity	Changes in desire for, comfort with or capacity for sex	
	38	Sleep disturbance ^{(c)(h)}	Sleep disturbance	Sleep disturbance score (>=60)
Reproductive ^(b)	39	Pelvic/genital pain ^(e)	Pelvis or genital pain	PROMIS Pain Score (>3)
Respiratory	40	Chronic cough	Persistent (chronic) cough	
	41	Shortness of breath ^(d)	Shortness of breath	MMRC Dyspnea scale (>1)
	42	Sleep apnea ^(h)	Sleep apnea	
	43	Throat pain ^(d)	Throat pain	PROMIS Pain Score (>3)
Urinary	44	Bladder ^(d)	Bladder problems (incontinence, trouble passing urine or emptying bladder)	

- 45 symptoms
- Multiple severity scales



Tiered Testing Adult Cohort: Symptoms-Triggered Assessments

Laboratory studies	Clinical Assessments	Clinical Procedures	Radiology studies
Comprehensive metabolic panel with cystatin-C	Symptom questionnaires and medical history	Pulmonary function testing (spirometry, DLCO and lung volumes)	Dual energy chest CT with contrast or if not available, volumetric non-contrast inspiratory/expiratory chest CT
Complete blood count with differential	Complete vitals, BMI and waist circumference	Nerve conduction study	Echocardiography
Lipid panel	Active standing test	EMG study	Fibroscan
Hemoglobin A1c	Home polysomnography	Skin biopsy	Renal ultrasound
Coagulation panel, d-dimer	6-minute walk test	Muscle biopsy	Brain MRI with and without gadolinium
Troponin, NT-pro BNP	Neuropathy exam	Lumbar puncture	Cardiac MRI
Thyroid panel	Rehabilitation exam	Facility-based sleep study	Cardiac imaging with mIBG
25-hydroxy vitamin D	Mini International Neuropsychiatric Interview	Cardiovagal innervation testing	Gastric emptying study
Urinalysis	Vision testing	Tilt table testing	
Urine microalbumin and creatinine	Smell test	Full cardiopulmonary exercise testing	
hsCRP	NIH Toolbox cognition tests	Bronchoscopy	
SARS-CoV-2 antibodies and NAAT	Complete eye exam	Right heart catheterization	
OGTT (time points 0, 30, 60, 90, 120 min)	Complete ENT exam	Upper endoscopy	
ACTH and cortisol	Comprehensive audiometry	Colonoscopy, with or without biopsy	
Serum B12 and methylmalonic acid	Complete neurocognitive testing		
Catecholamine testing	Endopat testing		





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