Researching COVID to Enhance Recovery (RECOVER) Adult Cohort Study Design

October 2024

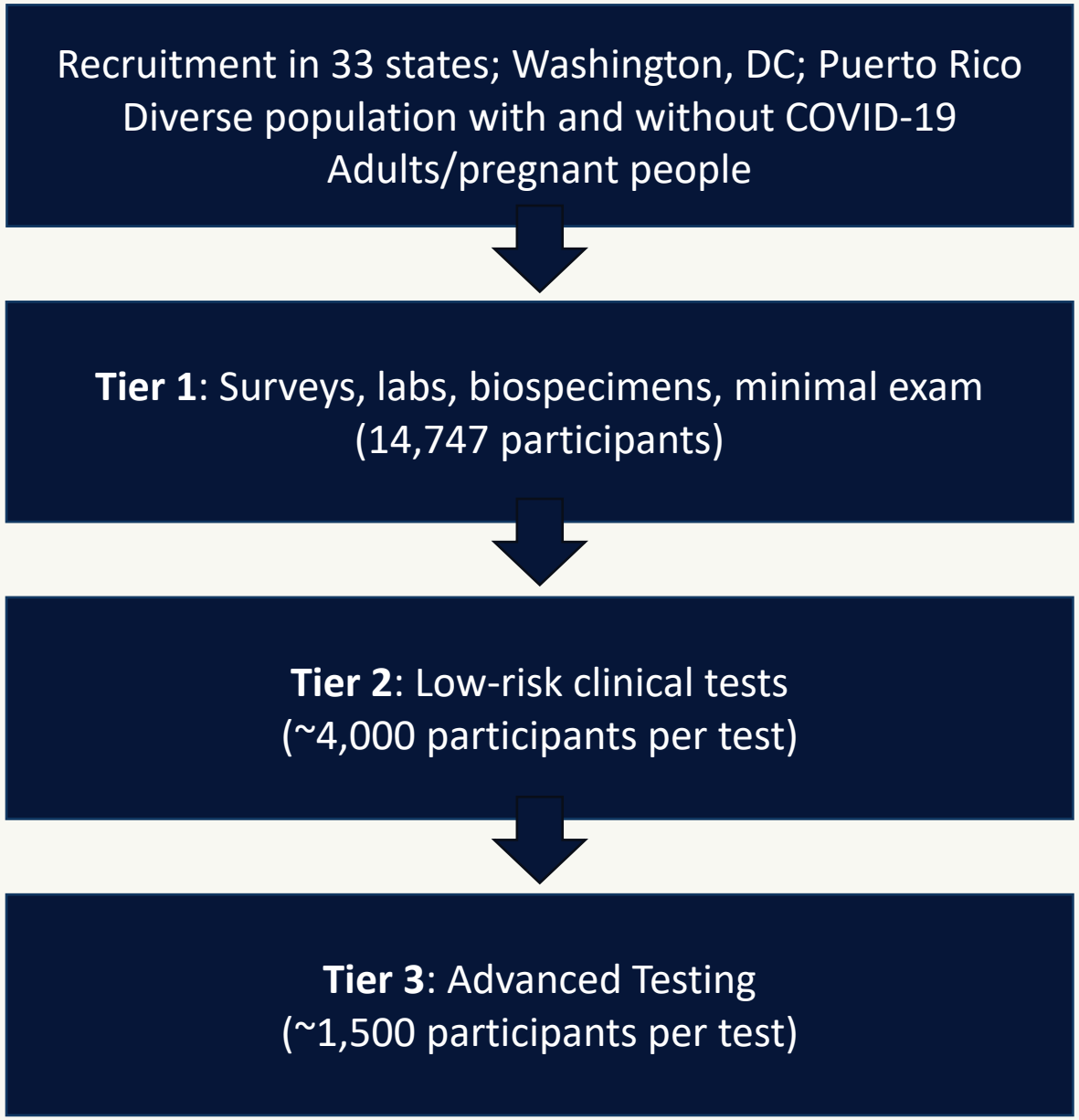
RECOVER
Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

Study Questions

- How **many** people are getting Long COVID or PASC (Post-Acute Sequelae of SARS-CoV-2 infection)?
- Why do **some** people get Long COVID or PASC and **others do not**?
- What **symptoms** do people feel when they get Long COVID or PASC?
- How **long** do people feel sick when they get Long COVID or PASC?
- What **causes** Long COVID or PASC to happen?

Adult Study Overview



RECOVER Adult Cohort

- **14,747** participants who are **18 years of age and older** and have reached the age of majority in their state of residence

- **People who have had COVID (12,296)**: Someone with a positive test showing they had an infection with the virus that causes COVID or had symptoms of COVID (“infected”)

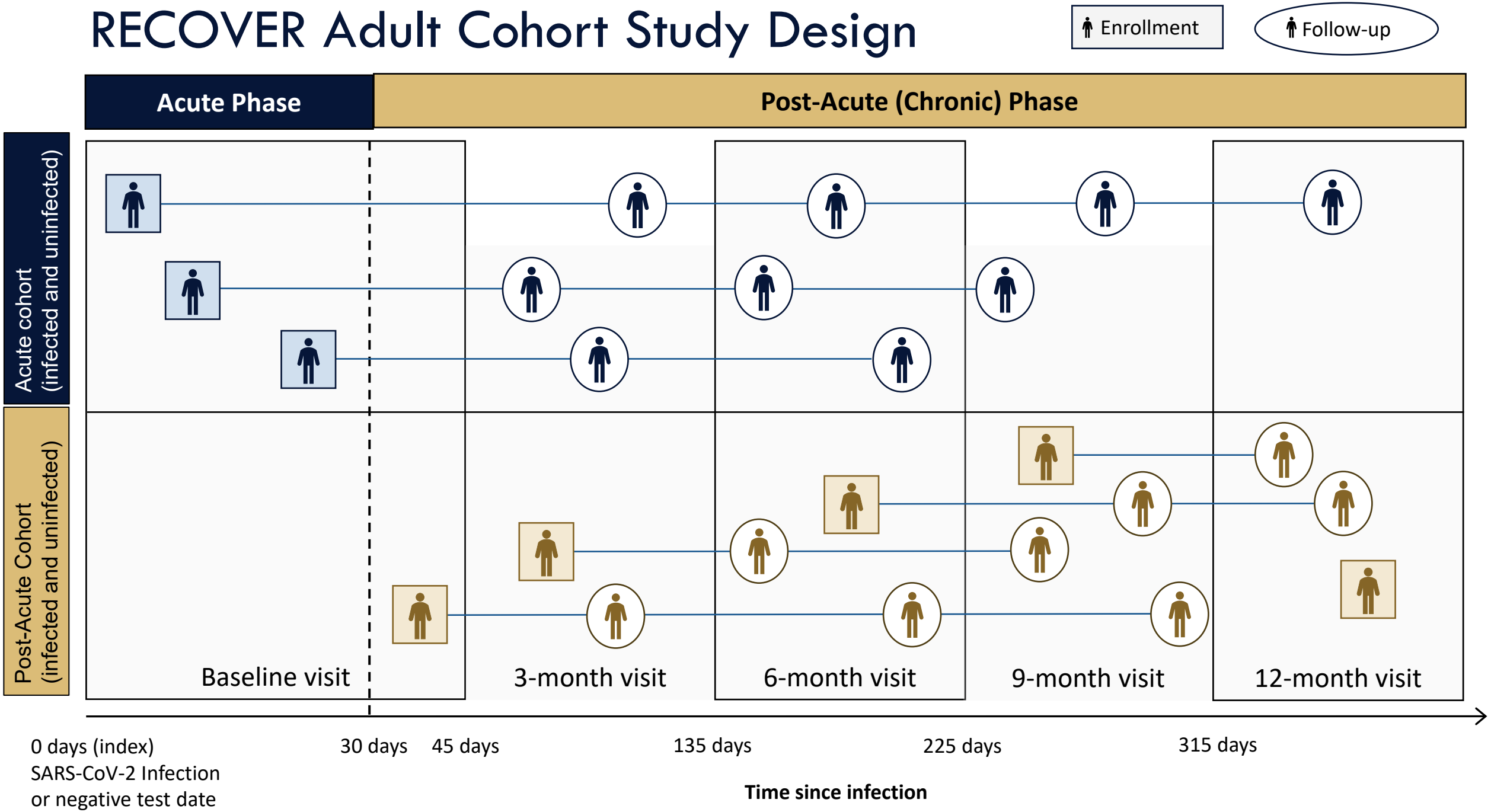
- **People who never had COVID (2,451)**: Someone who never had a positive test for COVID and never had any symptoms that make us think they had COVID (“uninfected”)

RECOVER Adult Cohort Study Design

Four groups

- **Acute infected cohort** (within 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)

RECOVER Adult Cohort Study Design



Schedule of Survey, Office Visit, Biospecimen Collection Timepoints (Slide 1 of 2)

eCRF	Baseline	Time Point after index date (minutes)															
		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Enrollment	x																
Tier 1-2 Consent	x																
Identity	x																
Visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comorbidities	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COVID Treatment	x																
Medications	x																
Change in Medications		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demographics	x																
PASC Symptoms	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vaccine	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SDoH	x																
SDoH Follow-up		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Alcohol/Tobacco	x																
Alcohol/Tobacco Follow-up		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Schedule of Survey, Office Visit, Biospecimen Collection Timepoints (Slide 2 of 2)

eCRF	Baseline	Time Point after index date (minutes)														
		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Disability	x																
Pregnancy	x																
Pregnancy Follow-up		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tier 1 office visit	x		x		x				x				x				x
Biospecimens	x	x	x	x	x				x				x				x
Lab Results	x	x	x	x	x				x				x				x

Key Procedures: Adult Tier 1

- Questionnaires (demographics, social determinants, medical history, COVID history, vaccination status, substance use, symptom screener (>50 symptoms plus follow up severity/validated instruments))
- Core physical exam (vitals, waist circumference, sit-to-stand, active standing test)
- Laboratory studies and biospecimens (blood, saliva, urine, stool, nasal)

Laboratory Studies	
Comprehensive metabolic panel with cystatin-C	TSH, free T4
Complete blood count with differential	25-hydroxy vitamin D
Lipid panel	hs-CRP
Hemoglobin A1c	Urinalysis
PT/INR/PTT, d-dimer	Urine microalbumin and creatinine
Troponin	SARS-CoV-2 antibodies and NAAT (uninfected only)
NT-pro BNP	SARS-CoV-2 NAAT

Key Procedures: Adult Tier 2

Laboratory studies
Oral glucose tolerance test (glucose, insulin, C-peptide at 0, 30, 60, 120 min.)
ACTH and cortisol
Hepatitis B and C testing

Clinical Assessments
Home polysomnography
6-minute walk test
Neurological exam
Rehabilitation exam
ENT exam
Mini-International Neuropsychiatric Interview (MINI)
Vision screen (Snellen chart)
Smell test
NIH Toolbox cognition tests

Radiology studies
Volumetric non-contrast inspiratory/expiratory chest CT or dual energy chest CT with contrast if available
Fibroscan
Renal ultrasound
Transthoracic echocardiography with strain imaging

Other Procedures
Electrocardiogram
Pulmonary function testing (spirometry, DLCO)

A random group of people without triggering symptoms will be assigned to each test to serve as controls.

Key Procedures: Adult Tier 3

Laboratory Studies
B12 and Methylmalonic Acid

Clinical Assessments
Comprehensive audiometry
Complete neurocognitive testing
EndoPAT testing

Clinical Procedures
Nerve conduction study
Electromyography
Skin biopsy
Muscle biopsy
Lumbar puncture
Facility-based sleep study
Autonomic testing (tilt table, Valsalva manuever, heart rate variability, catecholamines)
Cardiopulmonary exercise testing
Bronchoscopy
Right heart catheterization
Colonoscopy with biopsy

Radiology Studies
Brain MRI
Cardiac MRI
Gastric emptying study

Example: Triggered Phenotyping for Tier 2 and 3

6-minute walk test

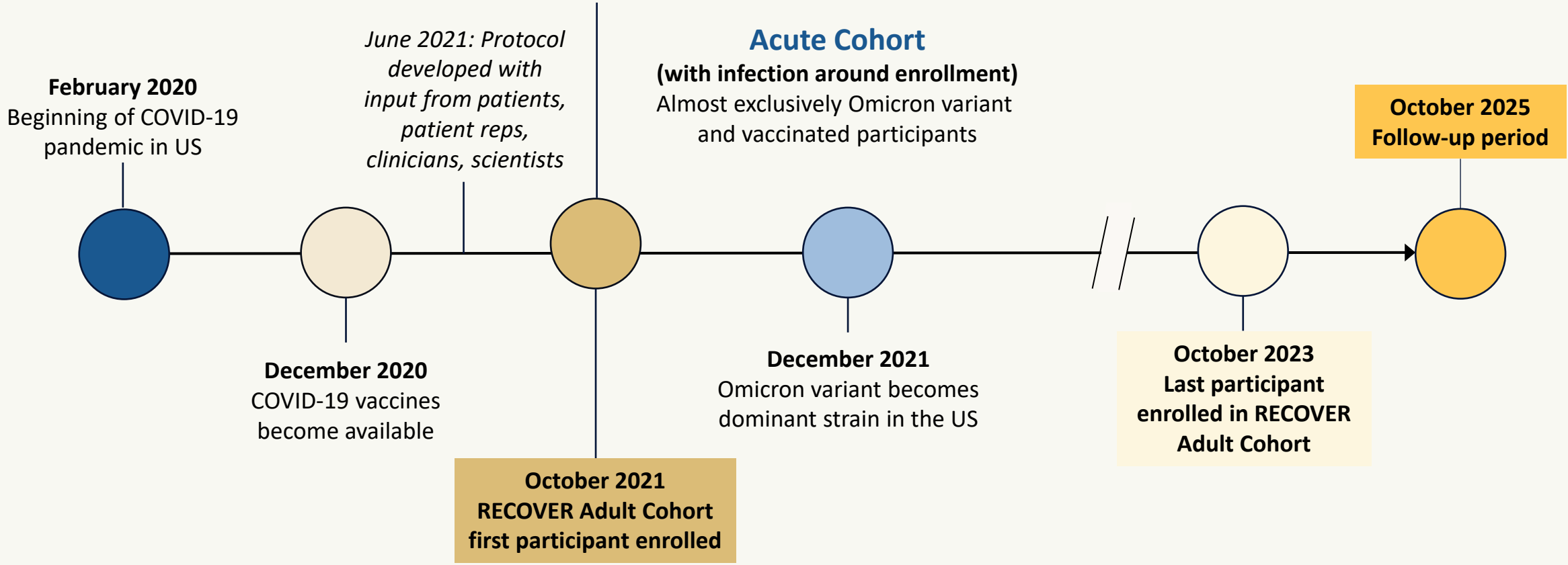
Test	Result	Condition
mMRC	Score of 1 or greater (any breathlessness)	OR
PROMIS-10 fatigue	Answer = 4 or 5 (severe/very severe)	
Persistent cough	Yes, currently have	
Post-exertional malaise	Yes, currently have	
Hypoxia (low oxygen saturation) at rest	Oxygen saturation <95% (93% at altitude)	
Mechanical ventilation during acute COVID	Yes	
Hypoxia during sleep without apnea	Oxygen saturation < 90% (88% at altitude) more than 10% of sleep; respiratory event index < 15	

A random group of people without triggering symptoms will be assigned to each test to serve as controls

83 Adult Enrolling Sites

Timeline

In 24 months, the cohort was fully accrued



Enrollment

Participant category	Enrolled	% of cohort
Infected, enrolled within 30 days of infection	4,965	34%
Infected, enrolled >30 days after infection	7,331	50%
Uninfected	2,451	17%
Total	14,747	

Data as of 6/17/2022

Demographics (Slide 1 of 2)

Identity group	Enrolled, %*	Target, %	US adult population
American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander	2%	1%	1%
Asian	8%	4%	6%
Black	16%	16%	13%
Hispanic	17%	27%	19%
White	60%	53%	59%
Other, prefer not to answer	1%		

** Among non-missing; data are missing for 238 enrollees (1.6%)*

Demographics (Slide 2 of 2)

	Characteristics	N	%
Sex	Female	10,522	71%
	Male	4,067	28%
Age	18 – 45	7,448	50%
	46 – 65	5,259	36%
	>65	2,023	14%
Rurality	Non-rural	14,028	95%
	Rural	684	4.6%

Exemplar Data Collected to Date

- >80,000 symptom surveys
- >1 million laboratory values
- >34,000 30-second sit-to-stand tests
- >3,300 spirometry tests
- >3,000 chest CTs
- >1,200 home sleep studies
- >1,000 brain MRIs

Example Analysis

- How can we identify people who may have post-acute sequelae of SARS-CoV-2 (PASC)?
- First: Identify which symptoms are more common in people who had infection versus those who didn't
  - Answer: All of them!
- Second: Reduce these to a parsimonious set using LASSO
- Third: Use the LASSO OR to assign points to each retained symptom; sum these to create a score for each participant
- Fourth: Identify an optimal threshold for categorization of PASC/Long COVID

Overview of All Survey Instruments

Time period	Instrument	Number of core questions	Total possible questions
Enrollment	Demographics	5	8
	PASC symptoms	44+8*	~210-220
	Vaccine status	1	2 + 2 more for each dose
	Social determinants of health	44	47
	Disability	6	6
	Alcohol and tobacco	10	14
	Pregnancy	1	19
	Comorbidities	27	138
	COVID treatment	12	24
	Long COVID treatment trial	1	9
	TOTAL	**152-155**	**>380**

** 8 symptom questions added in June 2023 (7 new symptoms and separate headache question)*

RECOVER Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Research Index

Thaweethai, et. al. JAMA

RECOVER Analysis Approach

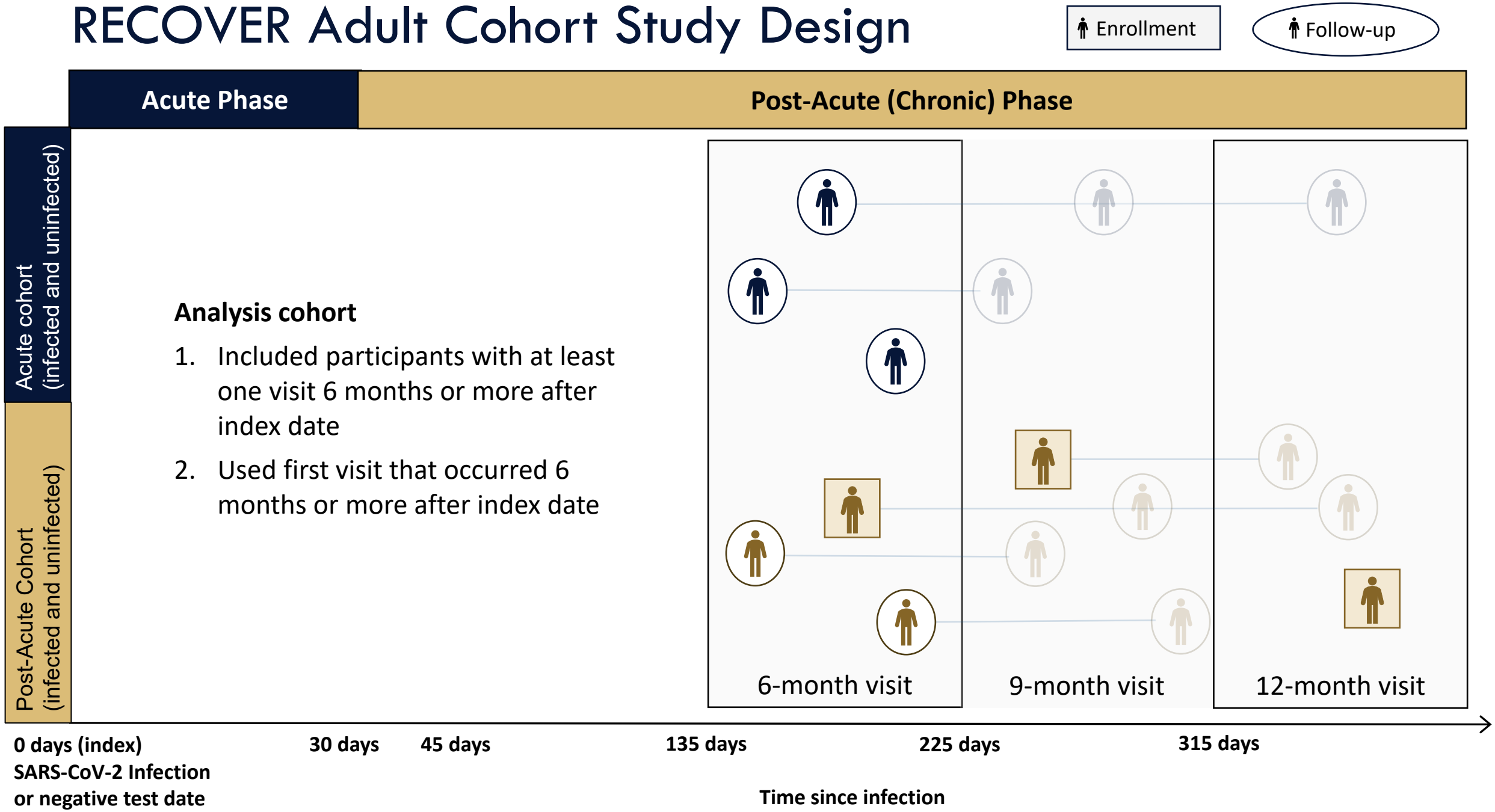
Goal

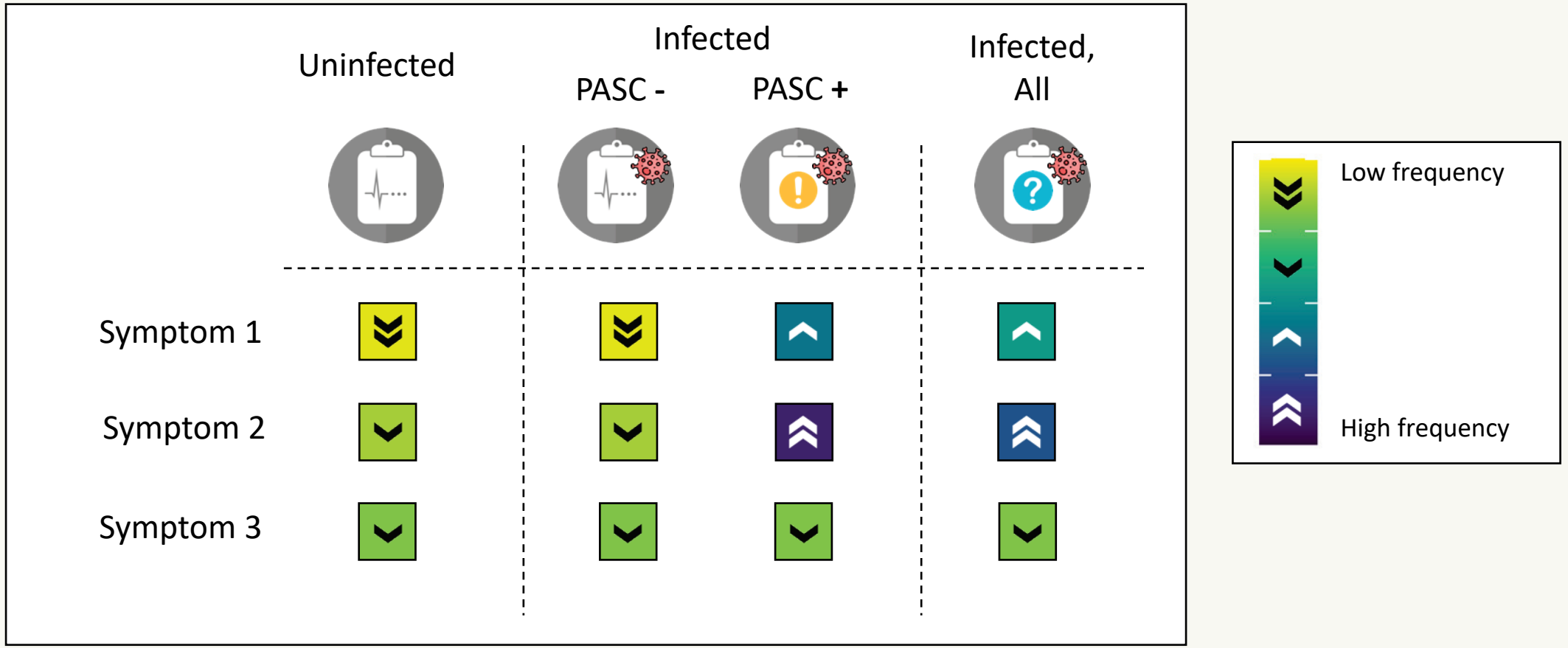
Pinpoint combinations of symptoms that can be used to identify people with Long COVID.

Approach

Identify combinations of persisting symptoms (6 months or more) that are different between people with and without a history of SARS-CoV-2 infection.

RECOVER Adult Cohort Study Design




Uninfected
Infected
PASC -
PASC +
Infected,
All
Symptom 1
Symptom 2
Symptom 3
Low frequency
High frequency

Analytic Overview

1. Symptom selection (LASSO)
2. Score assignment and calculation
3. Optimal threshold identification

RECOVER Adult Cohort Demographic Characteristics by Infection Status at Enrollment (Slide 1 of 3)

Characteristic	No./Total (%)	
	Infected (n = 8,646)	**Uninfected** (n = 1,118)
Age at enrollment, y		
Median (IQR)	45 (34-59)	55 (40-65)
No.	8,637	1,117
Age category at enrollment, y		
18-45	4,389 / 8,637 (51%)	377 / 1,117 (34%)
46-65	3,175 / 8,637 (37%)	502 / 1,117 (45%)
>65	1,073 / 8,637 (12%)	238 / 1,117 (21%)
Race and ethnicity		
Asian, non-Hispanic	428 / 8,558 (5%)	73 / 1,106 (7%)
Black or African American, non-Hispanic	1,220 / 8,558 (145)	197 / 1,106 (18%)
Hispanic, Latino, or Spanish	1,473 / 8,558 (17%)	119 / 1,106 (11%)
White, non-Hispanic	5,027 / 8,558 (59%)	685 / 1,106 (62%)
Multiracial/multiethnic	305 / 8,558 (4%)	26 / 1,106 (2%)
Other	105 / 8,558 (1%)	6 / 1,106 (1%)

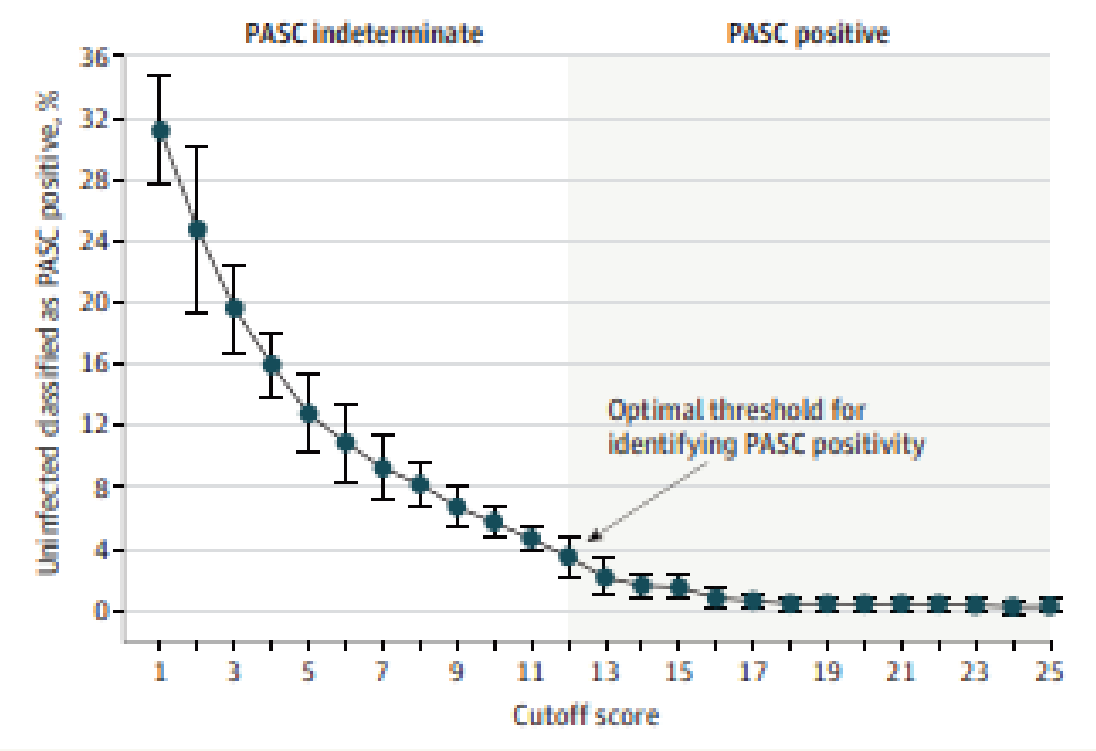
RECOVER Adult Cohort Demographic Characteristics by Infection Status at Enrollment (Slide 2 of 3)

Characteristic	No./Total (%)	
	Infected (n = 8,646)	**Uninfected** (n = 1,118)
Sex assigned at birth		
Female	6,221 / 8,602 (72%)	711 / 1,110 (64%)
Male	2,377 / 8,602 (28%)	399 / 1,110 (36%)
Intersex	4 / 8,602 (<1%)	0 / 1,110
Vaccination status at index date		
Unvaccinated	3,291 / 8,538 (39%)	161 / 1,095 (15%)
Partially vaccinated	154 / 8,538 (2%)	21 / 1,095 (2%)
Fully vaccinated	4,725 / 85,38 (55%)	860 / 1,095 (79%)
Date of last dose unknown	368 / 8,538 (4%)	53 / 1,095 (5%)
Cohort and prevalent SARS-CoV-2 strain at Index		
Acute pre-Omicron	17 / 8,646 (<1%)	2 / 1,118 (<1%)
Acute Omicron	2,231 / 8,646 (265)	388 / 1,118 (35%)
Postacute pre-Omicron	3,732 / 8,646 (43%)	290 / 1,118 (26%)
Postacute Omicron	2,666 / 8,646 (31%)	438 / 1,118 (39%)

RECOVER Adult Cohort Demographic Characteristics by Infection Status at Enrollment (Slide 3 of 3)

Characteristics	No./Total (%)	
	Infected (n = 8,646)	**Uninfected** (n = 1,118)
Medically underserved area		
Yes	2,369 / 8,646 (5%)	298 / 1,118 (27%)
No	6,277 / 8,646 (73%)	820 / 1,118 (73%)
Rural participate		
Yes	465 / 8,646 (5%)	45 / 1,118 (4%)
No	8,181 / 8,646 (95%)	1,073 / 1,118 (96%)
Education level		
Did not complete high school/no diploma	280 / 8,564 (3%)	44 / 1,107 (4%)
High school/GED/some college/vocational/technical	2,790 / 8,564 (33%)	306 / 1,107 (28%)
Bachelor's/advanced degree	5,494 / 8,564 (64%)	757 / 1,107 (68%)

LASSO-Selected Symptoms and Score Threshold

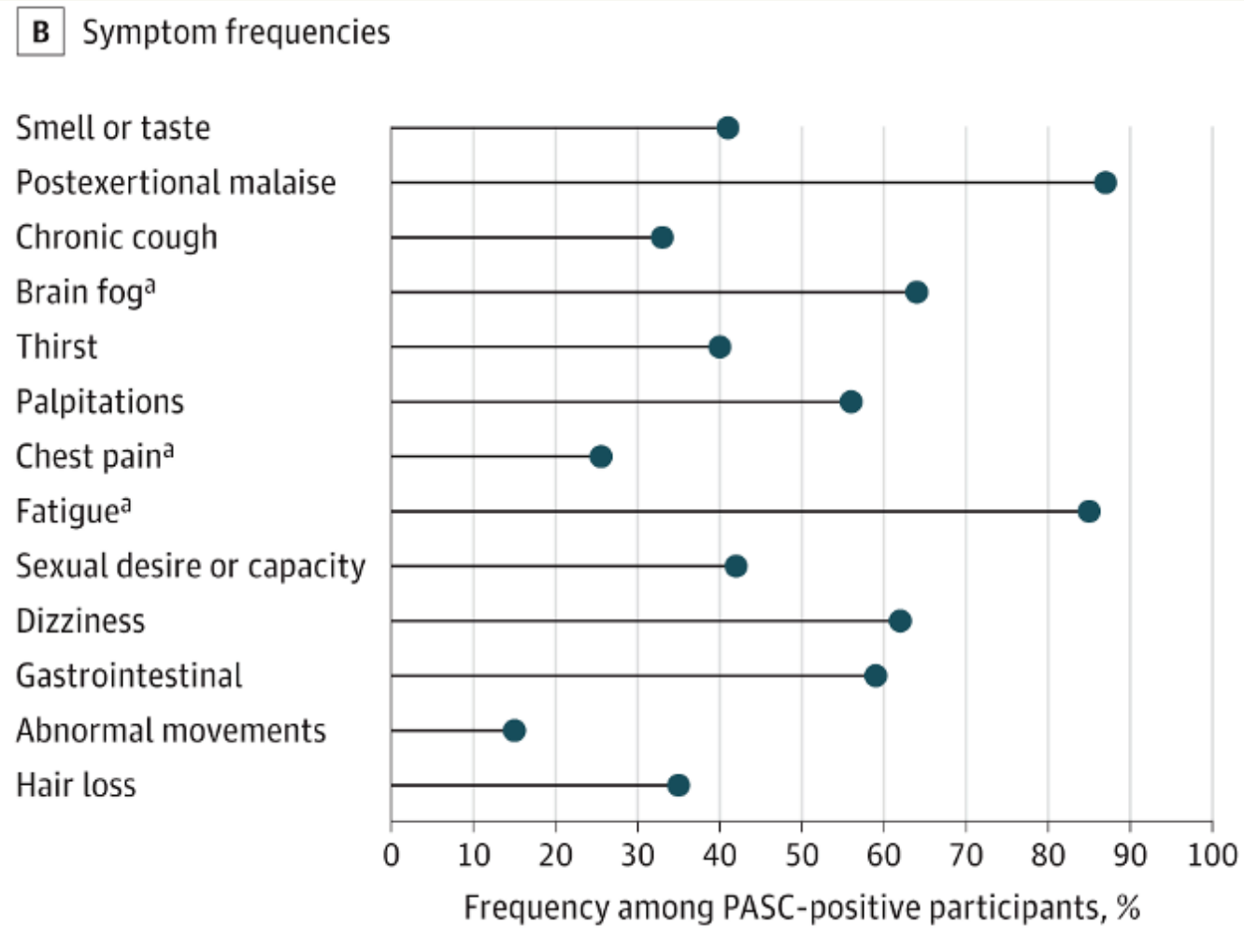


Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizziness	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Abbreviations: PASC, postacute sequelae of SARS-CoV-2 infection.
[a] Least absolute shrinkage and selection operator was used to identify which symptoms defined PASC. A symptom score was assignged by dividing the estimated log odds ration by 0.10 and rounding to the nearest integar. For each person, the total score was defined as the sum of the scores for each symptom a person reported.
[b] Additional severity criteria required.

Symptoms in Those with Score ≥ 12



Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

- The PASC score is calculated by adding up the scores for each symptom an individual has.

  Score < 12 ⇨ PASC-indeterminate

  Score ≥ 12 ⇨ PASC-positive

- Many other symptoms were highly correlated with these symptoms, including:
  - Dry mouth
  - Weakness
  - Headache
  - Tremor
  - Muscle and abdominal pain
  - Fever/sweats/chills
  - Sleep disturbance

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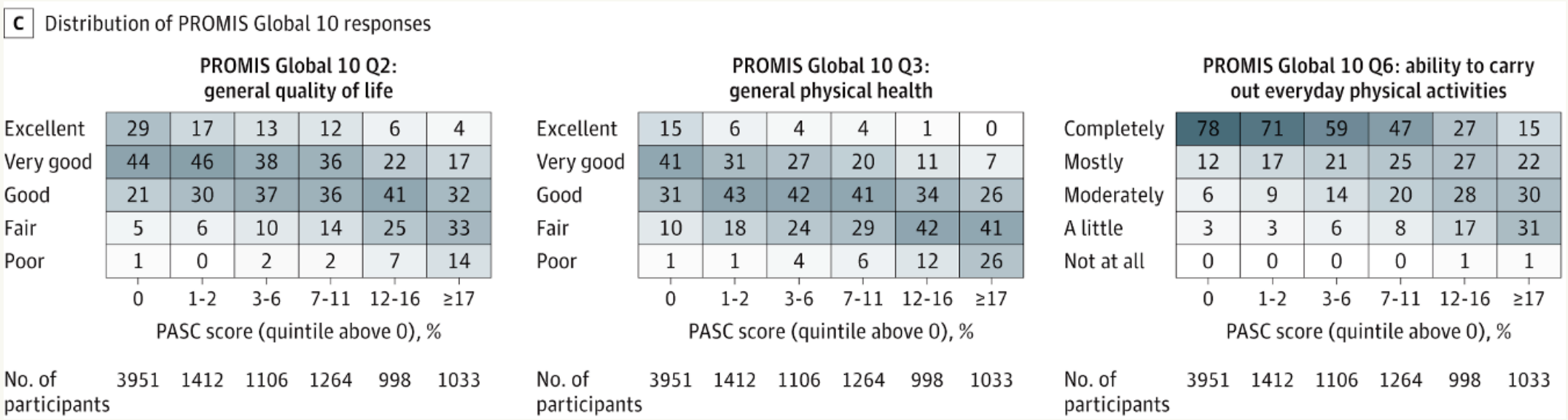
Face Validity: Association with Quality of Life



C Distribution of PROMIS Global 10 responses

PROMIS Global 10 Q2: general quality of life

	0	1-2	3-6	7-11	12-16	≥17
Excellent	29	17	13	12	6	4
Very good	44	46	38	36	22	17
Good	21	30	37	36	41	32
Fair	5	6	10	14	25	33
Poor	1	0	2	2	7	14
No. of participants	3951	1412	1106	1264	998	1033

PASC score (quintile above 0), %

PROMIS Global 10 Q3: general physical health

	0	1-2	3-6	7-11	12-16	≥17
Excellent	15	6	4	4	1	0
Very good	41	31	27	20	11	7
Good	31	43	42	41	34	26
Fair	10	18	24	29	42	41
Poor	1	1	4	6	12	26
No. of participants	3951	1412	1106	1264	998	1033

PASC score (quintile above 0), %

PROMIS Global 10 Q6: ability to carry out everyday physical activities

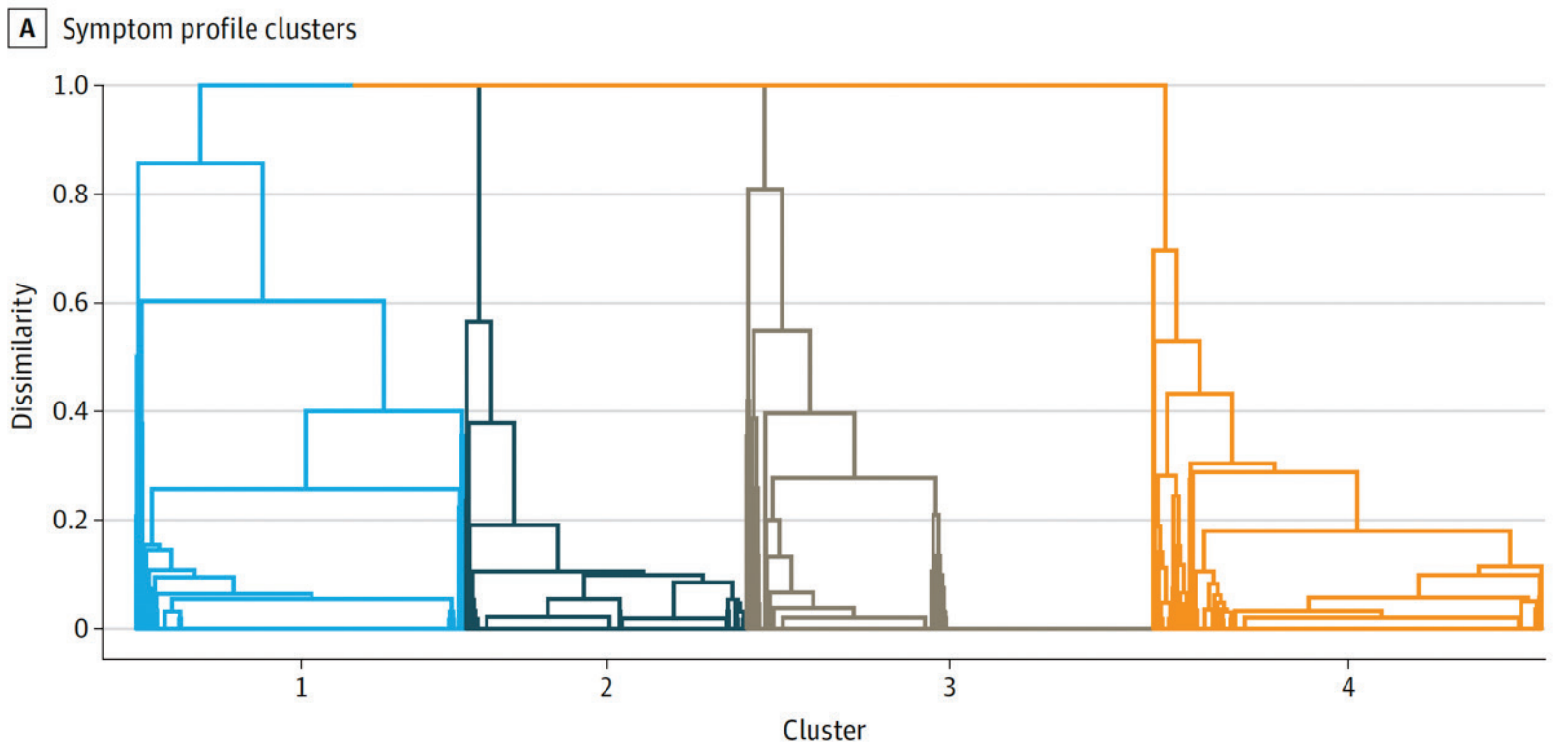
	0	1-2	3-6	7-11	12-16	≥17
Completely	78	71	59	47	27	15
Mostly	12	17	21	25	27	22
Moderately	6	9	14	20	28	30
A little	3	3	6	8	17	31
Not at all	0	0	0	0	1	1
No. of participants	3951	1412	1106	1264	998	1033

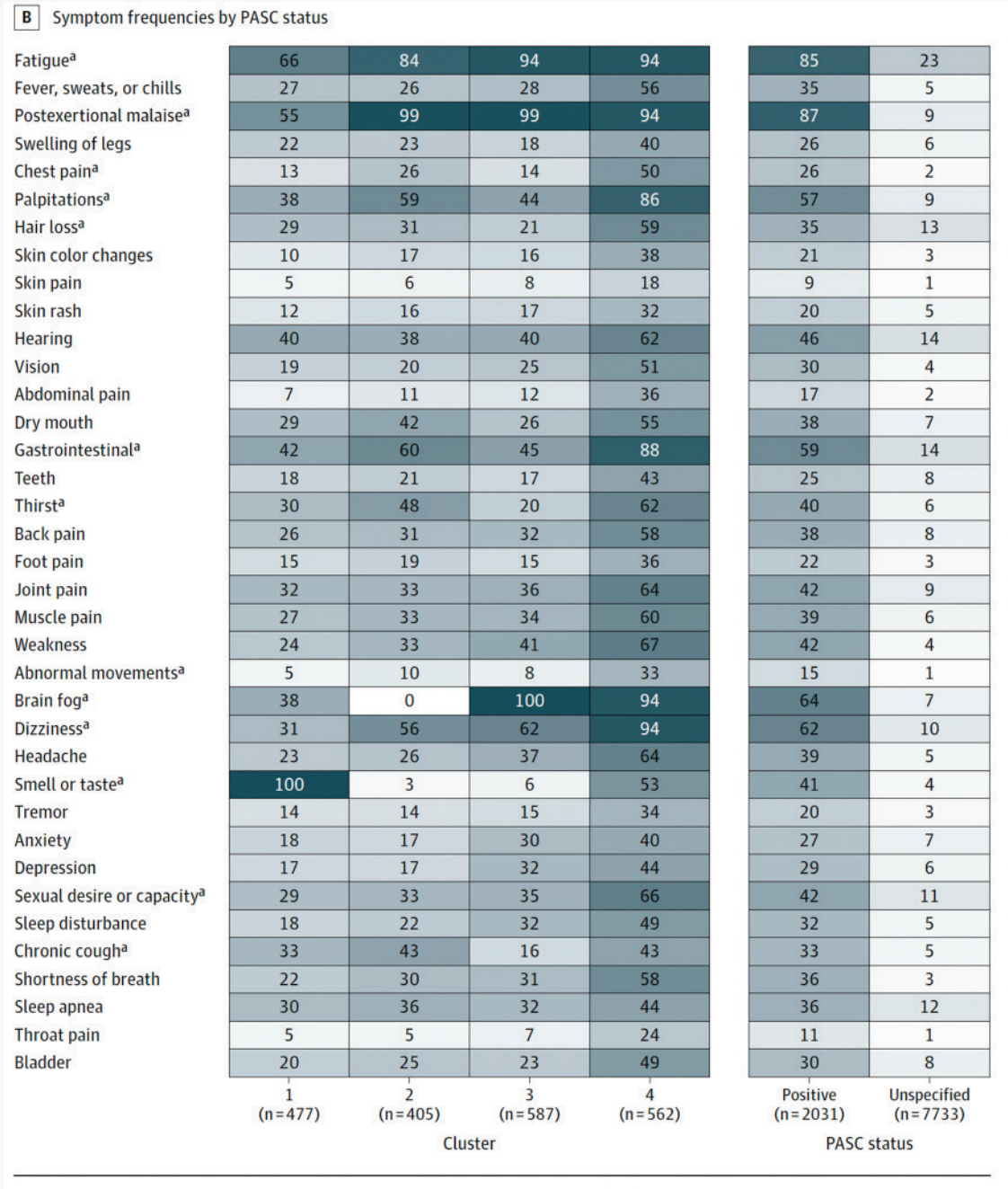
PASC score (quintile above 0), %

PASC Frequencies, Overall and Stratified by Subcohort, Infection, Vaccination, and Reinfection

	Total No.	PASC positive, No. (%)
PASC frequencies overall and stratified by subcohort and infection		
All participants (full cohort)	9,764	2,031 (21%)
Infected	8,646	1,990 (23%)
Uninfected	1,118	41 (3.7%)
Acute Omicron		
Infected	2,231	224 (10%)
Uninfected	388	18 (4.6%)
Postacute pre-Omicron		
Infected	3,732	1,320 (35%)
Uninfected	290	11 (3.8%)
Postacute Omicron		
Infected	2,666	442 (17%)
Uninfected	438	12 (2.7%)

Figure 3. Identification of Postacute Sequelae of SARS-CoV-2 Infection (PASC) Subgroups and Their Characteristics




B Symptom frequencies by PASC status
Fatigue[a] 66 84 94 94 85 23
Fever, sweats, or chills 27 26 28 56 35 5
Postexertional malaise[a] 55 99 99 94 87 9
Swelling of legs 22 23 18 40 26 6
Chest pain[a] 13 26 14 50 26 2
Palpitations[a] 38 59 44 86 57 9
Hair loss[a] 29 31 21 59 35 13
Skin color changes 10 17 16 38 21 3
Skin pain 5 6 8 18 9 1
Skin rash 12 16 17 32 20 5
Hearing 40 38 40 62 46 14
Vision 19 20 25 51 30 4
Abdominal pain 7 11 12 36 17 2
Dry mouth 29 42 26 55 38 7
Gastrointestinal[a] 42 60 45 88 59 14
Teeth 18 21 17 43 25 8
Thirst[a] 30 48 20 62 40 6
Back pain 26 31 32 58 38 8
Foot pain 15 19 15 36 22 3
Joint pain 32 33 36 64 42 9
Muscle pain 27 33 34 60 39 6
Weakness 24 33 41 67 42 4
Abnormal movements[a] 5 10 8 33 15 1
Brain fog[a] 38 0 100 94 64 7
Dizziness[a] 31 56 62 94 62 10
Headache 23 26 37 64 39 5
Smell or taste[a] 100 3 6 53 41 4
Tremor 14 14 15 34 20 3
Anxiety 18 17 30 40 27 7
Depression 17 17 32 44 29 6
Sexual desire or capacity[a] 29 33 35 66 42 11
Sleep disturbance 18 22 32 49 32 5
Chronic cough[a] 33 43 16 43 33 5
Shortness of breath 22 30 31 58 36 3
Sleep apnea 30 36 32 44 36 12
Throat pain 5 5 7 24 11 1
Bladder 20 25 23 49 30 8
1 (n=477)
2 (n=405)
3 (n=587)
4 (n=562)
Cluster
Positive (n=2031)
Unspecified (n=7733)
PASC status

Adult Cohort Insights: Conclusions and Next Steps

Implications for a Working Definition

- This is a symptom-based definition that is not intended for immediate clinical use for individuals; it is intended for research use for populations
- It should not be used to rule out PASC/Long COVID
- Individuals who do not meet the threshold may still have PASC/Long COVID
- Conversely, individuals above the threshold may not have PASC/Long COVID
- The symptoms included in the score are not necessarily the most common, burdensome, or severe Long COVID symptoms; they are the most distinctive
- Note that anxiety and depression were not distinctive enough to be included in the score; this is a not a syndrome primarily characterized by mental health problems

One of the Most Viewed and Discussed JAMA Articles

Top 3 most-viewed articles (page views)

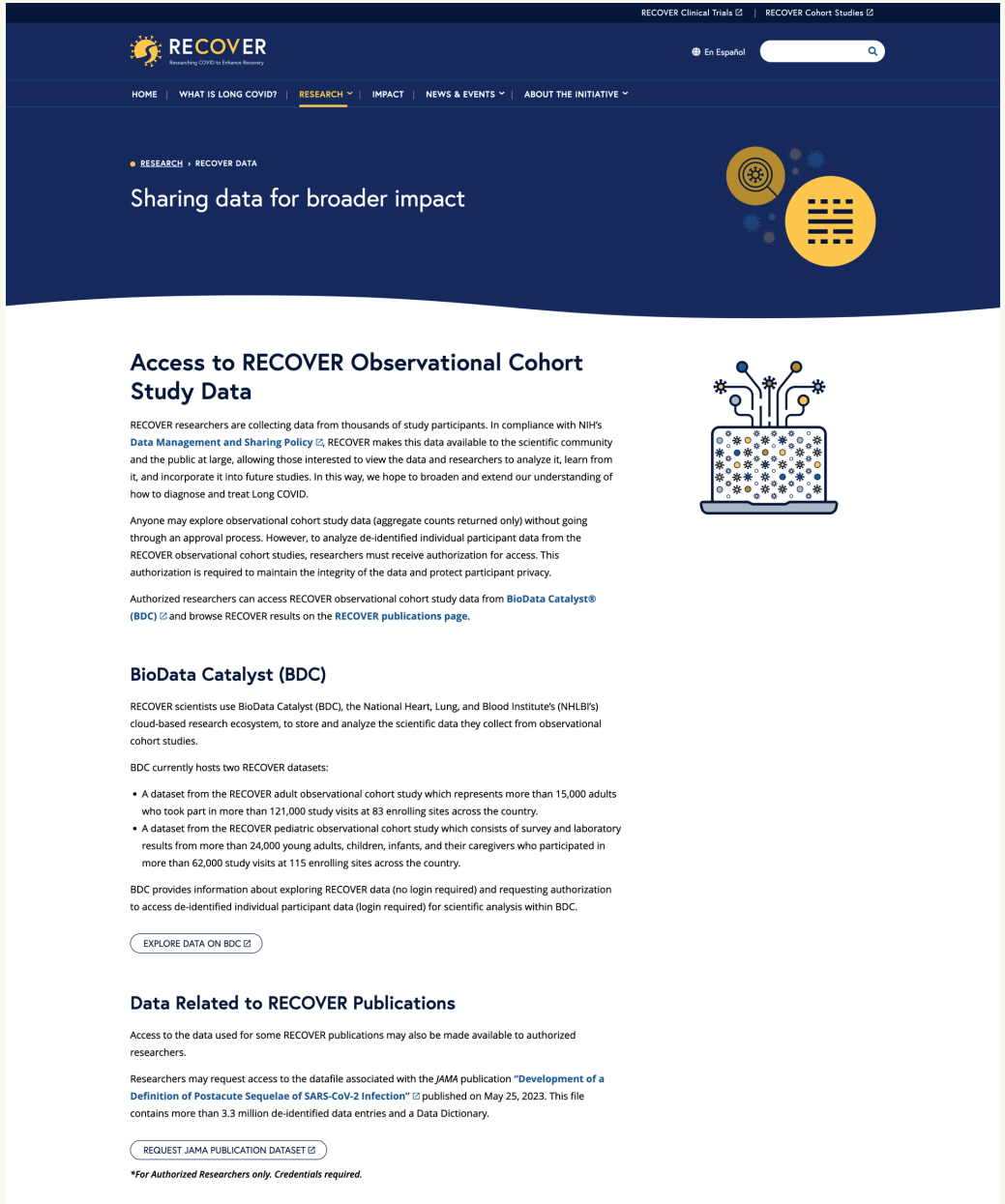
Articles	Page Views
Effect of Higher-Dose Ivermectin for 6 Days vs Placebo on Time to Sustained Recorvery in Outpatients with COVID-19: A Randomized Clinical Trial	385,366
Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial	226,715
Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection	213,155

Top 3 most-discussed articles (Altmetric score)

Articles	Altmetric Score
Effect of Higher-Dose Ivermectin for 6 Days vs Placebo on Time to Sustained Recovery in Outpatients with COVID-19: A Randomized Clinical Trial	5480
Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection	5167
Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial	4380

You Can Use the Data Too!

Visit RECOVER's Data page for more information.



recoverCOVID.org

Details of Survey Instruments: RECOVER Adult Cohort

Overview of All Survey Instruments as of 3/2024

Time period	Instrument	Number of core questions	Total possible questions
Enrollment	Demographics	5	8
	PASC symptoms	44+8*	~210-220
	Vaccine status	1	2 + 2 more for each dose
	Social determinants of health	44	47
	Disability	6	6
	Alcohol and tobacco	10	14
	Pregnancy	1	19
	Comorbidities	27	138
	COVID treatment	12	24
	Long COVID treatment trial	1	9
	TOTAL	**152-155**	**>380**

** 8 symptom questions added in June 2023 (7 new symptoms and separate headache question)*

Overview of Follow-Up Survey Instruments

Time period	Instrument	Number of core questions	Total possible questions
Follow up	PASC symptoms	44+8*	~210-220
	Vaccine status	1	2 + 2 more for each dose
	Social determinants of health	10	10
	Alcohol and tobacco	5	7
	Pregnancy	1	11
	Medication changes	1	2
	Comorbidities	27	138
	COVID treatment	12	24
	Long COVID treatment trial	1	9
	TOTAL	**103**	**>310**

RECOVER Adult Symptom Survey: Example Questions (Slide 1 of 4)

Category	#	Symptom short name	Symptom as it appears in the RECOVER questionnaire	Additional Severity criteria
General	1	Fatigue	Fatigue (being very tired)	PROMIS Fatigue Score (moderate or worse)
	2	Fever/sweat/chills	Fever, chills, sweats or flushing	
	3	P-E Malaise	Post-exertional malaise (Symptoms worse after even minor physical or mental effort)	
	4	Swelling of legs	Swelling of your legs	
	5	Unspecified pain	Unspecified pain	PROMIS Pain Score (<3)
Cardiac	6	Chest pain	Chest pain (including chest tightness, pressure)	SAQ-7 (<75)
	7	Palpitations	Palpitations, racing heart, arrythmia, skipped beats	
Musculoskeletal	8	Hair loss	Hair loss	
	9	Skin color changes	Color changes in your skin, such as red, white or purple	
	10	Skin pain	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	Vision problems (blurry, light sensitivity, difficulty reading or focusing, floaters, flashing lights, "snow")	VFQ-25 (composite <75)

Notes: 44 (males) – 47 (females) symptoms. Multiple severity scales.

RECOVER Adult Symptom Survey: Example Questions (Slide 2 of 4)

Category	#	Symptom short name	Symptom as it appears in the RECOVER questionnaire	Additional Severity criteria
Gastrointestinal	14	Abdominal pain	Abdomen (belly) pain	PROMIS Pain Score (>3)
	15	Dry mouth	Excessively dry mouth	
	16	GI	Gastrointestinal (belly) symptoms (feeling full or vomiting after eating, diarrhea, constipation)	
	17	Mouth pain	Mouth pain	PROMIS Pain Score (>3)
	18	Teeth	Problems with teeth	
Metabolic	19	Thirst	Excessive thirst	
Musculoskeletal	20	Back pain	Back/spine pain	PROMIS Pain Score (>3)
	21	Foot pain	Foot pain	PROMIS Pain Score (>3)
	22	Joint pain	Joint pain	PROMIS Pain Score (>3)
	23	Muscle pain	Muscle pain	PROMIS Pain Score (>3)
	24	Weakness	Weakness in arms or legs	PROMIS Physical Function Short Form 4a (T<=40) or Neuro-QoL Upper

Notes: 44 (males) – 47 (females) symptoms. Multiple severity scales.

RECOVER Adult Symptom Survey: Example Questions (Slide 3 of 4)

Category	#	Symptom short name	Symptom as it appears in the RECOVER questionnaire	Additional Severity criteria
Neurologic	25	Abnormal movements	Abnormal movements	
	26	Brain fog	Problems thinking or concentrating ("brain fog")	Neuro-QoL Cognition Score (<=40)
	27	Dizziness	Feeling faint, dizzy, "goofy," difficulty thinking soon after standing up from a sitting or lying position	
	28	Headache	Head pain/headache	HIT-6 (substantial or worse)
	29	Numbness/tingling	Numbness, tingling, burning	Michigan Neuropathy Score (>6)
	30	Paralysis	Inability to move part of body	
	31	Seizures	Seizures	
	32	Smell/taste	Loss of or change in smell or taste	
	33	Tremor	Tremor	
	34	Unspecified nerve problem	Unspecified	
Psychiatric	35	Anxiety	N/A	Anxiety (GAD-7>9)
	36	Depression	N/A	Depression (PHQ-8>9)
	37	Sexual desire/capacity	Changes in desire for, comfort with or capacity for sex	
	38	Sleep disturbance	Sleep disturbance	Sleep disturbance score (>=60)

Notes: 44 (males) – 47 (females) symptoms. Multiple severity scales.

RECOVER Adult Symptom Survey: Example Questions (Slide 4 of 4)

Category	#	Symptom short name	Symptom as it appears in the RECOVER questionnaire	Additional Severity criteria
Reproductive	39	Pelvic/genital pain	Pelvis or genital pain	PROMIS Pain Score (>3)
Respiratory	40	Chronic cough	Persistent (chronic) cough	
	41	Shortness of breath	Shortness of breath	MMRC Dyspnea scale (>1)
	42	Sleep apnea	Sleep apnea	
	43	Throat pain	Throat pain	PROMIS Pain Score (>3)
Urinary	44	Bladder	Bladder problems (incontinence, trouble passing urine or emptying bladder)	

Notes: 44 (males) – 47 (females) symptoms. Multiple severity scales.

RECOVER Adult Self-Reported Symptoms (47/57*)

General
- Fatigue
- Fever/swells/chills
- Swelling
- Post-exertional malaise of legs

Cardiac
- Chest pain
- Palpitations

Metabolic
- Thirst

Urinary
- Bladder

Ear/Eye
- Hearing problems
- Vision problems

Psychiatric
- Anxiety
- Depression
- Sexual capacity
- Sleep disturbance

Dermatologic
- Hair loss
- Skin color
- Skin pain
- Skin rash

Neurologic
- Abnormal movements
- Brain fog
- Dizziness
- Headache
- Numbness/tingling
- Paralysis
- Seizures
- Loss of smell/taste
- Tremor
- Unspecified nerve pain

Respiratory
- Chronic cough
- Shortness of breath
- Sleep apnea
- Throat pain

Reproductive
- Pelvic/genital
- Menstrual cycle changes
- Amenorrhea
- Fertility
- Menopause

Musculoskeletal
- Back pain
- Foot pain
- Joint pain
- Muscle pain
- Weakness

Gastrointestinal
- Abdominal pain
- Dry mouth
- GI symptoms
- Mouth pain
- Teeth

*** 10 new symptoms added in 6/2023**: Headache (separate); Soreness: Next day soreness or fatigue after non-strenuous, everyday activities; Temp: Feeling hot or cold for no reason; Cold: Cold limbs (e.g., arms, legs, hands); Smellsick: Some smells, foods, medications, or chemicals make you feel sick; Sinus: Runny nose (allergic rhinitis) or sinus problems; Headache: headache (as a separate question instead of listed under “pain in any part of your body”; Wheeze: Wheezing or whistling in your chest; Itching: Episodes of itching and/or hives; Anaphylaxis: Episodes of severe allergic reaction (anaphylaxis), with or without any known trigger; Bald: Hair loss

Core Questions/Instruments (Slide 1 of 6)

Instrument	Topic	N of core questions	Triggers additional question
PROMIS-10	Quality of life (overall health, quality of life, physical health, mental health, satisfaction with social activities and relationships, carry out usual social activities, carry out usual physical activities, anxiety/depression past week, fatigue past week, pain past week)	10	N/A
PHQ-2	Depression screen (little interest or pleasure, feeling down/depressed/hopeless)	2	PHQ-8
C-SSRS	Suicidality screener	2	MINI
GAD-2	Anxiety screen (feeling nervous/anxious, uncontrolled worrying)	2	GAD-7
PTSD screener	Ever experienced extremely traumatic event	1	PC-PTSD→PCL-5

Core Questions/Instruments (Slide 2 of 6)

Instrument	Topic	N of core questions	Triggers additional question
Loss	Ever lost anyone	1	6 additional questions→ PG-13-R
RECOVER symptom screener	Core PASC symptoms or symptom clusters	26-30	See next table
Utilization	Use of hospital or ED since diagnosis	1	--

Core Questions/Instruments (Slide 3 of 6)

Instrument	Topic	N of core questions	Triggers additional question
RECOVER Symptoms	Fatigue (being very tired)	1	--
	Post-exertional malaise (Symptoms worse after even minor physical or mental effort)	1	--
	Weakness in arms or legs	1	PROMIS PF, Neuro-QoL Fine Motor
	Fever, chills, sweats or flushing	1	--
	Loss of or change in smell or taste	1	--
	Pain in any part of your body (head, back, joint, foot, muscle)[a]	1	Pain locator[a]→HIT, SAQ
	Shortness of breath	1	mMRC
	Persistent (chronic) cough	1	--

[a]1, Head pain/headache|2, Chest pain (including chest tightness, pressure)|3, Abdomen (belly)|4, Pelvis or genitals|5, Joints|6, Muscles|7, Back/spine|8, Skin|9, Feet|10, Mouth|11, Throat; 6/23: Headache separated out as an individual symptom

Core Questions/Instruments (Slide 4 of 6)

Instrument	Topic	N of core questions	Triggers additional question
RECOVER Symptoms	Palpitations, racing heart, arrhythmia, skipped beats	1	--
	Swelling of your legs	1	--
	Gastrointestinal (belly) symptoms (feeling full or vomiting after eating, diarrhea, constipation)	1	COMPASS-31
	Bladder problems (incontinence, trouble passing urine or emptying bladder)	1	COMPASS-31
	Nerve problems (tremor, shaking, abnormal movements, numbness, tingling, burning, can't move part of body, new seizures)	1	Type of nerve problem, Michigan neuropathy, PROMIS PF, Neuro-QoL
	Problems with anxiety, depression, stress, or trauma-related symptoms like nightmares or grief	1	--

Core Questions/Instruments (Slide 5 of 6)

Instrument	Topic	N of core questions	Triggers additional question
RECOVER Symptoms	Problems thinking or concentrating (“brain fog”)	1	Neuro-QoL cognition
	Problems with sleep	1	Apnea, PROMIS sleep disturbance
	Feeling faint, dizzy, “goofy”; difficulty thinking soon after standing up from a sitting or lying position	1	COMPASS-31[b]
	Color changes in your skin, such as red, white or purple	1	COMPASS-31[b]
	Excessively dry mouth	1	COMPASS-31[b]
	Excessive thirst	1	--

[b] *Since 6/2023, COMPASS is asked of every participant on follow-up surveys*

Core Questions/Instruments (Slide 6 of 6)

Instrument	Topic	N of core questions	Triggers additional question
RECOVER Symptoms	Vision problems (blurry, light sensitivity, difficulty reading or focusing, floaters, flashing lights, "snow")	1	VFQ-25
	Problems with hearing (hearing loss, ringing in ears)	1	--
	Hair loss	1	--
	Problems with teeth	1	--
	Changes in desire for, comfort with or capacity for sex	1	SHOW-Q, UCLA Prostate
	Changes to menstrual cycle[c]	1	RECOVER female
	Changes to menopause symptoms[c]	1	RECOVER female
	Changes in fertility or difficulty getting pregnant[c]	1	RECOVER female

[c] *Female-only question*

Answer Options for Baseline RECOVER Symptoms

"Please tell us at what time(s) you have had any of the following symptoms. Check all that apply."

<table>
<tr><th>Category</th><th colspan="5">Response options</th></tr>
<tr><td>Baseline: Infected within last 30 days (Acute infected)</td><td rowspan="4">No, I have NOT had this symptom</td><td>Yes, I DID have it in the YEAR BEFORE my COVID infection on [date]</td><td colspan="2">Yes, I DID have it AROUND the time of my COVID infection on [date]</td><td rowspan="4">Yes, I have it NOW</td></tr>
<tr><td>Baseline: Uninfected, negative test within last 30 days (Acute uninfected)</td><td>Yes, I DID have it in the YEAR BEFORE [date of negative test]</td><td colspan="2">Yes, I DID have it AROUND the time of [date]</td></tr>
<tr><td>Baseline: Infected > 30 days ago
(Post-acute infected)</td><td>Yes, I DID have it in the YEAR BEFORE my COVID infection on [date]</td><td>Yes, I DID have it AROUND the time of my COVID infection on [date]</td><td>Yes, I DID have it BETWEEN 30 DAYS AFTER my COVID infection on [date] and NOW</td></tr>
<tr><td>Baseline: Uninfected, negative test > 30 days ago
(Post-acute uninfected)</td><td>Yes, I DID have it in the YEAR BEFORE [date of negative test]</td><td>Yes, I DID have it AROUND the time of [date]</td><td>Yes, I DID have it BETWEEN 30 DAYS AFTER [date] AND NOW</td></tr>
</table>

What it Looks Like to Participants on Baseline Forms

PASC Symptoms

AAA English

Please tell us at what time(s) you have had any of the following symptoms. Check all that apply.

	No, I have NOT had this symptom	Yes, I DID have it in the YEAR BEFORE my COVID infection on 2020-11-15	Yes, I DID have it AROUND the time of my COVID infection on 2020-11-15	Yes, I DID have it BETWEEN 30 DAYS AFTER my COVID infection on 2020-11-15 AND NOW	Yes, I have it NOW	I don't know or prefer not to answer
Fatigue (being very tired) * must provide value	☐	☐	☐	☐	☐	☐
Post-exertional malaise (Symptoms worse after even minor physical or mental effort) * must provide value	☐	☐	☐	☐	☐	☐
Weakness in arms or legs * must provide value	☐	☐	☐	☐	☐	☐
Fever, chills, sweats or flushing * must provide value	☐	☐	☐	☐	☐	☐
Loss of or change in smell or taste * must provide value	☐	☐	☐	☐	☐	☐
Pain in any part of your body * must provide value	☐	☐	☐	☐	☐	☐
Shortness of breath * must provide value	☐	☐	☐	☐	☐	☐
Persistent (chronic) cough * must provide value	☐	☐	☐	☐	☐	☐

	No, I have NOT had this symptom	Yes, I DID have it in the YEAR BEFORE my COVID infection on 2020-11-15	Yes, I DID have it AROUND the time of my COVID infection on 2020-11-15	Yes, I DID have it BETWEEN 30 DAYS AFTER my COVID infection on 2020-11-15 AND NOW	Yes, I have it NOW	I don't know or prefer not to answer
Problems thinking or concentrating ("brain fog") * must provide value	☐	☐	☐	☐	☐	☐
Stopping breathing during sleep or sleep problems (such as snoring, trouble falling asleep, nighttime awakenings, or trouble staying awake during the day) 3 or more times a week * must provide value	☐	☐	☐	☐	☐	☐
Feeling faint, dizzy, "goofy"; difficulty thinking soon after standing up from a sitting or lying position * must provide value	☐	☐	☐	☐	☐	☐
Color changes in your skin, such as red, white or purple * must provide value	☐	☐	☐	☐	☐	☐
Skin rash * must provide value	☐	☐	☐	☐	☐	☐
Excessively dry mouth * must provide value	☐	☐	☐	☐	☐	☐
Excessive thirst * must provide value	☐	☐	☐	☐	☐	☐

Answer Options for Follow-Up RECOVER symptoms

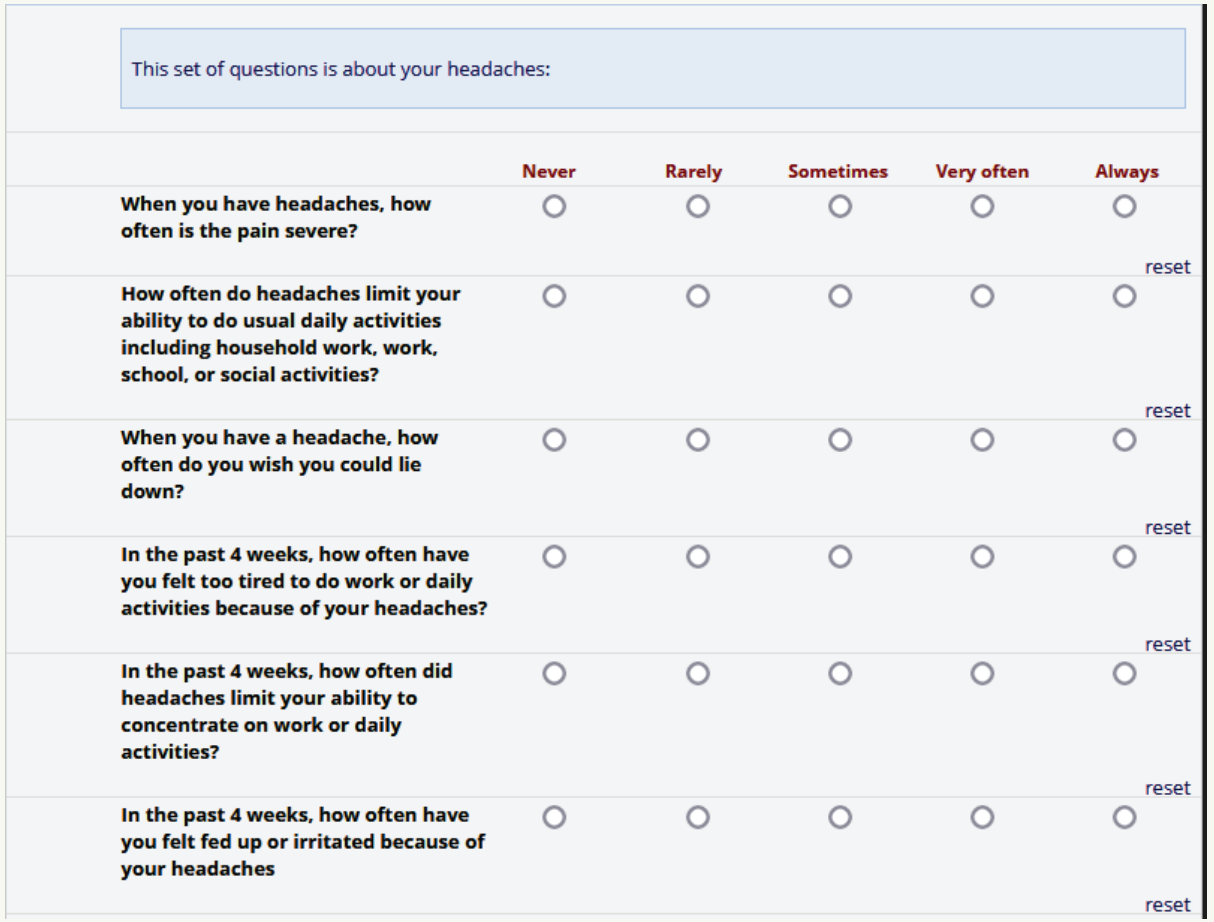
"Did you have any of the following symptoms in the LAST THREE MONTHS?"

Category	Response options		
3-month follow-up (everyone)	No	Yes, but I NO LONGER have it	Yes, and I STILL HAVE IT*

** 6/2023: Wording changed to "Yes, and I STILL HAVE IT (in the past 30 days)"*

Severity Scales

Headache Inventory: HIT



This set of questions is about your headaches:

	Never	Rarely	Sometimes	Very often	Always	
When you have headaches, how often is the pain severe?	○	○	○	○	○	reset
How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?	○	○	○	○	○	reset
When you have a headache, how often do you wish you could lie down?	○	○	○	○	○	reset
In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?	○	○	○	○	○	reset
In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?	○	○	○	○	○	reset
In the past 4 weeks, how often have you felt fed up or irritated because of your headaches	○	○	○	○	○	reset

Seattle Angina Questionnaire

Question	Response options
Walking indoors on level ground	1, Extremely limited | 2, Quite a bit limited | 3, Moderately limited | 4, Slightly limited | 5, Not at all limited | 6, Limited for other reasons or did not do the activity
Gardening, vacuuming, or carrying groceries	1, Extremely limited | 2, Quite a bit limited | 3, Moderately limited | 4, Slightly limited | 5, Not at all limited | 6, Limited for other reasons or did not do the activity
Lifting or moving heavy objects (e.g., furniture, children)	1, Extremely limited | 2, Quite a bit limited | 3, Moderately limited | 4, Slightly limited | 5, Not at all limited | 6, Limited for other reasons or did not do the activity
Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?	1, 4 or more times per day | 2, 1-3 times per day | 3, 3 or more times per week but not every day | 4, 1-2 times per week | 5, Less than once a week | 6, None over the past 4 weeks
Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (tablets or spray) for your chest pain, chest tightness, or angina?	1, 4 or more times per day | 2, 1-3 times per day | 3, 3 or more times per week but not every day | 4, 1-2 times per week | 5, Less than once a week | 6, None over the past 4 weeks
Over the past 4 weeks, how much has your chest pain, chest tightness, or angina limited your enjoyment of life?	1, It has extremely limited my enjoyment of life | 2, It has limited my enjoyment of life quite a bit | 3, It has moderately limited my enjoyment of life | 4, It has slightly limited my enjoyment of life | 5, It has not limited my enjoyment of life at all
If you had to spend the rest of your life with your chest pain, chest tightness, or angina the way it is right now, how would you feel about this?	1, Not satisfied at all | 2, Mostly dissatisfied | 3, Somewhat satisfied | 4, Mostly satisfied | 5, Completely satisfied

Modified Medical Research Council Dyspnea Scale

Question	Response options
Which of the following best describes your shortness of breath?	0, I only get breathless with strenuous exercise. | 1, I get short of breath when hurrying on the level or walking up a slight hill. | 2, I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level. | 3, I stop for breath after walking about 100 meters or after a few minutes on the level. | 4, I am too breathless to leave the house or I am breathless when dressing or undressing.

Michigan Neuropathy Screening Instrument

Questions	Response options
Are your legs and/or feet numb?	1, Yes | 2, No
Do you ever have any burning pain in your legs and/or feet?	1, Yes | 2, No
Are your feet too sensitive to touch?	1, Yes | 2, No
Do you get muscle cramps in your legs and/or feet?	1, Yes | 2, No
Do you ever have any prickling feelings in your legs or feet?	1, Yes | 2, No
Does it hurt when the bed covers touch your skin?	1, Yes | 2, No
When you get into the tub or shower, are you able to tell the hot water from the cold water?	1, Yes | 2, No
Have you ever had an open sore on your foot?	1, Yes | 2, No
Has your doctor ever told you that you have diabetic neuropathy?	1, Yes | 2, No
Do you feel weak all over most of the time?	1, Yes | 2, No
Are your symptoms worse at night?	1, Yes | 2, No
Do your legs hurt when you walk?	1, Yes | 2, No
Are you able to sense your feet when you walk?	1, Yes | 2, No
Is the skin on your feet so dry that it cracks open?	1, Yes | 2, No
Have you ever had an amputation?	1, Yes | 2, No

RECOVER Data and Sample Availability

Data/Sample Availability: RECOVER Adult Cohort

- Sample size = 14,754; Enrollment Ns:
  - 4,965 acute infected
  - 7,308 post-acute infected
  - 1,166 acute uninfected
  - 1,315 post-acute uninfected
    - 2,481 uninfected total
- Crossovers: Among the 2,511 uninfected individuals, N=1036 (41%) reported on-study infections and were assigned to the acute infected group
- Tier 2/Tier 3 tests are in the process of being scheduled/completed
- Sample types collected at baseline and specified f/u time points:
  - Serum
  - Plasma
  - PBMC
  - Whole blood (PAXgene)
  - Saliva
  - Nasal swab/nasopharyngeal swab
  - Urine
  - Stool

RECOVER

Researching COVID to Enhance Recovery

National Institutes of Health

Researching COVID to Enhance Recovery

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