The ‘Researching COVID to Enhance Recovery’ (RECOVER) Initiative

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NIH Mission

The mission of the National Institutes of Health are to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

Goals:

• Foster fundamental creative discoveries, innovative research strategies, and their applications to protect and improve health

• Develop, maintain, and renew scientific human and physical resources that will ensure the Nation’s capability to prevent disease

• Expand the knowledge base in medical and associated sciences in order to enhance the Nation's economic well-being and ensure a continued high return on the public investment in research

• Exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

https://www.nih.gov
COVID-19 Affects Multiple Organs

The Scientist, April 2020
# The Post-Acute Sequelae of COVID-19: Symptom clusters overlap with ME/CFS

Fatigue in almost 99% of those with PACS. Prevalence of post-exertional malaise maybe as high as 90%

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>CardioPulmonary</th>
<th>Gastrointestinal</th>
<th>Other</th>
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<tr>
<td>Memory/Word finding difficulties</td>
<td>Shortness of breath</td>
<td>Diarrhea</td>
<td>Elevated temperature</td>
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<td>Concentration difficulties/“brain fog”</td>
<td>Dry cough</td>
<td>Decreased appetite</td>
<td>Chills, flushing sweats</td>
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<td>Executive function difficulties</td>
<td>Chest pain</td>
<td>Nausea</td>
<td>Sore throat</td>
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<td>Sleep disorders</td>
<td>Exercise intolerance</td>
<td>Abdominal pain</td>
<td>Extreme thirst</td>
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<td>Pain syndromes- muscle, joint</td>
<td>Postural Orthostatic Tachycardia</td>
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<td>Skin changes</td>
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<tr>
<td>Abnormal sensations- tingling</td>
<td>Postural Orthostatic Tachycardia</td>
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<td>Menstrual changes</td>
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<td>Headache</td>
<td>Palpitations/ Fast heart rate</td>
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<td>Postural Orthostatic Tachycardia</td>
<td>Myocarditis</td>
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<tr>
<td>Abnormal smell/taste</td>
<td>Pulmonary fibrosis</td>
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<td>Visual abnormalities</td>
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<tr>
<td>Dizziness/balance problems</td>
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<td>? Confusional state/psychosis</td>
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</table>

**Mental Health**

- Post traumatic stress disorder
- Anxiety
- Depression

Assessment of Long-COVID Symptoms

Post-acute COVID-19 appears to be a multi-system disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of COVID-19 that was managed in the community or in a standard hospital ward.

An uncertain picture

The long-term course of COVID-19 is unknown. This graphic presents an approach based on evidence available at the time of publication. However, caution is advised, as patients may present atypically, and new treatments are likely to emerge.

Managing comorbidities

Many patients have comorbidities including diabetes, hypertension, kidney disease or ischaemic heart disease. These need to be managed in conjunction with COVID-19 treatment. Refer to condition specific guidance, available in the associated article by Greenhalgh and colleagues.

"Long covid” in primary care

Assessment and initial management of patients with continuing symptoms

Clinical testing is not always needed, but can help to pinpoint causes of continuing symptoms, and to exclude conditions like pulmonary embolism or myocarditis. Examples are provided below:

**Blood tests**
- Full blood count
- Electrolytes
- Liver and renal function
- Troponin
- C reactive protein
- Creatine kinase
- D-dimer
- Brain natriuretic peptides
- Ferritin

Other investigations
- Chest x-ray
- Urine tests
- 12 lead electrocardiogram

Social, financial, and cultural support

Prolonged COVID-19 may limit the ability to engage in work and family activities. Patients may have experienced family bereavements as well as job losses and consequent financial stress and food insecurity. 

Examination, for example:

- Temperature
- Heart rate and rhythm
- Blood pressure
- Respiratory examination
- Functional status
- Pulse oximetry
- Clinical examination

If indicated

Assess comorbidities

Social and financial circumstances

Proposed Treatment of Long-COVID Symptoms

Safety netting and referral

The patient should seek medical advice if concerned, for example:
- Worsening breathlessness
- $\text{PaO}_2 < 96\%$
- Unexplained chest pain
- New confusion
- Focal weakness

Specialist referral may be indicated, based on clinical findings, for example:
- Respiratory if suspected pulmonary embolism, severe pneumonia
- Cardiology if suspected myocardial infarction, pericarditis, myocarditis or new heart failure
- Neurology if suspected neurovascular or acute neurological event

Pulmonary rehabilitation may be indicated if patient has persistent breathlessness following review

Medical management

Symptomatic, such as treating fever with paracetamol
- Optimise control of long term conditions
- Listening and empathy
- Consider antibiotics for secondary infection
- Treat specific complications as indicated

Self management

- Daily pulse oximetry
- Attention to general health
- Rest and relaxation
- Self pacing and gradual increase in exercise if tolerated
- Set achievable targets

Mental health

In the consultation:
- Continuity of care
- Avoid inappropriate medicalisation
- Longer appointments for patients with complex needs (face to face if needed)

In the community:
- Community linkworker
- Patient peer support groups
- Attached mental health support service
- Cross-sector partnerships with social care, community services, faith groups

Diet
- Sleep
- Quitting smoking
- Limiting alcohol
- Limiting caffeine

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Researching COVID to Enhance Recovery

recoverCOVID.org
RECOVER Listening Session

Impressions and Observations

- Messaging needed on the **critical nature of research** and ability to inform treatments, clinical decisions, and health care policies around PASC.
- **Interest groups around Long COVID are engaged** and want to be involved.
- Currently a lack of public knowledge on the roles Federal agencies serve generally, especially as it relates to responding to COVID-19.
- **Strong desire to have patients** – and patient interest leaders – **integral to the planning and implementation** of the research.
- The **most powerful voice(s) are those of the people affected.**

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30
Of 40 RSVPs attended

At peak,

~140
people watched the NIH VideoCast live

recoverCOVID.org
Goal

- Rapidly improve our understanding of and ability to treat and prevent PASC

Key Scientific Questions

1. What are the clinical spectrum of and biology underlying recovery from acute SARS-CoV-2 infection over time?

2. For those patients who do not fully recover, what is the incidence/prevalence, natural history, clinical spectrum, and underlying biology of this condition? Are there distinct phenotypes of patients who have prolonged symptoms or other sequelae?

3. Does SARS-CoV-2 infection initiate or promote the pathogenesis of conditions or findings that evolve over time to cause organ dysfunction or increase the risk of developing other disorders?
PASC Initiative Components

SARS-CoV-2 Recovery Meta-Cohort

- Clinical Recovery Cohort
- Autopsy Cohort (Acute and PASC)
- EHR- and Other Real-World Data-Based Studies

Investigator Consortium

All study investigators will work together to:

- Conduct rapid systematic screening and follow-up evaluations of infected individuals, to provide a resource for in-depth multi-disciplinary phenotyping, and to pool data and share biospecimens and data from across studies
- Develop a streamlined set of common core protocol elements (specific hypotheses, design elements, screening evaluations, exams, lab tests, functional assessments, imaging, etc.) and to provide a collaborative for multi-disciplinary phenotyping
**Adult Population Awardees**

Brigham and Women’s Hospital  
Case Western Reserve University School of Medicine  
Howard University College of Medicine  
Icahn School of Medicine at Mount Sinai  
University of Alabama at Birmingham Heersink School of Medicine  
University of Arizona College of Medicine- Tuscon  
University of Illinois Hospital & Health Sciences System  
University of Texas Health Science Center  
University of Utah Health  
West Virginia University of Health Sciences  
Emory University

**Pediatric Population Awardees**

Arkansas Children’s Research Institute  
Children’s Hospital Los Angeles  
Rhode Island Hospital  
Rutgers Robert Wood Johnson Medical School

**Pregnant Population Awardees**

University of Utah Health

**Tissue Pathology Study Awardees**

Brigham and Women’s Hospital  
CVPath Institute  
Icahn School of Medicine at Mount Sinai

**Real-World Data Awardees**

University of Colorado
RECOVER Initiative Stats

39M+
People with a SARS-CoV-2 infection in the US … and counting

10%-30%
Preliminary estimate of the percentage of people infected with SARS-CoV-2 who will experience PASC

200+
Estimated number of RECOVER research clinical sites

Many 100s
Number of researchers involved in RECOVER
Ongoing PASC Clinical Trials

• Over 2 dozen studies in various stages of completion in adult patients:
  • Phase 2 trial in Long COVID Adults testing efficacy of RSLV-132 Remdesivir
  • Hyperbaric oxygen versus Placebo
  • Naltrexone
  • Serotonin enhances
  • Anti-fibrotic medication
  • Anti-inflammatory interventions
  • Sirolimus in Treating COVID019 Pneumonia for prevention of Post-COVID Fibrosis
• A pediatric trial studying efficacy of resistance exercise
Main conclusions:
• Instruments and measures of fatigue vary significantly in studies of different diseases making it difficult to compare across studies
• Very little research on the transition of acute fatigue to chronic fatigue in the setting of disease
• Neuroimmune interactions important, but mechanisms not understood
• Gut-brain interactions also important, but does it impact fatigue?
• Risk factors for post-infectious and post-cancer chronic fatigue not known
• New studies on glymphatics, CSF flow and relationship to sleep may be critical in understanding fatigue
• Need to apply new technologies to the study the neurobiology of fatigue
• Model systems are needed and will be critical in studying the cellular mechanisms of fatigue
Thank you!

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