Ongoing Research and Planning for New Research Program on Post Acute Sequelae of SARS-CoV-2 Infection (PASC)

Walter Koroshetz, MD, Director, NINDS

February 26, 2021
NIH Research on COVID-19

- Therapeutics
- Diagnostics
- Natural History
- Vaccines
- Research Resources
- Basic Research
NIH Research on COVID-19

How to address an emerging problem: recovery from SARS-CoV-2 infection?
The Post-Acute Sequelae of SARS-CoV-2 Infection: Symptom clusters overlap with ME/CFS

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

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

See Davis HE et. al. (2021) Characterizing Long Covid in an International Cohort: 7 months of symptoms and their impact. medRxiv preprint
There are many ongoing NIH resources that can be leveraged to better understand COVID recovery.

Electronic Health Records and Health Systems studies; 10 million+ collective participants. E.g.,
- National COVID Cohort Collaborative (N3C) (EHR-based COVID)
- eMERGE: combines DNA biorepositories with electronic medical record (EMR) systems
- North American – AIDS Cohort Collaboration on Research and Design
  - Corona infectious virus epidemiology team (CIVETs)
- All of Us: COVID survey, antibody testing, and more

40+ studies with cohorts of COVID-19 cases; 20,000+ collective participants. E.g.,
- NCCAPS: longitudinal study of patients with cancer/diagnosed with COVID
- COVNET: GWAS to identify genetic variants associated with susceptibility to COVID
- PETAL Network/BLUE CORAL: collect comprehensive data on hospitalized patients with COVID-19
- Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC)
- RADx-UP: diagnostics in underserved populations
- Pediatric studies: PRISM, PreVAIL kids, MUSIC, ARC, AICORE-kids

30+ studies with cohorts with pre-pandemic deep phenotyping (esp. neurologic, cardiac, or pulmonary); 100,000+ collective participants. E.g.
- Collaborative Cohort-of-Cohorts for COVID-19 Research (C4R)
  - Includes 14 cohorts: ARIC, CARDIA, Framingham, HCHS, Jackson, MASALA, MESA, Strong Heart, COPDGene, FIP, SARP, SPIROMICS, REGARDS, NOMAS
- HIV studies: REPRIEVE, CNICS,
- PARIS (pediatric AHRF), SPARTA (emphysema), ABCD (diabetes),
- ECHO (ped./environment)

Plus many more, including studies in special populations
NINDS supported projects related to COVID + ME/CFS

COVID Research Supplement Program

Notice of Special Interest (NOSI): Availability of Urgent Competitive Revisions and Administrative Supplements For Research on Biological Effects of the 2019 Novel Coronavirus on the Nervous System
Notice Number: NOT-NS-20-051

E.g., award to Leonard Jason (PI) at DePaul University (R01-NS111105)
- Add-on study to college student cohort (~4500 young adults) to assess long-term health of those that have contracted COVID-19
- This is building on an ongoing ME/CFS study re post EBV fatigue syndrome

NIH NeuroCOVID Project (at NYU Langone)

- Database will collect information from clinicians about COVID-19-related neurological symptoms, complications, and outcomes as well as COVID-19 effects on pre-existing neurological conditions
- Associated biospecimen bank

Ongoing Intramural studies: Led by Avi Nath, Brian Walitt, Bryan Smith, and others
Intramural studies addressing long term neurological symptoms associated with COVID-19

**Natural History of Post-Coronavirus Disease 19 Convalescence**
Avi Nath (NINDS), Brian Walitt (NINR)

To observe and describe the range of medical syndromes that occur following an acute COVID-19 infection

Study population: 1000 adults who are within six months of their convalescence from an acute COVID-19 infection

Starting with telephone interviews and internet-based questionnaires; following phases = in depth evaluation at CC; focus on identifying patients who overlap with ME/CFS; longitudinal follow up

**An Observational Study of Neurologic Function after COVID-19 Infection**
Avi Nath (NINDS), Bryan Smith (NINDS)

To investigate structural abnormalities by brain MRI and other components of neurologic function in those with prior SARS-CoV-2 infection and persistent neurologic symptoms
Is SARS-CoV-2 in the brain?

- Post-mortem study of brains of individuals who had COVID-19
- No evidence of viral infection in brain
- Widespread evidence of inflammation and damage, including:
  - Multifocal breakdown of the blood brain barrier, small infarcts, microhemorrhages, inflammatory infiltrates, and microglial nodules,
- Infection can lead to blood clots → stroke

Pathological Studies of Microvascular Injury in the Brains of Patients Who Died from COVID-19

Nath et al, *NEJM*, NINDS
COVID-19 Affects Multiple Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cells/Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>goblet/ciliated, secretory/mucous, AT2 cells</td>
</tr>
<tr>
<td>Lung</td>
<td>epithelial, fibroblast, myocyte, pericyte</td>
</tr>
<tr>
<td>Ileum</td>
<td>enterocytes, endothelial, fibroblast, myocyte</td>
</tr>
<tr>
<td>Heart</td>
<td>myocyte, pericyte, corneal epithelium</td>
</tr>
<tr>
<td>Eye</td>
<td>corneal epithelium, choroidal cells</td>
</tr>
<tr>
<td>Liver</td>
<td>epithelial, fibroblast, pericyte</td>
</tr>
</tbody>
</table>

The Scientist, April 2020
NIH Post Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative
NIH Post Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative

Coronavirus Response and Relief Supplemental Appropriations Act, 2021

- NIH Office of the Director received $1.15 billion over 4 years for research and clinical trials related to long-term studies of COVID–19

NIH is leveraging Other Transaction Authority (OTA), which offers flexibility and the ability to engage partners in collaborative innovation and problem solving.

Just announced!

https://covid19.nih.gov/funding/open-funding-opportunities

Recovery Cohort - Research Opportunity soliciting proposals for studies involving: (a) clinical recovery cohorts, (b) EHR and other real-world data, and (c) autopsy cohorts; proposals must be received by March 23

Cores - Research Opportunity soliciting proposals for: (a) a Data Resource Core, (b) a Clinical Studies Core, and (c) a Biospecimen Core; proposals must be received by March 16
**NIH PASC Research**

**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?
NIH SARS-CoV-2 Recovery Cohort
5-10K PASC over 3-6 months

Acute SARS-CoV-2 Infection Cohorts

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

Post-Acute SARS-CoV-2 Infection Cohorts

For those patients who do not fully recover or develop new sx/sequelae, what is the clinical spectrum and underlying biology?

EHR-/Health Systems-Based Studies

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?
Research Approach

1 Establish a SARS-CoV-2 Recovery Cohort to yield ~ 5-10K PASC cases over the next 3-6 months
   - SARS-CoV-2 infection case-driven and multi-disciplinary prospective assessment of PASC
     - Incidence/ prevalence, epidemiology, clinical spectrum, outcomes, risk factors
     - Leverage ongoing fit-for-purpose cohorts as well as new cohort studies
     - Includes children and adults (including pregnant women) and inclusive participation
     - Proactive community engagement as integral element
     - Will inform design of treatment and prevention strategies

2 Leverage EHR- and Other Real-World Data-Based analyses

3 Autopsy Studies
Clinical Characterization/Phenotyping

Streamlined core protocol elements (exam, labs, functional tests, imaging) to capture spectrum of PASC

Examples of assessments could include:
- Imaging (CT, MRI, Echo)
- Functional Assessments (PFTs, 6MW, ETT)
- Neuropsychiatric assessments (screening, questionnaires, testing)
- Psychosocial Factors, SDoH
- Immunophenotyping
- Biospecimens (Biomarkers, Multi-omics)
  - More in-depth assessments as indicated (e.g., fpgPET)
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
PASC Initiative Components

- The goals of the Recovery Cohort and Investigator Consortium will be supported by administrative coordination and oversight as well as three cores:
  - Clinical Science Core
  - Data Resource Core
  - PASC Biorepository Core
PASC Initiative Components

- The goals of the Recovery Cohort and Investigator Consortium will be supported by administrative coordination and oversight as well as three cores:
  - Clinical Science Core

Community and patient engagement

“The Clinical Science Core will provide.... Leadership of a Patient Engagement Working Group (e.g. a Community Advisory Board) to engage PASC patients, physicians and other stakeholders in shaping the research agenda initially and iteratively as research questions evolve, to work with investigators in disseminating information on the rationale and ethical basis for conducting the PASC studies, and to provide feedback from the community at large on the research. The Patient Engagement Working Group should be diverse and represent a broad range of patients and communities...”
Proposed NIH Workplan

Timeline is subject to change

January
- Issue “NOITP”
- Launch Administrative Coordinating Center

February
- Clinical Science Core
- Data Resource Core
- Biorepository Core

March
- Launch Clinical Science Core
- Launch Data Resource Core
- Launch Clinical Cased-Based Recovery Cohort
- Autopsy Study
- EHR-/Health Systems-Based Studies

April
- EHR-HS-Based Study
- COVID Case-Based Study (Adults)
- COVID Case-Based Study (Pediatric)

Iterative evolution of MP/eligibility criteria as PASC phenotype evolves

Early Deliverables

Initial Solicitations

Milestone-driven
Learn More: Technical Assistance Workshop

March 1, 5 PM ET

- **Audience:** Potential applicants for Research Opportunities
- **Purpose:** To enhance potential applicant understanding of the Research Opportunity Announcements and facilitate preparation of responsive applications
- **Topics:**
  - Overview of the vision and specific objectives of PASC initiative highlighting key scientific/research elements of the ROAs including the three cores and the three specific research components
  - Overview of the OT mechanism and application process and requirements
  - Answer prospective applicant questions

Registration available at: [https://covid19.nih.gov/funding/open-funding-opportunities](https://covid19.nih.gov/funding/open-funding-opportunities)
Discussion