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</table>
1) Problem statement
2) Clinical manifestations and knowledge gaps
3) Leveraging our assets and strengths
Post-Acute COVID-19 Syndrome

From ‘Brain Fog’ to Heart Damage, COVID-19’s Lingering Problems Alarm Scientists
J Couzin-Frankel

Long After the Fire of a COVID-19 Infection, Mental and Neurological Effects Can Still Smolder
E Cooney
Long-Term Effects of Covid-19 Infection

COVID-19 Affects Multiple Organs

The Scientist, April 2020
CLINICAL MANIFESTATIONS AND KNOWLEDGE GAPS
COVID-19: Persistent Symptoms in Hospitalized Patients
A Multi-Organ, Multi-System Clinical Presentation

Persistent symptoms

- Fatigue 55%
- Difficulty breathing 42%
- Memory loss 34%
- Sleep disorder 32%
- Attention disorder 27%
- Significant hair loss 20%
- Cough 17%
- Loss of smell 13%
- Chest pain 11%
- Loss of taste 11%

120 patients (mean = 111 days post admission)

143 patients (mean 60 days post onset)

https://doi.org/10.1016/j.jinf.2020.08.029

COVID-19: Persistent Symptoms and Health-related Quality of Life \(^1\)

**A Multi-Organ, Multi-System Clinical Presentation**

120 patients (mean = 111 days after admission for COVID-19)

### Professional and physical activities
- Not yet resumed to sports (engaged regularly pre-COVID) 28%
- Slower walking 29%
- Not yet returned to work (worked pre-COVID) 32%

---

Among symptomatic non hospitalized patients with positive test for SARS-CoV-2, 35% not returned to baseline health 2-3 weeks after testing

- Older age and comorbidities associated with lack of return to baseline health
- 19% of young adults (18-34) with no comorbidities had not returned to baseline health
- In contrast 90% of influenza outpatients recover within 2 weeks
New diagnoses of anxiety, insomnia, dementia and mood disorders as well as psychiatric disorders in general, were increased after COVID-19 illness.
Cross-talk among injured organs might explain post-acute COVID syndrome

- Lung
- Heart
- Liver
- Kidney
- GI Tract
- Fat

Microbial metabolites, Cytokines, Other circulating factors, Immune system dysfunction
cMRI revealed cardiac abnormalities in 78%, and gadolinium enhancement in 60%, (N-100), median 72d p dx.

- Independent of preexisting conditions, severity, and overall course of acute illness, and time from original diagnosis
- Lower EF, Higher LV volume, Higher hsTroponin
- 3 patients biopsied, demonstrate inflammatory infiltrates, no virus

15% of Ohio State University athletes had myocarditis after mild COVID-19, and fully half had CMR abnormalities
Cardiac Involvement in COVID-19

• Autopsy reports suggest direct cardiac involvement
  • Lindner showed virus in myocardium in majority of 39 autopsy cases with evidence of viral replication:
    ➢ Direct viral infection leading to myocardial injury??
  • Other reports have also shown myocardium infiltration of both innate and adaptive immune cells:
    ➢ Potential for cardiac fibrosis and decrease cardiac function in the long term??

• Conclusion: Long-term follow-up of recovered COVID-19 patients is necessary to assess risk of heart failure and other chronic CV complications


Potential common mechanisms between ischemic injury and COVID-19 induced cardiac remodeling; Unudurthi S. Life Sciences 2020; 260: 118482
COVID-19: Long-term lung sequelae

- Carvalho-Schneider et al. followed 150 patients with non-critical COVID-19 for 2 months after symptoms onset
  - Persistent dyspnea: 36.7% pts at 30d, 30% pts at 60d
  - Conclusion: A prolonged medical follow-up of patients with COVID-19 seems essential, whatever the initial clinical presentation (never admitted patients in this case)

- Zhao et al. analyzed 55 COVID-19 survivors (non-critical cases) 3 months after hospital discharge
  - Radiological abnormalities: 71% pts
  - Lung function abnormalities: 25% pts
  - Elevated D-dimer on admission predictive of impaired DLCO at 3 months post-d/c (in some pts, only abnormality)
  - Conclusion: It is necessary to follow up COVID-19 patients to appropriately manage persistent or emerging long-term sequelae
    - [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361108/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361108/)  July 2020
Nervous System and COVID-19

Manifestations during infection
- Stroke- large & small vessel occlusion, micro-bleeds
- Confusion and depressed level of consciousness
- Loss of smell
- Muscle/Nerve pain and weakness
- Meningitis/encephalitis
- Seizures
- Asymptomatic hypoxia

Rare Post-viral syndromes
- Delayed injury to brain and spinal cord (multiple sclerosis- like).
- Delayed injury to nerves (ie. Guillain Barre Syndrome)
- Parkinsonism
Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

LR Feldstein, S Li et al., for the Overcoming COVID-19 Investigators, and the CDC COVID-19 Response Team

- 186 patients in 26 states, median age 8.3 years
- 80% required ICU care, 20% required mechanical ventilation
- 71% with involvement of at least 4 organ systems
- 73% with no underlying conditions
Health Disparities in COVID-19 Risk and Mortality

Predisposing Conditions

- Cancer
- Chronic Kidney Disease
- COPD
- Heart Conditions
- Obesity
- Pregnancy
- Sickle Cell Disease
- Smoking
- Type 2 Diabetes

What we need to understand about recovery

• What is the spectrum of clinical “recovery” from COVID-19 infection?
  • Of those with symptoms 2-3 weeks post infection the rate of improvement is not yet known.

• What interventions might enhance or hasten recovery?
  • In the immediate post infection phase as well as in the more chronic phase

• What is the spectrum of tissue injury due to COVID-19 infection?
  • Are the various tissue injuries reversible, static, or contribute to progressive organ dysfunction
  • How to identify those with tissue injury in heart, lung, nervous system, kidney

• Will unabated symptoms lead to chronic illness(s) in a subset of people?
  • If so, what is its pathophysiology (s).
  • Is so, what are the drivers of special vulnerability or resilience across the lifespan and in special populations

• Will COVID-19 infection predispose people to other diseases in the future?
Preparing for the Possibility of a Post-COVID Storm

• Current expectation is that up to tens of thousands could suffer from sequelae of acute infection with COVID-19

• Time is of the essence - interventions are expected to have a greater effect the earlier they are employed

• The multi-organ involvement calls for a coordinated research program drawing on the expertise in multiple NIH Institutes and Centers
LEVERAGING OUR ASSETS AND STRENGTHS

A Few Examples
NIH Clinical Research Strategy to Understand and Treat Post-acute Sequelae of COVID-19

Note: Includes existing and new assets

Evaluation of Treatment and Preventive Strategies for Post-acute COVID-19 Sequelae

Longitudinal Community-Based Cohorts

- Large Scale EHR-/Health Systems-based Cohorts
- Longitudinal Deeply Phenotyped Community-based Cohorts

Case-based Registry Cohort of Persons with hx SARs COV-2 Infection

- Individuals Enrolled in NIH COVID-19 Clinical Trials
- Individuals Enrolled in NIH COVID-19 Case Registries/Observational Studies/Clinics

Data Coordination/Harmonization and Analytics Framework
NIAID: Observational Cohorts

- International Observational Study of Outpatients With SARS-CoV-2 Infection
- PREVAIL-XI: PREVAIL COVID-19 Observational Study
- Chasing COVID Cohort
- Immunophenotyping in a COVID-19 Cohort (IMPACC)
- Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)
- Observational study at San Antonio VA

- EHR based
  - Corona infectious virus epidemiology team (CIVETs)
  - Big Data Driven Clinical Informatics & Surveillance (BDD-CIS) project
Collaborative Cohort of Cohorts for COVID-19 Research (C4R)

- 70,000+ participants from 14+ longstanding longitudinal population- and disease-based cohorts
  - Highly diverse with multi-racial, multi-ethnic populations
  - Broad age range, national span of geographic reach
  - Enriched for at-risk populations (e.g., pre-existing lung disease)
  - Genotyped and deep phenotyping across multiple domains
    - Imaging, biomarkers, social determinants, lung function, anthropometry, vascular function, cognition, genetics and other -omics

- Leverage existing infrastructure, processes, data, and biospecimens from available cohorts/existing patient populations
  - Embed systematic protocolized assessment in existing cohorts
  - Include multiple nested sub-studies

- Collaboration with NHLBI, NINDS, and NIA
NHLBI platforms leveraged for development of COVID-19 Long term follow up cohorts

Registry and observational cohort study (CORAL) follow-up of COVID-19 inpatients (n = 3,000) leveraging critical care network

- Clinical characteristics, Rx, biology, and outcomes using retro/prospective methods
- Deidentified repository of clinical, imaging, and biologic data and biospecimens

*Serves as a pilot for:*

Larger Scale Multicenter Prospective COVID-19 Registry Cohort

- Leveraging the diagnosis, screening, and referral cores and clinical centers
- COVID-19 enriched and diverse cohort spanning pre-hospital, hospital, and post-discharge enrollment
- Systematic and protocolized collection of health data, biospecimens, and imaging on post-COVID pts for long-term, post-infection follow-up studies; utilizing full spectrum of data (EHR mining to IPLD)
- Fully consented for data sharing and follow-up
NIAID: A Longitudinal Study of COVID-19 Sequelae and Immunity

• Adults who have recovered from COVID-19 or were in close contact with someone with COVID-19 but did not become infected
• Evaluation includes history, physical exam, mental health exam, imaging and functional tests, laboratory draws
• Study visits at NIH Clinical Center every 6 months for 3 years
• Goal enrollment: 900
Funded programs to assess long-term neurological effects of 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 in 1000 adults within six months of their convalescence from an acute COVID-19 infection

- **Observational Study of Neurologic Function after COVID-19 Infection** Avi Nath, Bryan Smith (NINDS)
  - To investigate brain MRI and components of neurologic function in those with prior SARS-CoV-2 infection and persistent neurologic symptoms

- **NIH COVID-19 NeuroDataBank and NeuroBioBank** (at NYU Langone)
  - Building a national **(NeuroDataBank and BioBank)** to document and study neurological complications of COVID

- **Projects (through supplements)**
  - 2 studies examining **cognitive sequelae** of the biological effects of COVID-19 on the nervous system-cognitive batteries every 3 months for one year via phone to determine cognitive trajectories over time
  - **Neurofilament light chain (Nfl) protein in** predicting long term cognitive, behavioural and functional prognosis for ICU COVID patients
  - Add-on study to college student cohort (followed for post EBV **chronic fatigue** syndrome) to assess long-term health post COVID-19
## OVERALL AIM

To improve understanding of and develop strategies to treat and prevent post-acute manifestations of SARS-CoV-2 infection through a multi-pronged research framework.

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<th>To improve understanding of and develop strategies to treat and prevent post-acute manifestations of SARS-CoV-2 infection through a multi-pronged research framework</th>
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<tr>
<td>Understand</td>
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<td>Recognize</td>
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<td>Identify</td>
<td>Pathogenic mechanisms and therapeutic targets</td>
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<td>Develop</td>
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