Long COVID

- Current challenges and future solutions
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DISCLOSURES

United Therapeutics:

- Teton Studies of treatment for IPF and PPF

NIH:

- RECOVER-Adult Long COVID Research Index
- RECOVER ENERGIZE
- RECOVER TLC

Why talk about Long COVID in 2025?

Estimated that up to 8% of adult Americans have experienced long COVID (roughly 1 in 10 people)

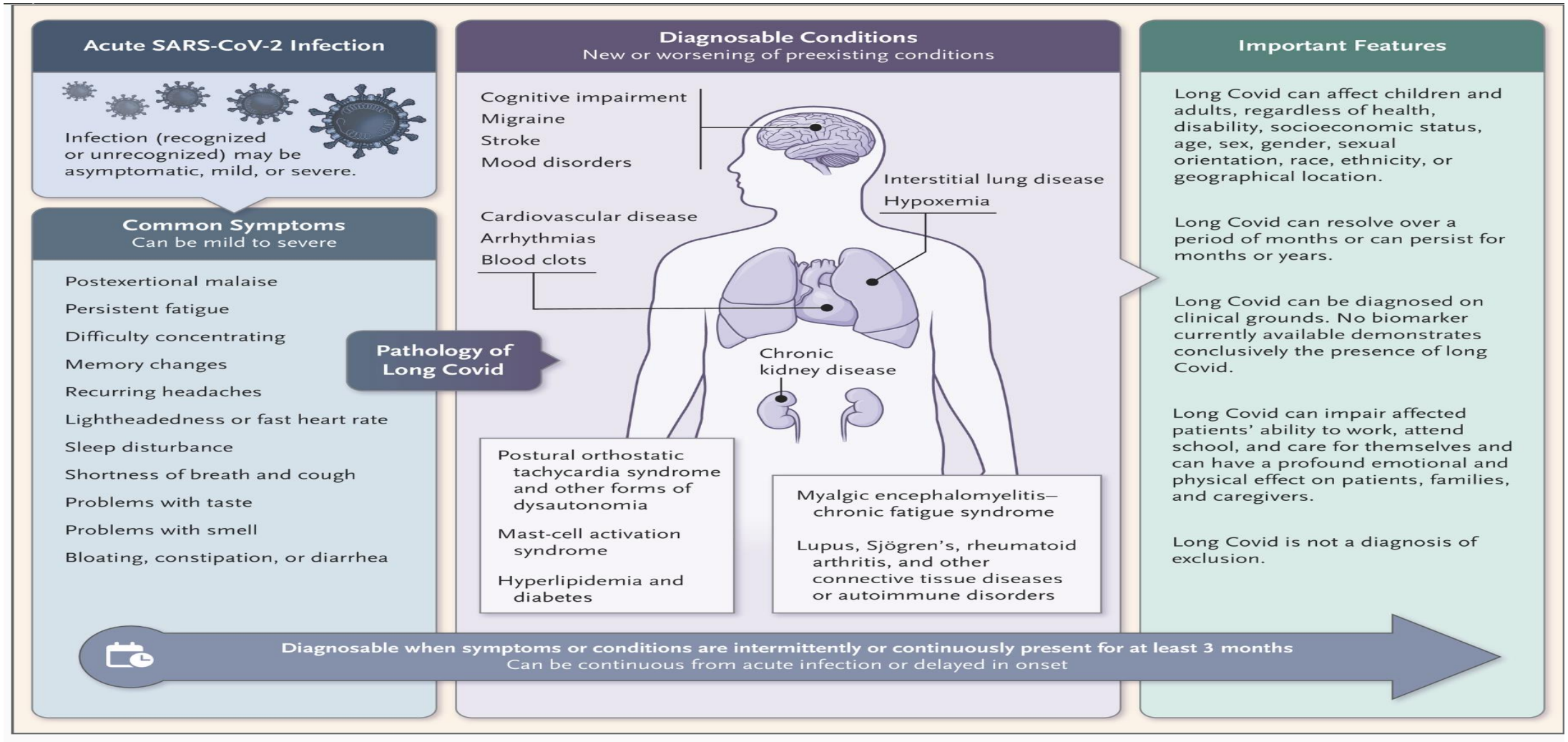
- Current estimate: 44-48 million Americans affected

- Economic impact:
  - (2022):
  - Total $3.7 trillion
    - QoL $2.2 trillion
    - Lost earnings $1 trillion
    - Additional medical expense $500 billion
  - (2025): Annually
    - Society $2.1-6.6 billion
    - Employers $1.99-$6.49 billion
    - Third party payers $21-$68 million

Why talk about Long COVID?

- Likely not a single disease with at least 4 root causes:
  - Persistent viral reservoir in different organs
  - Autoimmune reactions triggered by the infection
  - Tissue damage and organ dysfunction
  - Reactivation of latent viruses (e.g. herpes viruses like EBV)
- Definition:
  - A chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months (2/3/25: CDC)
    - Wide range of sx and conditions that can last for weeks, months, or even years.
    - Most people improve 3-6 months

Long COVID Disease State



Ely et al. N Engl J Med. 2024

Why talk about Long COVID?

Many clinicians unsure how to evaluate and manage individuals with health problems post-COVID

- Conflicting definitions
- Existence of multiple putative mechanisms
- Lack of a single, agreed upon and accessible biomarker for dx and for monitoring natural history

Lack of proven, effective therapy; No FDA-approved RX

”COVID fatigue”

- Frustration with lack of proven therapies
- Lack of awareness: approx. 1/3 of Americans not heard of Long COVID

Limitations of Multiple RX Studies for Long - COVID

- Observational
- Lack of randomization
- No control group
- Heterogeneous group of patients; selection bias
- Limited number of patients; often single center
- Results non-generalizable
- ? Improvement due to normal recovery
- No long-term follow-up

RECOVER TLC

Researching COVID to Enhance Recovery-Treating Long Covid

National Institute of Allergy and Infectious Disease (NIAID)

RECOVER – TLC Initiative

Goal: Develop safe and effective therapeutic interventions for Long COVID and provide these to health care providers and their patients as rapidly as possible

Key Scientific Aims:

1. ID pharmacologic and non-pharm interventions to treat Long COVID
2. Build on findings from RECOVER cohorts, pathobiology studies, and clinical trials
3. Develop rapid, nimble clin trials with direct and transparent engagement with scientific, industry, and patient communities.
4. Provide access and sharing of data with public and scientific communities

RECOVER – TLC Initiative

- Patient centered- participants as partners
- National scale with inclusive, diverse participation & community engagement
- Platform protocols- standardized methodologies, and common data elements
- Adaptive approaches based upon emerging science.

Agent Review Process

- Clinical Agents
  - Drugs
    - Antiviral; Immunomodulatory; Neuro; Cardiovasc; Metabolic
  - Devices
  - Manual and Physical Therapies
  - Complementary & Integrative Health
  - Nutrition & Diet
- Prioritization Activities
  - Score candidates based on pre-defined criteria
  - Utilize score as discussion points in debrief meetings
  - Assess supply, patient benefit, and other logistical need

RECOVER-TLC
Therapeutics Submission (9/30/2024-5/27/25)

357 distinct respondents

551 total submissions

- Submitter breakdown: 72% patient; 11% University; 7% caregiver; 4% Research institute
- 74% Drug; 12% Nutrition and Diet

Current Status of Agent Selection

- Potential agents for pivotal clinical trial : **Low dose naltrexone (LDN)**
- Scientific rationale:
  - In doses <5 mg acts as glial modulator (opioid production is increased, and opioid receptor synthesis is initiated). Some Long COVID patients have chronically activated microglia, resulting in increased pro- inflam cytokine levels that lead to neuro sx
  - LDN decreases pro-inflammatory cytokines and acts as immunomodulator

Low Dose Naltrexone (LDN)

Retrospective analyses: Reduction in fatigue, PEM, unrefreshing sleep

Some success in treating fibromyalgia & ME/CFS

Phase 2 trial U of British Columbia; completion in August/2025

Unproven efficacy. Widely used, felt to be safe (18% of adult Long COVID patients currently taking LDN).

No manufacturers of LDN; Compounders typically do not make investigational products for IND trials including matching placebo

Clinical Approach to Dyspnea/ Long COVID

- General medical evaluation
- Pulmonary assessment: PFT; CPET; Check for desaturation with activity; Chest Imaging; ? D-dimer
- Consider cardiac work-up: BNP; TTE
- Screen for PEM- (concentrate on pacing)
- Screen for orthostatic intolerance
  - ? POTS (Postural Orthostatic Tachycardia Syndrome
  - Autonomic conditioning therapy

Reminder-Keep an open mind:
New diagnoses in Patients referred with "Long COVID"

- Auto- immune disorders
- ANCA+ disease
- Asthma
- Bronchiectasis
- Bronchiolitis
- Organizing pneumonia
- Pulmonary fibrosis
- + ANA and other auto-antibodies
- Small fiber neuropathy
- Dysautonomia
- Fibromyalgia
- Sleep-related breathing problem
- Laryngeal abnormalities
- Malignancy