Toward a Common Research Agenda in Infection-Associated Chronic Illnesses

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Summary

- The Challenge – Translating the growing recognition of infection associated illnesses into advances in understanding and treatment.
  - Long Covid
  - Post-treatment Lyme
- The Role of the FDA
    - Support Patient Engagement
    - Explore innovation in clinical trials
    - Spur new methods of data collection
    - Hold public meetings, build and support public/private partnerships
    - Develop guidance
- Future Developments

The Challenge

- Finding solutions to respond to the growing recognition of chronic illnesses associated with prior infectious disease into solutions
  - Underscored by increase of Long COVID.

- The growing awareness is counteracted by a lack of treatment options, adequate patient care, barriers in diagnosis, and failure to fully recognize and understand these diseases
  - A lack of understanding of the cause and effect and links between initial infections and long term or chronic illness;
    - Confusion about lumping and splitting
  - A lack of resources devoted to study, research, trials.

The Opportunity

- Biomedical science and technology are in an amazing period of discovery and development.
- Yet these advantages are not resulting in superior health and outcomes for the U.S. population or for most individuals.
- The intersection of biomedical science, technology and communication, if handled with good policies, investment and communication, could usher in a new era of better health for the U.S. and the world.
- Previous policies and infrastructure investment provide a solid base from which to build an effective system for evaluation and implementation across the spectrum of development, pivotal trials and post-market evaluation.

The goal is to apply scientific and technological advances, new approaches to collecting data, as well as increased patient engagement to develop new approaches and solutions, and to build a base of evidence that can lead to effective treatments.

Long Covid –
Interim Federal Working Definition

- Long COVID is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection.
- The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing– remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection.
- Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes.
  - Additionally, symptoms and natural history of Long COVID, as well as diagnosis and management may be different among children, especially younger children.

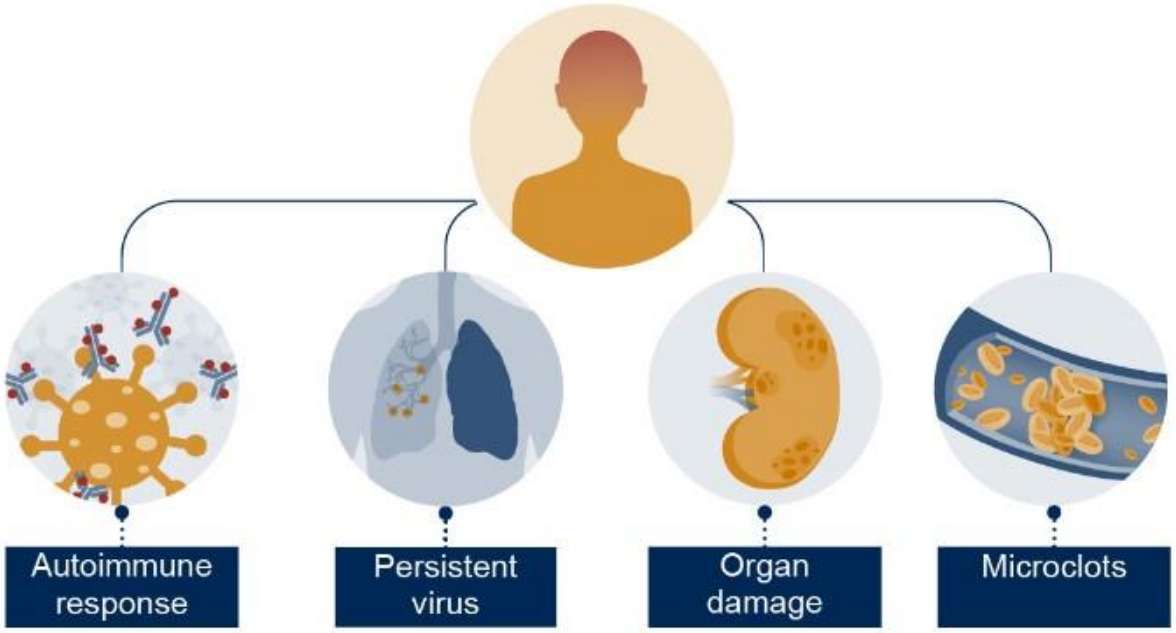
HHS Definition March 2023

Prevalence of Long COVID

- The prevalence has been challenging to estimate, with estimates ranging widely (5–30%).
- Based on March 2023 Household Pulse Survey results, the CDC/National Center for Health Statistics estimates that 6% of U.S. adults report currently having Long COVID symptoms.
- An estimated 65 million individuals globally may have Long COVID

Post-COVID Conditions: Information for Healthcare Providers (cdc.gov)
Long COVID - Household Pulse Survey - COVID-19 (cdc.gov)
Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study

Possible Causes of Long COVID



Source: GAO analysis of medical literature. | GAO-22-105666

Science & Tech Spotlight: Long COVID | U.S. GAO
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

In pediatrics, risk of long COVID poorly understood

Morbidity and Mortality Weekly Report (*MMWR*)

Post–COVID-19 Symptoms and Conditions Among Children and Adolescents — United States, March 1, 2020–January 31, 2022

Weekly / August 5, 2022 / 71(31);993–999

L Kompaniyets, L Bull-Otterson, et al.

Pediatric patients with COVID had higher rates of acute PE (aHR 2.01), myocarditis/cardiomyophathy (aHR 1.99) and venous thrombotic events (aHR 1.87)

THE LANCET
Child & Adolescent Health

Long COVID symptoms in SARS-CoV-2-positive children aged 0–14 years and matched controls in Denmark (LongCOVIDKidsDK): a national, cross-sectional study

S Kikkenborg Berg, P Palm, et al.

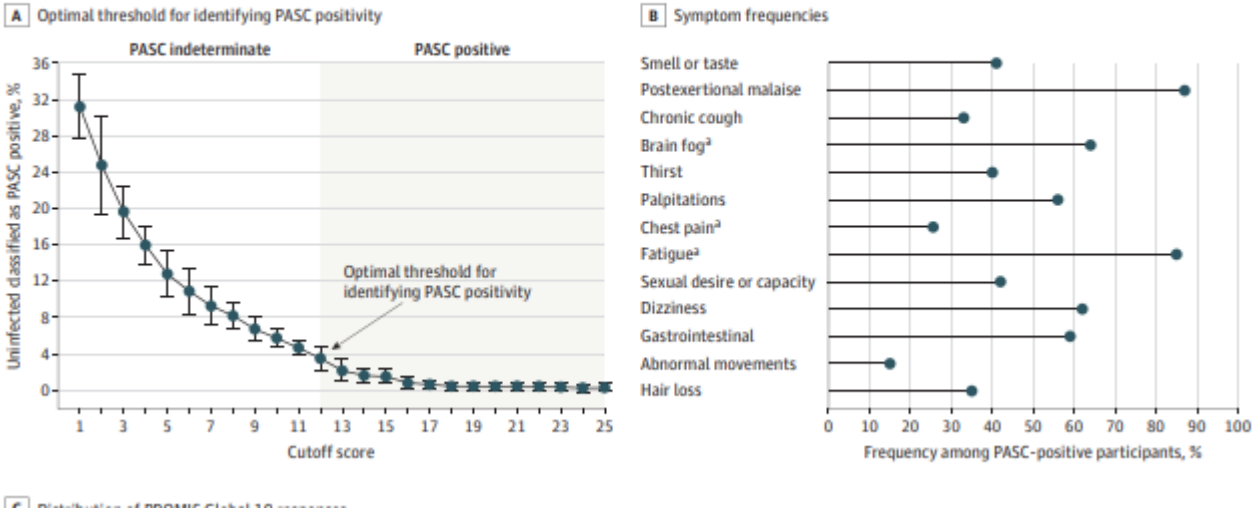
Nationwide survey showed cases had somewhat higher rates of persistent symptoms at 2 mos than controls (e.g., ages 4-11, 38.1% vs. 33.7% in controls)

JAMA | Original Investigation

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD; Sarah E. Jolley, MD, MS; Elizabeth W. Karlson, MD, MS; Emily B. Levitan, ScD; Bruce Levy, MD; Grace A. McComsey, MD; Lisa McCorkell, MPP; Girish N. Nadkarni, MD, MPH; Sairam Parthasarathy, MD; Upinder Singh, MD; Tiffany A. Walker, MD; Caitlin A. Selvaggi, MS; Daniel J. Shinnick, MS; Carolin C. M. Schulte, PhD; Rachel Atchley-Challenner, PhD; RECOVER Consortium Authors; Leora I. Horwitz, MD; Andrea S. Foulkes, ScD; for the RECOVER Consortium

Figure 2. Defining the Postacute Sequelae of SARS-CoV-2 Infection (PASC) Score and a Decision Rule



Treatment Options

- No drugs are FDA-approved for the treatment of Long COVID.
- For most patients, the goal of medical management is to optimize function and quality of life.
- Symptom management approaches may be helpful.
- Management may change as more evidence becomes available.

Post-COVID Conditions: Information for Healthcare Providers (cdc.gov)

Challenges to Drug Development

- Long COVID is a new entity and COVID-19 epidemiology is evolving.
  - Many knowledge gaps exist and features of Long COVID may change over time.
- Long COVID represents many potentially overlapping entities, with likely different biological causes and different sets of risk factors and outcomes.
  - Different treatment approaches may be needed for patients with different Long COVID symptoms, including **pediatric patients**
- Tools to reliably assess how new treatment impact how patients feel, function, or survive have not been established for Long COVID.

Challenges of Post-treatment lyme

- **Diagnosis issues** – may be based solely on clinical judgment and without laboratory evidence of *B. burgdorferi* infection or other direct connection.
- **Treatment issues** -- concern that after diagnosis is made, any alternative cause of a patient's symptoms might remain undiagnosed and untreated.
  - Antibiotics and immunoglobulin therapies are effective and necessary treatments for many conditions; however, unnecessary antibiotic and immunoglobulin use provides no benefit to patients while putting them at risk for adverse events
  - Treatments has sometimes have resulted in serious harm, including death.
  - Treatments have not proven effective.

    - "Serious Bacterial Infections Acquired During Treatment of Patients Given a Diagnosis of Chronic Lyme Disease," US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / June 16, 2017 / Vol. 66 / No. 23

The FDA's Role

Addressing multiple disciplines through multiple roles – Regulatory agency, Scientific agency, Public Health, Agency

- What we **can** do.
  - Strengthen Patient Engagement and input
    - PFDD, Patient Listening Sessions
  - Support Collaborative efforts
  - Encourage and respond to outside sponsors
  - Signal willingness to explore innovation in trials and provide feedback on trial design
  - Encourage Industry, academics, patient groups
    - Develop guidances
  - Help developers repurpose products through IND process
- What we **can't (don't)** do.
  - We don't develop drugs
  - We don't mandate research

How FDA can advance the discussion

- Spur **Patient Engagement** and respond to patient advocacy
- Signal willingness to explore **innovation in clinical trials** and provide feedback
- Facilitate consideration of viable **endpoints**
- Support collection of additional types of **data** (RWE, digital)
- Hold **public meetings**, build and support collaborative efforts, incl. **public/private** partnerships
- Develop guidances
  - E.g Draft guidance (June 2023) updated recommendations for good clinical practices (GCPs) aimed at modernizing the design and conduct of clinical trials.

Patient Engagement

- Patients are **experts** in their condition.

- *It is important to get patient input early in the drug development process.*

Courtesy: Patient Focused Drug Development Team, CDER

PFDD Meetings

Designed to engage patients and elicit their perspectives on two topic areas:

(1) the most significant symptoms of their condition and the impact of the condition on daily life;

(2) their current approaches to treatment.

FDA-led PFDD Meetings

In 2020 and 2021, FDA conducted 3 PFDD meetings

- Stimulant Use Disorder
- Systemic Sclerosis
- Vitiligo

Externally-Led PFDD Meetings

In 2020 and 2021, patient groups conducted 24 EL-PFDD meetings

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings

Courtesy: Patient Focused Drug Development Team, CDER

PFDD meetings follow a town hall style discussion format

Overview

Clinical Background and Current Available Treatments

Symptoms and Daily Impacts

- Panel of patients and caregivers
- Facilitated group discussion

Current Treatment Options

- Panel of patients and caregivers
- Facilitated group discussion

Clinical Trials

- Panel of patients and caregivers
- Facilitated group discussion

Courtesy: Patient Focused Drug Development Team, CDER

PFDD Meeting on Long Covid

- FDA was contacted by Solve ME/CFS about holding an Externally-led PFDD meeting for Long COVID

- FDA worked with other federal agencies to plan the meeting: OASH, NIH, CDC,
  - 1,800 people registered total
  - 1,000 patients and caregivers, including a diverse group of participants.
    - Hispanic/Latino, Black or African American, and Asian or Asian American individuals
    - Included Spanish-speaking individuals

Courtesy: Patient Focused Drug Development Team, CDER

Patient Perspectives on Symptoms and Daily Impacts

- "[Chronic fatigue symptoms] will pop up randomly (like yesterday) and I will miss a day of work. There does not seem to be any rhyme or reason for the flareup."
- "Many of us have exercise intolerance or "crash" (PEM) if we exert ourselves."
- "The random, unpredictable migraines are extremely difficult to deal with and plan life/work around."
- "My life is just "less" now. Less active, less capable, less intelligent, less able to interact socially and emotionally. Just less."
- "I tested positive for Covid April 2020. Three years later, I still struggle with fatigue, severe brain fog, migraines and the effects of POTS with includes heart palpitations, increased heart rate and painful blood pooling upon standing. I have extreme issues with ADL's such as showering and cooking."
- "I still experience a large constellation of symptoms, most likely due to autonomic nervous system dysfunction, that vary in their severity in a cyclical way… I also experience cognitive symptoms where it can feel like I'm thinking through mud, I often write or say the wrong words or have trouble finding words I'm looking for all together, my short and long-term memory are both significantly compromised, and I have issues focusing on things for more than 10 minutes at a time."

Courtesy: Patient Focused Drug Development Team, CDER

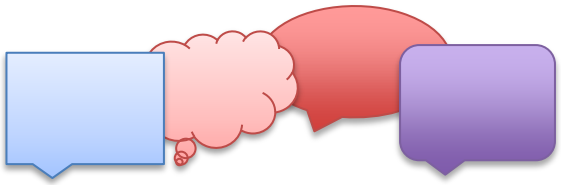
Patient Perspectives on Treatment --Approaches

- Patients used a variety of prescription and over the counter products
- Patients used other interventions including diet modifications, acupuncture and supplements
- Patients reported difficulty accessing treatment due to lack of physician education and geographic factors
- Patients expressed a desire for treatments that target the root cause of Long COVID, instead of treating only the symptoms
- Symptoms/aspects of Long COVID that patients would prioritize for treatment include:
  - Post-exertional malaise
  - Brain fog
  - Organ damage
- Patients described meaningful treatment outcomes
  - Reduction of fatigue/post-exertional malaise
  - Improved organ function
  - Reduction of brain fog

Courtesy: Patient Focused Drug Development Team, CDER

Patient Perspectives on Treatment -- Approaches

- "A successful treatment outcome would be me being able to be more functional in my daily life, work full-time, and get back to some of the physical activities (i.e. hiking) that I used to enjoy."
- "An ideal treatment would be addressing the mechanism(s) of long covid. This is because long-covid has been a dynamic disease for me, and I experience PEM/fatigue crashes that lead to worsening and new symptoms."
- "I have tried anything relatively accessible and relatively safe over the past 2.5 years – supplements, inhalers, beta blockers, antivirals, migraine medicines, acupuncture, meditation, breathing exercises, chiropractor, physical therapy, anti-inflammatory diet, intermittent fasting, resistance breathing training, pacing, increased hydration and salt for dysautonomia, compression stockings, etc."
- "The factors impacting selecting treatment are access to providers/treatment, insurance coverage/cost, time off work, and risk/benefit analysis based on the limited data."



Courtesy: Patient Focused Drug Development Team, CDER

Clinical Trial Innovation

- There exist numerous challenges relating to clinical trials with these diseases, as reflected in patient perspectives.
- Patients are desperate for treatment and eager to participate in research, but many are severely debilitated and/or located far from medical care, so a virtual, decentralized trial platform is essential
- Patients shared that they had difficulty accessing trials, especially rural populations
- Patients expressed desire for the following factors in clinical trial design: decentralized elements, permissive inclusion/exclusion criteria

Courtesy: Patient Focused Drug Development Team, CDER

Patient Perspectives on Clinical Trials

Measuring brain fog:

- "A number of patients I know are using games on their phone to assess processing speed. One woman has a racing game on her phone. If she can't beat the game, she doesn't try to drive in real life."

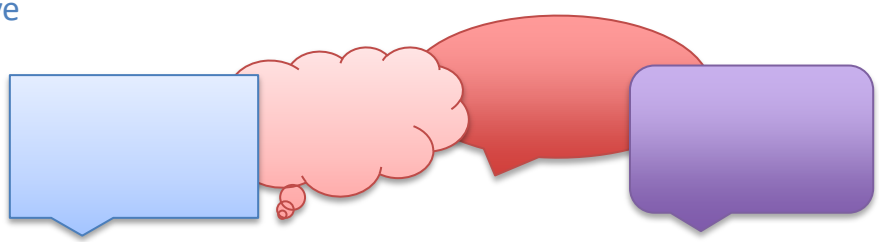
Side effects patients are willing to tolerate:

- "If there was fairly sound scientific evidence that a medication may benefit, I would be willing to tolerate any and all risks as this current state is ABSOLUTELY NO WAY TO LIVE."

- "I could put up with upset stomach.. and low blood pressure... but really, think about it. We are at the BOTTOM of quality of life now... any toxicities would have to be very minor."

- "Multiple clinical trials now exclude long covid patients like me because we've been sick "too long". Several I've wanted to participate in cut off the timeline at between 1 year and 18 months of illness. It is vital not to abandon 1st wavers."

- "I would be extremely hesitant to participate in any trial that does not screen for post-exertional malaise or that involves a form of graded exercise. I would be much more inclined to participate in trials that deal with the underlying cause of symptoms rather than just symptom management."



Courtesy: Patient Focused Drug Development Team, CDER

Translating patient input into research – what will you measure?

Clinical Outcome Assessment (COA) Fundamentals

clinical outcome
An outcome that describes or reflects how an individual feels, functions or survives.

Clinical Outcome Assessment

Assessment of a **clinical outcome** can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment. There are four types of COAs.
clinician-reported outcome
observer-reported outcome
patient-reported outcome
performance outcome

BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) https://www.ncbi.nlm.nih.gov/books/NBK338448/

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

Next steps

- FDA will continue to strengthen efforts to:
  - Advocate for innovative clinical trials
  - Advance methods of data collection
  - Encourage patients and patient advocates on clinical trial innovation
  - Strengthen collaborative efforts
  - Support patients, industry, academia on development issues
  - Increase coordination across FDA for addressing infection-associated illnesses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