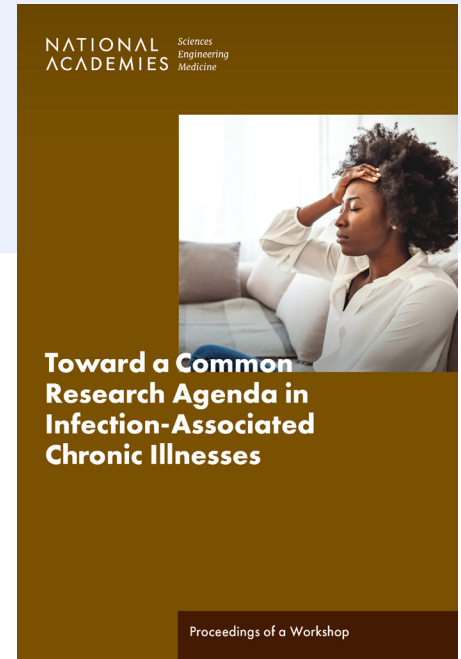# Toward a Common Research Agenda in Infection–Associated Chronic Illnesses

Infection–associated chronic illnesses, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), persistent or posttreatment Lyme disease (PTLD), and multiple sclerosis (MS), have traditionally been underresearched, underfunded, and met with skepticism. To address challenges and advance knowledge in research and treatment, the Forum on Microbial Threats, together with the Forum on Neuroscience and Nervous System Disorders, convened Toward a Common Research Agenda in Infection–Associated Chronic Illnesses: A Workshop to Examine Common, Overlapping Clinical and Biological Factors on June 29–30, 2023.[1] Since 2020, a growing recognition of conditions associated with COVID–19 (long COVID) has elevated attention to other chronic conditions that appear linked to infections, according to Lyle Petersen, U.S. Centers for Disease Control and Prevention. Collectively, infection–associated chronic illnesses can have debilitating physical effects on patients, as well as broader impacts on society through health care costs and loss of workforce, according to Anthony Komaroff, Harvard Medical School, and Lisa McCorkell, Patient–Led Research Collaborative. For example, between 31 and 70 percent of COVID patients remain absent from work after the acute phase of the disease (Nittas et al., 2022), and it is estimated that long COVID may be responsible for 1.6 million fewer full-time workers in the U.S. labor market (Bach, 2022).

Several speakers, such as Harlan Krumholz, Yale School of Medicine, and David Putrino, Mount Sinai Health System, noted that the many shared symptoms across different conditions led to an increasing recognition that research efforts would be more

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[1] A full workshop proceedings recounting the 2 full days of workshop discussions can be found at https://www.nationalacademies.org/event/06-29-2023/toward-a-common-research-agenda-in-infection-associated-chronic-illnesses-a-workshop-to-examine-common-overlapping-clinical-and-biological-factors.

effective by focusing on addressing common underlying pathophysiologies, rather than on individual conditions. Avindra Nath, National Institutes of Health, noted that research, patient care, and funding efforts are often carried out in condition-specific silos, and that collaboration between institutions is limited; advancing research will depend on interdisciplinary collaboration and assessing overlapping drivers among these conditions.

SHARED CHARACTERISTICS ACROSS CHRONIC CONDITIONS

Tim Henrich, University of California, San Francisco (UCSF), and Komaroff both commented on the clear overlap between postinfectious syndromes and chronic viral infections, saying that the scientific field is now more broadly acknowledging the potential for pathogen persistence to result in documented clinical morbidity. Henrich shared examples of documented persistence of infections, pointing to patients affected by human immunodeficiency virus, Ebola, or long COVID that express similar inflammatory biomarker profiles. Long COVID has also been shown to increase the likelihood of reactivating chronic viral infections such as Epstein-Barr virus (Gold et al., 2021). Henrich also highlighted the possibility of successive infections having an additive effect on chronic symptoms. This idea was also shared by Meghan O'Rourke, Yale University, as she spoke on her personal experience with Lyme disease and other infections, saying she felt the cumulative impact from each successive infection.

Komaroff presented data supporting the shared symptoms and underlying pathophysiology of ME/CFS and long COVID (Wong and Weitzer, 2021). While there are still questions of how these syndromes are triggered, he said both cases show evidence of mitochondrial dysfunction, oxidative stress, cellular aging, and chronic inflammation. These similar, ongoing symptoms may be in part attributable to the "sickness behavior" hypothesis, Komaroff explained, which posits that the protective response from the brain to temporarily conserve energy during an infection gets "stuck" because the neurochemical mechanism to turn it off becomes defective.

LISTENING TO AND ENGAGING PATIENTS

Across all highlighted disease areas, speakers emphasized the importance and opportunity for acknowledging and centering patients in all research and development efforts. O'Rourke and McCorkell highlighted their experiences with stigma and dismissal from health care providers, often because the mechanisms for disease are not well understood. Many speakers addressed the need for validation of these conditions in the eyes of the public, including Hannah Davis, Patient-Led Research Collaborative, who described the need for education campaigns to inform the public of potential risks, even if they have recovered from prior infections.

Patient engagement can improve research efforts. Krumholz presented on the importance of democratizing research and connecting researchers with patients in meaningful ways. This can lead to studies that are more efficient and relevant to patients, he said, and his team is continuing to pursue a model that includes patients at every stage, including initial designs, as well as learning from their experiences while unlearning the hierarchies of traditional research. McCorkell added that, in her experience, research that incorporates the patient's perspective is more relevant to the patient's lives, more effective, and leads to faster results.

Oved Amitay, Solve ME/CFS, and Putrino noted that with technological advances and increased use and application of telehealth modalities, there are more opportunities to democratize research even further, without requiring patients who are suffering and often bed-bound to come into a research center in person for studies. Amitay and Hilary Marston, U.S. Food and Drug Administration, supported the creation of a virtual, decentralized clinical trial platform to use these technologies and enable more research to be done from home, removing the barriers preventing many people from participating.

COMMON MECHANISMS OF INFECTION-ASSOCIATED CHRONIC ILLNESSES

Similar to the overlap in symptoms and underlying pathophysiology, Steven Deeks, UCSF, and Alessio Fasano, Harvard Medical School, also discussed common

potential mechanisms for infection-associated chronic illnesses, including viral persistence, viral reactivation, inflammation/immune dysregulation, autoimmunity, microbial translocation, and microvascular dysfunction (e.g., microclots) (see Figure 1). These mechanisms can be associated with long COVID, ME/CFS, MS, Lyme disease, postural orthostatic tachycardia syndrome, and dysautonomia.

Julia Oh, Jackson Laboratory, shared her research related to mediators of host–microbiome interactions, noting that the microbiome can contribute to disease severity in ME/CFS. She found that both early- and late-stage ME/CFS patients have microbial dysbiosis, with the beneficial microbes that produce short-chain fatty acids like butyrate being significantly depleted. This is also an important consideration for treatments, as Kim Lewis, Northeastern University, shared the presence of interactive feedback mechanisms between the immune system and the microbiome. Lewis stated that many conditions can be affected by this microbiome disruption, and current treatments for Lyme disease kill good flora in addition to the pathogen and may contribute to PTLD via microbiome disruption.

Brian Fallon, Columbia University, and Deeks both commented that even though the symptoms of various chronic illnesses are similar, the heterogeneity of symptoms for individual patients remains a challenge for developing treatments. Researchers have now documented more than 200 different symptoms experienced by long COVID patients, according to McCorkell. Fallon encouraged the creation of infection-associated, multisystem illness clinics in major medical centers with clinicians from multiple disciplines to help patients who are sick and need urgent care. John Aucott, Johns Hopkins University, shared a model of multifactorial potential mechanisms of chronic illness associated with Lyme disease that may drive the disease and inform diagnostic tests, noting that identifying the mechanism would inform the best type of therapy. This would likely be similar for other infection-associated chronic illnesses, Aucott said.

POTENTIAL FOR BIOMARKERS IN DIAGNOSTICS AND THERAPEUTICS

Several workshop discussions on research commented on current innovations and the infrastructure needed to accelerate clinical development, and a common theme was the use of biomarkers. Aucott, Nath, and Charles Chiu, UCSF, remarked on the potential for the identification and use of biomarkers in both diagnostics and therapeutics. For example, in PTLD, Aucott said, research found that inflammatory markers such as interleukin-23 could be an indicator for who is likely to develop persistent symptoms (Strle et al., 2014).
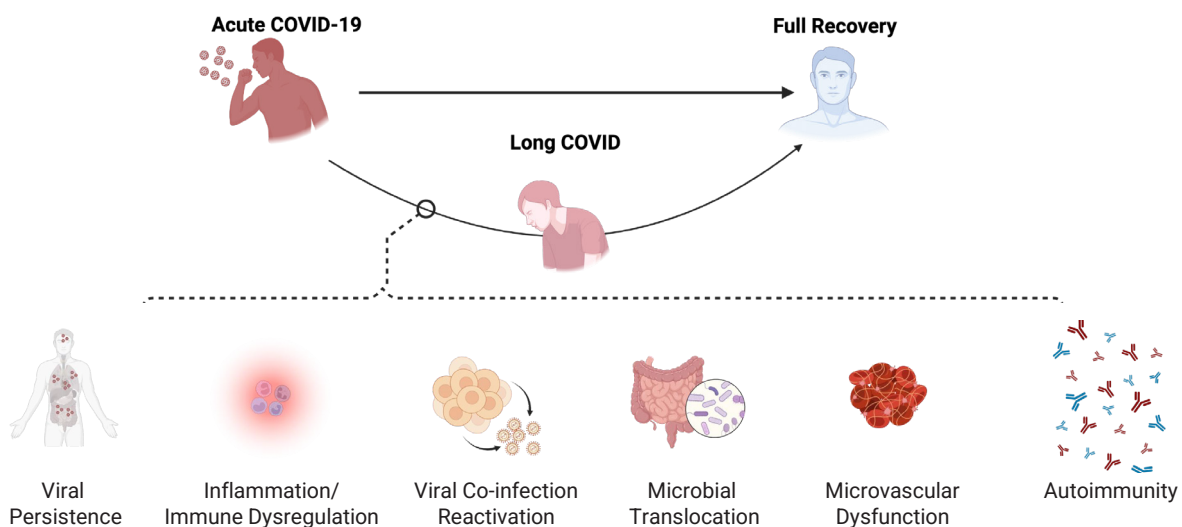

FIGURE 1 Proposed mechanistic pathways causing infection-associated chronic illness.
SOURCES: Steven Deeks presentation, June 30, 2023; Peluso and Deeks, 2022.

Given the challenges with timely and accurate diagnosis, Chiu discussed metagenomic sequencing as a potential method to improve diagnosis beyond antibody detection. Using artificial intelligence and machine learning, his models have obtained 90 percent accuracy for comparisons of spinal fluid samples, categorizing pathogens as bacterial, viral, fungal, and autoimmune. Chiu's team is also working to produce host-response classifiers that can identify specific types of infections and potentially noninfectious causes. Using this host-response profiling, he hopes they can identify biomarkers that can diagnose disease causes and monitor chronic disease.

Also related to diagnosis, Resia Pretorius, Stellenbosch University, spoke on her research team's discovery that the SARS-CoV-2 spike protein can trigger significant platelet hyperactivation and microclot formation. Both symptoms can be detected in long COVID patients as well as ME/CFS patients, Pretorius said (Nunes et al., 2022). However, biomarkers such as the spike protein may only be part of the equation, according to Alessio Fasano, Harvard University. Fasano reported that the presence of the spike protein in the bloodstream and elevated zonulin levels stemming from COVID-induced dysbiosis are both associated with long COVID and multisystem inflammatory syndrome in children, but an individual also needs to have a genetic predisposition. This explains why some people with the spike protein in their blood suffer from long COVID symptoms and others do not, he explained.

David Walt, Harvard University and Brigham and Women's Hospital, identified the role of different viral proteins as potential biomarkers, sharing his research showing that the detection of the spike protein seemed to be associated more often with gastrointestinal symptoms, detection of the nucleocapsid was associated more with neurological and musculoskeletal symptoms, and detection of persistent antigen was associated with more severe illness.

URGENT NEEDS IN RESEARCH AND PATIENT CARE
Lorraine Johnson, MyLymeData, quoted a 2017 article by Tom Frieden:

> There will always be an argument for more research and for better data. But waiting for more data is often an implicit decision not to act, or to act on the basis of past practice rather than on the best available evidence. (Frieden, 2017)

Many speakers, such as Johnson, McCorkell, and Nath, highlighted opportunities to take action now with the available information and lessons from other illnesses, as patient advocates and researchers have been examining Lyme disease and ME/CFS for decades. In addition to cross-pollination across disease areas, there are also ways to make ongoing research more robust, said Johnson. For example, by relaxing some of the inclusion criteria for studies, results can be made more generalizable to larger populations. Amitay also suggested engaging patient organizations to add value to research and recruit more patients with broad backgrounds.

In the earlier stages of research, Deeks stated that experimental medicine is a potential means of facilitating engagement with industry by conducting proof-of-concept studies and identifying pathways industry can pursue with therapeutics to address patient symptoms. He and Nath agreed on the need to break down silos across disease areas and fields to interact more and optimize outcomes. Linda Geng, Stanford University, also saw an opportunity for professionals across disease areas and disciplines to collectively build the knowledge base of potential mechanisms to generate better treatments and care. A better understanding of the model could also help validate many of these conditions in the eyes of the broader medical community, she said.

The invisibility that so many of these patients have experienced is starting to decrease, said Tim Coetzee, National Multiple Sclerosis Society, and while more work is needed, there is an opportunity to take action with the current hypotheses and available data. Peter Rowe, Johns Hopkins University, and Putrino agreed that research is important for the future, but they highlighted the critical need to treat the millions of people who are sick and suffering right now. They encouraged the prioritization of clinical care and multidisciplinary models for

infection-associated chronic illnesses to ensure that these patients will not be forgotten.

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