U.S. Senate Committee on Health, Education, Labor, and Pensions Committee Hearing

Addressing Long COVID: Advancing Research and Improving Patient Care

January 18th, 2024

Tiffany Walker, MD
Assistant Professor of Medicine
Division of General Internal Medicine
Emory University School of Medicine

Chairman Sanders, Ranking Member Cassidy, and Distinguished Members of the Committee:

My name is Tiffany Walker, and I am an assistant professor of internal medicine at Emory University. The views I express today are my own views and do not necessarily reflect the views of my employer, the RECOVER consortium, or AHRQ. I am honored to have the opportunity to share my testimony with you, and I hope to convey that Long COVID is a highly prevalent and often disabling disease. It is imperative that we continue to invest in and support research that defines the pathobiological drivers of this disease, and there is real urgency to identify effective treatments.

To review my experience in this field, I co-founded the Long COVID clinic at Grady Memorial Hospital. I serve as site principal investigator (PI) for the NHLBI RECOVER Initiative meta cohort and RECOVER VITAL (Paxlovid) clinical trial, and co-investigator for the RECOVER SLEEP (Modafinil/ Solriamfetol) clinical trial and the NIA REVERSE-LC (Baricitinib) clinical trial. I lead the Atlanta Long COVID Collaborative, a consortium of Long COVID providers and subspecialists in Atlanta and our site serves as a AHRQ Long COVID Center of Excellence. Additionally, I investigate health disparities and pathobiological mechanisms driving Long COVID.

Impact on the labor force

The COVID-19 pandemic has resulted in a conservative estimate of 20 million U.S. cases of Long COVID.[1] In fact, we have seen that 15% of those exposed to COVID-19 go on to develop long term sequelae.[2] To provide a stark comparison, this is commensurate to the rate of diabetes mellitus in our population,[3] a disease that receives substantial healthcare and research funding support. Long COVID can lead to significant impairments in quality of life and function.[4-6] We know that long haulers are more likely to be unemployed or work reduced hours,[2] with one estimate reporting nearly half were unable to work full time due to severity of symptoms and nearly a quarter were unable to return to work at all.[7] This is corroborated by recent CDC data showing that over a quarter of long haulers suffer from significant activity limitations.[1] This level of disability also mirrors that seen in diabetes, for which $30 billion of indirect costs is spent annually on reduced employment due to disability.[8] The duration of this disease remains uknown;[5,9] however, there is mounting evidence supporting significant overlap between Long COVID and pre-existing infection-associated chronic diseases such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and dysautonomia, which are known to be debilitating and can persist in individuals indefinitely.[9-11]

Health disparities

Minority populations and those experiencing economic disadvantage have been disproportionately affected by COVID-19.[12-14] These racial and ethnic disparities persist in the post-acute phase, with African and Hispanic Americans experiencing overall higher rates of Long COVID as well as higher rates of new-onset chronic diseases following COVID-19 infection, including diabetes mellitus and cardiovascular disease.[15,16] Impaired health literacy in economically-disadvantaged populations impacts recognition of symptoms and presentation to care. Furthermore, lack of coordination in Long COVID care has been identified as a key barrier

to optimizing health outcomes,[17] leading to increased healthcare costs and delays in care delivery[18]. These limitations are amplified in underserved, minority populations that have a long-standing history of poor access to affordable, quality healthcare.[19-22] I have seen this firsthand in our Grady Long COVID clinic. Even despite our efforts to minimize unnecessary diagnostic exams and subspecialty referrals, we have multiple patients who could not be retained in care due to insufficient funds for office visits and medication prescriptions.

Previously healthy adults

In acute COVID-19, older adults, minorities, and those with underlying comorbid medical conditions are at highest risk of developing severe illness, and young previously health adults have largely been spared.[14,23] Although these remain risk factors for development of Long COVID as well,[15] it is important to highlight that Long COVID, in contrast, can cause severe illness in anyone. Concerningly, Long COVID develops even in previously healthy patients who had mild acute COVID-19 infections,[24] and these patients make up a significant portion of patients presenting to Long COVID clinics.[25] In fact, some of the most devastating symptoms are those of dysautonomia, which causes heart racing and dizziness with standing, which are often seen in younger patients,[26] and data from the CDC suggests that those at highest risk for Long COVID may actually be those aged 30-60 years,[1] impacting our working aged adults and those of child rearing ages.

Limited access to care leads to increased healthcare expenses

Long COVID is a multisystemic and complex disease, which results in extensive and cost-prohibitive clinical evaluations. Primary care physicians are unprepared to provide this novel and labor-intensive clinical care. Patients are often referred to multiple subspecialty providers without answers. Lack of understanding of Long COVID among clinicians contributes to increased testing, delays in diagnosis, and impairment of triage to appropriate services,[17,27] further compounding healthcare spending burden and barriers to access. Long haulers continue to experience stigmatization from the community and clinicians who do not acknowledge it as a real disease despite objective pathobiological data establishing it as a distinct entity.[27,28] This lack of awareness can lead to feelings of isolation among long haulers and can have significant impacts on mental health in conjunction with the psychological stress from new-onset disability.[29] High rates of anxiety, depression, and PTSD are observed in this population and behavioral health services are often limited and disconnected.[17,30-32] Dedicated Long COVID clinics are equipped to provide this specialty care; however, these clinics remain rare and numbers continue to dwindle as clinics are shuttering. In the remaining Long COVID clinics, services are saturated due to high referral volumes.

AHRQ Long COVID Learning Community: Improving access to care

The AHRQ Long COVID Learning Community is a 5-year initiative supporting 9 Long COVID Centers of Excellence serving geographically- and demographically-diverse populations across the U.S. to provide coordinated, person-centered care to patients and caregivers affected by Long COVID.[33,34] The infrastructure provided through these grants supports increased clinical

capacity and expansion of multidisciplinary services. Through iterative programmatic evaluations, this consortium seeks to optimize Long COVID clinical management and guide healthcare policy. At each site, Long COVID teams will engage with the community to increase community-based referrals and ensure the needs of the population are met. Long COVID experts have designed robust peer education series to build capacity for Long COVID care throughout their region. We are grateful for the funding Congress provides to support AHRQ in this initiative, and we are grateful to AHRQ for prioritizing this important work to bridge clear gaps in Long COVID care quality. There is great value in establishing and supporting these Long COVID Centers of Excellence during these first 10 years, and we request continued support of this initiative. In addition to these centers, given the substantial prevalence of Long COVID, the permanence of COVID-19 in our environment, and the saturation of Long COVID clinics, it is imperative to support efforts to ensure primary care providers are appropriately trained and are competent to provide Long COVID care, with the ultimate goal of decentralization to ensure sufficient care access. There are multiple networks of Long COVID providers independent of the AHRQ Learning Community that are eager to contribute to this capacity building effort, and we request additional funding through AHRQ to bolster these activities, including primary care roadshows, development of adaptable protocols that can be implemented in community clinic settings, Project ECHO presentations, Long COVID podcasts and webinars.

RECOVER Initiative: A reason for hope and a reason for concern

Important steps have been taken to advance our understanding of Long COVID. Notably, Congress's investment in the RECOVER Initiative meta cohort has resulted in a successful demonstration of team-based science, with enrollment of over 14,000 patients in a little over one year and publications of meaningful data on Long COVID definition and phenotypes.[9] The robust infrastructure and data collection from this study well-positions investigators to define the clinical scope of Long COVID and characterize underlying mechanisms driving symptomatology. Meeting these objectives is critical as comprehensive understanding of organ system involvement can guide clinical care by mitigating unnecessary spending on diagnostic work-ups. Defining pathobiological pathways not only serves to promote credence of disease validity, but it also identifies biomarkers for Long COVID diagnosis and monitoring and defines intervenable targets for drug development. However, at this time, NHLBI anticipates concluding the cohort in May 2025, which is insufficient time to fully characterize this complex multisystemic disease and precludes long-term follow-up to monitor disease trajectory. This decision does not account for the ongoing high COVID-19 case rate, the protracted nature of Long COVID symptoms, or the concerning evidence of immune dysregulation observed in this population, including evidence of fatigability of T- and B-cell lineages that may indicate impending immunodeficiency that warrants long-term monitoring.[35,36] Despite the lack of coordinated, robust COVID-19 surveillance, we can estimate from wastewater analysis that new cases are occurring at very high levels and continuing to rise.[37] In fact, this may be the second largest COVID-19 surge to-date with an estimated 2 million cases per day peaking the second week of January 2024.[38] Now is not the time to deescalate funding for Long COVID.

A call for expansion of Long COVID clinical trials

Likewise, the RECOVER Initiative provides infrastructure for platform clinical trials hosted through the Duke Clinical Research Institute. These well-designed trials target evidence-based Long COVID manifestations and offer promising drug candidates that have potential for cure or for chronic symptom management. However, current funding for clinical trials is largely siloed through the RECOVER mechanism, stifling opportunities for further innovation. Given the prevalence and functional impact of this disease, funding for clinical trials needs to occur at a much greater scale and should not be limited to one institution or consortium. Despite RECOVER's best effort to roll out platform trials in parallel instead of in series, trials are launching sequentially because, despite admirable effort, there are finite resources for one institution to run all high-profile clinical trials for the U.S. population. In addition, these trials are designed as platform trials that allow multiple interventions to be trialed in tandem; however, many of the trials are only investigating 1-2 interventions at a time. Seasoned clinical trialists and Long COVID clinicians providing care on the ground level should have input into the treatments trialed in this patient population.

Innovative and efficient approaches to clinical trials

Several repurposed drugs have been investigated in the management of acute COVID-19, originating from a top-down approach to rapidly identify therapeutic options and mitigate severe outcomes. However, nearly 4 years from the pandemic onset, the same top-down approach has not been prioritized for Long COVID and as a result, there remain no effective, FDA-approved treatments. Investigating existing drugs as therapeutic options repurposed to treat Long COVID can safely expedite the timeline of identification, development, and time to market. I collaborate with the CURE Drug Repurposing Collaboratory, a public-private partnership between Critical Path Institute (C-Path) and the U.S. Food and Drug Administration (FDA) in partnership with the National Center for Advancing Translational Sciences (NCATS). We propose leveraging real-world data prospectively available from Long COVID patients and clinicians to identify promising repurposed drugs poised for rapid translation into patient-centered clinical trials. Real-world data, much like the CURE ID effort supported by the FDA/NCATS: Cure.ncats.io, can capture patterns of off-label uses of medications routinely occurring within and outside of the clinic, providing hypothesis generation that support rapid evaluation of common drugs in pragmatic clinical trials.[39]

Adaptive platform clinical trials

Adaptive platform clinical trials have an innovative design that allows for drug development expediency. This approach evaluates multiple drugs simultaneously, often with drugs administered in combination and with multiple drugs being compared to a single, common control. Adaptive designs use accruing, using real-time data to reallocate patients to drugs showing efficacy and retire drugs showing futility. As research uncovers novel pathophysiologic insights, treatments can be integrated seamlessly in this design. In contrast, traditional trials use fixed treatment arms, and data are typically not analyzed until trial completion, often years after trial initiation. This may result in a trial design that has insufficient patient enrollment to estimate the effect of the treatment. Advantages of adaptive platform design include smaller number of

participants, reduced patients on placebo, reduced costs, reduced timelines, and better inferences for regulators and researchers. These trials designs are gaining popularity following successes such as REMAP-CAP, ANTICOV, and ACTIV6.[40-43] Furthermore, many of these trials can be conducted remotely. Decentralized trials can enroll and complete all study visits through telemedicine, expanding participant network beyond institution-based recruitment. Traditional trials are predominately limited to recruitment of subjects who seek care at large academic institutions. In decentralized trials, participants throughout participating states will be able to enroll, promoting recruitment of marginalized populations with limited healthcare access as well as those with debilitating Long COVID symptoms which limit travel to study sites. Additionally, this model allows for a more demographically diverse study population, promoting inclusion of populations that are typically underrepresented in institution-based trials, such as rural and urban populations. This approach facilitates representative recruitment and ensures the greatest impact for those affected by this disease.

Barriers to RWD-guided adaptive platform clinical trials

This model demonstrates significant promise to provide sustainable infrastructure that can be employed not only to identify effective treatments for Long COVID but also can be rapidly scaled to efficiently identifying treatments in future outbreaks of existing and emerging infectious diseases; however, there are key barriers to timely implementation. As mentioned previously, funding for adaptive clinical trials in the Long COVID space is limited and primarily siloed to the RECOVER Initiative. There is concern in scientific and patient communities that interest in funding Long COVID research may be waning. In addition, the novelty of these approaches can be challenging for regulatory bodies who have limited precedence to provide guidance and approval. I have encountered this difficulty engaging with the FDA on a sponsor-investigator adaptive repurposed drugs trial. Despite their many advantages and gain in popularity, regulators remain unsure of how to interpret data from adaptive trials, impeding drug development and approval for market. In addition, there is no FDA division specific to Long COVID and recommendations across Long COVID studies have proven to be disparate and inconsistent.

Summary of recommendations:

1. Expand RECOVER Initiative funding to support extension of the observational cohort.
2. Expand funding for Long COVID adaptive platform repurposed drug trials, independent of the RECOVER mechanism.
3. Request a report from FDA detailing protocols for expedited Long COVID drug development and strategic planning for support of adaptive platform clinical trials.
4. Continue funding for AHRQ Long COVID Initiatives and expand resources for education and capacity building among primary care providers.
5. Establish a new institute at NIH to address Long COVID, ME/CFS, and other infection-associated chronic diseases.

References

1. Ford ND, Slaughter D, Edwards D, et al. Long COVID and Significant Activity Limitation Among Adults, by Age - United States, June 1-13, 2022, to June 7-19, 2023. *MMWR Morb Mortal Wkly Rep*. Aug 11 2023;72(32):866-870. doi:10.15585/mmwr.mm7232a3
2. Perlis RH, Santillana M, Ognyanova K, et al. Prevalence and Correlates of Long COVID Symptoms Among US Adults. *JAMA Netw Open*. Oct 3 2022;5(10):e2238804. doi:10.1001/jamanetworkopen.2022.38804
3. CDC. National Diabetes Statistic Report. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed 1/15/2024
4. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. Aug 28 2021;398(10302):747-758. doi:10.1016/s0140-6736(21)01755-4
5. Seeßle J, Waterboer T, Hippchen T, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. *Clin Infect Dis*. Apr 9 2022;74(7):1191-1198. doi:10.1093/cid/ciab611
6. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med*. Sep 2021;18(9):e1003773. doi:10.1371/journal.pmed.1003773
7. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. Aug 2021;38:101019. doi:10.1016/j.eclinm.2021.101019
8. Parker ED, Lin J, Mahoney T, et al. Economic Costs of Diabetes in the U.S. in 2022. *Diabetes Care*. Jan 1 2024;47(1):26-43. doi:10.2337/dci23-0085
9. Thaweethai T, Jolley SE, Karlson EW, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *Jama*. May 25 2023;doi:10.1001/jama.2023.8823
10. Bonilla H, Quach TC, Tiwari A, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is common in post-acute sequelae of SARS-CoV-2 infection (PASC): Results from a post-COVID-19 multidisciplinary clinic. *Front Neurol*. 2023;14:1090747. doi:10.3389/fneur.2023.1090747
11. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology*. 2023/01/13 2023;doi:10.1038/s41579-022-00846-2
12. Millett GA, Jones AT, Benkeser D, et al. Assessing differential impacts of COVID-19 on black communities. *Ann Epidemiol*. Jul 2020;47:37-44. doi:10.1016/j.annepidem.2020.05.003
13. Vasquez Reyes M. The Disproportional Impact of COVID-19 on African Americans. *Health Hum Rights*. Dec 2020;22(2):299-307.
14. DiMaggio C, Klein M, Berry C, Frangos S. Black/African American Communities are at highest risk of COVID-19: spatial modeling of New York City ZIP Code-level testing results. *Ann Epidemiol*. Nov 2020;51:7-13. doi:10.1016/j.annepidem.2020.08.012
15. Khullar D, Zhang Y, Zang C, et al. Racial/Ethnic Disparities in Post-acute Sequelae of SARS-CoV-2 Infection in New York: an EHR-Based Cohort Study from the RECOVER Program. *J Gen Intern Med*. Feb 16 2023:1-10. doi:10.1007/s11606-022-07997-1
16. Xie Y, Bowe B, Al-Aly Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. *Nat Commun*. Nov 12 2021;12(1):6571. doi:10.1038/s41467-021-26513-3
17. Robinson, E. Long COVID is a Case Study of Our Fractured Healthcare System. Content last reviewed March 2023. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/news/blog/ahrqviews/long-covid.html. Accessed 6/1/2023.
18. Cutler DM. The Costs of Long COVID. *JAMA Health Forum*. May 6 2022;3(5):e221809. doi:10.1001/jamahealthforum.2022.1809
19. Garcini LM, Pham TT, Ambriz AM, Lill S, Tsevat J. COVID-19 diagnostic testing among underserved Latino communities: Barriers and facilitators. *Health Soc Care Community*. Sep 2022;30(5):e1907-e1916. doi:10.1111/hsc.13621
20. Baker DR, Cadet K, Mani S. COVID-19 Testing and Social Determinants of Health Among Disadvantaged Baltimore Neighborhoods: A Community Mobile Health Clinic Outreach Model. *Popul Health Manag*. May 24 2021;doi:10.1089/pop.2021.0066
21. Snowden LR, Graaf G. COVID-19, Social Determinants Past, Present, and Future, and African Americans' Health. *J Racial Ethn Health Disparities*. Feb 2021;8(1):12-20. doi:10.1007/s40615-020-00923-3

22. Maness SB, Merrell L, Thompson EL, Griner SB, Kline N, Wheldon C. Social Determinants of Health and Health Disparities: COVID-19 Exposures and Mortality Among African American People in the United States. *Public Health Rep*. Jan/Feb 2021;136(1):18-22. doi:10.1177/0033354920969169
23. CDC. COVID-19:People with Certain Medical Conditions. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed 1/16/2024.
24. Walker TA, Truong AD, Summers A, et al. Mild antecedent COVID-19 associated with symptom-specific post-acute sequelae. *PLoS One*. 2023;18(7):e0288391. doi:10.1371/journal.pone.0288391
25. Vanichkachorn G, Newcomb R, Cowl CT, et al. Post-COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the Initial Patient Cohort. *Mayo Clin Proc*. Jul 2021;96(7):1782-1791. doi:10.1016/j.mayocp.2021.04.024
26. Reis Carneiro D, Rocha I, Habek M, et al. Clinical presentation and management strategies of cardiovascular autonomic dysfunction following a COVID-19 infection - A systematic review. *Eur J Neurol*. May 2023;30(5):1528-1539. doi:10.1111/ene.15714
27. List JM, Long TG. Community-Based Primary Care Management of 'Long COVID': A Center of Excellence Model at NYC Health+ Hospitals. *Am J Med*. Oct 2021;134(10):1232-1235. doi:10.1016/j.amjmed.2021.05.029
28. Pantelic M, Ziauddeen N, Boyes M, O'Hara ME, Hastie C, Alwan NA. Long Covid stigma: Estimating burden and validating scale in a UK-based sample. *PLoS One*. 2022;17(11):e0277317. doi:10.1371/journal.pone.0277317
29. Efstathiou V, Stefanou MI, Demetriou M, et al. Long COVID and neuropsychiatric manifestations (Review). *Exp Ther Med*. May 2022;23(5):363. doi:10.3892/etm.2022.11290
30. Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry*. Oct 2022;9(10):815-827. doi:10.1016/s2215-0366(22)00260-7
31. Han Q, Zheng B, Daines L, Sheikh A. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. *Pathogens*. Feb 19 2022;11(2)doi:10.3390/pathogens11020269
32. Xie Y, Xu E, Al-Aly Z. Risks of mental health outcomes in people with covid-19: cohort study. *Bmj*. Feb 16 2022;376:e068993. doi:10.1136/bmj-2021-068993
33. AHRQ. Long COVID Grant Awards. https://www.ahrq.gov/coronavirus/long-covid-grant-awards.html. Accessed 1/16/2024.
34. AHRQ. AHRQ Awards $45 million in Grants to Expand Access to Care for People with Long COVID. https://www.ahrq.gov/news/newsroom/press-releases/long-covid-grant-awards.html. Accessed 1/16/2024.
35. Peluso MJ, Deitchman AN, Torres L, et al. Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms. *Cell Rep*. Aug 10 2021;36(6):109518. doi:10.1016/j.celrep.2021.109518
36. Woodruff MC, Bonham KS, Anam FA, et al. Chronic inflammation, neutrophil activity, and autoreactivity splits long COVID. *Nature Communications*. 2023/07/14 2023;14(1):4201. doi:10.1038/s41467-023-40012-7
37. CDC. National Wastewater Surveillance System (NWSS): COVID-19 Wastewater Data. https://www.cdc.gov/nwss/rv/COVID19-currentlevels.html. Accessed 1/16/2024.
38. Today. The US is starting 2024 in its second-largest COVID surge ever, experts say. https://www.today.com/health/news/covid-wave-2024-rcna132529.
39. von Delft A, Hall MD, Kwong AD, et al. Accelerating antiviral drug discovery: lessons from COVID-19. *Nat Rev Drug Discov*. Jul 2023;22(7):585-603. doi:10.1038/s41573-023-00692-8
40. Angus DC, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *Jama*. Oct 6 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022
41. ANTICOV. https://anticov.org/ Accessed 7/30/2022
42. ACTIV-6: Operationalizing a decentralized, outpatient randomized platform trial to evaluate efficacy of repurposed medicines for COVID-19. *J Clin Transl Sci*. 2023;7(1):e221. doi:10.1017/cts.2023.644
43. McCarthy MW, Naggie S, Boulware DR, et al. Effect of Fluvoxamine vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *Jama*. Jan 24 2023;329(4):296-305. doi:10.1001/jama.2022.24100