ME/CFS in the Long COVID World
A White Paper

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As we begin the 2nd quarter of the 21st century, there is reason to be optimistic about progress being made in ME/CFS research and patient care. First quarter developments offer that promise: The Institute of Medicine offered physicians easy-to-use diagnostic criteria for ME/CFS, the similarities between symptoms of ME/CFS and Long COVID have been rigorously demonstrated and offer indirect proof that ME/CFS is neither an imagined or psychosomatic disease, the National Academy of Medicine offered Long COVID diagnostic criteria which are inclusive of many ME/CFS patients, and a report emerged at a recent rheumatology meeting which stated that some arthritis patients exhibit post-exertional malaise (PEM) – the cardinal symptom of ME/CFS. Used properly, these developments could move ME/CFS into the mainstream of medicine which would facilitate diagnosis and treatment of many more ME/CFS patients. Where ME/CFS was once wrongfully characterized as "yuppie flu" or a women's disease, or a disease which was imagined because its viral trigger could not be found, or considered by some to be a disease so devoid of physical symptoms that it could only be explained as an imagined or psychosomatic illness, those characterizations are difficult to sustain as we enter the second quarter of the 21st century.

Here is a closer look at some recent developments and why they hold promise:

1. The Department of Health and Human Services let a contract in 2013 to the Institute of Medicine ostensibly to review the diagnostic criteria of ME/CFS. The Committee had no way of knowing that the criteria it developed [1] would also embrace yet-to-emerge Long COVID patients. Since few doubt the infectious, viral origin of Long COVID, the similarity of symptoms between ME/CFS and Long COVID suggests that ME/CFS can also be caused by a viral vector. Few if any clinicians are accusing Long COVID patients of having an imagined or psychosomatic illness. There is now a clear example of an ME/CFS-like illness with a viral origin.
2. A previous winner of the New Jersey Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (NJME/CFSA) Medical Scholarship partnered with her residency supervisor to write a statistical analysis of the similarities between ME/CFS and Long COVID. [2] No longer can there be doubt that the cluster of symptoms once thought to be unique to ME/CFS is unique to ME/CFS. With many ME/CFS symptoms now present in the much larger group of Long COVID patients whose viral trigger is not disputed, the possibility and plausibility of ME/CFS being imagined or psychosomatic is diminished.
3. In 2024, the National Academy of Medicine (NAM) produced diagnostic criteria for Long COVID that permit the inclusion of ME/CFS patients. [3] The intent of NAM diagnostic criteria was to facilitate healthcare provider diagnosis of Long COVID. The NAM criteria

require only the presence of specific symptoms. The criteria do not require proof of previous COVID-19 infection or of any previous viral infection. Because of the overlap of ME/CFS and Long COVID symptoms, the NAM Long COVID diagnostic criteria are inclusive of most ME/CFS patients.

4. Given the current consideration of Long COVID Moonshot legislation [4], with an impressive budget to investigate and treat Long COVID, and the inclusion of most ME/CFS patients under the NAM Long COVID diagnostic criteria, ME/CFS patients should be able to present themselves for treatment at all federally funded Long COVID treatment centers and be included in federally funded Long COVID research studies.
5. Also reported in 2024 is that some arthritis patients exhibit post-exertional malaise (PEM), considered by many to be the cardinal symptom of ME/CFS. [5] That PEM occurs in arthritis patients suggests either that PEM can occur in patients who suffer from non-infective disease and, therefore, PEM is not a direct consequence of infection, or that arthritis is an infectious disease. In either case, arthritis is a disease which has a well-established funding mechanism (the Arthritis Foundation) [6] and a professional medical organization which overviews patient care (the American College of Rheumatology). [7] To have PEM come under the purview of the Arthritis Foundation and/or the American College of Rheumatology holds great promise for PEM becoming an accepted symptom of disease, of it becoming a symptom of increased research, and of it being treated more aggressively by healthcare providers.

But the promise of these 21st century developments does not guarantee achievement:

- Senator Bernie Sander's proposed Long COVID Moonshot legislation for Long COVID research funding and treatment is reminiscent of the unsuccessful congressionally-mandated Chronic Fatigue Syndrome research funding of the 1990's: Despite a federally-mandated disbursement of funds for Chronic Fatigue Syndrome research, the U. S. Government's General Accounting Office would eventually conclude that the monies allocated were spent on such "diverse" activities by different agencies so as to raise the question of whether the money was appropriately spent. [8]

- The creation of a Long COVID Advisory Committee (LCAC) for the DHHS by the Office of the President [9] was announced April 5, 2022. As of January, 2025, the LCAC has not met. The proposed members of the LCAC [10] may benefit from knowing the history of the Chronic Fatigue Syndrome Advisory Committee (CFSAC): The CFSAC was formed in 2003 and abruptly terminated in 2018. Chat GPT summarizes the DHHS's responses to the CFSAC's recommendations this way: *(1) The level of research funding fell short of patient's needs. (2) Despite recommendations to improve healthcare provider awareness of CFS, widespread recognition and understanding of the disease remain a challenge. (3) Recommendations regarding DHHS policies were not fully implemented or acted upon in a timely matter. (4) Advocacy groups and public pressure led to more attention than the policymakers.* Chat GPT concludes: *While the CFSAC secured some funding and increased awareness, more needs to be done. Continued advocacy and engagement with the government are essential for further*

progress. Despite there being Committee work on the table, the DHHS disbanded the CFSAC subsequent to the IOM's unfavorable report of the federal government's management of Chronic Fatigue Syndrome, raising the issue of whether the IOM report [11] contributed to the demise of the CFSAC?

What efforts are likely to promote ME/CFS research and patient care in the second quarter of the 21st century?

1. ME/CFS advocates and organizations should align with their Long COVID counterparts so as to represent a larger constituency. The CDC estimates the number of ME/CFS patients in the United States is 1.3 percent of the population [12] while it estimates the number of Long COVID patients as being 6.9 percent of the population [13]. Thus, the combined estimate of patients suffering ME/CFS-like disease in the United States is 8.2 percent of the adult population. By comparison, the percentage of the U. S. population currently living with HIV is estimated to be 0.36 (or 1.2 million people) [14]. Thus, the combined ME/CFS and Long COVID patient population has a 24 times greater chronic disease burden than HIV/AIDS in the United States.
2. ME/CFS advocates and organizations should learn from the history of similarly, "wrongly perceived," diseases. Other diseases which have had to overcome initial, "skepticism," and/or misdiagnoses include HIV/AIDS [15], multiple sclerosis [16], systemic lupus erythematosis [17], and Lyme disease [18]. Efforts need to be undertaken to change societal attitudes towards ME/CFS through public and healthcare provider education, and scientific research. A better understanding and proof of the underlying pathophysiology have overcome the misperceptions of other diseases and are likely to assist in overcoming the skepticism/misdiagnoses found for ME/CFS.
3. ME/CFS should be reclassified and placed into the proposed category of Post Active Phase of Infection Syndromes (PAPIS). ME/CFS is one of many chronic conditions triggered by one or more previous infections. As early as the 18th and 19th centuries lingering symptoms were observed for influenza [19, 20], typhoid [21] and tuberculosis [22]. In the 20th century, post-polio syndrome affected polio patients years after "recovering" from polio [23, 24], and rheumatic fever led to chronic disease through autoimmune mechanisms. [25, 26, 27, 28, 29, 30] The concept of PAPIS (Post Active Phase of Infection Syndromes) was proposed in 2021 [31] based upon the commonality of symptoms between ME/CFS and Long COVID and expanded to include other diseases in 2024 [32]. One year later, the term Post Acute Infection Syndromes (PAIS) was introduced into the literature [33] but the two terms are similar in concept. By emphasizing that PAPIS is a large group of chronic diseases, PAPIS diseases rise to the level of a significant, public health concern with all included diseases receiving increased attention. Without group inclusion some of the individual chronic diseases might receive less or little attention.
4. Assuming that the LCAC will eventually meet, those wishing it success can improve the Committee's chances of success by knowing the history of its predecessor – the Chronic Fatigue Syndrome Advisory Committee. The probability of success of the LCAC can be

enhanced by avoiding the previous Advisory Committee's missteps: Now would be the time to negotiate the diversity of the Committee's membership (to ensure all stakeholders are adequately represented) and that they or their alternates are present at all meetings. Now would be the time to negotiate the types of meetings (physical, virtual, or combined) and the frequency of those meetings (quarterly or biannual). Virtual meetings deprive committee members and patients the opportunity of important, informal interactions and infrequent meetings slow the momentum and the progress of the Committee's work. Now is the time to negotiate a time frame for receipt of responses from the Secretary of Health to submitted recommendations. The Committee needs to receive responses to its submitted recommendations in order to proceed with and plan future work. Now would be the time for DHHS to assure the LCAC that an appropriately educated Designated Federal Officer (DFO) will be assigned so that the LCAC does not need to spend committee time educating the DFO. Now is the time for the DHHS to assure the LCAC that the designated DFO will be appointed for the lifetime of the Committee. The LCAC needs a DFO who understands the Committee's previous efforts and who partners with the Committee to ensure that the workflow continues smoothly and is translated into effective recommendations. It is not the function of the LCAC to educate multiple DFO's.

Summary and Conclusions:

At the beginning of the 2nd quarter of the 21st Century, we know that ME/CFS frequently occurs subsequent to a viral infection and may be triggered by other life events. Similarly, Long COVID occurs as a sequel to COVID-19 in approximately 6 percent of COVID-19 patients and exhibits a cluster of symptoms which overlap with ME/CFS. The Institute of Medicine's diagnostic criteria for ME/CFS, which are inclusive of some Long COVID patients, and the National Academy of Medicine's diagnostic criteria for Long COVID, which are inclusive of a larger percentage of ME/CFS patients, are evidence of the similarities between the two diseases. These overlapping sets of diagnostic criteria support the hypothesis that both diseases should be considered Post Active Phase of Infection Syndromes or PAPIS. A recent Oxford University Press publication supports and extends this hypothesis to other viral and bacterial diseases, and even a helminthological disease. To address the conservatively estimated 8 percent of the U.S. population disabled by ME/CFS and Long COVID, the U.S. Government may provide moon shot funding for Long COVID and a Long COVID Advisory Committee for the U.S. Secretary of Health. These efforts parallel previous efforts for ME/CFS which fell short of their expectations and goals. To promote better outcomes of these new government initiatives, a historical review of the previous efforts should be undertaken and remedies provided for the shortfalls of the previous efforts. Greater stakeholder involvement in all aspects of these proposed government initiatives is likely to enhance the chances of more successful outcomes.

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