Addressing Lacunas in Diagnostic and Treatment Models for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Issuing the Necessary Clarion Call toward Clinical Reformation and a Patient-Centered Approach

New Jersey Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Association Medical Education Award Program

Sarah Armenia
New Jersey Medical School
Class of 2019

Submitted in Partial Fulfillment of Requirements of
NJME/CFSA Medical Education Award

Seated upon an examining table, Dorothy Zbornak, a middle-aged woman and one of the four protagonists of the comedic series *The Golden Girls*, maintained a tight grip on the hospital gown with which she had been provided. The fabric, uncomfortably aged and gossamer, was on the precipice of disintegration; lacking buttons or ties, it draped Dorothy's body and provided only as much protection as her strength could muster. For five months, Dorothy had been suffering from an illness she could not identify. Constant and acute throat pain, muscular weakness, and an unending and encompassing sense of exhaustion had eroded Dorothy's previous quality of life. After the doctor whom she waited over two hours to see asked her whether she felt that her lack of romantic or sexual partners might be the cause of this belated depression and inescapable fatigue, Dorothy stated the following:

> Look, Doctor Stevens, I don't think you understand, so I'm going to tell you again. I am at a point now where I am so exhausted that sometimes I cannot speak – literally, cannot speak. There are days when I can't get out of bed. Raising my arms to wash my hair in the shower is too exhausting for me. I can't even do that! I have heart palpitations. I forget things. I…I get confused.[1]

Dorothy's doctor found her complaints rooted in an etiology of loneliness, likely exacerbated by her gender. He counseled her to avoid wasting further money on unnecessary medical expenses and washed his hands of her complaints. As Dorothy would eventually learn, it was not her loneliness that left her so debilitated – Dorothy suffered from Chronic Fatigue Syndrome (CFS), known also as Myalgic Encephalomyelitis (ME), a disease then lacking and still lacking a universal case definition. Despite the absence of medico-scientific consensus on the diagnostic standards for identifying ME/CFS, the condition is often defined by a painful assemblage of symptoms including "immunologic and inflammatory pathologies, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities."[2] Fatigue, which long served as the cornerstone of ME/CFS diagnosis, is now

understood to inadequately capture the immensely complex nature of the illness. A dearth in clinical evidence has rendered it difficult to conclude whether the aforementioned symptoms are characteristic of the illness at all stages of life or only at particular stages. The neurocognitive deficits and general malaise that inhibit the adult and mature body may not be manifest in the pediatric patient despite the operation of ME/CFS within that patient's body.

The episode from which the above quote is excerpted first aired in late 1989; it is thus unusually unsettling that in December 2014 the National Institutes of Health would state in its final *Pathways to Prevention* report regarding ME/CFS that patients continue to be treated with skepticism and disregard, with doctors forcing patients to make extraordinary physical and financial efforts merely to have diagnoses made and treatment plans coordinated. The National Institutes of Health was not alone in acknowledging the acutely impoverished state of clinical knowledge surrounding the pathogenesis and symptom profile of ME/CFS. Both the Institute of Medicine (IOM) (now known as the Health and Medicine Division (HMD) of the National Academies of Science, Engineering, and Medicine) and the Agency for Healthcare Research and Quality (AHRQ) of the federal Department of Health and Human Services (HHS) would release extensive documentation regarding the state of ME/CFS research and the incongruous constellation of approaches to patient care in late 2014 and early 2015. These three reports each articulated significant concerns about the inchoate, fractured, and almost absent universal diagnostic and treatment standards for ME/CFS. If clinicians intend to transform the unacceptably underdeveloped quality of ME/CFS research into a burgeoning field, it must be done with an eye toward both the concerns these documents express and a constant privileging of the physical, psychological, and emotional needs of patients as the very nexus that drives this demand for funding, research, and the highest and most uncompromised quality in care.

I. Inquiries of Context: The State of ME/CFS Research and the Concerns Articulated by IOM, NIH, and AHRQ.

To better situate the intense immediacy with which discourse on ME/CFS must begin, the debilitating effects of the illness should be contextualized. Anywhere between 836,000 to 2.5 million Americans have been clinically diagnosed with ME/CFS, a numerical gap admittedly erroneous, as it is estimated that well over 80 percent of individuals living with ME/CFS have not yet been diagnosed. This conservative estimation would suggest that the disease could be affecting over 4 million American lives.[3,4] The inability to diagnose the presentation of ME/CFS is partially a function of the illness' multifactorial origin. Researchers and clinicians remain unable to penetrate the complexity that characterizes the pathophysiology of ME/CFS'.[5] IOM, for example, has suggested that the presence of three symptoms – debilitating fatigue, post-exertional malaise, and unrefreshing sleep – are necessary for diagnosis of ME/CFS, along with the manifestation of either cognitive impairment or orthostatic intolerance. However, the nature and intensity of symptoms vary widely among patient populations, thereby confounding doctors and perpetuating the cycle of misdiagnosis and mistreatment.[6] These variations in symptom profiles have further aggravated the delay in standardizing diagnostic criteria. As will be subsequently discussed, the IOM's *Pathways to Prevention* document offers its own set of distilled diagnostic criteria for ME/CFS; these criteria are the most recent to be published, with eight preexisting case definitions with conflicting clinical criteria having already been published over the last twenty-five years.[7–14]

The following three documents, each prepared by an organization committed to galvanizing the urgency so needed in support of research on ME/CFS, contemplates the required steps that must be taken for patients living with ME/CFS to lessen the illness' impact on their lives. While the documents explore many avenues, of salience here are the proposals and

recommendations each makes to transform the very nature of ME/CFS treatment. These concerns, when interwoven, serve as the collective fabric upon through which the future of ME/CFS treatment will be tailored. Specifically, they will inform the subsequent discussion that responds to the IOM's clarion call for the creation of ME/CFS Centers of Excellence across the nation.

A. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness (Institute of Medicine).*[15]

At the request of HHS' Chronic Fatigue Syndrome Advisory Committee (CFSAC), IOM convened a task force to structure evidence-based clinical diagnostic criteria for ME/CFS, to determine whether new terminology for ME/CFS should be adopted, and to develop outreach strategies for the dissemination of these new criteria to healthcare professionals nationwide. The task force was to place emphasis on the unique diagnostic issues facing persons with ME/CFS, related specifically to gender and the compounding impacts of disability.

The primary message of the report underscored the severity of ME/CFS as a chronic, complex, and systemic disease that dramatically alters the lives of affected patients. It was this central insight that helped shape the proposed diagnostic criteria for ME/CFS found within the report. As mentioned, those criteria focused on extensive fatigue, post-exertional malaise, unrefreshing sleep, and the presence of either cognitive impairment or orthostatic intolerance. In addition, the task force released four explicit recommendations to be immediately implemented in order to effectuate the heightened standard of care that ME/CFS patients deserve.

First, the committee suggested that the diagnosis of ME/CFS should be met not only if the diagnostic criteria are met but also after physicians have done thorough evaluations of their patients' health histories and have completed diligent medical work-ups. To ensure that physicians are able to meet this standard of proper diagnosis, the task force also recommended

that HHS develop and make available a clinical toolkit for screening and diagnosing patients with ME/CFS in clinical settings beyond the scope of primary care, including emergency departments, behavioral health clinics, occupational therapy units, and during subspecialty examinations. Third, the task force instituted a mechanism of self-accountability, suggesting that a multidisciplinary group should be convened within five years of the publication of the recommendations to determine whether the issuance of these new diagnostic criteria improved the quality of care impacted individuals received. Finally, after extensive consideration of the misconceptions often elicited by the very name of the illness and the inaccurate symptom profile it suggests, the task force became convinced that there was value in proposing an alternative name for ME/CFS that conveyed the central elements of the disease. The task force felt that the suggested name, "Systemic Exertion Intolerance Disease (SEID)," captured the reality that any form of exertion – physical, cognitive, emotional – causes patients to pay a profound tax on their quality of life.

B. *Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (National Institutes of Health).*[3]

At the conclusion of 2014, NIH convened a workshop of clinicians, doctors, and scholars to illuminate lacunas in existing ME/CFS discourse and begin remedying those fissures. An independent panel, organized by NIH, evaluated the scholarship and scientific evidence marshaled by workshop participants to offer recommendations on the future direction of ME/CFS research. The panel first noted undergirding paradox of ME/CFS diagnosis and treatment: despite the overwhelming panoply of symptoms identified and associated with ME/CFS, there exists no universally accepted standard of diagnosis. And, while the absence of such a standard misleads doctors into erroneous diagnoses, physicians should not be held singularly accountable. The dearth of research funding to better understand the pathogenesis of

ME/CFS binds clinicians' capacity to identify the illness and prescribe appropriate treatment.

Those clinical trials researchers have completed have been skewed disproportionately toward particular subpopulations and have failed to delineate between conditions caused by ME/CFS and comorbidities bearing a positive correlational relationship with ME/CFS. The panel found that the research presented generally neglected to place emphasis on the biological factors underlying ME/CFS onset and progression; if research is to improve patient quality of life, the panel found that it would need to be shifted to include basic science and mechanistic inquiries that will expand a too shallow group of tools and measures to identify the illness.

The panel offered several immediate recommendations whose implementation would begin to stymy the increasing paralysis of ME/CFS study. The panel stated that a gold standard for diagnosis had to be adopted, even if the standard were one upon which scholars and researchers disagreed. The universal utilization of this standard will allow for a collective drive toward new prognostic tests that can guide treatment strategies as well as research that employs an integrated, systems-level approach that will unearth how immunologic, neurologic, and metagenomic factors may contribute to the onset and progression of ME/CFS. Multimodal therapies and treatment programs which acknowledge differences in ability among patients can expand access to healthcare for those persons afflicted by ME/CFS while igniting physicians and researchers to continuously reimagine the approach taken toward ME/CFS diagnosis and treatment.

C. *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (Agency for Healthcare Research and Quality).*[16]

AHRQ, commissioned by various divisions within NIH, sought to evaluate and summarize existing research on methods for diagnosis of ME/CFS, the benefits and harms of treatments, and lacunas in current research that should serve as the impetus for future clinical

examination. The agency's review proceeded along two distinct but conceptually interrelated axes: the clinical sufficiency and quality of currently existing methods used to diagnose ME/CFS and the impacts of specific therapeutic interventions on patients with ME/CFS, partitioning the efficacy of such treatment approaches among various subpopulations.

Of the various clinical criteria that have been published and made accessible to physicians, AHRQ noted the difficulty of determining which collective was the most accurate for diagnostic use in the absence of an established reference standard. Studies evaluating potential relationships between diagnostic criteria and subpopulations were found to be lacking, and multiple studies documented the intense emotional and financial distress ME/CFS patients experience because of overt stigmatization among healthcare providers. With regard to treatment, AHRQ found that completed randomized trials analyzing the benefits and harms of ME/CFS interventions employed fair- or poor-quality research methods and had insufficient sample sizes that did not reflect the diversity of patients afflicted by ME/CFS. AHRQ analyzed treatment interventions that were cross-modal and multimodal, including treatment via medication, via complementary and alternative therapies, via behavioral therapy, and via exercise therapy. AHRQ concluded that the body of research examined was insufficient to draw conclusions regarding desirable treatment methods for ME/CFS.

II. Centers of Excellence: Transforming the Face of Treatment for ME/CFS.

The reality of ME/CFS research is a stark one: in 2014, among the 234 disease categories financially supported by NIH, ME/CFS ranked 228th, with an estimated $5 million in funding.[17] Realizing that this yearly sum was woefully insufficient for the clinical task at hand, the CFSAC recently re-recommended the establishment of ME/CFS Centers of Excellence (COE), the purpose of which would be to provide complete and comprehensive patient care and

unprecedented clinical and research opportunities for scholars and clinicians. In its issued recommendation, the CFSAC outlined seven benchmark standards for the program, including the number of COE to be established, the ideal locations for the COE, and the necessary funding for the COE to successfully achieve their intended objectives.[18] These seven criteria, however, were not robustly developed in the issued recommendation. If the quality of care for patients afflicted by ME/CFS is to change, there must be explicit focus on questions regarding the number of needed COE, the locations of COE that will provide both clinicians and patients with the highest yield in knowledge production, the research activities and therapeutic interventions that will be offered at the COE, and the funding that will be necessary for the COE to change the very nature of ME/CFS treatment and diagnosis.

A. *Determining the Necessary Quantity and Locations of COE Nationwide*

In determining both the number of COE to establish and the ideal locations of the Centers to maximize their impact, the CFSAC suggested that COE should be housed in or near academic centers with preexisting medical institutions to properly foster the required multidisciplinary approach to research and patient care. The Advisory Committee recommended the establishment of twelve COE that will serve the diverse patient communities that constitute the United States population. However, the CFSAC did not provide further insight into the proper methodology for selecting these locations, nor did it offer justification or reasoning as to why twelve COE would be preferable to a greater or fewer number. Despite the realistic concern that fiscal constraints engender, it would be imprudent to narrow the horizon of the COE program because of projected uncertainties. If the COE are to reach the largest number of patients possible and are to provide telemedical services to care for rural populations too far removed to access the sites, a wiser approach would be to develop of methodology of determining the number of COE by

considering the most ideal locations for their establishment. Such a determining system would explore how the COE could be integrated within existing academic medical institutions known for their innovative research agendas and excellence in scholarship. Further, this system would remain cognizant of population density throughout the United States, allowing for an increased number of COE in portions of the country where population sizes so demand.

Employing the selection methodology just described, the ideal number of COE to be established would be sixteen rather than twelve. Each COE would be affiliated with an academic medical institution geographically located at the central nexus of the collective area it is intended to serve. Additionally, the establishment of these sixteen COE should not be construed as sixteen independent research and treatment enterprises; the sixteen COE would represent a fully integrated and systematized network of clinical resources, collegiate consulting, and novel therapeutic interventions developed within the very walls of the Centers.

A hypothetical distribution of COE among academic medical institutions and the geographic areas such distributions would cover might look as follows: 1) COE at Harvard Medical School, Boston, Massachusetts, to serve Massachusetts, New Hampshire, Connecticut, Rhode Island, Vermont, and Maine; 2) COE at University at Buffalo School of Medicine and Biological Sciences, Buffalo, New York, to serve northern and eastern portions of rural New York; 3) Rutgers New Jersey Medical School, Newark, New Jersey, to serve New Jersey and the New York City area; 4) Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, to serve Pennsylvania, Washington, D.C., and northern portions of Delaware and Maryland; 5) Johns Hopkins University School of Medicine, Baltimore, Maryland, to serve Maryland, Delaware, and the Washington, D.C., metropolitan area; 6) University of Virginia School of Medicine, Charlottesville, Virginia, to serve Virginia, West Virginia, and

southern portion of Maryland; 7) Emory University School of Medicine, Atlanta, Georgia, to serve North Carolina, South Carolina, Georgia, Florida, Alabama, Tennessee, and eastern Mississippi; 8) University of Michigan Medical School, Ann Arbor, Michigan, to serve Michigan, Indiana, and Ohio; 9) University of Chicago Pritzker School of Medicine, Chicago, Illinois, to serve Wisconsin, Illinois, and the eastern portion of Iowa; 10) Washington University School of Medicine, St. Louis, Missouri, to serve Kansas, Missouri, Kentucky, and Nebraska; 11) Mayo Clinic College of Medicine, Rochester, Minnesota, to serve Minnesota, North Dakota, and South Dakota; 12) Dell Medical School at the University of Texas at Austin, Austin, Texas, to serve western Texas, Louisiana, western Mississippi, Arkansas, and Oklahoma; 13) University of Colorado School of Medicine, Aurora, Colorado, to serve Colorado, Utah, New Mexico, western Texas, and southern Wyoming; 14) University of Washington School of Medicine, Seattle, Washington, to serve Washington, Oregon, Idaho, Montana, Alaska, and northern Wyoming; 15) University of California, San Francisco School of Medicine, San Francisco, California, to serve northern California and Nevada; and 16) Keck School of Medicine of University of Southern California, Los Angeles, California, to serve southern California and Arizona.

While several different inquiries led to the genesis of the above list of academic medical institutions, the most important questions asked by the proposed methodology dealt with whether an institution had the necessary resources to willingly pioneer a COE for ME/CFS when it is well-known within the medical community that funding and support for research are rare treasures to be found. Each of these medical centers has the institutional capacity and the potency of scholarly ingenuity to power a COE and transform each individual site into a constituting element of a vibrant mosaic of large-scale and path-breaking research.

B. *Research Activities and Therapeutic Interventions at National COE*

The consideration of COE research agendas (and the therapeutic interventions those agendas will subsequently fuel) requires examination of an antecedent inquiry: who will constitute the multi-specialty clinical and research team present at the COE to ensure both quality of research and quality of care? Numbers of required clinical personnel will be driven by caseloads at each individual COE, and this inherent variability cannot be easily predicted, which suggests that a framing of sheer volume would not prove useful. An alternative and more pragmatic and efficacious approach would be to select the individuals who should constitute a single clinical-treatment unit (CTU) at individual COEs; these CTUs, each with a set number of individuals who can perform both discrete and collaborative tasks, can then be multiplied in order to meet the patient needs of various COE.

Leading the CTU should be two physicians, each with differing but complementary specialties that will encourage robust discussion during the diagnostic phase of ME/CFS treatment. A potential coupling might include a primary-care physician and a rheumatologist. While a primary-care physician would be able to develop, maintain, and evaluate a patient's medical history (which, in the context of ME/CFS, is likely to be historically longitudinal and complex) and prescribe the necessary diagnostic testing to determine the patient's overall state of health, a rheumatologist will have a developed and unique facility for the diagnosis of complex illnesses affecting multiple organ systems. Additionally, a rheumatologist will have a balanced and knowledgeable approach toward the management of chronic inflammation and pain and toward the intricacies of autoimmune pathophysiology. Supporting these physicians would be two Physician Assistants (PA) on the clinical-treatment end, one of whom could serve as a liaison for clinical studies in which the patients for whom they care may wish to participate.

Specifically, this PA would be charged with speaking with patients about available trials at the particular COE in question and whether the trial might prove beneficial to the unique profile of ME/CFS symptoms the patient is experiencing. Additional members of the core CTU should include a Registered Nurse (RN) who is able to oversee and coordinate multidisciplinary care for patients and a Medical Assistant (MA) to perform required logistical and operational work so that patient records are accurately maintained. The MA will play a particularly vital role in the consistency of telemedicine delivery, as much of this care will need to be scheduled around the availabilities of patients and the physical abilities of patients to access the COEs. These six individuals represent the core of a CTU, and the CTU model can be multiplied as necessary to ensure that ME/CFS patients at the COE receive the highest quality of care. To ensure operational and logistical functioning, each COE should also have a Clinical Research Coordinator and a Statistical Programmer who can work collaboratively with colleagues at other COE to bring together acquired clinical data in preparation for review and publication.

With the core CTU in place, the twin questions of research and treatment are brought to the fore. It is only by advancing ME/CFS-targeted research agendas that the enormous gaps in clinical knowledge enveloping the illness can be addressed. Without such reorientation, treatment modalities will remain ineffective and improperly prescribed, resulting in patients' further debility. From a normatively empirical perspective, clinical research on ME/CFS must move away from heightened focus on the efficacy of cognitive behavioral therapy (CBT) and graded exercise therapy (GET). For example, while clinical evidence supports the notion that CBT has proven effective in addressing patients' sense of psychological wellbeing, it does little to improve "cognitive function" or "quality of life."[19] In the absence of such improvements, CBT cannot be considered to be an appropriate primary treatment strategy. Instead, research should

prioritize the development of biomarkers for ME/CFS and objective diagnostic criteria. Imaging technologies, cytokine abnormalities, genetic or metabolic signatures, and other potential markers must be shifted to the center of new research agendas. Research in more specialized areas should not preclude inquiry into gaps in basic, translational, clinical, and epidemiological scholarship on ME/CFS. Indeed, clinical inquiries must be operating at both macrocosmic and microcosmic levels if innovative approaches to treatment are to be discovered.

While each of the COEs may have the capacity to engage diverse clinical trials of significant impact, there must also be a research inquiry that unites the COEs and drives forward the overarching mission that led to their conception. As discussed, one of the most vexing issues facing ME/CFS today is the failure to identify a unique etiology. The documentation of countlessly varying triggers for what is then concluded to be the same illness should indicate that the narrowness that accompanies the clinical conception of ME/CFS is itself disorienting. Each COE must be connected to the others in order to determine whether ME/CFS should be understood as a series of interrelated illnesses rather than as one illness that must have a concretely delineated etiology. One might consider as an example the perplexing convergence of diagnoses of Lyme disease and ME/CFS documented by Associate Clinical Professor Samuel Shor of George Washington University. In the research Dr. Shor conducted, 209 patients both satisfied the International Case Definition for CFS, which is based on fatigue and were also seronegative for Lyme disease. Through treatment with antimicrobials pursuant to Lyme disease protocols, 62% of patients achieved a 50% improvement in clinical status and an additional 26% self-reported a subjective sense of improvement.[20] If all patients who reported improvement following treatment for Lyme disease also matched the symptom profile for ME/CFS, it is clear that the diagnostic criteria currently used for ME/CFS have such substantial overlap with other

illnesses and conditions that it may be imprudent to characterize ME/CFS as a single illness or an illness that presents identically in every patient. The COEs must be working constantly to unravel the multiple layers of ME/CFS in order to determine whether what has long been thought of as a singular illness actually represents an umbrella of similar symptoms.

If the sixteen proposed COEs are to provide excellence in clinical research and excellence in clinical care, it will be because their research agendas are driven by the impetus to understand the multiplicities of ME/CFS. It is the ingenuity of such a research agenda that will transform the menu of therapeutic interventions and that will therefore ensure that ME/CFS patients receive the highest quality of healthcare.

C. *Fiscal Considerations for the Establishment and Long-Term Maintenance of COE*

What remains as the most daunting aspect of the establishment of the sixteen COEs is the question of funding. Funding issues pertain not only to the financing of research and clinical trials; they deal also with the construction and maintenance of the sixteen COEs, the payment of medical personnel who run the COEs, and the ongoing costs of ensuring that the latest and most cutting-edge technology is available for ME/CFS research and treatment. In its recommendation, the CFSAC stated that $60 million should be spread across its proposed twelve centers over a five-year period, thereby providing each center with $1 million per year. The state of urgency that characterizes current ME/CFS knowledge and research cannot depend solely upon a singular governmental sub-entity to ensure its continued functioning. While each COE should have *at minimum* $1 million per year in funding, requests for capital financing must go beyond HHS and federal agencies also known for supporting medical research, such as Department of Defense or the Department of Veteran Affairs. The need for change is at its apex, which means that each COE must consider how it can leverage its unique relationship with its affiliated academic

institution, the state in which it is located, and the private foundations that continue to support ME/CFS research.

Pragmatically, this will require COEs to explore how their research and clinical work might be supported through grants from organizations such as the Solve ME/CFS Initiative or the Chronic Fatigue Initiative at the Hutchins Family Foundation. These organizations have preexisting relationships with several of the academic institutions chosen to house COEs. It is likely that medical faculty have worked through the grant process before and have a sophisticated level of knowledge with regard to applications and new research approaches. Finally, the COEs must be willing to turn to the states in which they are located for additional funding. If COEs bring patients from various parts of the country into the states in which they are housed, this gravitational draw injects the COEs directly into state economies. This relationship can and should be symbiotic.

III. Moving Forward, Moving Center: The Patient as Nexus and Lodestar of ME/CFS Treatment.

As the next generation of research and treatment begins for persons living with ME/CFS, it is of elemental necessity that healthcare providers begin to learn about ME/CFS and understand its complex and evolving character. Perhaps this transformation can begin at the very site that first proposed the question of this discussion – a medical school. A step toward including ME/CFS in medical school curricula is a step toward recognizing the role that future generations of doctors must play in ameliorating the impacts of this illness.

References

[1] Witt PJ, Thomas T, Harris S. "Sick and Tired, Pt. 1," The Golden Girls. Los Angeles (CA): National Broadcasting Company; 1989 Sept 23.

[2] Green CR, Cowan P, Elk R, O'Neil KM, Rasmussen AL. Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Final Report. 2014 Dec 9-10; 3. Sponsored by National Institutes of Health.

[3] Institute of Medicine of the National Academies. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Key Facts. 2015 Feb.

[4] Jason L, Torres-Harding S, Njok M. The Face of CFS in the U.S. CFIDS Chronicle 2005-2006; 16-21.

[5] de Korwin JD, Chiche L, Banovic I, Ghali A, Delliaux S, Authier FJ, et al. Chronic fatigue syndrome: a new disorder? Rev Intern Med. 2016. doi: 10.1016/j.revmed.2016.05.003. Epub 2016 May 31.

[6] Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness, Report Guide for Clinicians. 2015.

[7] Carruthers BM, Jain AK, de Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. J Chronic Fatigue Syndr. 2003;11(1):7-115.

[8] Carruthers BM, van de Sande MI, de Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270(4):327-38. PMID: 21777306.

[9] Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12):953-9. PMID: 7978722.

[10] Dowsett E, Goudsmit E, Macintyre A, et al. Report from the National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME). Westcare; 1994.

[11] Holes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. Ann Intern Med. 1988;108(3):387-9. PMID: 2829679.

[12] Jason L, Evans M, Porter N, et al. The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. Am J Biochem Biotechnol. 2010;6(2):120-35.

[13] Reeves WC, Wagner D, Nisenbaym R, et al. Chronic fatigue syndrome–a clinically empirical approach to its definition and study. BMC Med. 2005;3:19. PMID: 16356178.

[14] Sharpe MC, Archard LC, Banatvala JE, et al. A report–chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991:84(2):118-21. PMID: 1999813.

[15] Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC): The National Academies Press; 2015.

[16] Beth Smith ME, Nelson HD, Haney E, Pappas M, Daegas M, Wasson N, et al. Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Evidence Report/Technology Assessment No. 219. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 15-E001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014.

[17] Chronic Fatigue Syndrome Advisory Committee. Comments, Draft Report, Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Washington (DC). 2015 Jan. 2 p.

[18] Centers of Excellence Workgroup Recommendations [Internet]. Washington (DC): U.S. Department of Health & Human Services; [updated 2016 Jul 11, cited 2016 Aug 10]. Available from: http://www.hhs.gov/advcomcfs/recommendations/centers-of-excellence-workgroup-recommendations.html.

[19] O'Dowd H, Gladwell P, Rogers C, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Tech Assessment. 2006 Oct;10(37):39.

[20] Shor S. Retrospective analysis of a cohort of internationally case defined chronic fatigue syndrome patients in a Lyme endemic area. Bulletin of the IACFS/ME. 2011;18(4):109-123.