NATIONAL INSTITUTES OF HEALTH

Pathways to Prevention Workshop:

Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Comments on the Draft Executive Summary

From Massachusetts CFIDS/ME & FM Association

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Note: The line numbers in this document refer to the 389-line version.

General comment: Thank you to the panel for producing a thoughtful and strong report in a very short amount of time, with limited input (Evidence Review and 1 ½ day Workshop with presentations from a variety of "experts"). We consider this report a major contribution to help get our disease the recognition and attention that is greatly needed to advance research, awareness and education in the health care provider community, and care for patients. The comments below are offered in the spirit of making the final report even better, with clearer statements about the definition of the disease being studied (critical to patients), and stronger recommendations particularly with regard to funding needs.

We particularly appreciate the following points which were strongly stated in the report:

- That ME/CFS is a biological, not psychological disease
- That greatly increased funding is needed to research many and varied aspects of the disease, emphasizing biological studies
- The need for agreement on an accurate case definition, recognizing that the use of multiple and sometimes inappropriate clinical criteria to select research subjects has contributed to the lack of progress
- The need for all patients to have access to high quality care
- The need for education about this disease for all levels of health care providers

- Outreach to underserved and diverse populations, and including children and youth, men, and the severely ill.

Introduction

[2-4] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi- faceted condition characterized by extreme fatigue and other symptoms that are not improved by rest. The etiology and pathogenesis remain unknown; there are no laboratory diagnostic tests;

We ask: Revise this statement to use the current CDC definition of CFS, to add a separate statement about ME, and to delete the phrase "there are no laboratory diagnostic tests."

> *"Chronic fatigue syndrome, or CFS, is a debilitating and complex disorder characterized by profound fatigue that is not improved by bed rest and that may be worsened by physical or mental activity. Symptoms affect several body systems and may include weakness, muscle pain, impaired memory and/or mental concentration, and insomnia, which can result in reduced participation in daily activities*[1]*. Myalgic Encephalomyelitis, or ME, as originally defined by Ramsay in 1986*[2]*, has as a hallmark symptom profound fatigue that is worsened by physical or mental activity and is not improved by bed rest (note the rearrangement of phrases). The etiology and pathogenesis remain unknown, and there are no known cures. Whether ME and CFS, which are hereinafter referred to jointly as ME/CFS, are one entity, two separate entities, or part of a continuum, is not addressed in this report. We recognize and acknowledge that patients who meet the ME criteria are more severely ill, with significant and often devastating impact on their lives."*

This statement is out-dated and highlights "fatigue" and "other symptoms." This is one of the central controversies of this illness. To acknowledge it at the beginning, and to state clearly that the Panel is not taking a specific position with regard to the various case definitions which have

[1] *http://www.cdc.gov/cfs/*

[2] Ramsay AM. Myalgic Encephalomyelitis and Postviral Fatigue States: The saga of Royal Free disease. 1st ed. London: Gower Medical Publishing; 1986.
Cited in: Myalgic Encephalomyelitis Case Definitions, Leonard A. Jason, Dylan Damrongvachiraphan, Jessica Hunnell, Lindsey Bartgis, Abigail Brown, Meredyth Evans, and Molly Brown, Automatic Control of Physiological State and Function Vol. 1 (2012):1-14.
http://www.iacfsme.org/LinkClick.aspx?fileticket=5rQ3LXEp4WE%3D&tabid=512

contributed to the methodological problems in ME/CFS studies as noted in lines 48 and 49 of the report, would help to promote more widespread acceptance of the report's excellent findings. A more robust introduction, summarizing salient facts, would help to educate those who may only read the Introduction. It is also worth noting that while there may be no laboratory diagnostic tests currently in use in the primary care setting, the presence of post-exertional malaise as a symptom is a key diagnostic factor and can be definitively demonstrated in a laboratory setting.

[5] "one million" "mostly women"

Add *in the U.S.* after "one million." The number of patients world-wide is widely quoted to be 17 million[3].

Delete "mostly women" and add sentence: "*Although both men and women have the illness, it appears to be more common in women."*

[6-7]: ME/CFS is an unmet public health need with an economic burden estimated to be greater than $1 billion.

We ask: Revise this statement to reflect both direct and indirect costs.

"The economic burden of ME/CFS in the US, including annual health care costs, is estimated to be between $1.9 billion and $7.2 billion. When factoring in indirect costs to society as a whole, the annual estimate jumps to between $18.7 and $23 billion in the US alone.[4,5,6]"

What is the incidence and prevalence of Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and whom does it affect?

[32] "ME/CFS exists."

We ask: Consider adding: "*It is a biological illness with reproducible evidence of a variety of bodily dysfunctions and pathologies [described in lines 82-86]; this is not a psychological disease in etiology [92-93]."*

[3] http://www.microbediscovery.org/about-mecfs/

[4] The economic impact of CFS. K Reynolds et al. Cost Eff Resour Alloc. 2004, 2: 4. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC449736/

[5] Jason L et al. The economic impact of ME/CFS: Individual and societal costs. Dynamic Medicine. 2008, 7:6. http://www.dynamic-med.com/content/7/1/6

[6] Lin J et al. The economic impact of CFS in Georgia: direct and indirect costs. Cost Effectiveness and Resource Allocation. 2011, 9:1. http://www.resource-allocation.com/content/9/1/1

We need a clear, strong statement right up front that ME/CFS is a real, physical illness, not psychological in origin. The misperceptions about this, especially from health care providers, are a major source of harm to patients.

[33 and repeated on line 94] "ME/CFS…overlaps with many other diseases (e.g., fibromyalgia, major depressive disorder, chronic pain)."

We ask: Reword this sentence to state: "*…often exists with many other diseases as co-morbidities."*

ME/CFS often occurs with one or more co-morbid conditions from a long list, fibromyalgia being likely the most common. More research is needed to determine the prevalence of each of these in ME/CFS patients. A clear distinction should be made between **co-morbid conditions** which occur in ME/CFS patients, and those **conditions which have symptoms which are similar** (overlapping symptoms) to those which occur in ME/CFS. The word "overlap" when applied to co-morbidities is confusing as it may suggest to some readers that the diseases are part of the same continuum and have the same etiology, whereas even though symptoms are similar, two illness may have quite different etiology and pathophysiology (e.g., ME/CFS and fibromyalgia[7]).

For a complete list of common co-morbid conditions, please see the 2003 Canadian Consensus Criteria[8] which states (p. 13): *"Co-Morbid Entities: Fibromyalgia Syndrome, Myofascial Pain Syndrome, Temporomandibular Joint Syndrome, Irritable Bowel Syndrome, Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities, Hashimoto's thyroiditis, and Sicca Syndrome. Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes."*

[34] "…There is no agreement from the research community on what needs to be studied.."

In fact, there is considerable agreement. Please reference the National Institutes of Health State of the Knowledge Workshop Report, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research, April 7-8, 2011, and the numerous recommendations regarding research which have been made regularly by the Chronic Fatigue Syndrome Advisory Committee (from 2004 – 2014).

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[7] QJM. 2013 Jan;106(1):3-9. doi: 10.1093/qjmed/hcs156. Epub 2012 Aug 26. Is chronic fatigue syndrome the same illness as fibromyalgia: evaluating the 'single syndrome' hypothesis. Abbi B[1], Natelson BH. http://www.ncbi.nlm.nih.gov/pubmed/22927538

[8] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols, Carruthers, et al. J.ChronicFatigueSyndrome 11:7-97 (2003) http://www.fm-cfs.ca/pdfs/CFS-Protocol.pdf

[49] "…there are no agreed-upon parameters for defining ME/CFS, no accurate ways of identifying and diagnosing ME/CFS."

Many ME/CFS experts, both clinicians and researchers, as well as the Chronic Fatigue Syndrome Advisory Committee (October 2012, March 2014), have recommended the adoption of the 2003 Canadian Consensus Criteria for both research and clinical use, recognizing that it is the best definition we have and could be used as a starting point for further refining both a research and a clinical case definition. This choice is reinforced by the selection of this case definition as the basis for the ME/CFS Primer for Clinical Practitioners[9], published by the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in 2012, and revised in 2014.

While we fully support your recommendation to convene a national and international group to clarify the case definition [lines 202-204] we respectfully point out that similar recommendations have been made before by the Chronic Fatigue Syndrome Advisory Committee (October 2009 and October 2012) and no action has yet been taken.

We further ask that a statement be made that once agreement has been reached on a case definition, all other case definitions be retired from further use, at least in the U.S.

[50-51] "…and 163 symptoms have been associated with ME/CFS."

We ask: Replace this phrase with "*…and the most commonly used case definition (Fukuda, 1994) allows for diagnosis using any one of 163 combinations of symptoms."*

Dr. Nacul stated during the workshop that using Fukuda, there could be *163 unique combinations* of symptoms, pointing out how non-specific it is as a case definition.

[52] "research focus on men"

Please clarify. Perhaps this is a typo?

Most of the ME/CFS research to date has used predominantly women subjects.

[54] "many instruments"

Please clarify this statement. Examples would be helpful to support this statement.

[58] "Fatigue has been the defining focus of recent research"

We ask: Consider changing this sentence to clarify. "*Fatigue was the defining focus of the research in the Evidence Review provided for this study*."

[9] http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509

Recent research explores many other topics, but this statement may be true of the research review that was provided in the EPC report because of the way the search was conducted. "Fatigue" is also a very non-specific symptom. There are many different kinds of fatigue. Research on different types of fatigue should not be lumped together. In particular, the type of fatigue that is often described as "post-exertional malaise" is the most relevant to ME/CFS, since PEM is a hallmark symptom of the illness.

Patients agree that "fatigue," as it is generally understood, does not begin to describe their experience, and many say that fatigue is not even the most troublesome symptom.[10]

[58] "…many other symptoms need to be explored"

We ask: Could you could add to this list: "sleep disorders, immunological changes, orthostatic intolerance, metabolic basis of energy production, as examples"

Examples would be helpful.

[60] "Most ME/CFS studies focus on adults, excluding children with similar symptoms."

We ask: Consider suggesting that this omission should be rectified (both here and in the Recommendations section). "*Children and youth were not part of the present study; however such a study should be done. ME/CFS in children and youth often presents somewhat differently from that in adults. Symptoms more prominent in children include gastrointestinal upset, orthostatic intolerance, and headaches, among others*[11,12]."

In his presentation Dr. Nacul referenced a Norwegian study that showed two peaks of age of onset, 10-19 years and 30-39 years,[13] a fact which makes this group an important one to study. Given that ME/CFS in children and youth was specifically not addressed in the P2P study, a strong statement that such a review should be done (and this included in the Recommendations

[10]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Chronic Fatigue Syndrome and Myalgic Encephalomyelitis, Voice of the Patient, September 2013, p. 6. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf

[11] Jason et al., A Case Definition for Children with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Clinical Medicine: Pediatrics 2008:1 53-57

[12] Chronic Fatigue Syndrome Myalgic Encephalomyelitis Primer for Clinical Practitioners 2014 Edition, published by the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, p.29

[13] Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008–2012, Bakken, et al., *BMC Medicine* 2014, **12**:167 doi:10.1186/s12916-014-0167-5 http://www.biomedcentral.com/1741-7015/12/167

section) would be appropriate. Australia and Great Britain in particular have focused more ME/CFS research on children and youth.

[65-66] "often, patients with ME/CFS are labeled as lazy, deconditioned, and disability-seeking; this hampers scientific progress."

We ask: Insert "*attitude is unprofessional and disrespectful to patients*" before "hampers scientific progress."

Clinicians who label patients with derogatory terms are unprofessional. This attitude does great harm to patients. When these attitudes are conveyed to legal and insurance professionals, they contribute to the financial decline of patients.

[68-70] "Patients usually have to make extraordinary efforts, at extreme personal costs, to find a physician who will correctly diagnose and treat ME/CFS symptoms. In addition to high medication costs…"

We ask: Insert this sentence before "In addition to high medication costs": "*It is estimated that only 20% of people with the illness are correctly diagnosed*[14]."

This fact raises the question, What happens to patients who cannot afford the long search for diagnosis and treatment, and those who do not know how to search/advocate for themselves? These people need to be found and studied/helped. Perhaps this is why patients in the tertiary treatment centers tend to be white, middle class, and well educated. It is not that they are the only patients; more likely they are the only people who have the resources required to find adequate help.

Given the unique challenges to ME/CFS, how can we foster innovative research to enhance the development of treatments for patients?

[88-89] "Clinical studies have focused on predominantly Caucasian, middle-aged women."

[14] Reynolds et al, 2004. Ibid http://www.ncbi.nlm.nih.gov/pmc/articles/PMC449736/ cites the two references:

Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994;121:953–9. [PubMed]

Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, et al. Prevalence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003;163:1530–6. doi: 10.1001/archinte.163.13.1530. [PubMed] [Cross Ref]

We ask: add after "middle-aged women" "*as these are the patients who have found their way to tertiary treatment centers, leaving out pediatric patients, the severely ill, and members of ethnically and economically diverse communities*."

The report should acknowledge and highlight the skewing of research results resulting from lack of knowledge about ME/CFS by the great majority of health care providers, and the extreme inequality in access to adequate care that results from this.

[90-91] "Investigations of natural history and familial linkages may identify genetic predispositions and lead to early identification and primary prevention."

We ask: Insert after "natural history" *", age and type of onset*,"

There is some preliminary evidence that the disease process may be different in the early years of the illness (<3 years). Therefore special effort needs to be made to find newly ill patients (this implies early and correct diagnosis) for research studies. (CFI presentation at IACFS/ME conference, March 2014) In addition, Dr. Nacul's presentation made at the Workshop showed 2 peaks of age at illness onset, 10-19 and 30-39 (referenced earlier); these groups of patients could be studied to see if there are significant differences between them. Finally, studying patients who are part of cluster outbreaks vs. isolated cases may lead to clues about infectious origins. All of this work depends on obtaining a faster and more accurate diagnosis.

[94] "…substantial overlap with other pathologic diseases (e.g., fibromyalgia, major depressive disorder…"

See earlier comment [line 33] re: including major depressive disorder as an "overlap" condition. This paragraph refers specifically to **symptoms** which overlap. ME/CFS patient have a high burden of co-morbid conditions so in research studies these need to be separated out. This needs to be made clearer – perhaps the last sentence of the paragraph should be put first.

[95-96] "Focusing on fatigue alone may identify many ME/CFS cases."

This statement is misleading. It could be true if the fatigue is moderate-to-severe and is present at least 50% of the time (Dr. Jason's presentation). It could be true if the type of "fatigue" is post-exertional malaise. But otherwise the statement is too broad to be helpful.

[102] "defining the spectrum of ME/CFS in urban and rural communities"

Substitute for "spectrum": "*incidence and prevalence*"

[107] "post-exertional malaise, neurocognitive deficit, and pain."

Add to list "*sleep disorders*" which was mentioned consistently in the expert presentations as a major symptom.

[113-116] "Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy [GET]) demonstrate measurable improvement, but this has not translated to improvements in quality of life (QOL). Thus, they are not a primary treatment strategy and should be used as a component of multimodal therapy."

Suggested rewording: "*Some studies of cognitive behavioral therapy [CBT] and graded exercise therapy [GET] have demonstrated some improvements, but these have not translated to improvements in quality of life. Thus, they are not a primary treatment strategy and should be used only as a component of a multidisciplinary approach. Exercise as therapy should be carefully supervised by knowledgeable clinicians who will help patients understand how to stay within their capabilities and avoid doing harm."* Results from the PACE study should be disregarded since study participants were selected using the Oxford case definition. "Multi-modal therapy" is commonly understood as a term developed to describe a psychological approach to psychotherapy, and is inappropriate in this context.

What does research on ME/CFS tell us about the presentation and diagnosis of ME/CFS in the clinic?

[120-121] "Limited time during the clinical encounter has impaired patient/clinician communication and quality of care for patients with ME/CFS."

We ask: consider adding, "*Patients who struggle to describe a multitude of symptoms while experiencing cognitive difficulties also contributes to difficulties with communication. Lack of time to do an adequate history impedes diagnosis."*

[123] "…physical consequences of the illness…"

Insert after "physical consequences of the illness" *", including months or even years confined to bed in severe cases*,".

[130-131] "In general, little attention was given to how self-management may empower and improve health and QOL for patients with ME/CFS"

We ask: substitute for "empower and improve health and QOL" the following: "*help to stabilize symptoms and improve QOL."*

Many patients benefit from learning coping skills, especially how to manage their day-to-day life and pace their activities so as to stay within their personal "energy envelope."

[135-136] "…lack of instructions of guidance for including graded exercise therapy often causes additional suffering…"

"Graded Exercise Therapy" is a dangerous treatment for patients with ME/CFS, and great harm has been done to individuals who are pushed to participate in a one-size-fits-all regimen. Introducing exercise as a component of treatment should be supervised by knowledgeable clinicians or exercise physiologists, and tailored to each patient's individual capabilities.

What tools, measures, and approaches help define individuals with ME/CFS? How are tools and measures used to distinguish subsets of patients with ME/CFS?

[145-146] "There is a failure to give adequate attention to the severity of the physical, social, and emotional implications of ME/CFS."

We agree with this statement. A word of caution may be in order: when considering including the severely ill in clinical studies, great care must be taken not to require action that may do harm to these vulnerable individuals.

[154] "…include only a short follow-up"

We agree that studies of chronic illness need long-term followup. It should be noted that these types of studies are expensive and that lack of funding for such studies has contributed to the small size and limited duration of many studies of ME/CFS.

[160-161] "…simple statements need to be developed to ensure that the patients understand the questions"

This may not be a question of complexity, but of speed of information processing. Some patients may require more time to process the information given to them and to formulate their response.

[172 – 177] [list of 5 questions needing answers]

These questions (and probably many others) could be added:

- *What are the characteristics of cluster/outbreaks of ME/CFS? Are the symptoms of patients from these cluster/outbreaks different from those in cases with isolated origin?*
- *Are there fundamental differences between acute onset vs. gradual onset cases?*
- *Why is the illness more common in adult women than adult men? Does it manifest differently in women vs. men?*
- *Do subgroups with different constellations of symptoms have similar or different underlying pathologies?*

[176] “Is ME/CFS a spectrum disease?”

The term “spectrum disease” is often associated with autism. We suggest substituting “*disease with a continuum of severity”*.

Future Directions and Recommendations

General comment:

All of these recommendations for future directions in research require significant funding. It would be useful if the Panel could make an estimate of the amount of total funding that is needed over 5 years to implement the report’s recommendations, perhaps separate estimates for general research and for funding the Centers of Excellence. That would give NIH and other funders a realistic idea of the need to compare with the actual amount of funding allocated.

NIH has never funded this illness commensurate with its impact on patients and society. While it may be possible to cobble together small amounts of funding from different agencies for some specific initiatives (e.g., the recommendation for supporting new researchers, specifically minorities and women), why not just recognize the inequality here and deal with it? The types of research recommended here cannot be done on nickels and dimes. Already there are efforts to fund important research by “crowdfunding” from the patient community because it has been turned down by NIH (see Dr. Ian Lipkin’s microbiome discovery project, http://www.microbediscovery.org/*).* ME/CFS research has been mired for years in the NIH “explanation” that they need more good quality applications in order to fund more research, while researchers with excellent reputations who submit applications over and over which are not funded eventually stop submitting new applications.

Many of the recommendations call for the involvement of patients. Patients have been active partners with federal agencies for years. Patients are also active in their own care; they have to be. However some patients are so ill that they cannot participate in the search for knowledgeable (or at least open-to-learning) physicians, the many laboratory and other tests needed, the fruitless trips to the psychiatrist, managing the multiple specialists and keeping track of medical records and test results, and researching and trying out numerous alternative medicine suggestions from other patients.

On the other hand, the recommendation to involve all stakeholder groups, including patients (and patient/advocates) in determining priorities for research and care (line 284), creating improved outcome measures (line 278), putting patients at the center of research efforts (line 184), reaching consensus on a definition for the disease (which is already widely agreed upon by all

but the federal agencies) (lines 202-204), creating a web page for information about ME/CFS clinical trials (lines 340-341), and improving treatment decision-making (line 344) are very welcome. Patients should be regarded as partners and not adversaries.

Absent funding, the one thing that would make the most fundamental difference is a strong, clear description of the illness, which states categorically that the illness is real, with a biological not psychogenic basis. Then have all the federal websites update their descriptions accordingly. A corollary of this would be to emphasize that GET and CBT are ancillary treatments only, NOT the primary treatment, and NOT intended as a cure. **The CDC's "Chronic Fatigue Syndrome A Toolkit for Providers[15], which gives major emphasis to Cognitive Behavioral Therapy and Graded Exercise Therapy as primary treatments, must be revised or removed.**

[180] "nothing has improved the lives of the patients."

This statement is misleading. Often just getting a diagnosis greatly relieves patients, since they now have something to research and they can begin to take control of their condition. Having an explanation of their illness to share with family and friends, treatment of the most bothersome symptoms (sleep disturbances, pain, autonomic symptoms) and learning pacing can improve quality of life.

[183] "The subjective nature of ME/CFS, associated stigma, and the lack of a standard case definition has stifled progress."

Suggest rewording this sentence as follows: "*The lack of comprehensive tools to objectively describe and quantify the multiple aspects of ME/CFS, the persistent myth that ME/CFS is a psychological illness and the associated stigma, and the lack of a standard case definition have stifled progress.*"

As an example of the kind of psychological bias patients face, see this example[16]:

> *"UNDIFFERENTIATED SOMATOFORM DISORDER*
>
> *The diagnosis of undifferentiated somatoform disorder is a less-specific version of somatization disorder that requires only a six-month or longer history of one or more unexplained physical complaints in addition to the other requisite clinical criteria.*

[15] http://www.cdc.gov/cfs/toolkit/index.html

[16] Oyama et al., Somatoform Disorders, Am Fam Physician 2007; 76:1333-8 (excerpt from page 1335). https://edulibs.org/get_paper.php?id=36623891.

Chronic fatigue that cannot be fully explained by a known medical condition is a typical symptom. The highest incidence of complaints occurs in young women of low socioeconomic status, but symptoms are not limited to any group.[1] (Reference is: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. rev. Washington, D.C.: American Psychiatric Association, 2000.)"

[188-189] "The influence of health literacy and cognitive impairment on informed consent must be considered."

It is important to note that the impairment is not in the patient's intelligence or ability to understand, but in the speed of information processing[17]. Patients may simply need more time to digest and respond to information given to them.

[192] "…should focus on primary care providers."

Insert after "primary care providers": " *(including pediatricians) and certain specialty groups (Infectious Disease, Rheumatology, Neurology, Allergy and Immunology, Psychiatry)*"

1. Define disease parameters

[203] "…to reach consensus on the definition…"

It should be noted that the Chronic Fatigue Syndrome Advisory Committee (CFSAC) has been calling for exactly this. This P2P and the parallel IOM efforts are apparently the federal response to this strong request.

[322-323] "Opportunities exist within HHS to engage new ME/CFS working group members..."

Expanding the Trans-NIH Working Group, **and especially, ensuring that all members of this group are sufficiently educated about ME/CFS to make good decisions**, is a no-cost action that might improve the NIH response to this illness. This worthy suggestion **must** be accompanied by education of all Trans-NIH ME/CFS Working Group members about the illness. Persons making important funding decisions should have at least basic, if not expert, knowledge. We should not expect that experts in other fields will know anything about ME/CFS, except perhaps holding popular mis-conceptions. Previous federally-funded reports, such as the FDA's Voice of the Patient report for ME/CFS, the NIH State of Knowledge for ME/CFS 2011, and this report when finalized would be good starting places.

4. Provide training and education

[17] http://www.masscfids.org/resource-library/15-conference-reports/395-dr-gudrun-lange-reviews-neuropsychological-testing-for-cfs-and-fm

Education of health care providers has proven to be very challenging. Although excellent "primers" for physicians exist (CCC, IACFS/ME), it is difficult for busy physicians to accept and absorb new material, especially that brought to them by patients. Misinformation about ME/CFS (e.g., that it is psychological in origin) has been very difficult for patients to challenge. Strong, clear statements about the nature of the illness from respected groups such as this panel may be helpful in changing these entrenched attitudes and improving medical care for patients. All stakeholders, including patients, should be involved in developing training and educational materials.

[315-316] "…patients must become active participants in their overall treatment."

Many patients, especially those who are better educated and have more financial resources, are already very active in their own treatments; however there are only a very few doctors who are knowledgeable about ME/CFS. Many areas of the country have none. Local patient organizations often maintain lists of ME/CFS-aware physicians and struggle to serve all the requests they get from patients requesting suggestions. Many patients are too sick to participate much in their own care, or to do the research required to find physicians who can provide appropriate treatment. On the other hand, patient groups often have excellent suggestions to help patients help themselves, and are sources of accurate information about ME/CFS in general, and new research in particular. They could be engaged to review federal and private websites; develop educational programs; help with distribution of written material to patients, health care providers and medical organizations; and expand access to self-help through online communities and in-person support groups. Established non-profit patient organizations, such as ours, could be enlisted to assist in these efforts.

5. Finding new funding resources

[323] "…to create efficiency, and to co-fund research…"

We respectfully suggest that creating efficiency and co-funding research projects will not provide the amount of new funding required to really advance the field, and new scientists entering the field need to be able to anticipate at least a potential for on-going support.

[328] "Create a network of collaborative centers…"

This essentially calls for creating "Centers of Excellence," a recommendation the Chronic Fatigue Syndrome Advisory Committee has made 8 times since 2004, the last in May 2013. This cannot be done without new and substantial funding. ME/CFS research is not exactly a prestigious field, given the "popular" perception of the illness, and is unlikely to attract the attention of major private money.

[334] "…as well as those who recover from ME/CFS."

The definition of Recovered must be carefully looked at. It should apply only to people are living without ME/CFS energy envelope restrictions. They must also be free of all symptoms for an extended period of time, minimum of 1 year, not just managing their symptoms. This should be established with the use of standard scales of functioning, not simply self-reports[18].

7. Improve treatment

[344] "…patients should be active participants in care and decision-making."

See comments for lines 315-316.

[348-350] "The modest benefit from CBT should be studied as an adjunct to other modalities of treatment….Future treatment studies should evaluate multimodal therapies."

We respectfully suggest that more studies of CBT and "multimodal therapies" (from a psychological perspective) **are not required**, and that any funding available should be directed to biological research. Supportive education should always be provided to patients with chronic, serious illnesses. "CBT" aimed at "changing illness beliefs" is entirely inappropriate and demeaning to patients with ME/CFS. Patients often report that learning "pacing" and other coping techniques is an important element in helping them to manage daily life. We concur with the recommendation to educate health care providers about this illness, and to educate them about self-management and coping strategies that may help patients **as part of the treatment plan as in any chronic illness**. This does not require more funding.

[351-352] "We recommend that the NIH and the FDA convene a meeting on the state of ME/CFS treatment."

We respectfully suggest that instead of convening another meeting on "the state of ME/CFS treatment" use the money to fund treatment studies or to educate primary care physicians. We know what to do, at least based on the research done to date, and it isn't generally available to patients who cannot find their way to tertiary treatment centers. Federal partners should collaborate with patients to review and update the information on federal websites and provide authoritative information to private sites used by physicians in primary care offices or emergency rooms (such as www.uptodate.com) to reflect the state of current knowledge.

Conclusions

[18] Understanding Long-Term Outcomes of Chronic Fatigue Syndrome, Brown et al., J Clin Psychol. Sep 2012; 68(9): 1028–1035. Published online Jun 29, 2012. doi: 10.1002/jclp.21880
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3940158/

[359-361] "Patients and their advocates may benefit from education on how to effectively communicate their symptoms and concerns to clinicians, while health care providers could benefit from enhanced active listening skills and increased education."

Sad, but true. Many patient associations (such as ours) already provide such information to patients, and also advise taking a companion along to medical appointments to help advocate for the patient and be a second set of eyes and ears. While necessary, this is not always appreciated by health care providers.

[366] "the ME/CFS community agree on a single case definition…"

This plea has been made by patients and researchers for several years; it has been actively resisted by our federal partners. How do we implement it? Likewise, CFSAC has requested a workshop of researchers to discuss and agree on a single definition (October 2012); this request has been rejected by our federal partners as well.

[370] "…clarifying endpoints that suggest improvement and quality care."

It is very important that an endpoint not be used by insurance companies or courts as a marker to stop covering treatments or disabilities. Endpoints must never be used as a justification for the medical practitioner to declare that this patient is no longer ill and no longer needs care. Endpoints must be 'clinical' or 'research'-based milestones that determine that a trial has reached a milestone, not an endpoint that will push a patient into a situation that may cause more damage either physically or emotionally.

[370-371] "We believe there is a specific role for multimodal therapy."

We do not agree that there is a specific role for multi-modal therapy (psychological treatment approach), and we suggest deleting this sentence. Further we suggest re-wording the previous sentence as follows: "*Attention should be focused on biological research; providing broad access to high quality, knowledgeable, multidisciplinary care; refining assessment; clarifying endpoints that suggest improvement; and quality care*."

[378-380] "The NIH should work with the Centers for Medicare & Medicaid Services (CMS) and the Patient-Centered Outcomes Research Institute (PPCORI) to develop demonstration projects of patient-centered medical homes for people with ME/CFS."

ME/CFS patients are desperately in need of a new financial model for their care. As pointed out earlier in this report, the 20-minute encounter and fee for service is not sufficient for a provider to adequately care for an ME/CFS patient. Perhaps new economic models ("medical homes") could be part of the multidisciplinary centers (Centers of Excellence). Without an economic model for care that works for both patients and the Center, Centers cannot be sustained.

[381-382] "…comparative effectiveness research framework with clear endpoints and continuous evaluations to improve health care and to determine best practices that are evidence-based."

How will best practices become "evidence-based" and then "translated" to primary care clinicians without major new funding and several years of time? We need broad access to knowledgeable care and treatment NOW. Establishing a network Centers of Excellence (even "virtual centers" at first) with formal and regular information-sharing between them (perhaps via scheduled conferences or workshops) would be a huge advance. Responsible, concerned clinicians can discuss, develop and share "best practices" without waiting years for "evidence." Again, regional patient organizations which have long experience in identifying knowledgeable and helpful health care providers may be of assistance.

[383-388] Lines beginning "Federal agencies…"

This is suggested in every report. We need an actual plan and leadership to get agreement/commitment among the parties to make this happen, and funding to support it. Who or what agency do you suggest should do this (NIH? Perhaps the Trans-Working Group?). Otherwise this statement is meaningless. Also we won't need another Expert Panel unless there is actual action.

[388-389] "We hope our work has dignified ME/CFS and those affected, while providing expert guidance to the NIH and the broader research community."

Thank you for your work on this topic. Strong, clear statements that ME/CFS is a real, physical illness, not psychological in origin, will bring dignity to patients and provide hope that at last sufficient attention will be given to accelerate the pace of research and bring better treatments to all patients, eventually leading to prevention and a cure. Providing expert guidance to the NIH, along with strong calls for greater funding (with a dollar estimate of urgent needs) and adequate education about ME/CFS to members of the Trans-NIH ME/CFS Working Group, is an important step in advancing the research on ME/CFS and helping patients so desperately in need.