To: Dr. Carmen Green, Penny Cowan, Dr. Ronit Elk, Dr. Kathleen O'Neil, and Dr. Angela Rasmussen
From: Denise Lopez-Majano
Date: January 16, 2015

Re: Comments on the Draft Statement on Advancing the Research on ME/CFS

I believe that all of my line references are from the 403 line (19 page) draft report.

I appreciate the panel sorting through and figuring out which line numbers referenced in submitted comments refer to which of the two versions of the draft report that have been released. It is regrettable that circumstances have necessitated your devising a workaround for this complicated situation.

I also appreciate the panel's concern and recommendations regarding patient care, stigma, etc. In case you are not aware, the IOM report to be released on February 10th on "Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome" may recommend better and more appropriate care for patients than we currently receive and we understand that a dissemination plan is supposed to be part of the release. We hope that the recommendations of your report and those of the IOM report align well.

Your openness to listening and learning, and your diligent work in developing this report is appreciated. Please remain engaged with us and help us monitor progress on the implementation of your recommendations.

You (the panel) managed to grasp many concerns despite having been given an incomplete picture of this illness and its complexity. Some of the missing pieces include findings in pediatrics, neurological findings, and autonomic nervous system dysfunction. Those missing pieces are however, significant and need to be detailed in your report.

It is gratifying that you understand (among other things) that:

- there is an imperative need for an agreed upon definition that accurately identifies patients
- this illness results in severe disability for a large portion of its population
- there is an ongoing failure to accurately assess and treat patients
- the Oxford definition needs to be retired - I hope you recommend the retirement of the Fukuda definition also
- stigma, disdain, disrespect of patients is widespread and unfounded
- outcome measures that are meaningful to patients must be used
- this is a physiological illness through and through – this bears emphasizing throughout the report
- for over 20 years scant progress has been made on successful treatments, etiology, prevalence, incidence, longitudinal, epidemiological, studies, etc
- funding is needed
- healthcare professionals need appropriate education.

I hope that the panel will strengthen its research recommendations which I understand to be the focus of the workshop. "After weighing evidence from the evidence report, expert presentations, and public comments, an unbiased, independent panel prepares a draft report that identifies research gaps and future research priorities."[1]

The draft report uses the terms disease, condition and illness interchangeably. For consistency I suggest using one term throughout the report.

I believe your entire report will be strengthened by :

- the inclusion of references, including incorporating comments and references submitted regarding the draft report
- your prioritization of the research recommendations with emphasis on biomedical research (from basic laboratory science to clinical research). As Dr. Anderson indicated in his opening remarks on 9 Dec. 2014 "Ultimately we should remember that it's the voices of the patients who will help advance the future of research on ME/CFS. … Those affected are seeking the best possible research on the cause, development of treatments and a cure for ME/CFS." [2]
- stipulating an implementation time-line for your recommendations.

During the course of the workshop, it seemed that very little information was presented about post-exertional malaise (PEM). Understanding PEM is critical to understanding ME. PEM has little correlation to the fatigue experienced by people who do not have ME. Episodes of PEM can be brought on by minimal physical or cognitive exertion and episodes vary in triggers, symptoms, severity and duration. The Canadian Consensus Criteria [3] explains post-exertional malaise thusly:

> "Post-Exertional Malaise and/or Fatigue: There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period–usually 24 hours or longer." [3] p. 22

Additional information about PEM is available here [4] and includes references that may also be of benefit to the panel. This video [5] includes descriptions of the devastating impact of post-exertional malaise (aka post-exertional collapse, post-exertional crash) as experienced by one of my sons.

Lines 3, 58, 95-7,106 - fatigue - It feels that the term "fatigue" is overused/overemphasized in the report and in the term "chronic fatigue syndrome" as its applicability to this population is limited. As you say – fatigue does not capture the essence of this illness which is PEM. And research focusing on fatigue alone does *not* accurately or specifically identify ME – it does however identify fatigue which occurs in many illnesses – chronic and acute (Ehlers-Danlos Syndrome, MS, cancer, lupus, dysautonomias, among others). For many patients with ME, fatigue is not their most debilitating or primary complaint. Patients with ME describe a feeling of pathological exhaustion but this exhaustion is magnitudes more intense than what is understood by the term fatigue. Instead it is symptoms such as PEM, cognitive dysfunction and autonomic nervous system dysfunction that patients often describe as those of greatest impact on their lives. I suggest that beginning with the introduction, the report focus much more on the hallmark symptoms of this illness rather than fatigue.

Line 6-7 - "... economic burden is estimated to be greater than $1 billion..." is more correctly :

"...the direct and indirect cost of ME/CFS to society was estimated to be $18,677,912,000 for the community sample and $23,972,300,000 for the tertiary sample." (in 2008 dollars) [6]

Lines 8, 10, 63, 108, 158-9, 16177, 182, 184, 186, 201, 204, 213 (NOTE – the term INVEST is critically important), 219, 220-221, 236, 244, 291-2, 329, 334, 390-1, 399-401 - funding – Yes. The existing NIH infrastructure and dollars must be leveraged. But these scant resources don't go very far – as evidenced by the need for biomedical research utilizing large-scale studies, replication studies, clinical trials and the continued need to discover etiology(ies). To move things forward in this field funding levels must be increased. One benefit would be that the much needed (as you correctly say) large-scale replication studies of promising pilot studies could finally be undertaken. Funding increases for biomedical research must be clearly understood to be and agreed to be **long term increases**. In other words, as you also say, this requires investment in biomedical research funding, not just temporary funding spikes. This investment must be commensurate with the burden and severity of the illness. NIH's current allocation of $5 million/year is nowhere near enough for an illness whose economic impact is at least $20 billion/year and funding increases must be sufficient to appropriately fund biomedical research as well to fund your other recommendations.

Despite NIH's response to CFSAC's June 2014 recommendations that funds are not available, there is ample evidence that if there's a real will on the part of NIH to find funding, there is a way. Here are some examples of recent NIH funding increases:

Category	Change in funding level FY 2010-FY2013 (US dollars)
Chronic Fatigue Syndrome	**6M to 5M (yes, a decrease)**
Burden of Illness	**48 M to 72M**
Headache and migraine	**33M to 45M**
Dementia, Alzheimer's & Frontotemporal Dementia (FTD)	**468 M to 1.186 BILLION**
PTSD	**0 M to 77M**
Pain	**360M to 901M**
Stem Cell Research	**2.398 Billion to 2.698 Billion**

(See Appendix for additional details)

(FY 2014 and 2015 have not yet been confirmed by NIH. Therefore changes noted only include FY2010 to FY2013)

Additionally NIH should issue RFA's for biomedical research in ME, and these must be in addition to long-term significant NIH funding increases for biomedical research.

Lines 64, 121-124, 219- 221, 399-401 – private funding - The funding burden should not even be implied to be a responsibility of this impoverished patient population. As you note, most patients are isolated and stigmatized, meaning that few outside the community pay any heed to our requests for contributions for research. We willingly fund what we can, but we don't have funds individually or collectively, nor do we currently have access to those with deep pockets to provide funding. We will however be very glad for connections to funding sources. Meanwhile NIH must commit to significant funding increases for ME biomedical research.

Lines 33-34, 94 - overlap with major depressive disorder (MDD) - Is what the panel is referring to, perchance depression as secondary to (consequence of) chronic illness, which is something that occurs at one point or another, in most, if not all chronic illnesses? I suggest that if there is literature indicating some sort of overlap of MDD with ME, it is likely due to defining the illness too broadly while not requiring the hallmark symptom of post-exertional malaise, and thus encompassing illnesses other than ME.

Lines 34-35 – what needs to be studied - Several study areas were discussed by ME experts during the Workshop – including treatment studies, outcome measures, diagnostic markers.

As stated in the report from the NIH State of the Knowledge Workshop held in 2011:

> "moving forward
>
> Throughout the Workshop, participants discussed opportunities for improvements in the current research paradigm for ME/CFS, beginning with a need to define and standardize the terminology and case definitions. This need applies to simple definitions of "fatigue," as well as how to use the words "diagnostic" and "screening tests." Workshop participants also suggested more interdisciplinary research, as seen in a systems biology approach. Creating coordinated and collaborative systems for sharing research was an important topic that included creating standard operating procedures for the field, within and across labs, as well as common data elements. The Workshop pointed to gaps in the ME/CFS field, including gaps in study design and types of studies. There is a lack of longitudinal, natural history, early detection, pediatric-versus-adult-onset, and animal model studies. In addition, few studies look at comorbid conditions, biomarkers, or genetics. Moreover, study designs needed for clinical trials require further refinement. Improved and more extensive data from patient-derived and reported outcomes will better define the successes or failures of treatment interventions. To capture the extensive information from such studies, a centralized interactive database, using common data elements and accessible to everyone, is sorely needed to collect, aggregate, store, and analyze results." [7]

If this has a familiar ring to you, it's not a surprise, as the gaps and concerns are still the same as they were in 2011.

Line 52 - a research focus on men - Is this an error? (If not, please share the literature indicating that men have been the focus of research - I am not familiar with it and would like to be.)

Lines 59, 107 – many other symptoms, constellation of symptoms - Autonomic dysfunction must be added to this list.

Line 60 - - children with similar symptoms - This illness affects people of all races, genders, socioeconomic status, educational backgrounds and all ages. It therefore affects pediatric patients. *Please* make sure your report speaks to the necessity of biomedical research on ME in pediatric patients. Children, adolescents, teens are also deserving of biomedical research that will yield treatments.

Your report mentions that young people have "similar" symptoms – does this imply that my sons don't have ME,

but instead have something that has similar symptoms? Clarification would be appreciated.

The evidence review asserts that young people have better outcomes. It is true that some do. There can be many reasons for this. If they have an advocate (parent/other) who perseveres, quickly gets the patient to a specialist, and if the patient responds to treatment, their function and QOL may well improve.

Early intervention likely plays a role in degree of improvement as is the case with many illnesses. It is likely that there is a better chance for early intervention when one has an advocate/parent "breaking down doors" to try to help their child. Sadly early intervention is much less likely for newly ill adult patients struggling to understand what is happening to them and struggling to make it from one day to the next let along getting to see a specialist. BUT, "improvement" could also be a perception of improvement because the young person makes adjustments to the illness-imposed limitations and stays within the boundaries of their resources as Bell, Jason et al.[8] OR, they may not improve at all or even get worse, even *with* strong advocates, treatment and specialist care.

Lines 76 -81 - For decades, overly broad, non-specific definitions have hampered ME research and confused the medical and scientific communities about ME. We need to study ME using disease appropriate criteria.

When a case definition (such as Oxford, Fukuda or Reeves) is not specific enough in its characterization of patients, study samples will include people who do not have the condition being studied, thereby contaminating the study sample and rendering the results inapplicable.

As Dr. Smith noted during the P2P Workshop, Fukuda encompasses the less severely ill at least some of whom may well be suffering from primary psychiatric illness or deconditioning. They therefore should not be included in studies of ME

Several workshop presenters and participants pointed out that in order for advancements to be made in ME research, the patients being studied must be accurately characterized. Dr. Nacul noted that with all of the symptoms encompassed by Fukuda, there are 163 possible symptom combinations which indeed indicates quite a broad spectrum of patients.

However, Dr. Nacul also noted that requiring post-exertional malaise (PEM) as a symptom reduces the number of possible combinations to 35 – making diagnosis easier and more accurate. Accurate diagnosis yields less noise in research findings, leading to greater clarity on signals, which in turn leads to more applicable research results.

More accurate diagnosis also means less likelihood of misdiagnosis.

I urge that the Fukuda and Reeves definitions also be retired along with the Oxford definition, so that from here on out research on ME will benefit from more accurately characterized patients.

Originally this workshop was supposed to address the issue of whether ME and CFS are the same illness. Not addressing this question of distinction has led to continued reference to ME and CFS as being one and the same in this report. This ignores and downplays the distinctiveness of the illness that is characterized by - PEM, immune dysfunction, sleep disturbances, cognitive dysfunction and autonomic dysfunction. That illness is ME.

ME is best described by the 2003 Canadian Consensus Criteria and the 2011 ME International Consensus

Criteria[9], is a complex, disabling disease characterized by unrefreshing sleep, flu-like symptoms, impairment of memory and other cognitive issues, orthostatic intolerance, debilitating weakness, pain, fever and the hallmark symptom of post-exertional malaise. It has been shown to cause dysfunction of the neurological, immune, endocrine and energy production systems.

Lines 211, 218, 220, 322, 334, 387-9, 400 – HHS, NIH, openness, collaboration, transparency - During (at least) the past 2 decades, progress towards successful treatment and/or cure of this illness has been imperceptible because of lack of funds, stigma, lack of commitment, etc.

There is also a lack of follow-through. The 2011 NIH State of the Knowledge Workshop assessed the state of ME science and assessed research gaps. The subsequent report [7] included suggestions, but no firm recommendations, plans or prioritization of research. And lamentably no increased funding.

There is a history of lack of openness, transparency and accountability by HHS and its agencies regarding this illness. HHS developed and implemented the contract for the IOM project in total secrecy. An advocate found the signed contract by accident. You likely are not aware that the patient/advocate community has tried many times, in many ways, to engage with HHS and its agencies. Among other efforts we have asked HHS to work with us to develop a comprehensive, strategic plan for ME[10]. HHS rebuffed us (yet again).

As others have pointed out, many of your recommendations are very worthwhile and have been made, often repeatedly, by the CFSAC[11] and advocates. However - stigma, lack of funding, barriers at NIH and HHS have led to a failure to seriously consider or implement recommendations.

A couple of recent examples regarding communication difficulties, and lack of openness and transparency from NIH/ODP (Office of Disease Prevention).

1) The public was never alerted that there are two versions of the report in circulation. People trying to discuss the report, and referring to line numbers, were understandably confused. This confusion was unnecessary for any people discussing the report, but was particularly bad for this community, because the confusion exacerbated cognitive impairments and triggered post-exertional malaise for some patients. Notifying the community about the two versions might have prevented some of those crashes.
2) Several advocates asked for clarification from NIH regarding the closing time for submitting comments. They did not receive replies and the information appears to have only been disseminated via Twitter leaving many unaware of the closing time.

> "**NIH ODP @NIHprevents** Jan 13
> Don't forget to submit comments on the **#NIHP2P** ME/CFS draft report. Comments close 11:59pm EST on January 16, 2015. http://1.usa.gov/1z1PCX1
> 0 replies 6 retweets 2 favorites" [12]

The closing time has not been posted to the P2P website, nor has it been sent out via the ListServ.

> "**Comments on the Panel's Draft Report**
> Public comments on the panel's draft report will be accepted from Thursday, December 18, 2014 through Friday, January 16, 2015. **Please reference the corresponding line number of the report**, and submit your comments via:
> **Email**
> prevention@mail.nih.gov
>
> Or
>
> **Postal mail**
> Office of Disease Prevention
> National Institutes of Health
> ATTN: Paris A. Watson

6100 Executive Boulevard, Suite 2B03
Bethesda, MD 20892
…..**Email**
prevention@mail.nih.gov

Or

Postal mail
Office of Disease Prevention
National Institutes of Health
ATTN: Paris A. Watson
6100 Executive Boulevard, Suite 2B03
Bethesda, MD 20892
…
This page was last updated 12/18/2014" [13] accessed 15 Jan 2015

Because the current system has failed for decades, perhaps the system needs to be revamped to appropriately address this illness. And because neither (HHS') Office of Women's Health (OWH) or (NIH's) Office of Research on Women's Health (ORWH) are disease researching entities they are not suitable NIH/HHS homes for ME. In addition – ORWH is home to no other illness and has no research budget. In fact it has no budget at all which likely makes it difficult for NIH employees to justify the time that would be necessary to truly move things forward for research on ME.

This illness needs a home that fosters biomedical research.

WHO categorizes ME as a neurological illness[14]. (p.233 - G93.3 includes: benign myalgic encephomyelitis) Therefore, a more suitable home would be NINDS, or perhaps NIAIDS. In addition to increased funding, moving ME to a suitable NIH home, may well result in the elimination of the institutional barriers, stigma, bias, and ameliorate funding difficulties, while attracting additional researchers to conduct biomedical research to help patients with ME.

Any and all detailed plans for ME must be developed collaboratively and openly with the community (advocates, patients, etc), and experts on a level playing field with NIH, etc. and with ongoing input and feedback from the community and experts.

To effect the necessary changes, a firm mandate, structure and commitment must be made so that 20 years from now, we are not still in the same place research and treatment-wise. I strongly urge the panel to recommend congressional oversight to ensure that patients' voices are heard and that appropriate biomedical research and medical education take place.

Lines 92-93 – physiological illness - The report states that this illness is not psychological/psychiatric in etiology. And the report must be clear that this ongoing chronic illness is not psychologically/psychiatrically based.

Lines 116, 130, 132, 134, 137, 283, 303-305, 314, 360, 363, 364, 383, 385 – and any other references to multi-modal, self-management, multidisciplinary, biopsychosocial and mind-body connections. While the mind-body connection can be of intellectual interest, one does not suggest that patients with, for example, cancer or MS can be cured by changing their illness beliefs. Because of the often inappropriate referral of patients with ME to psychosocial specialists, the above-mentioned terms are viewed with skepticism by patients who all too often are told they have false illness beliefs or illness behaviours that CBT (or similar) can cure them of.

In the context of this illness, the biopsychosocial model has been described by Larun:

> "The etiology and pathophysiology of CFS are controversial. Models of understanding can be broadly divided into biomedical and biopsychosocial models. The biomedical model explains the illness as caused by abnormalities of the immune, central nervous (Nijs 2011) or endocrine systems and/or a persistent infectious agent. The multifactorial biopsychosocial model (Moss-Morris 2012) distinguishes between precipitating and maintaining factors. Precipitating factors may include acute infective illness and/or excessive stress, while the illness is maintained by the interaction of behavior, thoughts, emotions and physiology. For example, after a severe infection or other illness, attempts to get back to normal life may result in bursts of activity punctuated by the need to rest up to recover, known as all-or-nothing behaviour (Moss-Morris 2010; Spence 2005). These periodic bursts of activity may exacerbate symptoms and result in failure, which further reinforces sufferers' belief that they have a serious, ongoing illness. As time goes by, efforts to meet previous standards of achievement are abandoned and patients become increasingly inactive and distressed by their ongoing symptoms. Inactivity in turn leads to physiological changes such as cardiovascular and muscular deconditioning, dysregulation of the hypothalamic-pituitary-adrenal axis and disrupted circadian rhythms. In this deconditioned state, any activity is liable to produce symptoms, the experience of which reinforces the fearful beliefs and hence reinforces the avoidance of activity (fear avoidance)."

> "Various models exist to explain why exercise therapy might be a viable treatment for CFS. The deconditioning model suggests that CFS is perpetuated by a chronic reduction and avoidance of activity leading to reversible physiological changes of deconditioning (Clark 2005; White 2011). In support of the model, CFS patients show a decreased exercise capacity when compared to sedentary controls (Fulcher 2000), but to date, improvements in fitness fol- lowing exercise therapy have not been linked to improvements in fatigue in people with CFS (Fulcher 2000; Moss-Morris 2005). The biopsychosocial model emphasises the role of patients' cognitions and behaviours in the perpetuation of CFS. One variant of this model suggests exercise therapy reduces the focus on symptoms and avoidance of feared activity through showing that gradual increases in activity do not unduly exacerbate symptoms (Moss-Morris 2005),thereby engendering belief change. Reductions in beliefs about the harmful effects of exercise have also been related to improved outcomes in CFS (Deale 1997). A second variant suggests that graded exposure to the previously-avoided exercise extinguishes the conditioned response to exercise." [15]

Ten years ago, the nightmare that is this illness was thrust upon us - unbidden and totally unwelcome. During this time I have met quite a few patients. My sons and every patient I know would very much like to be productive members of society.

We have had more than enough research on biopsychosocial, CBT and such and yet we are still no closer to getting people well or knowing why they are sick.

Biomedical research should be the highest priority. Because patients want to get better!

Regarding self-management – many patients are pros at managing themselves, if only to be able to help themselves feel less awful than if they over do physical or cognitive activities. Rather than self-management studies what is desperately needed is biomedical treatments to help patients.

I am certain that many who have submitted comments have discussed the harms of the PACE trial and I too am concerned about those harms. I recommend this valuable resource on said harms - Kindlon T. Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Bull IACFS ME. 2011;19(2). [16]

I would like to note another harm of the PACE trial in relation to stigma and misinformation. As recently as 13 January 2015, the PACE trial authors published yet another article [17] (in The Lancet Psychiatry Journal) using

PACE trial data. Remember that the Pace trial used the OXFORD definition (requiring one symptom only – 6 months of unexplained fatigue). Several main stream news sources have written articles about this new study, the headlines and content of which have spewed misinformation such as:

Chronic fatigue syndrome sufferers 'can benefit from exercise'

ME: fear of exercise exacerbates chronic fatigue syndrome, say researchers

Chronic fatigue syndrome patients' fear of exercise can hinder treatment - study

Chronic Fatigue: 'No need to fear exercise' (See Appendix for additional details)

The panel and evidence review have called for the retirement of the Oxford definition. There are now at least 7 articles from the PACE trial data and indications of more to come. They must be stopped! The continued release of articles that use the Oxford definition causes harm and significantly delays progress in changing the public perception of this illness. In addition to calling for the retirement of the Oxford definition, the panel must address the harms caused by said continued publications.

Given that ME is a severely debilitating physiological illness, there is great need for specialty care for patients with ME. It must be biomedical specialty care provided by neurologists, rheumatologists, immunologists, endocrinologists, specialists in infectious disease, cardiologists, pediatricians, as well as other biomedical specialties. These are the sorts of specialties that treatment teams should be comprised of in order to provide the care that patients need and deserve.

Lines 79-81, 87, 311–327, 354, 373-5 – education of healthcare providers – There is a definite need for healthcare providers to be accurately educated about this illness. They also need to be active listeners and they need to be supportive of patients. Currently, patients are usually far more knowledge about this illness than healthcare professionals and patients have to try to educate healthcare providers – but are met with disdain, disbelief and lack of engagement.

Lines 115-116, 360–4 – treatment recommendations - The treatment recommendations in your report lean heavily on biopsychosocial, multi-modal therapy, etc in your report. This is inappropriate given that this is not an illness of psychiatric or psychologic etiology.

Lines 134-8 – focus on exercise programs – As I mentioned in the IOM presentation referenced above, exercise in relation to this illness is something most healthcare providers do not understand. And as discussed by Dr. Snell at the Workshop and as shown most recently in the 2014 study by Keller et al. [18] patients with ME have an impaired physiological response to exertion. Because of this impaired response, patients have justifiable concerns about exceeding their exertion (cognitive or physical) limits. This justifiable concern may be termed by some to be a fear but patients know all too well, the harms of exceeding those limits. Post-exertional malaise (collapse) is something every patient I know does their utmost to avoid.

Lines 166-7 - meaningful symptoms - Symptoms meaningful to patients are in the literature – PEM, cognitive impairment, autonomic dysfunction appear regularly in studies.

Line 173 - "... Does mononucleosis lead to ME/CFS in adolescents?" - It is worth noting that several studies about mononucleosis and ME have been done including one that was the focus of Dr. Taylor's presentation[19] - and at least one is currently underway as Dr. Jason mentioned during the workshop.

However, ME is not confined to sudden onset in adults or in children and only suggesting that mononucleosis be looked into as a trigger, overlooks many other things that seem to be triggers – giardia [20], Parvo B19 [21] among others.

The panel's report also should not ignore ME with a gradual onset and ME with no apparent trigger. And the panel should additionally be aware that sudden onset and gradual onset ME do occur within the same family.

Line 191 – dissemination to primary care providers – Several points here

> Why should dissemination be limited to primary care providers, when realistically patients with ME need to be seen by specialists (in addition to ME specialists) and therefore specialists also need to be educated about this complex illness.
>
> Primary care providers aren't set up to handle complex illnesses such as ME which encompasses dysfunction in multiple body systems. They don't have enough knowledge about this illness and most can't allot the time required to assess/manage such a complex illness.
>
> Therefore patients should be treated by specialists in ME with referrals to other specialists as warranted.

Lines 204-211 – Criteria for research networks, biobanks, repositories, registries, etc. need to begin with the Canadian Consensus Criteria (CCC) until such time as research and expert consensus warrants change.

Line 217 - fwiw -National Center for Complementary and Alternative Medicine (NCCAM) is now National Center for Complementary and Integrative Health (NCCIH).

Lines 227-232 - diagnostic tools - It would strengthen the report to add 2 day CPET with gas exchange (with neurocognitive testing) to the list of diagnostic tools that should be further studied. The 2 day CPET with gas exchange test is already used as objective proof of disability. As indicated in several studies (including Keller et al referenced above) and during the Workshop, the 2 day CPET with gas exchange accurately demonstrates the abnormal physiological response to exertion in patients with ME.

Lines 277 - psychiatric drugs - Your report states that ME is not an illness of psychological etiology. Specifically including psychiatric medications when discussing background medications weakens your assertion of the physiological nature of this illness . Your report must be emphatic throughout that this illness is physiological. Doing so will help dispel misinformation .

Line 281 - homeopathy - I strongly urge the panel to remove all suggestions for studies of homeopathy. The field of ME needs appropriate biomedical research.

The 2014 AHRQ evidence review says:

> Different complementary and alternative (CAM) therapies have been studied only in small pilot trials with methodological limitations, and although homeopathy, pollen extracts, and carnitine preparations showed some benefit, the results have been inconsistent across different measurement tools precluding any determination of potential effectiveness. (p.97)

and concludes that there is insufficient evidence of benefit. [22]

In 2014, the NHMRC study conclusion (from their evidence review) that "…the assessment of the evidence from research in humans does not show that homeopathy is effective for treating the range of health conditions considered" cannot be ignored or dismissed by your report.

The NHMRC study specifically noted (on page 14):

"There is no reliable evidence that homeopathy is more effective than placebo for the treatment of these health conditions:

....chronic fatigue syndrome...."

Even if research funding is significantly increased, there is a lot of catching up to do in ME biomedical research and therefore there is no extra to allocate to something that has not demonstrated effectiveness such as homeopathy. [23]

Line 294 - PROMIS - There is a PROMIS scale that can assess fatigue, but I find no PROMIS scale that can assess PEM, its triggers, symptoms or severity. In order for it to be applicable, the PROMIS fatigue (or other) scale would require significant alteration (and validation) by ME experts in order to accurately assess PEM.

Lines 326-7, 357-8 - patients as active participants - Patients *are* active participants. That's how we have gotten to the few specialists we have, that's how we choose which other healthcare providers are active listeners who can understand. We also read, discuss, investigate and try to help ourselves as much as illness parameters allow. Few patients have friends/family who can help them, but those friends and family members tend to work tirelessly to move things forward for patients with ME.

IF however, you are referring to newly ill patients, I agree that they need to be active participants – as much as they are cognitively able to manage.

Line 365 – NIH and FDA meeting – The report calls for an FDA meeting with NIH regarding the state of ME/CFS treatment. Please note that there was an FDA meeting 2013 on drug development for ME(CFS). Outcomes of that meeting include the Voice of the Patient [24] report and Guidance for Industry Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment.[25] If the panel feels another meeting is appropriate, the report should provide specific details about the proposed goals and purpose of such a meeting.

Line 373 – patients communicating with healthcare professionals – As I said in my May 2014 IOM presentation, it is imperative that healthcare professionals know more about this horrid illness and have sufficient breadth of knowledge about ME to be able to ask questions about PEM and cognitive dysfunction. A newly ill patient likely won't have the language to describe PEM or cognitive dysfunction and healthcare professionals. Healthcare

providers who can successfully identify patients with PEM and or cognitive dysfunction will be able to help patients stay within their energy limits. Hopefully being able to do so early in the illness will keep them from getting worse.

Lines 381-2 – Again everything needs to be on a level playing field with patients/advocates/experts involved as equal participants in defining meaningful recovery

Lines 401-2 – ODP convene another ME/CFS Expert Panel – A mechanism to monitor progress is well worthwhile. Specifics about who will monitor progress (stakeholders, NIH employees, subject matter experts, etc), in what capacity, and who is answerable for ensuring progress would further strengthen your report

Many people have submitted comments regarding your report. I hope that you will incorporate these comments as you strengthen your report.

Thank you for your time and attention.
Denise Lopez-Majano

References

1 - P2P webpages: https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs

2 -At about minute 4:55 http://videocast.nih.gov/summary.asp?Live=14723&bhcp=1

3 - Canadian Consensus Criteria: http://www.mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Document.pdf

4 - PEM articles: https://dl.dropboxusercontent.com/u/57025850/pem-series.pdf

5 - Panel 1 - Lopez-Majano https://www.youtube.com/watch?v=_U35icetbzw

6 - **J**ason 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

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25 - Guidance for Industry Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM388568.pdf%20

Appendix

Additional details
(FY 2014 and 2015 have not yet been confirmed by NIH. Therefore changes noted only include FY2010 to FY2013)

Chronic Fatigue Syndrome change in funding level (US dollars) FY 2010 to FY 2013 6 million to 5 million (yes, a decrease)

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Chronic Fatigue Syndrome (ME/CFS)	$6	$0	$6	$5	$5	$5	$5

Burden of Illness change in funding level FY 2010 to FY 2013 48 to 72 million

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Burden of Illness	$48	$8	$40	$84	$72	$74	$74

Headache and migraine change in funding level FY 2010 to FY 2013 33 million to 45 million

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Headaches	$18	$1	$21	$24	$25	$25	$25

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Migraines	$15	+	$16	$18	$19	$20	$20

Dementia, Frontotemporal Dementia (FTD) & Alzheimer's change in funding level FY2010 to FY2013 468 million to 1.186 BILLION

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Dementia	$0	$0	+	$0	$650	$666	$666
Frontotemporal	$18	$1	$23	$26	$32	$33	$33

Dementia (FTD)							

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Alzheimer's Disease	$450	$79	$448	$503	$504	$566	$566

PTSD **change in funding level FY 2010 to FY 2013** **0 to 77 million**

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Post-Traumatic Stress Disorder (PTSD)	$0	$0	+	$0	$77	$78	$78

Pain **change in funding level FY 2010 to FY 2013** **360 million to 901 million**

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Pain Conditions - Chronic	$360	$44	$386	$396	$402	$413	$413
Pain Research	$0	$0	+	$479	$475	$488	$488

Stem Cell Research **change in funding level FY 2010 to FY 2013** **2.398 billion to 2.698 billion**

Research/Disease Areas (Dollars in millions and rounded)	FY 2010Actual (Non-ARRA)	FY 2010Actual (ARRA) 10/	FY 2011Actual	FY 2012Actual	FY 2013Actual	FY 2014 Estimated	FY 2015 Estimated
Stem Cell Research	$1,099	$187	$1,179	$1,374	$1,273	$1,306	$1,306
Stem Cell Research - Embryonic - Human	$126	$40	$123	$146	$146	$150	$150
Stem Cell Research - Embryonic - Non-Human	$175	$20	$165	$164	$154	$157	$157
Stem Cell Research - Nonembryonic -	$341	$74	$395	$504	$431	$443	$443

Human							
Stem Cell Research - Nonembryonic - Non-Human	$570	$74	$620	$653	$613	$629	$629
Stem Cell Research - Umbilical Cord Blood/ Placenta	$42	$8	$41	$47	$40	$41	$41
Stem Cell Research - Umbilical Cord Blood/ Placenta - Human	$40	$7	$36	$43	$35	$36	$36
Stem Cell Research - Umbilical Cord Blood/ Placenta - Non-Human	$5	$1	$10	$8	$7	$8	$8

http://report.nih.gov/categorical_spending.aspx

Re. News headlines re 13 January 2015 article using PACE trial data
https://news.google.com/news/story?ncl=dX6YnAHz36m3uvMa_6BI4Q4zwGhZM&q=chronic+fatigue+syndrome&lr=English&hl=en&sa=X&ei=DgS3VOCWGZXIsASslYDIBA&ved=0CCUQqgIwAA (copied from page1 of Google search returns regarding the article - 16 January 2015)

Chronic fatigue syndrome

The Economist - 5 hours ago
CHRONIC fatigue syndrome (CFS) is an illness that robs its victims of concentration, sleep and—as the name suggests—energy. What causes it is a puzzle. Hypotheses include it being the long-term consequence of viral infection, some sort of autoimmune ...

'Fear of exercise' is biggest barrier to chronic fatigue syndrome recovery

Medical News Today - Jan 15, 2015
According to trial data reported in the journal The Lancet Psychiatry, one of the most important elements of improving

physical function in patients with **chronic fatigue syndrome** is using therapy to reduce fear that exercise will worsen rather than improve ...

Chronic fatigue syndrome sufferers 'can benefit from exercise'

The Independent - Jan 14, 2015
Exercise therapy and cognitive behavioural therapy were shown to be the most effective treatments for **CFS**, also known as myalgic encephalomyelitis (ME), in a major trial in 2011. The condition has been subject to controversy in the past. Some doctors once ...

Chronic fatigue syndrome: the symptoms

Telegraph.co.uk - Jan 13, 2015
Most people with **CFS** describe this fatigue as overwhelming, and a different type of tiredness from what they have experienced before. Exercising can make symptoms worse. This is called post-exertional malaise, or 'payback'. The effect of this is sometimes ...

ME: fear of exercise exacerbates chronic fatigue syndrome, say researchers

Telegraph.co.uk - Jan 14, 2015
Professor Trudie Chalder, of Kings College London said: "**CFS** is a **chronic** and debilitating condition which is characterised by severe **fatigue**. "People may experience sleep disturbance and muscle and joint pain. It stops them engaging in normal activities ...

Chronic fatigue syndrome patients' fear of exercise can hinder treatment - study

The Guardian - Jan 13, 2015
Patients' fear that exercise or activity will make **chronic fatigue syndrome** worse can significantly hinder treatment of the debilitating condition, according to researchers. Exhaustion is a defining condition of CFS, also known as myalgic encephalomyelitis (ME), ...

Therapists Must Ease Patients' Fear When Treating Chronic Fatigue Syndrome ...

U.S. News & World Report - Jan 14, 2015
WEDNESDAY, Jan. 14, 2015 (HealthDay News) -- Easing fears that exercise may worsen symptoms of **chronic fatigue syndrome** is crucial in efforts to prevent disability in people with the condition, a new study says. **Chronic fatigue syndrome** is a complex ...

Sufferers of chronic fatigue syndrome 'can benefit from exercise'

Irish Independent - Jan 15, 2015
Fear that exercise could lead to a worsening of symptoms was an “understandable reaction” to having **CFS**, researchers said, and some patients have reported that too much exercise too soon does indeed lead to even more extreme exhaustion. The findings ...

Key to warding off chronic fatigue syndrome identified

Zee News - Jan 14, 2015
London: Reducing fears that exercise or activity would make symptoms worse is the key to treating people with **chronic fatigue syndrome** (CFS), says a study. CFS is a condition whose defining symptom is exhaustion. It affects everyday life with varying ...

Chronic fatigue victims 'suffer fear of exercise' and are anxious activities could ...

Daily Mail - Jan 13, 2015
Sufferers of **chronic fatigue syndrome** are being held back from recovery by fears about exercise, claim researchers. A new study found some people with the disorder were worried about doing activity such as walking in case it aggravated their symptoms.

CBT, graded exercise therapy challenged fears of those with chronic fatigue ...

Healio - Jan 13, 2015
“So far, process research shows that change in proposed mediators and outcome occur mostly simultaneously during CBT for patients with **chronic fatigue syndrome**,” they wrote. Disclosure: See the study for a full list of relevant financial disclosures.

Chronic fatigue syndrome patients may see benefits in exercise

helpmeoutDOC News - A consistent flow of medical news - Jan 14, 2015

For people who suffer from **chronic fatigue syndrome** (CFS), researchers suggest they can improve exhaustion symptoms by reducing the fear associated with exercise as a source of making the condition worse. The new study, from the same team at Kings ...

Chronic Fatigue: 'No need to fear exercise'

WebMD.Boots.com - Jan 14, 2015
14th January 2015 – People who have **Chronic Fatigue Syndrome** (CFS) should be encouraged to see exercise as a way of easing their symptoms of exhaustion rather than fearing that activity will make them feel worse, say researchers. CFS, which is also ...

Helping chronic fatigue patients over fears eases symptoms

Reuters - Jan 13, 2015
Presenting an analysis on a trial showing how cognitive behavior therapy (CBT) and graded exercise therapy (GET) help reduce fatigue and improve physical function in people with **chronic fatigue syndrome** (CFS), the researchers said misguided but ...

Reducing fears key to success of CBT or GET in people with chronic fatigue ...

News-Medical.net - Jan 14, 2015
... behaviour therapy (CBT) or graded exercise therapy (GET) in reducing fatigue and improving physical function in people with **chronic fatigue syndrome** (CFS), according to new analysis of data from the PACE trial, reported in The Lancet Psychiatry journal.

Providers Urged to Address Patient Fears in Chronic Fatigue

Doctors Lounge - Jan 14, 2015
14, 2015 (HealthDay News) -- Easing fears that exercise may worsen symptoms of **chronic fatigue syndrome** is crucial in efforts to prevent disability in people with the condition, according to research published online Jan. 13 in The Lancet Psychiatry.

Reducing fear avoidance beliefs key to improving symptoms and reducing ...

Medical Xpress - Jan 14, 2015
We assume that an increase in physical activity is nothing more than a catalyst for the change in cognitions about activity and symptoms in patients with **chronic fatigue syndrome**. Future studies should focus on how these beliefs can be changed more rapidly ...

How therapy and exercise 'may help some with CFS'

NHS Choices - Jan 14, 2015
Chronic fatigue syndrome (CFS) is a long-term condition that causes persistent and debilitating fatigue. We do not know what causes the condition and there is no cure, though many people improve over time. Treatments for CFS aim to reduce symptoms, but ...