To: Dr. Carmen Green, Penny Cowan, Dr. Ronit Elk, Dr. Kathleen O'Neil, and Dr. Angela Rasmussen
From: Jennifer Spotila
Date: January 16, 2015
Re: Comments on the Draft Statement on Advancing the Research on ME/CFS

I wish to thank the members of the Panel for your efforts in drafting recommendations to advance ME/CFS research. You were asked to master a great deal of information in a short period of time, and it is clear that you truly heard the voices of patients at the Workshop. My comments on your Draft Statement are intended to improve upon what you have already done, and to take the recommendations from good to great. You have my thanks for your willingness to engage on these issues in service to ME/CFS patients.

I must also note that I am commenting on the original (403 line) version of your statement, published on the NIH website on December 18, 2014. I believe you are aware that some time after December 18th, NIH published a second version of your statement that is 389 lines long. No notice of this change was given to the public, and so you are likely to receive comments using conflicting line numbers. It may seem like this is a simple formatting error, and not a major problem. But it is mistakes like these – and a pattern of failing to communicate openly and immediately to acknowledge and address those mistakes – that contribute to the frustration and abandonment that ME/CFS advocates feel in light of NIH's paltry investment in ME/CFS research. I hope that my comments, and those submitted by other members of the public, can contribute to changing this situation.

Broad Issues with Report

I have two comments about your report that do not relate to a single section or line number. The first relates to trusting the evidence base, and the second to research funding.

Trusting the Evidence Base

Evidence-based reviews rely upon the fundamental premise that the evidence base is an accurate reflection of what is known about a disease. The assumption is that science is a level playing field: the best ideas are funded, the best data are published, and our understanding progresses as more and more knowledge is accumulated. Systematic evidence reviews then select the papers most applicable to the topic being reviewed.

However, there are two problems with making this assumption in ME/CFS. First of all, the systematic evidence review excluded most of the papers applicable to the issues examined in the Workshop. Exclusionary criteria eliminated many treatment studies, and an *a priori* decision was made to exclude studies "intended" to investigate etiology. The Workshop presentations addressed some of the many excluded topics, but by no means all (e.g. autonomic dysfunction, cognitive dysfunction). You were provided with a great deal of information but not the full picture, and thus your evidence base is not complete.

The second problem with trusting the evidence base is the limiting factor of funding. With little money available, researchers have conducted smaller and shorter studies, used case control

design, and failed to extend their work beyond pilot data. Furthermore, until very recently NIH grant review was conducted by scientists who were not ME/CFS experts, and this may have allowed bias and misinformation to play a role in funding decisions, which in turn would affect the ME/CFS evidence base.

For example, Dr. Ian Lipkin of Columbia University stated at the March 2014 IACFS/ME conference that NIH denied his application for an ME/CFS microbiome study after one reviewer commented that ME/CFS is a psychological disorder. One can see how bias like this would impact funding decisions, both in low funding levels overall and the particular focus on psychological studies. There is also a general perception among ME/CFS researchers that NIH does not assess ME/CFS research applications with ME/CFS experts, and this has likely contributed to low numbers of applications. All of these factors have resulted in an evidence base that may be biased.

I believe it is critical for you to be mindful of this potential bias as you review the ME/CFS evidence base. There has not been a level playing field at NIH, and this has hindered the accumulation of data and advancement of science in ME/CFS. While that does not automatically invalidate the data that have been published, it is an important factor that must be taken into account in any review of the field.

Recommend More Funding

There is one key priority that your report barely addresses at all, and that is the need for a significant increase in investment. NIH allocates approximately $5 million per year to ME/CFS research. This is wildly out of step with the economic burden of the disease, and pennies on the dollar compared to what many other disabling diseases receive. I will address the details of your recommendation #5 on funding sources below. However, I must urge you to explicitly recommend that NIH immediately and significantly increase its investment in ME/CFS research. Such a recommendation would be even stronger if you specified the level of investment that is required. The bottom line is this: if NIH does not begin to add zeroes to the ME/CFS spending figure, then none of your recommendations will be accomplished and this entire process will have been a waste of time and money.

Lines 6-7: "economic burden estimated to be greater than $1 billion"

This is incorrect, and I do not know the origin of the number. The correct number is approximately $20 billion in direct and indirect costs per year.[1]

Line 32: "ME/CFS exists."

I thank you for the simple clarity of this statement. However, I respectfully suggest that you repeat here what you say in lines 92-93, "this is not a psychological disease in etiology." CDC data from 2011 show that 85% of healthcare professionals surveyed believe that ME/CFS is wholly or partially psychological.[2] To say this disease exists is insufficient, because of course

[1] Jason LA, Benton MS, Valentine L, et al., The Economic impact of ME/CFS: Individual and societal costs. Dynamic Medicine 2008, 7:6.

[2] http://www.iacfsme.org/LinkClick.aspx?fileticket=%2bG6GTkbP33I%3d&tabid=499 (p. 130).

psychological disorders also exist. I believe your report must state clearly and consistently that ME/CFS is a real, physiological disease that is neither wholly nor partially psychological.

Line 33: "overlaps with . . . major depressive disorder"
I do not recall any data from the systematic review or the Workshop that indicated an overlap with MDD. Dr. Jason presented data that show definitions focused on fatigue instead of post-exertional malaise (PEM) erroneously capture people with primary MDD, but that is a different problem from an overlap or higher rate of MDD in ME/CFS. Given your statement that ME/CFS is not a psychological disease, the reference to overlap with MDD in the absence of such data seems misplaced. The reference to MDD should be deleted here and at line 94.

Lines 34-35: "There is no agreement from the research community on what needs to be studied"
I am not certain this is true, or at least it is no more true in ME/CFS than in any other disease area. ME/CFS researchers presenting at the Workshop identified diagnostic biomarkers, outcomes measures, and treatment studies as priority areas. A number of the presentations on possible etiology (Dr. Hornig, Dr. Natelson) linked the significance of that research to developing biomarkers and treatments. Very similar needs were identified at the 2011 NIH State of the Knowledge Workshop on ME/CFS.[3]

The one major disagreement among researchers is over the value of continued investment in psychological and behavioral studies. Most ME/CFS researchers (and advocates) believe that this area has received a disproportionate amount of funding to date. A small group of researchers continue to investigate the psychosocial theory and treatments based upon it. But competing schools of thought can be found in most areas of science. Your report identifies many areas for future research, and I think there is general agreement among ME/CFS researchers on many of those points.

Lines 40-43: "preventing ME/CFS from being considered as a distinct pathologic entity."
This is very true, and the point needs to be emphasized. But to say that ME/CFS should be recognized as a distinct entity begs the question of which version of ME/CFS is the correct distinct entity?

The systematic evidence review and Workshop agenda is based on the assumption that the eight case definitions describe the same population. The paradigm is of one illness characterized by debilitating fatigue not explained by any of the exclusionary conditions, and accompanied by a shifting list of other symptoms that may or may not be categorized into subtypes. That is representative of HHS's official views. In describing the CDC multisite study at the FDA's meeting in April 2013 on Drug Development for ME/CFS, Dr. Unger said that CFS or CFS/ME is a generic term, and an "umbrella diagnosis."[4] Oddly, CDC continues to promote the broad umbrella approach while simultaneously acknowledging that ME is a different disease. In one

[3] http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf
[4] FDA Center for Drug Evaluation and Research, Drug Development for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: Public Workshop Day Two, April 26, 2013. Transcript, page 227. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (retrieved January 18, 2014).

paper, CDC went so far as to say, "The 1994 International CFS case definition and the Canadian Consensus Criteria are different and do not necessarily identify similar groups of ill persons."[5]

In contrast, Dr. Jason's presentation and the experiences related by patients at the Workshop clearly show that the Fukuda and Reeves definitions are too broad, as they both focus on fatigue. It is a similar problem as with the Oxford definition. Patients collectively described symptoms along common themes aligned more closely with the Canadian criteria than the Fukuda definition. ME/CFS experts and advocates have promoted the adoption of the Canadian criteria in part because it is more focused than Fukuda, and requires post-exertional malaise. This more precise view of the disease characterized by PEM, cognitive dysfunction, sleep disturbances, along with immune and autonomic dysfunction does represent a discreet entity – distinct from the conditions captured by Oxford, Fukuda and Reeves.

The umbrella or combination approach is emblematic of the mushy thinking that has hindered this field for thirty years. If we fail to acknowledge and grapple with this problem, then we perpetuate that sloppy thinking as well as the detrimental effects on patients. There is a distinct entity, which is referred to as ME/CFS or ME, characterized by PEM, cognitive dysfunction, sleep disturbances, along with immune and autonomic dysfunction. Your report needs to be crystal clear that this is the distinct disease at issue.

Lines 49-50: "no agreed upon parameters for defining . . . no accurate ways of identifying and diagnosing ME/CFS"
I think it would be more precise to say that there are no universally accepted parameters for defining ME/CFS, because there are certainly schools of thought within the field, e.g. PEM is required or not. In addition, it would be more precise to say there are no widely validated and accurate ways of diagnosing ME/CFS. The clinicians and researchers who presented at the Workshop believe it is very possible to accurately identify the disease. The dearth of funding has been the main barrier to conducting large validation studies, and disputes between groups of experts and CDC have hindered progress.

Lines 50-51: "163 symptoms have been associated with ME/CFS"
This is incorrect. I believe this point was taken from Dr. Nacul's talk, and I understood him to say that there were 163 different combinations of symptoms possible within the Fukuda case definition. He further stated that only 35 of those combinations require PEM, which means there are 128 Fukuda symptom combinations that do not require PEM. This is a critical point to note in light of the controversy over making PEM a required symptom for diagnosis of ME/CFS.

Line 52: "and a research focus on men"
The phrasing of this sentence is confusing. Do you mean to say that the lack of a research focus on men limits the applicability of current studies? Because the sentence currently reads as if you are saying there is a research focus on men that limits applicability of studies.

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[5] Switzer WM, Jia H, Hohn O, Zheng HQ, Tang S, Shankar A, Bannert N, et al. Absence of evidence of Xenotropic Murine Leukemia Virus-related virus infection in persons with Chronic Fatigue Syndrome and healthy controls in the United States. Retrovirology 2010; 7:57.

Line 87: "limited patient and professional education"
There is no doubt that limited professional education has impaired progress. However, I do not understand your statement that limited patient education has impaired progress. No data were presented on this point. Speaking from my own experience, I have to educate my doctors (with very few exceptions) and I have heard the same from every other patient I know. I think you may have a point that the patients who are not accurately diagnosed or who do not have access to expert care may not be as well equipped to manage their healthcare. In that case, I respectfully suggest that the sentence be rephrased to be more descriptive of those patients.

Lines 92-92: "this is not a psychological disease in etiology."
This is a critically important statement. I believe this point should be emphasized throughout the report because of the legacy of the psychogenic view.

For more than thirty years, the psychogenic model dominated the medical mainstream view of ME/CFS. Patients were labeled malingerers with "yuppie flu." Allegedly, they could not cope with stress, indulged their psychosomatic symptoms, received secondary gain from disability, and simply needed to get therapy and more exercise. This perception continues today, as I have never met an ME/CFS patient who did not receive this message from at least one doctor. Many of us followed the advice of well-meaning healthcare providers and tried to exercise ourselves out of disease. This therapy is not a treatment, and adverse side effects include relapse, exacerbation of the disease, and increased disability.

Science has emerged to confirm what ME/CFS patients and doctors already knew empirically. Abnormal two day CPET results, abnormal post-exercise gene expression, abnormal spinal fluid proteomics, abnormal immunological findings – and multiple studies that find different results in ME/CFS patients compared to controls with depression or anxiety – conclusively establish that ME/CFS is not the result of deconditioning, poor coping skills, or a mental disorder. But these views persist, sometimes in the guise of claiming the disease is born of both physical and psychological factors. For example, a recent systematic review of ME/CFS case definitions stated: "The futile dichotomy of 'organic' versus 'psychic' disorder should be abandoned. Most medical disorders have a complex aetiology."[6]

To say that physical and psychological attributions of illness are a "futile dichotomy" is to ignore how diseases are diagnosed and treated in the real world, and obscures the relevance of such classification in research as well. No one could credibly claim that the physical-psychological dichotomy should be abandoned in cancer, heart disease or MS because the origin of disease as physical or psychological does not matter. In fact, patients with any of these diseases would rightly be offended at such a suggestion. Making such an argument in ME/CFS is born from the perception that this disease has a psychological etiology.

There are dangers in the persistent framing of ME/CFS as a morass of poor coping skills, deconditioning, and secondary gain. First, such a view ignores and diminishes the significance of the amassed physiological evidence. Second, it leads to the prescription of exercise as a

[6] Brurberg K, Fonhus MS, Larun L, Flottorp S, Malterud K. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. BMJ Open2014;4:e003973 doi:10.1136/bmjopen-2013-003973

treatment for ME/CFS and the predictable harm that comes from provoking PEM. Third, it obstructs progress towards developing more appropriate and effective treatments. Fourth, it perpetuates the common misconception among healthcare professionals and the general public that ME/CFS isn't "real." The psychosocial trap not only fails to account for the physiological evidence, but it excuses the continuing failure of the government and medical community to respond to ME/CFS as the public health crisis that it is.

The psychogenic model of ME/CFS should have faded into obscurity by now. But it persists in open supporters of the hypothesis, and in less overtly expressed attitudes among scientists, doctors, and policy makers. CBT aimed at correcting false illness beliefs is part of this psychosocial view. Claims that the mind-body connection trumps the either-or debate leaves the psychogenic theory on the table. Our long experience with the destructive effects of psychogenic pronouncements has taught ME/CFS advocates to be wary of these unseen and unvoiced assumptions. You must be crystal clear throughout your report that ME/CFS is not a psychological disease. Very few things have hindered progress in research and patient care more than the psychogenic view of this disease. It is past time to declare a clean break from the psychosocial paradigm.

Lines 95-97: "Focusing on fatigue alone . . . fails to capture the essence of this condition."
You have made a critical point here. Fatigue is not the essence of the disease that the ME/CFS patients and experts addressed at the Workshop. Post-exertional malaise (PEM) and cognitive deficits (as you correctly noted at lines 106-107) are the essential core of this disease. However, as Dr. Nacul and Dr. Jason presented to you, the Fukuda and Empirical definitions do not require these core features for diagnosis. Unfortunately, you were not presented much data or descriptions of PEM beyond the statements of patients at the meeting. PEM is not just severe fatigue; it is the exacerbation of cognitive, immune and autonomic symptoms after even minor activity (e.g. taking a shower). I urge you to be clear throughout your report on the primary importance of PEM as the distinguishing feature of this disease.

Lines 105-106: "A clear case definition with validated diagnostic tools is required before studies can be conducted."
I find this statement to be confusing. I completely agree that a clear case definition and validated diagnostic methods are the top priority in the field. This may be what you intend (i.e. the very first action taken from this report should be the resolution of the case definition and validation of diagnostic tools). However, to say that these must be resolved before studies can be conducted casts doubt upon the thousands of studies already published. This sentence could also be interpreted to mean that previous studies should be interpreted with caution due to the lack of a clear case definition. I suggest that the sentence be edited to more clearly reflect your intention.

Lines 113-115: "[CBT and GET] demonstrate measurable improvement"
This brings us to the thorny problem of CBT and GET. There are several issues that need untangling here.

First, what is meant by "CBT" and "GET"? The studies included in the systematic evidence review in those categories actually encompass very different therapies based on conflicting theories of disease. For example, some studies focused on support, stress management, or pacing.

In stark contrast, other studies challenged somatic attributions, addressed activity avoidance and unhelpful beliefs, or reduced perfectionism and self-criticism. Counseling that seeks to support and improve coping is at the opposite end of the disease theory spectrum from counseling that challenges somatic attributions, unhelpful beliefs or seeks to reduce perfectionism. In terms of "graded exercise therapy," there are two competing schools of thought. One school increases activity on a schedule, regardless of the symptoms experienced by subjects. The other school increases activity only to the extent it is tolerated by subjects and does not cause an increase in symptoms. Dr. Snell's presentation on VO2max and two-day CPET provides a strong basis for why the former is dangerous for ME/CFS patients. Lumping all CBT or GET studies together, as if one type of counseling or exercise is as good or as applicable as another, introduces more heterogeneity into the analysis than already exists.

Second, the statement that these studies demonstrate measurable improvement is exaggerated. To take the PACE trial as an example, the only objective measure of improvement was the six-minute walking test, with the biggest improvement reported in the GET arm of the trial (an increase of 67 meters over baseline to 379 meters). However, the PACE authors fail to note that this improvement still left the subjects below the 400 meter threshold qualifying for lung transplantation. Dr. Snell presented to you on the insignificance of this small improvement. There are other reasons to question the PACE results: the study abandoned the plan to use actigraphy as an objective measure of improvement; a *post hoc* change to the definition of recovery made it possible for a subject to worsen on the SF-36 scale and be considered recovered; and PACE data show that there was a slight increase in the number of participants receiving illness and disability benefits by the end of the trial. Most of these data were not included in the draft systematic evidence review nor were they presented at the Workshop. Given these multiple problems with the largest trial of CBT and GET, the conclusion that these demonstrate measurable improvement is highly questionable.

Finally, the evidence review pooled the results of trials conducted using different case definitions. I will address this in more detail in my comments on lines 379-381 below. However, if the CBT and GET trials that used the Oxford definition were separated out from Fukuda trials in the analysis, the measurement of improvement would be even less significant than it appears.

For all of these reasons, I recommend that the Panel modify its statements (here and at line 362) about the benefits of CBT and GET to more accurately reflect the evidence.

Lines 115-116: "they are not a primary treatment strategy and should be used as a component of multimodal therapy." (see also lines 364 and 385)
Just as references to CBT should define exactly what type of approach is meant, the same must be done for "multimodal" therapy. If you are referring to Multimodal Therapy (MMT) as pioneered by Dr. Arnold Lazarus, then it is inappropriate and inapplicable here. MMT is an extension of CBT and was designed to treat psychological problems. You have already acknowledged that ME/CFS is not a psychological disorder, so to recommend MMT as a treatment is contradictory.

However, if by "multimodal therapy" you mean a multidisciplinary approach to treatment that includes medications, supportive counseling, pacing, and safe physical activity, then I suggest

that you select a different descriptive phrase to distinguish it from MMT. Replacing references to multimodal therapy at lines 116, 364, and 385 with "multidisciplinary" or "team" approach would better represent your intent.

Lines 134-138: "focus on exercise programs . . . "
You are correct that a focus on studying exercise programs as a "treatment" for ME/CFS has discouraged research participation. However, your next sentence seems to state that patients are afraid of attempting even mild stretching because of a lack of instruction in graded exercise therapy. I strongly disagree.

Everyone – family, friends, healthcare providers – tell people with severe fatigue to exercise more. Even before receiving an ME/CFS diagnosis, patients have made numerous attempts to increase activity. For many of us, even the activities of daily living cause severe PEM and our worlds quickly shrink to our bedrooms. But every single patient with ME/CFS that I have met wants to be more physically active. The fear of harm from exercise programs does not come from a lack of instructions. The "fear" of harm is based on repeated hard experience of attempting physical activity and being slammed with the repercussions of PEM. Sometimes, I can walk through a grocery story with no adverse consequences. Other times, I can't walk around my living room without my heart rate spiking above my anaerobic threshold and a sudden onset of autonomic symptoms.

The data that show exercise is harmful to ME/CFS patients were largely excluded from the systematic evidence review. But it is this "strong evidence of impaired physiological responses to exercise" that explains why "incautiously applied GET is likely to result in exacerbation of fatigue and other symptoms of ME/CFS patients."[7] This is precisely what ME patients have reported regarding exercise for years, both in patient surveys and at the FDA Patient Focused Drug Development Initiative. The evidence review also ignored the fact that a trial of CBT and GET found an increase in SF-36 pain scores at follow-up in the intervention group.[8] The review also failed to examine two important papers that addressed increased harms associated with GET.[9, 10]

Your statement on exercise begs the question: what is sufficient instruction for engaging in safe levels of physical activity? Given the dropout rates from many studies, coupled with patients' reported experiences and results of studies that use exercise challenges to provoke PEM, there

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[7] Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. J Transl Med. 2014;12:104.
[8] Nunez M, Fernandez-Sola J, Nunez E, et al. Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomized controlled trial with 1 year of follow-up. Clin Rheumatol. 2011;30(3): 381-9.
[9] 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).
[10] Twisk FN, Maes M. A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. Neuro Endocrinol Lett. 2009;30(3): 284-99.

are limited data on designing such programs. Almost none of that data were included in the evidence review and Workshop.

This may not have been your intent, but stating that there is fear from harm from mild stretching places the blame and onus on the patient for being afraid, and further says that adequate instruction will overcome that fear. The reality is that virtually no resources have been invested in studying the design and implementation of safe, individualized activity programs, let alone training healthcare professionals in carrying out such methods. This is not the fault of ME/CFS patients, whose fear of harm from unsafe exercise or activity is very reasonable and realistic.

Lines 142-143: "Many patients with ME/CFS are misdiagnosed and treated erroneously with potentially toxic therapies"

There are several issues here that need clarification. As worded, this sentence seems to state that patients with ME/CFS are misdiagnosed with other conditions, and therefore receive erroneous and potentially dangerous treatment. This is true, in that patients who have been misdiagnosed with primary psychiatric disorders or Lyme disease (as just two examples) are given inappropriate treatments for conditions they do not have.

But it is also true that patients with diseases such as MS or Lyme disease or psychiatric disorders are misdiagnosed with ME/CFS.[11] These patients are erroneously denied treatments that they need, such as immune modulators, antibiotics or psychoactive drugs. It is not clear to me if you intended to describe this problem here. Conversely, it is also true that patients who have been correctly diagnosed with ME/CFS may receive potentially toxic therapies, but your sentence does not describe this problem.

It would also be useful here to give examples of the toxic therapies you have in mind. The list could include off-label use of anti-retrovirals, fecal transplants, and hookworm – all of which have been tried by ME/CFS patients. But the list could also include antidepressants, steroids, and exercise. Specificity is needed to avoid creating the impression that you are referring only to medications as being toxic, and not to alternative treatments and exercise which can be just as harmful to ME/CFS patients as inappropriate medications.

Lines 166-167: "The symptoms patients consider clinically meaningful are not in the scientific literature."

This is not the case. PEM, cognitive impairment, and autonomic dysfunction are all present in the scientific literature. These studies, however, were missing from the systematic evidence review conducted for the Workshop. I respectfully suggest that the discordance between the systematic evidence review and patients' experiences be noted.

Lines 169-177: "Research priorities should be shifted . . ."

I am in complete agreement with your statement that priories should shift to focus on work that will identify biomarkers and therapeutics. However, I would like to ask if the bullet point

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[11] Berger JR, Pocoski J, Preblick R, Boklage S. Fatigue heralding multiple sclerosis. Multiple Sclerosis Journal 2013; 10(11): 1526-1532.

questions that follow this statement are meant to be all-inclusive? If not, it would be helpful to state that these questions are among the many more that need to be answered.

Line 181: "failure to implement what we already know"
I am unclear on what is meant by this sentence. The risk, in my opinion, is that this sentence could be interpreted as, "failure to implement the CBT and GET approaches proven in the PACE trial," just as easily as, "failure to implement two-day CPET protocols." The sentence is too nonspecific, leaving its meaning to the eye of the beholder.

Line 184: "Patients must be at the center of the research efforts"
I agree 100% with this, and with the similar statement at lines 189-191. ME/CFS research could be a demonstration project for the value patients can bring to the scientific enterprise. I would welcome a strong recommendation from the Panel encouraging NIH to incorporate patients at all stages of research, similar to FDA's efforts through its Patient Representative Program.

Lines: 191-192: "dissemination of diagnostic and therapeutic recommendations should focus on primary care providers."
Why? Are such recommendations for diagnosis and treatment of multiple sclerosis focused on primary care providers? For lupus and rheumatoid arthritis? For cancer and heart disease? For those diseases, primary care providers must know the signs that indicate a patient should be referred to the relevant specialty for evaluation, diagnosis and treatment. Primary care providers are not expected to manage such complex health conditions directly. It is true that ME/CFS patients likely begin their search for answers with primary care providers. In the current healthcare environment, patients with many complex diseases begin in primary care, but they do not remain there. What data support leaving ME/CFS to the care of providers who are unfamiliar with the complexity and course of the disease?

Line 199: "Is ME/CFS one disease?"
I believe it is very clear that the symptoms and signs captured by the eight case definitions combined in the systematic evidence review represent more than one disease (See also my comments on lines 40-43 above). In fact, this very question was one of the original questions proposed for this P2P Workshop and evidence review. At some point in the process, the question was dropped because it was decided *a priori* that the evidence base could not answer this question.[12] This question is not merely a gap. It is foundational to the entire ME/CFS field. I submit to you that achieving consensus between ME/CFS experts, NIH and CDC on this single question is the greatest priority in the field, and one of the most difficult because scientific data has not yet succeeded in overcoming the political issues entwined in this question.

Research Strategy Recommendations (Lines 202-366)
I recommend that you explicitly prioritize the recommendations. It is not clear if the numbered items are listed in order of priority, and there is no indication of prioritization among the sub-items. It is critical to take this step because, given the very limited resources available, all of this work will not be done at once. Hard decisions will be made about allocating those scarce resources, and your guidance could greatly influence those decisions. I am acutely aware of how

[12] http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-june-17-2014.pdf, p. 38.

difficult it is to prioritize in a field that desperately needs advances on every front. My six years of service on the board of an ME/CFS non-profit required decision making on program priorities and individual research projects. It is precisely because I know how difficult these decisions are that I ask you to explicitly address prioritization, because without it we run the risk of scattershot approaches that make no advances at all.

Lines 202-204: "Assemble a team of stakeholders . . . to reach consensus on the definition"
Very little time at the Workshop was spent on reviewing past and current efforts to reach consensus on an ME/CFS case definition. I would like to bring to your attention the following:

- In April 2011, the NIH State of the Knowledge Workshop concluded: "working toward a single, more usable, and accurate case definition for this illness would create a more solid foundation for research."[13]
- In October 2012, the CFS Advisory Committee recommended that HHS convene a "stakeholders' (ME/CFS experts, patients, advocates) workshop in consultation with CFSAC members to reach a consensus for a case definition useful for research, diagnosis and treatment of ME/CFS beginning with the 2003 Canadian Consensus Definition for discussion purposes."[14]
- In October 2012, HHS first announced the intent to hold what became this P2P Workshop, and the stated purpose was to create a research case definition.[15] This goal was subsequently dropped with no public explanation (despite our repeated requests for one).
- In September 2013, HHS contracted with the Institute of Medicine to create new clinical diagnostic criteria for ME/CFS. The controversies surrounding the contract are beyond the scope of these comments. However, the IOM report is expected in early February 2015.

In light of the recent history of case definition efforts, let alone that of the previous thirty years, I believe your recommendation can be strengthened. Should the IOM clinical criteria be adopted for research? Which stakeholders should participate in decision-making, and at what level of representation? Should stakeholders work together to reach consensus, and if so, how and under whose auspices? My personal opinion is that, without significantly more teeth and specificity, it is unlikely that your recommendation to bring stakeholders together will be any more successful than previous similar recommendations have been. At a minimum, your recommendation should acknowledge that similar recommendations to involve all the stakeholders in the case definition effort have been made and ignored.

Lines 209-210: "Additional NIH Institutes and Centers not presently represented in the Trans-NIH ME/CFS Working Group should be included"
I am not certain what adding representatives to the Trans-NIH Working Group will achieve. There is no doubt that multiple institutional and systemic obstacles hinder progress for ME/CFS at NIH. One such obstacle is that the Working Group is housed in the Office of Research on

[13] http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf
[14] http://www.hhs.gov/advcomcfs/recommendations/10032012.html
[15] http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac10032012.pdf, p. 5.

Women's Health (ORWH), despite the fact that at least 25% of ME/CFS patients are male. A similar male-female ratio is found in diseases like MS, yet those diseases are not confined to the realm of women's health. Furthermore, neither the ORWH nor the Working Group has any research budget. The Working Group has had little success in increasing investment by or through the represented Institutes. What purpose is served by adding more representation? It would be more effective, and have a great impact, if ME/CFS were assigned to an Institute home and allocated a research budget.

Lines 216-217: "e.g., [NCATS] . . . [NCCAM] [*sic*]**"**
I agree that NCATS could play a powerful role in coordinating research efforts. However, I object to your inclusion of NCCAM (now NCCIH) rather than Institutes such as NIAID, NINDS, or even the BRAIN Initiative. ME/CFS has long been relegated to the fringes of both biomedical research and clinical care. Patients turn to unproven alternative therapies because they have nowhere else to go. Assigning a pivotal role to NCCIH does nothing to correct this situation, and will likely only perpetuate the popular view that ME/CFS is not a serious disease because it is largely treated and researched in alternative medicine.

Lines 220-221: "leverage and catalyze the use of existing NIH infrastructure and dollars."
I strongly disagree. While existing resources can and should be maximized, no meaningful progress can be made without substantial new investments by NIH in ME/CFS research. Your report cannot be silent on this desperate need. Five million dollars per year equals no diagnostics, no biomarkers, and no treatments. By comparison, NIH spends $9 million per year on hay fever.[16] If you do not recommend a significant increase in spending, it is all but guaranteed that we will get precisely that: no increase. And no increase all but guarantees that none of your most important recommendations will be followed.

Lines 233-236: "registry/repository"
I agree. Your recommendation would be stronger if it referenced the recommendation from the CFS Advisory Committee (CFSAC) for a data repository and sharing platform.[17] CFSAC is also currently working on recommendations for a national biobank or registry.[18] Your recommendation would also be strengthened if you expressly encouraged NIH to reexamine its rejection of CFSAC's recommendation on the data repository because it is "cost prohibitive."[19]

Lines 254-256: "diagnostic and prognostic algorithms"
I believe that this is a forward-looking recommendation, and fits squarely with the goals of the Pathways to Prevention program. However, it seems to me that a great deal of discovery and epidemiology work will have to precede development of these algorithms. This is why I suggested above that your recommendations should be prioritized. Resources should not be allocated to theoretical algorithm work before undertaking a study such as the Framingham-like study suggested by Dr. Taylor.

[16] http://report.nih.gov/categorical_spending.aspx
[17] http://www.hhs.gov/advcomcfs/recommendations/cfsac-scientist-work-group-bkgrnd-6-16-17-2014.pdf
[18] http://www.hhs.gov/advcomcfs/meetings/presentations/day-1-combined-deck-dec-2014.pdf
[19] http://www.hhs.gov/advcomcfs/recommendations/hhs-cfsac-recommendations-response.pdf

Lines 281-282: "Studies investigating homeopathy . . ."
I strongly disagree. First, I note that there is no evidence that homeopathy is effective in any condition, including chronic fatigue syndrome.[20] Second, research into complementary or alternative treatments should not be prioritized over biomedical research into diagnostics, biomarkers, and treatments.

Lines 282-284: "Studies addressing biopsychosocial parameters . . ."
Again, I disagree. Such studies should not take precedence over the biomedical research so desperately needed. Examination of function and QOL can readily be incorporated into biomedical studies. For decades, research into psychosocial parameters has been front and center, to the detriment of other areas of ME/CFS research. I respectfully suggest that this imbalance be corrected through heavy investment in biomedical research.

Lines 289-290: "NIH should develop an ME/CFS methodological workgroup."
I agree. However, it would be helpful if your report could recommend more specifics, such as whether nonfederal members should be included and to what extent, and the need for patient representation (not merely non-profit representation) on this workgroup. Any such workgroup must be transparent and accountable to the public. I believe it is important to make this explicit because, in the past, NIH has made statements about creating action plans and priorities and then refused repeated requests from multiple parties to share those plans with the public. This has made it impossible to track progress or internal decisions.

Lines 301-327: "Provide training and education."
I am concerned about all of your recommendations on clinical care and education, as this was examined only in a cursory fashion at the Workshop. There is a risk that you don't know what you don't know. Clinical care of ME/CFS patients is not only complex, but also the doctors who specialize in this disease use a range of testing, treatments, and approaches that was not even mentioned in passing at the Workshop. If you make recommendations for clinical care based on the evidence review and presentations, then you will grossly underrepresent what specialists are using with varying degrees of success.

A broader understanding of what education has been attempted in the past, and what is currently being done (or not done), would better inform these recommendations. I am particularly concerned because ME/CFS advocates have expressed dismay over the federal government's education efforts for years, and this recommendation could simply be used to justify no change in the government's course.

Furthermore, education efforts should not proceed until there is consensus and acceptance of a case definition. For example, CDC's education materials use the Fukuda and Reeves definitions, and CDC has expressly rejected requests to make PEM a mandatory part of diagnosis. In addition, the Institute of Medicine committee I mentioned above was tasked with not only

[20] NHMRC Draft Information Paper: Evidence on the Effectiveness of Homeopathy for Treating Health Conditions, April 2014, p. 14, http://consultations.nhmrc.gov.au/files/consultations/drafts/nhmrcdrafthomeopathyinformationpaper140408.pdf

creating a new clinical case definition, but also recommending a program to disseminate that definition to healthcare professionals. Depending on the specifics, the IOM report may or may not be accepted by ME/CFS advocates/experts and/or the federal government.

Finally, your suggestions to engage health professional agencies, HRSA, professional societies and others have previously been recommended by CFSAC.[21] However, these recommendations became controversial when advocates discovered that HHS had illegally altered the recommendations after the CFSAC's vote.[22] To date, HHS Secretary Burwell has not seen the corrected legal recommendations.

Line 317, et seq.: "Finding new funding resources"
Your recommendations on new collaborative models, co-funding research across Institutes, and developing new researchers are welcome. But these recommendations are doomed to fail and ME/CFS research consigned to stagnation without a substantial increase in investment by NIH.

As I previously noted, NIH currently spends approximately $5 million per year on ME/CFS research. CFSAC has recommended increases in NIH funding seven times in the last ten years, inspired in part by the success of an RFA issued by NIH in 2005.[23] Most recently, CFSAC recommended that NIH issue an RFA with set aside funds to study many of the same questions and priorities that you identify in your report.[24] In 2014, both the IACFS/ME[25] and eleven members of Congress[26] also made requests for an RFA.

NIH has remained obdurate in its refusal to set aside funds for ME/CFS research. NIH answered the most recent CFSAC recommendation by saying "there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment for ME/CFS. As such issuing a Request for Applications (RFA) would not be an effective strategy as RFAs generally encourage a narrowly defined research area that addresses more specific gaps in scientific knowledge."[27] It is not clear to me why an RFA could be issued in 2005, but not ten years later when more data have been accumulated.

Also troubling are Dr. Susan Maier's comments to you at the opening of the Workshop that ME/CFS researchers should look to "other areas" of research for funding. Both her comments and the presentations from Drs. Buchwald, Clauw and Afari reflect the "lumping" paradigm: ME/CFS should be studied with other pain conditions based on the theory that they share an underlying mechanism. Yet your report recognizes that ME/CFS is distinct and must be studied as such.

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21 http://www.hhs.gov/advcomcfs/recommendations/03112014.html
22 http://www.occupycfs.com/2014/11/24/another-cfsac-violation/
23 http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html
24 http://www.hhs.gov/advcomcfs/recommendations/06142014.html
25 http://www.iacfsme.org/LinkClick.aspx?fileticket=tnCp3meyVmU%3D&tabid=36
26 https://dl.dropboxusercontent.com/u/57025850/Congressional%20letter%20-%20Dr.%20Collins%20-%20March%202014.pdf
27 http://www.hhs.gov/advcomcfs/recommendations/hhs-cfsac-recommendations-response.pdf

I urge you to recommend that NIH dedicate set aside funds for ME/CFS research. Your recommendation should specify the amount of funding and over what period of time, as earlier recommendations have done. There is simply no way to move this field forward and accomplish your recommendations without a substantial and sustained increase in funding.

Lines 340-349: "Create a network of collaborative centers"
This was discussed to some extent at the Workshop. The CFSAC has recommended the creation of "Centers of Excellence," which would undertake clinical care and research such as you delineate, a total of six times in the last ten years. NIH has refused to restore the funding to the defunct CFS research centers from a decade ago. Dr. Clauw spoke about the MAPP Initiative at the Workshop, a collaborative research center network established by NIH to investigate pelvic pain conditions. However, MAPP was created with dedicated set aside funding, something that NIH has refused to allocate to ME/CFS research. It would be a mistake to piggyback ME/CFS centers onto the MAPP or other network. I urge you to add specifics to this recommendation for centers focused on ME/CFS clinical care and research: number of centers, amount of funding, and period of time.

Lines 350-351: "Establish a central archive of de-identified data and tissue samples"
This seems duplicative of your recommendation at lines 233-236. You may wish to refer to that earlier recommendation here, or explain how the two are distinct from one another.

Lines 353-355: "NIH should . . . create a website for . . . educational materials as well as information regarding clinical trials."
With all due respect, this is nowhere near the top of the priority list. It would be a diversion of resources better spent on actually conducting clinical trials and biomedical research. Generally speaking, the problem is not that we need more education materials or information on clinical trials. The problem is that there are virtually no clinical trials! Dr. Natelson and Dr. Fletcher both appealed to the Workshop audience for research participants, but I believe that there are other ways to solve the recruitment problem than to encourage NIH to spend money on something like this. Double the amount of research money NIH invests in ME/CFS each year for the next five years, and then I think you would see the recruitment problem addressed as well.

Lines 359-362: "Studies examining the role of self-management techniques"
Respectfully, this is not a high priority area for research. Self-management techniques and studies are more or less stabs in the dark. How can we draw conclusions about self-management without thoroughly investigating the abnormal response to exercise and cognitive challenges? Continuing to study self-management without the data needed to guide creation of these programs is a wasteful distraction. Your report correctly points out that case definition, outcomes measures, large-scale analysis such as genomic studies, biomarkers and clinical trials are critical needs in this field. If you undertake prioritization, as I have suggested, then self-management studies should rank near the bottom.

Lines 362-363: "The modest benefit from CBT should be studied"
First, I believe that if the Oxford definition studies of CBT are removed from the analysis, this "modest" benefit will disappear. Second, as I stated at lines 113-115 above, CBT should not be used as a catch-all term for counseling, correction of false illness beliefs, etc. These approaches

are not synonymous. Third, CBT studies share the same low priority as self-management techniques and biopsychocial parameters. Enough money has been spent with little results to show. Priority and emphasis must shift to biomedical studies and clinical trials.

Lines 365-366: "We recommend that the NIH and the FDA convene a meeting on the state of ME/CFS treatment."
I am not certain if the Panel is aware of FDA's April 2013 Workshop on Drug Development for CFS and ME.[28] It may be that this meeting is similar to what you envision. If not, then it would be helpful to add specifics to your recommendation so that it is clear that another meeting is required.

Lines 373-374: "Patients and their advocates may benefit from education on how to effectively communicate their symptoms"
ME/CFS patients and advocates are highly sensitized to language that blames or shames them for their disease or how they manage it. This sensitization is due to the hundreds of times patients are told to get over it, stop being lazy, change what they eat, change doctors, get exercise, deal with stress, and so on. Seen in that light, this sentence can be interpreted as "Patients and advocates have failed in communicating with their providers, and would get better care if they just changed how they spoke to doctors." This is a paternalistic view, and it is not supported by data.

Dr. Klimas has said that many of her ME/CFS patients have PTSD caused by their interactions with the healthcare system.[29] This is not the patients' fault, and telling them that they would not have been traumatized if they just communicated correctly blames them for something they did not cause. I realize that this interpretation may not be what you meant at all. I respectfully request that you edit the sentence to remove any hint or interpretation of blame. You correctly described the situation at lines 10-11: "ME/CFS is an area where the research and medical community has frustrated its constituents, by failing to assess and treat the disease and by allowing patients to be stigmatized."

Lines 379-380: "recommend . . . the Oxford definition be retired"
I thank you for this recommendation. However, I disagree with the discussion at the Workshop on why Oxford based studies should be retained, and I ask that you make recommendations on that point.

Imagine a hypothetical breast cancer chemotherapy study from the 1960s. Patients are enrolled based on the presentation of tumor in the breast, and receive a chemotherapy treatment. Modest effectiveness is found. But fast forward to today, when research discoveries have shown that breast cancer is not a monolithic disease. It is a disease with many different biomarkers that help predict which treatments may be most effective, as in the case of estrogen antagonists in the treatment of estrogen receptor positive breast cancer. The modest effect of that 1960s trial could very well be explained by the heterogeneous nature of the subjects, i.e. some with estrogen sensitive tumors and some without. If tissue were not available to reanalyze the data based on the

[28] http://www.fda.gov/Drugs/NewsEvents/ucm369563.htm
[29] http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac20081028min.html

presence of those receptors, the continued use of the drug could not be recommended because it would be impossible to predict who would benefit.

The same is true of studies using the Oxford definition. You are absolutely correct that the Oxford definition hinders progress because it identifies a heterogeneous cohort that includes people who do not have ME/CFS. You cannot take the results of studies done on subjects who do not have ME/CFS and simply apply those results to those that do. It is unscientific and unethical. The "modest" benefit reported in flawed studies like the PACE trial could have been experienced by the patients who do not have ME/CFS. It will further hinder progress to continue to view Oxford based studies as a part of the ME/CFS literature because those studies included subjects without the disease. You must make a strong recommendation that the Oxford studies not be applied to the ME/CFS population.[30]

Lines 380-381: "the ME/CFS community agree on a single case definition"
This recommendation needs more specificity. There is broad agreement among ME/CFS researchers and patients that PEM must be mandatory for diagnosis of ME/CFS, and therefore many have adopted the Canadian Consensus Criteria. CDC, NIH and FDA have all refused to do so. We have been at this impasse for years. Can you propose a way to solve this problem? As I commented on lines 202-204 above, this recommendation needs more teeth and specificity to have any hope of success. Who is part of the "community"? How should they come together and under whose auspices? How can the disagreements, particularly over the central feature of PEM, be resolved? What needs to change in order to break the thirty-year logjam?

Lines 381-382: "patients, clinicians, and researchers agree on a definition for meaningful recovery."
Agreed, as long as patients are equal participants in the decision making process.

Lines 384-385: "We believe there is a specific role for multimodal therapy."
See my comments on Lines 115-116, above.

Lines 401-402: "recommend that ODP convene another ME/CFS Expert Panel in the future to monitor progress"
Two specifics should be added to this recommendation. First, add a specific timeline (e.g. three years, five years or ten years?). Second, be specific about the composition of the Panel. The ODP P2P process convenes Panels of non-subject matter experts. There can be value to this approach, but if you believe ME/CFS subject matter experts should be the ones to monitor progress then you should specify this in the recommendation.

Lines 402-403: "We hope our work has dignified ME/CFS and those affected"
It has, and I thank you.

[30] I acknowledge that the PACE authors claim to have tested treatment effect using the Fukuda definition as well. However, they did not apply Fukuda correctly. They required subjects to have symptoms for one week, rather than the six months required in Fukuda.