Comments on the "Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Draft Executive Summary"

>> Using the original version of the Draft Report (lines 1-403).

First, I will restate and reaffirm my opposition to both the P2P and IOM, and my unequivocal disapproval of these redundant and unscientific efforts. HHS and NIH have repeatedly acted in ways which have gone against the expressed wishes of patients, and have caused them harm. I join multitudes of advocates, patients, caregivers, ME/CFS researchers and clinicians, and other stakeholders, in mass opposition.

The effort to redefine ME/CFS is redundant because a research and clinical definition has already been developed and adopted by leading independent ME/CFS international expert biomedical professionals, who have reached a concensus and also agreed to refine it as necessary; the 2003 Canadian Consensus Criteria (CCC), updated in 2011 by the International Consensus Criteria (ICC). These critera is very well accepted by the international ME/CFS medical community.

It is interesting to note that the vast majority of the ME/CFS community; clinicians, researchers, advocates and patients were in agreement with CFSAC's recommendation of adopting the Canadian Consensus Criteria (CCC) now, and working on improving it. This is evidenced by the letter to the Secretary of HHS that 50 ME/CFS expert clinicians and researchers signed, informing her that they have in consensus, adopted the CCC and were urging HHS to do so as well. This letter was later endorsed by over 170 patient advocates.

The people on the P2P panel have done a remarkable job given the circumstances, and I do not fault them at all. However, P2P is inappropriate and unscientific by design for many reasons, mainly because it precludes anybody with ME/CFS experience or expertise from being a member of the P2P panel, because of outrageous time frames, and because of a seriously flawed Evidence Review. Good definitions are good because they correspond closely an accurately to the reality of the disease state being described. Therefore, it's crucial that those that attempt to define any disease or illness or the best way forward for research, have long term clinical experience with patients with this illness (and, in certain cases, direct personal experience from having or having had the disease). There is simply no place for the bureaucrat in defining illness or research objectives and needs in this way. The utilization of the jury-model approach in this context is scientifically indefensible and irresponsible, totally inappropriate. I protest this dangerously unscientific process in the strongest way possible.

What we really need is experienced expert biomedical specialists in the disease who understand the science. We need to adopt current criteria based on science, like the CCC and/or ICC, and use them as a starting point. We urgently need research to find real biomarkers.

Like so many others, I agree with our biomedical ME/CFS experts that HHS in all their agencies should adopt current criteria based on science like the CCC and/or ICC as well as the medical ME/CFS expert researchers and clinicians' concensus recommendations on research focus. Historically, diagnostic and research criteria for diseases are created by the expert medical community, not the Government. The money for bureaucratic process like these would be much much better spent on critical and urgently needed biomedical research and to find real biomarkers.

Having said that, the Draft Report contains a number of valid, helpful and sensible conclusions and

recommendations. I'll return to them below.

First, there are a number of conclusions and recommendations in the Draft Report that I would not agree with.

THE EMPHASIS ON 'FATIGUE' INSTEAD OF PEM/PENE

The Draft Report fails to adequately address the crucial importance of Post-Exertional Malaise (PEM)/Post-Exertional Neuroimmune Exhaustion (PENE), the data that shows how essential it is to understanding this disease, and how PEM/PENE is clearly distinguishable from general fatigue - not only by how it is physically experienced by the patient, but also in objectively measurable ways such as abnormal biological response to exertion as shown by the 2-day Cardiopulmonary Exercise Testing (CPET) [1, 2]. This confirms yet again that ME is not characterized by a subjective feeling of fatigue, and that PEM/PENE is not fatigue-based (although fatigue can be one of many accompanying symptoms).

The emphasis on 'fatigue' is hugely problematic, particularly given the difficulty of measuring, or even defining, 'fatigue'. Several other essential hallmark symptoms need close consideration in defining this disease, much more so than 'fatigue': PEM/PENE, neurocognitive dysfunction, immune abnormalities, orthostatic intolerance, sleep disturbances and pain. Stating that this is an illness characterized by 'fatigue' as opposed to PEM/PENE, is incorrect, misleading and unhelpful, and will only perpetuate old harmful misconceptions of this disease. By focusing on fatigue only, you are studing a very different group of patients than those with neurological/immunological ME, as defined by CCC and/or ICC. (Line 3)

The ICC document states that ME is characterized by an abnormal biological response to exertion or exercise that is objectively measurable by the 2-day cardiopulmonary exercise test (CPET). [Carruthers, 2011; VanNess, 2007] According to the ICC, "Pain and fatigue are crucial bioalarm signals that instruct patients to modify what they are doing in order to protect the body and prevent further damage." The fatigue experienced by ME patients is the result of an underlying disease process and cannot be considered as medically unexplained, nor lumped together with the same, any more than can be the fatigue experienced by for example cancer and MS patients.

Calling Myalgic Encephalomyelitis (as defined by CCC and/or ICC) 'Chronic Fatigue Syndrome' is like calling Parkinson's disease 'Chronic Shaking Syndrome' — equally misleading and demeaning. One could argue that using 'fatigue' is even more unhelpful given it is one of the most common symptom found across basically all known illnesses.

There needs to be an agreement that PEM/PENE (as defined by the CCC and/or ICC) is worth treating as a clue to a more specific mechanism. It seems likely that there will be no substantial advancement science-wise until an official adoption of PEM/PENE as a cardinal symptom is accepted. Otherwise, it's unfortunately highly likely that ME/CFS will be stuck as an diffuse umbrella 'fatiguing' illness, perpetually. In other words, by using "ME" criteria in research, there is an attempt to look at a pattern of specific symptoms, with some similarity between patients, other than the simple presence of fatigue.

The CPET is already being used sucessfully clinically and in legal representation (for making disability decisions, measure treatment outcomes, etc), and has potential as a treatment biomarker. There is a need for larger studies, consistent with the future research needs identified in the Evidence Report: "Further studies are needed to determine the utility of 2-day cardiopulmonary exercise testing to identify or monitor symptoms of post-exertional malaise." (page 90)

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

Patient advocate Erica Verillo makes a powerful argument in her comments to this Draft Report, saying: This statement is incorrect. Focusing on fatigue alone may identify many chronic fatigue patients, including people with leukemia, MS (1/3 of patients with early MS present with fatigue as a primary symptom and are misdiagnosed with CFS), incipient cancers, Hashimoto's disease, Ehlers-Danlos, and a multitude of other illnesses. Focusing on fatigue alone not only has led to the misdiagnosis of significant numbers of patients with other treatable conditions, it does not identify many ME/CFS cases. The symptom that identifies ME/CFS patients is post-exertional malaise, also known as post-exertional collapse. As Dr. Jason and Dr. Nacul pointed out, this is the hallmark symptom of ME/CFS.

ME, CFS, FATIGUE, SUBGROUPS..?

One of my most fundamental concerns is the continued lack of clarity on the disease to which this report applies. The Draft Report does not state that hallmark criteria like PEM/PENE must be mandatory, only that PEM should be studied further. The Draft Report recommends against Oxford but says nothing of Fukuda's failure to require hallmark criteria or its lack of specificity. Its focus regarding treatment outcomes is only on 'fatigue'(!) instead of cardinal symptoms such as PEM/PENE, immune abnormalities and cognitive dysfunction. This lack of clarity on the scope of this disease is the root cause of the lack of progress and needs to be addressed. Implementing this report without doing so would be harmful, wasteful and worse, bad science.

99 […] Future
100 studies should distinguish between ME/CFS alone, ME/CFS with comorbidities, and other
101 diseases to better define cellular and molecular mechanisms for targeted treatments.

Yes, this needs more attention. However, probably even more important than that is to consider subgroups within the label "ME/CFS". I would like to see an honest effort (by properly funded expert biomedical scientists, both clinicians and researchers -- not the Government or its bureucrats) to define and investigate a cohort of patients with PEM/PENE (as defined by CCC/ICC, and using CCC and/or ICC criteria as a starting point); in other words, ME distinguished from CFS.

95 […] Focusing on fatigue alone may
96 identify many ME/CFS cases. However, this symptom taken in isolation fails to capture the
97 essence of this complex condition. Prior studies may have inadequately excluded individuals
98 with the distinct diseases listed above, leading to delayed diagnosis, conflicting diagnoses,
99 contradictory treatments, suboptimal care, and inappropriate health care utilization.

For this reason, I believe the focus needs to be on PEM/PENE, not fatigue.

147 Carefully defining comorbid conditions is
148 necessary to define ME/CFS subgroups and to move the field forward.

Comorbid conditions have already been carefully defined in the CCC, which should be a good starting point. I agree that it's very important to define subgroups, but I again question the focus on comorbid conditions at this time. Why not start by looking at subgroups within the strictly defined group of neurological/immunological ME (as defined by CCC, ICC) patients?

199 […], and there are many gaps (e.g., Is ME/CFS one disease?).

Very important question, yes. Wasn't this originally supposed to be one of the main questions for the P2P-agenda? Why was it taken out?

To my mind, a good start would be to follow the lead of the international ME consensus panel of experts. They recommend that patients meeting the International Consensus Criteria (ICC) be given the name ME, and that those meeting the criteria for CFS but not the ICC for ME be given the name CFS. The vast majority of ME/CFS experts don't prefer a broad 'fatigue-based' approach, on the contrary.

"Research on ME:
The logical way to advance science is to select a relatively homogeneous patient set that can be studied to identify biopathological mechanisms, biomarkers and disease process specific to that patient set, as well as comparing it to other patient sets. It is counterproductive to use inconsistent and overly inclusive criteria to glean insight into the pathophysiology of ME if up to 90%of the research patient sets may not meet its criteria (Jason 2009). Research on other fatiguing illnesses, such as cancer and multiple sclerosis (MS), is done on patients who have those diseases. There is a current, urgent need for ME research using patients who actually have ME." [3]

PACING

The Draft Report completely fails to recognize the immense importance and great value of pacing as a treatment approach, and has failed to take account of the very robust and consistent patient evidence that CBT is ineffective for the vast majority of people with ME/CFS, and that around of 50% of people consistently report that GET makes their condition worse, whilst over 90% report that pacing is the most effective and safe form of activity management.

There is a great amount of solid evidence detailing the risks of great permanent harm to the ME/CFS patients posed by exercise and overexertion. All possible efforts to help patients limit risks of harm and avoid permanent severe disability caused by such often manageable factors must be recognized as indispensable and given top priority. One crucial and acutely needed step in this direction is to start focusing on PEM/PENE, pacing and biomedical research, instead of unhelpful things such as 'fatigue', multimodal approaches and CBT/GET.

CBT AND GET

I disagree in the strongest way possible with the Draft Report's conclusions and recommendations regarding CBT and GET.

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

135 stigmatized and discouraged research participation. In many cases, lack of instructions or
136 guidance for including graded exercise therapy often causes additional suffering, creating fear of
137 harm from a comprehensive self-management program that may include some physical activity
138 (e.g., mild stretching).

113 Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy
114 [GET]) demonstrate measurable improvement, but this has not translated to improvements in

115 quality of life (QOL). Thus, they are not a primary treatment strategy and should be used as a 116 component of multimodal therapy.

This is seriously misleading: it gives the untrue impression that the CBT/GET studies assessed were studies on ME/CFS patients, and it conflicts with the acknowledgement in lines 38-39 that the criteria are flawed and include people with other conditions. Again, please do consider and acknowledge the crucial fact that no severely affected patients took part in any of these trial.

It is of crucial importance to clarify the statements made on lines 113-114, to make it absolutely clear that CBT and GET studies on ME/CFS patients do not demonstrate any kind of measurable improvement or objectively measurable changes in physical disability.

I notice that the Draft Review seem to use CBT as a catch-all term, not considering the significant differences between the various approches, such as for example using CBT for counseling and developing coping skills, versus CBT as a tool used to ”correct false illness beliefs”, etc. I find this problematic, seeing that these approaches are clearly not synonymous.

ME/CFS advocate Sten Helmfrid’s (PhD, Associate Professor of Physics) comments below – with my own additional comments shown between *...* - shows clearly that in fact no CBT/GET studies have demonstrated improvements in objective outcomes. I quote:

“I am concerned about the claim on rows 113–114 in the draft statement that studies on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) demonstrate measurable improvement for patients with ME/CFS. There are two underlying biopsychosocial assumptions in these studies: firstly, that the illness is perpetuated by behavioral factors and deconditioning; and secondly, that behavioral intervention in combination with exercise can reverse the condition. There have been several studies of this kind during the last twenty years. Although some of them show small improvements, the only outcome measures that actually have improved are subjective. It is well known that there is a placebo response in subjective measures. This response is likely to cause large bias in studies on cognitive behavioral therapy and graded exercise therapy, as it is part of the protocol to convince patients that the treatment works.

To my knowledge, there are only two studies that have analyzed objective outcome measures. A Dutch group made a post-hoc analysis of actometer data from three of their own CBT studies and concluded that although the fatigue score was reduced in the subjective self reports, there was no objective improvement in the activity levels of the patients [13]. In another study, the same group showed that patients who reported reduced cognitive impairment after CBT did not improve their performance in neuropsychological tests [14].

In the British PACE study, patients made a six-minute walk test before, during and after intervention [15]. Such tests are regularly used to evaluate patients with heart or lung conditions. A healthy person covers about 600 m *(Healthy adults aged 55-75yrs - 659m [26], Healthy elderly adults 50-85 yrs - 631m [27])*, whereas 400 m corresponds to severe disability *(Patients with class III heart failure - 402m) [28]* and is suggested as a limit for lung patients when transplantation is justified.

For the six-minute walk test, CBT failed to improve outcomes when compared to the usual care (specialist medical care) control group. GET did a little better than the usual care control group, but failed to achieve a clinically useful outcome. All four groups in the study showed small improvements, but the GET group improved slightly more than the others, from 312 to 379 m *or from 344 to 379m when adjusted for the improvements seen in the usual care control group.* This is, however, a poor measure of objective improvement. In contrast to cardiopulmonary exercise

tests (CPET), there is no way to control what efforts the patient is making during the test. The performance of ME/CFS patients is affected by post-exertional malaise, and there was no follow-up on how the patients were doing the day after the test. Moreover, as actometers were not used, there is no way to determine how the general functionality of the patients was affected by the treatment.

It should also be emphasized that there is no theoretical foundation for the treatment strategies used in CBT and GET. The cognitive behavioral therapy in the PACE study, for example, was administered on the basis of the fear avoidance theory [15]. There are no supporting references cited in the paper, and the theory strikes a discordant note with our knowledge of ME/CFS. Many patients report crash periods caused by overexertion, which is inconsistent with fear of exercise. Moreover, it was shown in a prospective study that increased level of activity is a predictor for developing ME/CFS [16]. Participants who later developed ME/CFS continued to exercise more frequently even after they started to experience fatigue.

The statement on rows 113–114 in the draft completely ignores the evidence for adverse reactions due to graded exercise therapy. Patient associations in several countries have used surveys to compare the outcome of different therapies. There are now data from ten independent surveys in four different countries with more than 13700 participants. About 4600 patients had tried GET, and 52 % reported that they felt worse [17,18]. The largest survey was carried out by the ME Association in the UK [19]. More than 56 % of the participants said that they felt worse, and 33 % reported that they felt much worse. (The number of false negative reports in these surveys is expected to be low. For example, only 3 % of patients treated with homeopathy—which most scientists regard to be completely ineffectual—felt much worse [19].) This large body of evidence for the adverse effects of graded exercise therapy cannot be ignored.

There is also a growing amount of biomedical evidence for physical deterioration after exercise. Several independent groups have shown that ME/CFS patient are unable to reproduce physical measures in cardiopulmonary exercise tests, which are repeated after 24 h [20,21]. Studies have also demonstrated changes in the gene expression and increased pro-inflammatory cytokine levels after exercise [22,23].

There have been few reports of adverse reactions in the published studies on cognitive behavioral therapy and graded exercise therapy. It should be pointed out, however, that the dropout rate in many of these studies has been high, up to 42 % [24]. Patients may leave the program because they deteriorate, and adverse reactions are therefore likely to be underreported. Moreover, there rarely are any objective measures of adherence.

In the PACE study, there were comparatively few dropouts (8 %). The number of serious adverse events in the GET group was about the same as in other groups. The authors conclude that graded exercise therapy is safe if administered as described. However, no objective measure of adherence such as actometers was used. After following the program for one year, the patients in the GET group on average managed to cover 379 m in the six-minute walk test. The goal of the study was complete recovery, and although the authors were confident that the acceptance and adherence to manuals were high, the poor test performance and the lack of objective measures raise serious doubts about the adherence to the exercise protocol. The conclusion that graded exercise therapy is safe if administered as described therefore is dubious.

In conclusion, there is no objective evidence for the efficacy of cognitive behavioral therapy and graded exercise therapy based on a biopsychosocial model as a treatment for ME/CFS. The only available objective data suggest that the self-reported improvement in some of the studies is due to the placebo effect. Moreover, there is no theoretical support for the underlying hypothesis that behavioral factors and deconditioning perpetuate the condition. I suggest that this is clearly pointed

out in the final report. This does not mean that all forms of cognitive behavioral therapy and exercise should be dismissed. CBT may help some patients to deal with a chronic debilitating disease, and many patients use pacing strategies to maintain the activity level that the disease permits.

There are numerous reports of adverse reactions after graded exercise therapy. Although controlled studies report fewer and less severe reactions than surveys from patient associations, high dropout rates and lack of objective measures of adherence in these studies make all claims of safe treatments unconvincing. As long as there is no credible explanation why adverse reactions are so common and no way to separate patients that are at risk from other patients, the use of graded exercise therapy should be discouraged and the risk for deterioration should be acknowledged.

The need for objective measures in future studies should be emphasized. Double blinding should be used whenever possible, and when this is not possible—for example in psychological interventions —actometers or other objective measures of functionality must be employed instead."

Many papers have been written about the significant methodological and scientific issues with the 2011 PACE trial, the refusal to release results for the outcome measures laid out in the trial's protocol, their unfounded and spun claims about 'recovery' (described as being "contradictory" in the evidence review), and failure to account for potential problems with response bias in the subjective self-report measures used as primary outcomes. I urge you yet again, to remove it from the evidence base, and along with it any conclusions and recommendations that have been unjustly made based on its highly problematic content. Many eloquent and well-researched critical comments have already been submitted by others, and they have my full support.

Seeing that the Draft Report recommends that the Oxford criteria be retired, all studies based on the same or equivalent critera should be dropped and excluded from the evidence base too. And, according to repeated statements in the Evidence Report, CBT/GET treatment findings can't be generalized to ME patients (pages ES-7, 26, 54, 57). What evidence is then left to draw these harmful recommendations on?

The Evidence Review ignored substantial evidence of harms associated with GET, thereby failing to recognize the evidence of well-known correlations between abnormal physiological responses to exercise (as evidenced by significant, distinct responses to exercise in gene expression and cardiopulmonary measures), PEM/PENE, and harms following GET. This underplays the serious risk of harm for ME patients who are prescribed exercise, and creates a high risk that the Evidence Review and this Report will be used to perpetuate or worse, exacerbate, the harmful prescription of exercise to ME patients who are physically incapable of exercising without incurring harm. Patients who have an organic disease characterized by neurological, immunological and metabolic impairments would not have a meaningful therapeutic response to CBT (based on hypothetical "false illness beliefs") and would be at higher risk for harm.

Contrary to the findings presented in the Draft Report, the very robust and consistent patient evidence shows that CBT is ineffective for the vast majority of people with ME/CFS, and that around 50% of people consistently report that GET makes their condition worse [17, 29, 30]. Also very important to note is that over 90% report that pacing is the most effective and safe form of activity management.

As a ME/CFS patient, I'm one of the many people who have been severely and permanently harmed by CBT/GET within a multimodal context. I was never informed about the risks posed by exercise and overexertion(!), and the concerns I expressed when I kept getting worse was repeatedly dismissed(!), my questions brushed away. I was told that pacing was harmful(!), and repeatedly told

not to trust my own experience which was insisting on the opposite. At that point in time I was willing to do anything, in the passionate hopes of getting better, but knowing what I know today I wouldn't recommend these kind of "treatments" even to my worst enemy, if I had one. I experienced continued severe deterioration and went from moderately affected (being able to drive a car to the store once every couple of weeks to buy a few groceries, visit a friend for a few minutes for a cup of tea, and independently taking care of myself and my home, despite not being well enough to hold down a job), to very severely affected (bed/sofa-bound 24/7 and completely unable to leave the house not even for medical appointments, unable to take a shower, cook food, take out the trash, clean up, see a friend etc). This was 8 years ago, and I still haven't recovered the functional ability I lost back then, as a direct result of being subjected to GET. I never even got so much as an apology, and the "therapists" still get to keep doing the same thing to other ME/CFS patients. How many more people will get their lives completely destroyed before further abuse like this is ended?

I urge you to clearly acknowledge that unjustified claims about CBT/GET leading to recovery from ME/CFS have been made – and are still being made – to patients, that this is unethical, and has done a lot of real, lasting harm. Patients need to be able to trust their doctors, to know that they will not be harmfully manipulated – unknowingly and against their will – by doctors and therapists who wrongly believe that patient cognitions play a key role in perpetuating their disability. The problems that have occurred here need to be fully recognised.

Many patients can attest to having been manipulated into taking anti-depressants and/or doing GET, despite a lack of evidence for efficacy, and despite evidence for them often being harmful for patients suffering from ME/CFS. Many patients have been harmed for life, myself included. This unethical behaviour should be recognised and put an end to.

This therapy is not a treatment, and adverse side effects include relapse, exacerbation of the disease, and increased disability. I urge you to clearly state the fact that CBT/GET should never ever under any circumstances be considered or used as a recovery treatment for ME/CFS.

67 Patients are frequently treated with psychiatric
68 and other inappropriate drugs that may cause harm.

Yes, I agree. It can't be stressed strongly enough that treatment by antidepressants and other psychotropic intervention can cause severe harm to patients. However, it is not just pharmacological psycho-therapy that is problematic and often inappropriately prescribed, but also non-pharmacological psycho-therapies as well.

MULTIMODAL THERAPIES

(Lines 92-93) Although psychological repercussions (e.g., depression) often follow ME/CFS, this is not a psychological disease in etiology.

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

(Lines 282-284) Studies addressing biopsychosocial parameters (including the mind-body connection), function, and QOL should be encouraged.

(Lines 359-360) Studies examining the role of self-management techniques

(Lines 362-364) The modest benefit from CBT should be studied as adjunct to other modalities of treatment such as self-management. Future treatment studies should evaluate multimodal therapies. (Lines 384-385) We believe there is a specific role for multimodal therapy.

(Lines 296-298) Although ME/CFS is not a psychiatric disease, exploring psychiatric comorbidities such as depression, anxiety, and fear is critical to improve quality of life.

The Draft Report (lines 92-93) acknowledges that ME/CFS does not have a psychological etiology. However, the Draft Report recommends 'multimodal therapies' with CBT as a component (lines 113-116, 362-364, and 384-385), and that studies addressing biopsychosocial parameters and function, the mind-body connection, biopsychosocial function, and QOL should be encouraged (lines 282-284).

I do not agree with these recommendations, and I protest this dangerously unscientific approach in the strongest way possible. I urge you to completely remove these recommendations from the Report.

The basic and acute need for biomedical treatments for the ME/CFS patients has not been met, and this urgently has got to change before any kind of rehab is even suggested, before precious and scarce resources are allocated to educate other professions and create multidisciplinary teams.

Self-management and multimodal therapies for ME/CFS research and/or care is absolutely the wrong direction to move in! What ME/CFS trials are these recomendations based on, if any? Would you recommend to cancer patients "self management" as a way to improve their health too? This approach has already been going on for quite a while in many places, since there's no other option for most patients, and it's not curing anyone, nor significantly improving patients' quality of life. On the contrary, there is much ongoing harm being done, much harmful and unhelpful "therapies" being wrongly pushed, mainly GET but also CBT because of how it is being misused. Social workers, therapists or homeopathy practicioners have such a small role in this context that they shouldn't even be mentioned here, and to assume that these multidisciplinarians have even an ounce of the skills and specific ME/CFS knowledge required would be to take a completely unreasonable leap of faith. Recommendations for treatment teams has to focus on the role of specialist physicians.

The multimodal model mentioned in the Draft Report has been applied to ME/CFS in a few places in Scandinavia, among others Stockholm, Sweden. Now, around 5 years later, the project has been evaluated and it has been concluded that this model did not at all meet the needs of the ME patients. Many patients actually experienced deteriorated health. In Stockholm there is now agreement between the multi-team project management and other caregivers, patients and politicians, that the multimodal model did not serve the ME patients well. Instead, what is needed is biomedical specialist care.

Research shows that patients with ME/CFS have no more psychological troubles than patients suffering from other chronic diseases. It makes no sense to push psychological interventions on people who don't need them. Let the possible support from nurses, case managers, social workers and psychologist be something that is optional and only offered on an individual basis as needed, not pushed on ME/CFS patients as a group. To suggest that ME/CFS patients as a group need these kind of "therapies" is very unhelpful and will only help perpetuate old harmful misconceptions of this disease.

What patients actually need, when struggling to cope, is financial, practical and social support.

While the panel stated that neither CBT nor GET should be considered a primary treatment it might reflect that given the historical bias in this disorder, recommending multimodal clinical trials could be interpreted as recommending a biopsychosocial approach to treatment – an approach that is largely based on disease theories that have repeatedly been scientifically proven to be false, that has failed over and over again, and keeps causing much unneccesary and unacceptable harm to patients. Enormous damage has been done to patients by treating their organic disease as though it is due to false illness beliefs and an irrational fear of exercise. CBT has unsucessfully been used to deliver 'treatment' designed to rid patients of these supposed beliefs and irrational fears. This inexcusable abuse has got to stop immediately and the approach as a whole must be firmly rejected.

While the Draft Report states that this illness is not psychiatric, its recommendations on treatments seem to have an unjust and highly disproportionate focus on psychosocial, CBT, GET and multimodal approaches; all of which, particularly in this disease, are based on unproven psychosocial disease theories. (If you recall, at the end of Chris Snell's presentation during the Workshop, he put on the screen two quotes from the manual used in PACE, which clearly shows that their approach to CBT depends on persuading the patients that they do not have a serious disease(!).) After decades of prolific research dedicated to this particular hypothesis, there is still no evidence whatsoever to support it. On the contrary. It's high time to move on and to disown the "biopsychosocial model".

The overriding need is for biomedical research into the disease. This wish to do ME/CFS-specific psychological research is a harmful hangover from the false illness belief model and should be firmly rejected. Psychological therapies should not be recommended as a standard part of treatment.

The focus here has got to be on the acute need for biomedical specialist care by medical treatment specialists as the key role in ME/CFS care. Such as, for example, a multidisciplinary care team of biomedical specialists consisting of ME/CFS knowledgeable and properly trained physicians including neurologists, cardiologists, immunologists, infectious disease specialists, endocrinologists, rheumatologists, and specialists in orthostatic intolerance etc.

Multimodal therapy is already a past failure that should not be repeated. Patients urgently need biomedical research and properly trained biomedical treatment specialists. Nothing less will ever suffice.

BIOMEDICAL RESEARCH

I believe that much more effort should have been made in the Evidence Review and Draft Report to make use of, and reference, the developing biomedical research in this field. Failing to do so gives a very unbalanced and incomplete view of ME/CFS; I feel this is hugely problematic, and words are not enough to express my immense disappointment. While problems with limited funding often mean that studies are often not of the size we would all like to see in the future, there have still been many successful pilot studies indicating changes in the immune, endocrine and nervous systems of ME/CFS patients. The failure of the bodies such as the NIH in following up with larger studies means that hugely important evidence regarding promising biomarkers and treatment research has been excluded from consideration.

What is really needed is NIH financing to expand or replicate the promising biomedical studies already made by the experts, so that those can result in diagnostic markers, tests and treatments. There are already a lot of really good biological research to build on, promising work that has already been started. These most expert biomedical researchers deserve to be adequately funded in

order to expand their work and clinical care — to use and build upon the intelligent expertise already present.

The P2P approach stands in stark contrast to the science presented at the 2011 State of the Knowledge [4] meeting. That workshop dove deep into infectious disease, systems biology, immunology, neurology, exercise physiology, diagnosis and biomarkers, and treatments. While there was no panel to produce a set of recommendations, the meeting participants identified a number of opportunities for advancing ME/CFS research, including: define and standardize case definition and terminology; conduct more cross-system research; develop standard procedures and common data elements across the field; address gaps in study design, biomarkers and clinical trials, outcome measures, and reproducibility; create a centralized data repository; and attract new investigators. All of these issues remain unaddressed and unsolved three years later.

Of course, we need not look back three years for examinations of ME/CFS science and priorities. For example, the May 2014 Invest in ME conference [5] focused on autoimmunity, infection, immunological biomarkers, brain imaging, the autonomic nervous system, markers for post-exertional malaise, and diagnostic and treatment strategies. Then there was the March 2014 Stanford ME/CFS Symposium [6], which examined epidemiology, cytokine and gene expression patterns, cardiovascular aging, MRI and EEG findings, inflammatory/autoimmune profiles, and microbial investigations [7].

Finally, there was the March 2014 IACFS/ME Meeting: Translating Science into Clinical Care [8]. This four day meeting was even more comprehensive than the 2011 State of the Knowledge workshop, covering immunology, exercise and metabolism, treatments, orthostatic intolerance, pediatric issues, autoimmunity, biomarker and pathogenesis findings, case definition issues, brain function and imaging, and much more. There is a detailed summary [9] available, as well as Dr. Komaroff's conference summary talk [10].

There is also an excellent document from the Invest in ME meetings in May 2014 [11]. It contains a summary from the researchers' colloquium written by Prof Jonathan Edwards plus the abstracts from the IiMEC9 conference. On page 2 the priorities identified by the researchers at the colloquium are listed:

"The dominant impression from the meeting was a consensus that although much research into ME/CFS remains exploratory there are strong leads pointing in specific directions that deserve focus of further study. The following points were highlighted as of particular relevance to future strategy.

1. A pressing need to identify clinical and biological subgroups in ME/CFS.
2. The value of further exploration of the possibility that a subgroup of ME/CFS is autoimmune, drawing on progress in other neurological and inflammatory disorders.
3. Clarification of the effector mechanisms of fatigue including central nervous, vasoactive and metabolic pathways and mediators such as cytokine or antibody.
4. Continued debate on the role of micro-organisms, with a focus on modulation of the immune response by viruses and microbiota in particular.
5. The potential importance of mitochondrial dysfunction in linking pathogenesis to symptoms.
6. A need for better communication within the research community to make optimum use of data resources.
7. The potential value of genome analysis to identify genetic risk factors for ME/CFS"

Another initiative which produced a thorough discussion of the ME/CFS research field was the OMI-MERIT meeting in 2012 [12], where a group of high-profile, international researchers and

clinicians identified the top-ten priorities within ME/CFS research:

There is a lot to build on for NIH, if they wanted to approach this in a constructive way – starting with their own 2011 workshop.

REFERENCES TO PATIENTS' 'FEAR'

References to patients' supposed 'fear' must be removed from the Report.

A small but very vocal group of psychiatrists have pushed the idea that ME/CFS is a form of deconditioning maintained and exacerbated by the patients' supposed false illness beliefs such as an irrational fear of exercise. There is no evidence whatsoever to support this 'kinesophobia' theory. There is, however, substantial research and studies documenting the actual harm and risk inherent in "treatments" such as CBT and, in particular, GET [17, 29, 30]. To suggest that patients hold such irrational fears and that they require exploring is greatly misleading and unhelpful, has no basis in evidence, and will only help perpetuate old harmful misconceptions of this disease.

The Draft Report acknowledges that labelling patients with ME/CFS as deconditioned has hampered scientific progress, that there is reproducible evidence of organic pathology and that ME/CFS is not a psychological disease. (Lines 65-66, 82-86, 92-93)

The statements about patients' 'fear' should therefore be removed from the Report. (lines 134-138 and 297-298)

DEPRESSION

It's very unhelpful to suggest that there is a significant overlap with major depressive disorder (line 33), as it is not supported by the evidence. Depression is given way too much weight and significance (line 33, 92-94, 297-298). Several studies have shown that ME/CFS patients in general are no more depressed than other chronically ill people are, on the contrary.

Dr. Natelson's presentation on subtyping during the Workshop showed distinct objective markers between ME/CFS, major depressive disorder and fibromyalgia, indicating that there aren't substantial overlaps with either condition. Dr. Klimas's research shows that depression does not often follow ME/CFS. Psychometric testing shows that patients with ME/CFS score much better on role emotional that patients with depression. There is, to date, no valid psychometric instrument that has shown that depression, major depressive disorder, or any other psychiatric conditions frequently occur either with or after ME/CFS.

Also, many of the studies that show high rates of depression in ME/CFS patients use inappropriate questionnaires which take physical and cognitive symptoms as an indication of depression, not taking into account that the outward expression of some symptoms of the two very different conditions might appear similar to the untrained eye.

I believe it's also very important in this context to consider the difference between major depression, and situational/secondary depression (in relation to a chronic and severely disabling illness).

THE EVIDENCE REVIEW

27 We critically reviewed the scientific literature and opinions presented by a group of experts and 28 the ME/CFS community

This part needs to be clarified to reflect the truth, to highlight that it was only a extremely small and subjectively selected part of the total body of scientfic literature and experts, and that a lot (most?) of what was included was not even about the neurological/immunological illness Myalgic Encephalomyelitis (ME) but general 'fatigue'. The limitations of the Evidence Review need to be declared in the Report, for clarity.

The only published case definition using the term "ME/CFS" is the 2003 Canadian Consensus Criteria (CCC) document [Carruthers, 2003]. However, both the Evidence Report and the Draft Report use the term "ME/CFS" differently and in a broader sense than the CCC, with a completely different meaning. The Draft Report fails to define what they mean by "ME/CFS", and how/if their definition is different from 'fatigue'. This is highly confusing and misleading, and needs to be clarified.

Obviously, there is great danger in lumping things together indiscriminately. Please allow me to use a metaphor to illustrate how the P2P process appears from my perspective. Say you have a generous fruit platter in front of you, filled with a wide variety of fresh fruit and berries. You are given the assignment to, within a few minutes, describe the properties of that fruit platter as a whole, in as much detail as possible. You are not allowed to touch or taste the fruit. Would you say that your description will be scientifically comprehensive and valid? Will it fairly and in a scientifically relevant way describe the essential properties of, for example, a single orange? Would you say that you know that orange as intimately as someone who has tasted it? How would you be able to describe its texture, its sweetness? And if you were to instruct another peson about how to best treat or approach this fruit platter as a whole, for example how to peel a fruit, would your description of how to peel be equally applicable to the orange and the banana as well as the grape and the melon?

To my mind, a good start would be to recognize ME as the distinct neurological/immunological disease that it is and removing ME from the broader inappropriate CFS category, as called for by the ICC.

Basing a process like this on a fundamentally flawed Evidence Review will never result in any scientifically valid outcome. This concerns me deeply. (Line 27)

I was deeply disappointed and hugely concerned to discover that the vast majority of flaws in the Evidence Draft Report were not corrected in its final version. I will restate and reaffirm my main points from the comments I submitted, here:

* The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, calls into question the entire Review and all conclusions made about diagnostic methods, the nature of this disease and its subgroups, the benefits and harms of treatment, and the future directions for research.

* Accepting eight disparate ME or CFS definitions as equivalent in spite of dramatic differences in inclusion and exclusion criteria - even contradictory/mutually exclusive in some aspects - , the Review draws conclusions on subgroups, diagnostics, treatments and harms for all CFS and ME patients based on studies done in any of these eight definitions. In doing so, the Evidence Review disregards its own concerns, as well as the substantial body of evidence that these definitions do not all represent the same disease and that the ME definitions are associated with distinguishing

biological pathologies. It is unscientific, illogical and risky to lump disparate patients together without regard to substantive differences in their underlying conditions.

* Compounding this flawed assumption are the a priori choices in the Review Protocol that ignored critical questions and instead focused on a narrowly defined set of questions and applied restrictive inclusion and exclusion criteria. As a result, evidence that would have refuted these flawed starting assumptions or that was required to accurately answer the questions was never considered.

* Flawed search methods. Inclusion/exclusion choices shaped what evidence was considered and what conclusions were drawn. All of the most promising biomarker and treatment research was ignored, along with a huge amount of other highly relevant and essential biomedical studies, including critical evidence on diagnostic methods and subgroups.

* Treatment outcomes associated with all symptoms except fatigue were disregarded, resulting in a biased view of treatment effectiveness and harm. Examining data on objective measures of physical function like activity would have not only broadened the evidence base, but would have introduced data that call into question the assessment of CBT/GET benefits.

* Severe well-known quality issues with individual studies were either not considered or ignored. The PACE trial in particular; the Review failed to examine any of the well-documented methodological issues and deficiencies in this study.

* Regarding treatments, the Review explicitly decided to focus on changes in only one(!) symptom, fatigue, and almost exclusively self-reported subjective measures over objective measures of functional capacity and activity levels, thereby choosing to ignore the critical component PEM (correctly noted by the Review to be a hallmark characteristic of the disease), as well as all other well documented and studied symptoms such as pain or neurological, endocrine, cardiovascular, immunological, cognitive and muscular abnormalities; most of them objectively measurable/verifiable. There is still no reliable way of measuring, or even defining, 'fatigue'. Inexplicably reducing a neurological/immunological illness such as ME to just one single diffuse symptom that can also be found in a myriad of other illnesses, and that can't even be measured objectively, is unacceptable.

* The Review never questioned whether the disease theories underlying these treatments were applicable across all definitions. Yet again the failure to be clear and specific about what disease was being studied muddles the findings. It simply isn't reasonable comparing treatments like Rituximab/Rituxan or Ampligen (targeting a very specific objectively measurable biological issue) with talk and/or exercise therapies (thought to reverse what is assumed to be the patient's "false illness beliefs") by pretending that both types are about aimed at the one and same disease.

* The issue of harms associated with CBT and Graded Exercise Therapy/GET has not been adressed adequately. Again a problem likely caused by the failure to be clear and specific about what disease was being studied. The Review ignored substantial evidence of harms associated with GET, thereby failing to recognize the evidence of well-known correlations between abnormal physiological responses to exercise (as evidenced by significant, distinct responses to exercise in gene expression and cardiopulmonary measures), Post Exertional Malaise/PEM, and harms following GET. This underplays the serious risk of harm for ME patients who are prescribed exercise, and creates a high risk that the Review will be used to perpetuate the harmful prescription of exercise to ME patients who are physically incapable of exercising without incurring harm. Patients who have an organic disease characterized by neurological, immunological and metabolic impairments would not have a meaningful therapeutic response to CBT (based on hypothetical "false illness beliefs") and would be at higher risk for harm.

* The Review excluded all studies examining biomarkers or physiological tests “because the intent of these was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment.” This choice means that hundreds if not thousands of studies were not considered at all, which had the indisputable effect of narrowing the evidence base monumentally

* The Review failed to acknowledge that poor study quality is largely a result of the low levels of research funding available. It must be acknowledged as a factor affecting the evidence base. The ME evidence base cannot be properly assessed without understanding this critical limitation.

* The Review correctly noted, “treatment of ME/CFS often involves multiple concurrent therapies” but also claimed that the Review’s “interventions and comparators represented most of the therapeutic modalities commonly used in clinical practice.” This is not true. Treatments used for ME patients include a number of medications and therapies excluded from the review including immune modulators, beta blockers, antihypotensives, antidepressants, antivirals, antibiotics, antifungals, stimulants, pain medications, sleep medications, IV saline, and manual physical therapy. The protocol used for the Review excluded almost all of this research. The Evidence Review must explicitly acknowledge this weakness in the applicability of its findings.

FUNDING, COST

The Draft Report completely fails to address the total lack of funding by the NIH for any research on the neurological/immunological disease ME with subjects selected using specific ME criteria such as CCC or ICC (as opposed to general, so called unexplained, fatigue).

Biomedical research into ME/CFS is grossly underfunded and not anywhere near proportionate to the vast number of people affected along with the high level of disability and ill health that this disease causes. A direct correlation exists between the near non-existent funding provided by the NIH over the last two decades and the lack of progress made in treatments and causes of ME/CFS. The fact that NIH has historically denied proper funding for good scientific research that is based on the biology of the disease is inexcusable. Funding can no longer be largely left to the charity sector.

The Draft Report fails to address the acute need for a hugely substantial and immediate raise in funding from NIH for biomedical ME/CFS research, in particular biomedical research using specific ME criteria (using CCC and/or ICC as a starting point). The new funding levels then need to be sustained long term at a level commensurate with the burden of the disease. Further, NIH has to make targeted efforts, such as issue specific RFAs for ME/CFS.

The economic burden in America must be well in excess of £1(!) billion. Several studies of the overall economic burden of ME/CFS indicate a minimum figure at least one order of magnitude greater. (lines 6-7).

OBJECTIVELY MEASURABLE IMPROVEMENTS

The Draft Report fails to mention that one of the main problems regarding the ME/CFS treatment research is the lack of objective measures of changes in physical disability.

The Report needs to ensure that all future clinical research is obligated to include such objective measures, for example long-term actometer data, and data on how many of the participants were

able to return to full time studies or work, changes regarding private insurance claims and welfare claims etc, all with long-term follow-ups as well.

128 […] and do not
129 provide information on why there were high dropout rates.

153 […] fail to adequately
154 address harms or who dropped out and why; and include only a short follow-up.

I agree, this is very very important and can't be stressed enough.

THE OXFORD DEFINITION AND OTHER FATIGUE-BASED CRITERIA

I strongly support the Panel's recommendation that the Oxford definition be retired immediately. It is very good to see that the Draft Report recognizes the damage that it has done to research. (lines 378-380) I'd like to stress that the problems with Oxford also apply to a certain extent to Fukuda and, therefore, Fukuda and its equivalents should be retired too.

In order to capture the right patient population for this Report, it would seem obvious that all Oxford-based research used as reference immediately be dropped and excluded too. 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. To keep these studies would not be logical, scientifically valid or medically ethical. This includes the 2011 PACE trial as well as any other research evidence that is based on Oxford-equivalent general 'chronic fatigue' (no other symptoms required) recruitment criteria. Any treatment recommendations based on these findings should be excluded and dropped immediately.

I would like to see the CDC stop all studies based on Oxford and Oxford-equivalent general 'chronic fatigue' (no other syptoms required) criteria from being used as references in their ME/CFS continuing medical education course.

This yet again stresses the need for a specific definition like the CCC or the ICC that describes ME with its hallmark PEM/PENE, immune abnormalities and cognitive dysfunction; clearly separating ME from general fatigue and psychological/psychiatric-based illnesses. One can not recommend treatments or research objectives for one group of patients based on studies in another group of patients.

COMORBID CONDITIONS

100 studies should distinguish between ME/CFS alone, ME/CFS with comorbidities, and other

116 component of multimodal therapy. Overall, agreeing on a case definition and clarifying
117 comorbidities could launch bench-to-bedside science.

147 symptoms are often "lumped" into ME/CFS. Carefully defining comorbid conditions is
148 necessary to define ME/CFS subgroups and to move the field forward. There is also a lack of

198 that there are many unresolved issues, including overlapping comorbid conditions. Findings in

288 comprehend variability (e.g., onset, time course, comorbid conditions), and to identify

296 encouraged. Although ME/CFS is not a psychiatric disease, exploring
297 psychiatric comorbidities such as depression, anxiety, and fear is critical to
298 improve quality of life. Response burden must be considered; a battery of

345 treatment studies, and the role of comorbidities in clinical and real-life

The P2P process claims to invite innovative research by looking at overlapping and co-morbid conditions. Sadly, and for some unexplicable reason, a disproportional weight was given to pain disorders, functional somatic syndromes and suchlike during the Workshop. Why did the Workshop not look at the comorbidities of for example orthostatic intolerance, Lyme disease, reactivated viral infections, cancers, or Ehlers-Danlos syndrome? Seeing how many people get ME after vaccinations (especially Hepatitis A and B), the various ASIA syndromes should be of great interest too, one would think.

In the same vein, the Draft Report fails to adequately acknowledge the many occurrences of cluster "outbreaks". This strongly argues for a cause that is either a communicable infectious disease or common exposure to an environmental factor, and would suggest there's a value in studying similar outbreaks of that which is labelled post-SARS, post-Q fever etc.

Dr. Natelson's presentation on subtyping during the Workshop showed distinct objective markers between ME/CFS, major depressive disorder and fibromyalgia, indicating that there aren't substantial overlaps with either condition. Dr. Klimas's research shows that depression does not often follow ME/CFS. Psychometric testing shows that patients with ME/CFS score much better on role emotional that patients with depression. There is, to date, no valid psychometric instrument that has shown that depression, major depressive disorder, or any other psychiatric conditions frequently occur either with or after ME/CFS.

AUTONOMIC DYSFUNCTIONS

The Draft Report fails to adequately recognize the importance of autonomic dysfunctions and in particular orthostatic intolerance. It can be argued that orthostatic intolerance should be considered a key symptom in ME/CFS.

SEVERELY AFFECTED PATIENTS

Although it is briefly mentioned, the Draft Report fails to adequately stress the acute need for biomedical research focus on the severely and most severely affected patient. (line 52, 104-105)

"Estimates suggest that up to 25% of people with CFS/ME are so seriously affected that they are unable to perform most basic personal tasks and are confined to bed or spend the majority of the day in bed. Such patients feel particularly alone and isolated. The severity, complexity, and longevity of the illness are poorly understood." [25]

CASE DEFINITION AND VALIDATED DIAGNOSTIC TOOLS

"A clear case definition with validated diagnostic tools is required before studies can be conducted." (lines 105-106)

I strongly disagree. Although a clear case defnition and validated disagnostic tools are needed, a lot

of great and highly valuable biomedical research has already been done with successful results. Much of it based on CCC and/or ICC. Developing validated diagnostic tools can happen simultaneously, and side-by-side with mutually beneficial synergetic effects, with much of the biomedical research that is already happening today.

LABORATORY DIAGNOSTIC TESTS

4 […] there are no laboratory diagnostic tests;

One could argue that this is too much of a simplification. The 2012 ME International Consensus Primer (IC Primer or ICP) [Carruthers. 2012], lists over 30 laboratory tests and imaging studies specifically useful in diagnosing ME, in addition to standard laboratory screening tests.

EDUCATION

79 Educational efforts are needed to help patients and their health care providers better understand
80 this disease and scientific processes. […]

87 Overall, limited patient and professional education has impaired progress in managing ME/CFS.

I respectfully suggest that the bulk of education needed is for both the professional medical (clinical and research) community, and the broader general community. The vast majority of patients are already strongly motivated to do everything they can to improve their life situation despite the illness, any way they can, and without being told by others to do so. Seeing that clinicians have such a poor understanding of this disease, patients have no other option than to go out and find this factual and experience-based knowledge for themselves, which they already are doing. The problem is inadequate biomedical research, and clinical and community support.

GENDER BIAS?

The reference to the gender imbalance in research is ambiguous and need rephrasing. Is it trying to say that men have not been studied enough? If so, I agree. One would think it would be a good idea to move research out of the Office of Research on Womens Health since an estimated 25-30% who have ME/CFS are men. As it stand now, there is a discriminatory component to the research. This bias isn't helpful from a scientific perspective either. (Line 52)

PRIORITIES

I notice that the Draft Report doesn't prioritize among its recommendations. This could be seen as a problem.

281 Studies investigating homeopathy, non-pharmacologic, complementary, and
282 alternative medicine treatments are needed.

This, for example. I personally welcome complementary and alternative medicine, but I feel that the main focus needs to be on biomedical research (lines 222-276). An overwhelming part of the funding has already been poured into overly broad fatigue-based studies and (bio)psychosocial

approches over the years, with no success. I urge you to stop wasting time and money, and focus on the most acute needs: biomedical research and properly trained biomedical treatment specialists. Nothing less will ever suffice.

HELPFUL CONCLUSIONS AND RECOMMENDATIONS

2 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-
3 faceted condition

6 ME/CFS is an unmet public health need with an [large!] *economic burden*

7 […] ME/CFS results in major disability for a large proportion of the people affected. Limited
8 knowledge and research funding creates an additional burden for patients and health care
9 providers.

10 Unfortunately, ME/CFS is an area where the research and medical community has frustrated its
11 constituents, by failing to assess and treat the disease and by allowing patients to be stigmatized.

38 […] The Oxford criteria (published in the Journal of the Royal
39 Society of Medicine in February 1991) are flawed and include people with other conditions,
40 confounding the ability to interpret the science. The lack of a consistent, specific, sensitive
41 diagnostic test and set of criteria has hampered all downstream research on pathogenesis and
42 treatment, causing harm and preventing ME/CFS from being considered as a distinct pathologic
43 entity.

45 […] Patients are typically underserved, and clinicians have a poor understanding of
46 ME/CFS. We heard throughout the workshop that ME/CFS can affect anyone.

I agree with all of this.

58 Fatigue has been the defining focus of recent research, but many other symptoms need to be
59 explored, primarily neurocognitive deficit ("brain fog"), post-exertion malaise, and pain

I agree with this, and would also like to add immune abnormalities and orthostatic intolerance.

60 […] We noted few
61 disease-specific clinical trials; a disconnect on ways in which patients, clinicians, and researchers
62 define meaningful outcomes; the lack of well-controlled, multifaceted studies using large,
63 diverse samples; and the limited research dollars directed at ME/CFS from both the public and
64 private sectors.

65 Often, patients with ME/CFS are labeled as lazy, deconditioned, and disability-seeking; this
66 hampers scientific progress. Both society and the medical profession often treat patients with
67 ME/CFS with disdain, suspicion, and disrespect. Patients are frequently treated with psychiatric
68 and other inappropriate drugs that may cause harm. Patients usually have to make extraordinary
69 efforts, at extreme personal costs, to find a physician who will correctly diagnose and treat
70 ME/CFS symptoms. In addition to high medication costs, the debilitating effects of ME/CFS can
71 result in financial instability due to the physical consequences of the illness (e.g., the loss of
72 employment, home, and other basic necessities).

I agree with all of this. Very important that it's acknowledged. However, would like to see "wrongly" or "unfairly" or "unjustly" added before the word "labeled" on line 65.

76 Over the last 20 years, minimal progress has been made to improve the state of the science for
77 patients with ME/CFS, and the public and provider community is frustrated. Patients want their
78 concerns to be heard, a meaningful recovery (not just incremental improvement), and a cure.
79 Educational efforts are needed to help patients and their health care providers better understand
80 this disease and scientific processes. The scientific community also has a responsibility to
81 address issues that are meaningful to patients.

82 There is reproducible evidence of neurocognitive dysfunction with abnormalities in functional
83 magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies. Strong
84 evidence indicates immunologic and inflammatory pathologies, neurotransmitter signaling
85 disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities in ME/CFS,
86 potentially important for defining and treating ME/CFS.

I agree, all of this is very important.

92 Although psychological repercussions (e.g., depression) often follow ME/CFS, this is not a
93 psychological disease in etiology.

I agree. However, please see my comments on depression further down.

96 [...] However, this symptom taken in isolation fails to capture the
97 essence of this complex condition. Prior studies may have inadequately excluded individuals
98 with the distinct diseases listed above, leading to delayed diagnosis, conflicting diagnoses,
99 contradictory treatments, suboptimal care, and inappropriate health care utilization.

Agreed.

104 Specifically, it is critical to include patients with limited access to clinical services (e.g., non-
105 ambulatory patients).

Agreed. This is extremely important.

122 […] They often experience financial instability due
123 to the physical consequences of the illness and the inability to continue employment. Negative
124 interactions with the health care system are frequent,

142 Many patients with ME/CFS are misdiagnosed and treated erroneously with potentially toxic
143 therapies that may cause harm

166 […] The symptoms patients consider clinically meaningful are not in
167 the scientific literature; this discordance must be rectified.

169 Research priorities should be shifted to include basic science and mechanistic work
170 that will contribute to the development of tools and measures such as biomarker

179 […] We have learned
180 some about the mechanisms of the disease, but nothing has improved the lives of the patients.

186 Innovative biomedical research is urgently needed

Yes, I absolutely agree. This can't be stressed enough!

222-276 Developing valid prognostic tests that can guide treatment strategies using…

I agree, biomedical research and finding biomarkers — this is hugely important.

303 Telemedicine or home visits for those unable to participate in clinical
304 trials/treatment in person…

Yes, I agree. There is acute need for this.

371 For example, patients do not want to be labeled as complainers and want their stories to be heard.

Yes, this is true.

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