

Comments to the P2P report on ME from Kati Debelic

Essentially I have found your report expedited and weak. I worry about how it could be interpreted by others including the NIH, scientists and physicians who are not currently specializing in ME.

I will review the line by line and comment as needed. I urge you to 'get it right' for the patients sake, who have been waiting for decades for recognition of their illness, for a government body to truly care for them, and for research funding to commensurate the disability of these folks. You need to be aware that there are thousands of the very severe patients out there who live totally shut in, unable to tolerate light or sound, needing to be fed, and requiring around the clock care. The spectrum of the illness varies greatly, but 25% is either housebound or bedbound.

1) First, while you are saying that Oxford definition needs to be retired (and I agree) in Line 2-3 you cannot seem to explain ME beyond fatigue. ME is not being tired. It is about the inability to produce energy to perform any activity of daily living. It's about documented cognitive dysfunction. It is about documented immune dysfunction and viral reactivation.

2) Line 6-7 mentions an economic burden of 'more than 1 billion dollars.' This was also mentioned in Dr Carmen Green's workshop introduction. This value is wrong. Jason et al. (2008) place a cost-to-society value of roughly between \$19b to \$24b.

"...the direct and indirect cost of ME/CFS to society was estimated to be \$18,677,912,000 for the community sample and \$23,972,300,000 for the tertiary sample"

Reference: The Economic impact of ME/CFS: Individual and societal costs.

Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S.

2008

Dyn Med. 7:6.

<http://www.dynamic-med.com/content/7/1/6>

3) Line 10-11, I really wish you could stay away from reporting that patients are frustrated, because your wording makes it sound like we are a whining community. The truth is that we are a community with enormous unmet health care needs, experiencing social, medical and governmental stigma. How about mentioning that NIH and other agencies have failed the patients for 30 years? in this case, the wording truly hurts the patients further.

4) Line 33-34 ME also overlaps with autonomic nervous system disorders like POTs and NMH, and immune abnormalities like inflammation markers (cytokines) Immune globulin deficiencies and natural killer cell dysfunctions. if you mentioned this instead of co-morbidities that are just as stigmatized like fibromyalgia, depression and chronic

pain, there would already be increased credibility that ME exists and that ME is a serious disease.

5) Line 34 mentions 'there is no agreement in the research community on what should be studied'. This is not true. The ME experts all agree there is immune abnormalities, and gene expression is a worthwhile avenue to explore. A few are experts in system biology, and Ian Lipkin has been refused a NIH grant to research the microbiome in 2014. Suffice to say that the blocks to ME research do not stem from the medical community disagreement, but stems from the lack of funding and the difficulty in getting grants approved. Moreover, NIH grants usually allocate 30% and greater of the total research funding to psychological and behavioral research. Fred Friedberg mentioned that his drop-out rate in his clinical research was nearing 50%, research aimed at behavioral changes. His grant totalled over 600,000\$ as I recall. This in my view should send a message to NIH that biomedical research needs to be the major focus for the next few years, including biomarker discovery, brain imaging, microbiome, system biology, gene expression and the like. Grants need to be awarded so adequate cohort are used so they can count when there is a review such as the P2P

6) Line 44-47 Thank you so much for summing it all. This is a very important paragraph.

7) Line 56-57 The lack of medical education regarding ME needs to be highlighted too. Physicians who are kind enough not to label patients with this disease knowing about the stigma, and others who have never been thought in school that ME is a very serious, life altering disease characterized by low natural killer cells, autonomic nervous system dysfunctions and brain structural abnormalities (recent paper from Stanford). Instead, many physicians believe that patients are faking an illness in order to get access to benefits.

8) Line 58-59. Symptom by symptom research will not get us far. i would say that researching fatigue has been the focus of the psychiatrists who have not been able to find an adequate measure, staying well away from measurable outcome such as 2 consecutive days CPET testing. With the advances of science and technology, it is remarkable that an entire disease has been prevented access to adequate research and treatments. Considering that most symptoms reported by patients with ME are shared by many other conditions such as lupus, MS and many other diseases, it becomes urgent to compare patients with Me and these conditions to see how they are similar and hpw they are different. i will comment further that many chronic conditions experience depression as a result of being diagnosed with these chronic conditions and ME is not any different.

9) Line 65-73 Please also note that our physician experts are also stigmatized and shunned from their community of physicians. Take Dr Dan Peterson for instance. He has cared for patients with ME for over 30 years now. He has blood and CSF samples from his original cohort in his freezer. This physicians deserves recognition and respect. Their clinical expertise is not recognized and these physicians have not been invited in providing any opinions. These are our heros. Several have lost tenure in prominent universities because their research was not popular and they were told to change their

practice.

10) Line 79-80 you said " Educational efforts are needed to help patients and their health care providers better understand this disease and scientific processes"

i am sorry, patients do not need to be educated. Most patients I know would have sufficient knowledge to give a 3 hour lecture to family physicians and oftentimes even specialists. i have read and re-read this sentence and it can be interpreted as patients need education. I agree that enormous education program needs to be put in place for physicians and med students. However with the current stigma happening at all level of society, it would be risky for the patients to have the education program promoting the wrong research, the kind which mentions that patients need cognitive behavioral therapy and graded exercise therapy. Patients need to be involved at all levels of education and research policies.

11) line 87 "Overall, limited patient and professional education has impaired progress in managing ME/CFS." Patients once more do not need to be educated. Patients are educating their health care professionals and directing their care through their own online research. Patients desperately need and deserve biomedical research, and treatments. I vehemently disagree with the allusion that patients need to be educated.

12) Line 88 "treatment remain unproven". NIH and other governments around the world can be blame for that for only with adequately funded research and clinical trials, only through well defined patient population, and only with statistically significant cohort can we find treatment modalities for ME, and by this I do not mean behavioral research, i mean biomedical treatments. Patients look for biomedical treatments because they know that what they have is not in their heads. We are thankful of the few Me experts who believe them.

13) Line 93-95 "A multitude of symptoms are associated with ME/CFS, with substantial overlap with other pathologic diseases (e.g., fibromyalgia, major depressive disorder, and a variety of chronic pain or inflammatory conditions)"
Overlap with common variable immune deficiency, Postural orthostatic tachycardia syndrome, EBV response deficiencies which are also found in HIV and HCV. Please stop insinuating that this disease overlaps with other stigmatized illnesses or psychiatric illnesses it is not helpful. We know that depression is very prevalent in chronic diseases at large. The prevalence of depression in Me is no more than with other life altering chronic diseases.

14) Line 110-111 "Clinical trials require large investments of time and energy, and may be associated with other harms (e.g., increased symptoms, medication toxicity)" there is a dire need of drug clinical trials in this field.

A) While Ampligen has been deemed safe this drug is still not approved for use for ME. Why?

B) drug clinical trials are widely used in other diseases (HIV, cancers, etc) and are the only way to go to move the field forward. Moreover, associated risk of harm is widely accepted in patients undergoing these experimental drugs, so why not ME? Why is there

the belief that patients with ME are not worth the investment?

15) line 113-115 "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" to be fair P2P panel recognized that Oxford criteria needed to be retired. Studies using the Oxford criteria should not be accepted as being valid and conclusions should not be drawn by the P2P panel. Patients around the world are saying CBT and GEt are unhelpful. we do not need further psychiatric studies, nor do we need further studies which disregard completely the current biomedical knowledge we have of the illness.

16) Line 115-116 "Thus, they are not a primary treatment strategy and should be used as a component of multimodal therapy" multimodal therapy? What do you exactly mean by multimodal therapy?

17) Line 120-124 " Limited time during the clinical encounter has impaired patient/clinician communication and quality of care for patients with ME/CFS. Patients experience stigma from the diagnosis of ME/CFS, including social isolation and judgment. They often experience financial instability due to the physical consequences of the illness and the inability to continue employment. Negative interactions with the health care system are frequent, and the emotional burden is heavy."

i could not agree more with this, however there needs to be the recognition that at least part if the problem is due to the fact that no medical specialty is embracing the diseases. This results in family practice sending the patients to a specialty for further testing, for opinion and for specialized care, and the specialist sending back the patient because ME is not their specialty.

18) Line 130-134" In general, little attention was given to how self-management may empower and improve health and QOL for patients with ME/CFS. Physicians are inadequately trained to instruct patients in self-management skills (e.g., pacing, realistic goals, physical self-awareness, basic rights, understanding emotions, exercise, relaxation), and there is a lack of data demonstrating the efficacy of self-management on health outcomes"

Patients do not need self-management skills. Patients have learned the skills themselves because there is usually no better option in their community. moreover, patients forums provide peer-to-peer advice in regards to lifestyle and disease management. What is most needed currently is a clear understanding of the pathology and physiology of the illness, understanding subsets, understanding the interactions between systems like immunology, hormones, neurology and mitochondria. Please, NIH, save yourself some money, and invest in science, not behavior models of the illness.

19) Line 134-138 "The focus on exercise programs has further stigmatized and discouraged research participation. In many cases, lack of instructions or

guidance for including graded exercise therapy often causes additional suffering, creating fear of harm from a comprehensive self-management program that may include some physical activity (e.g., mild stretching)"

The media propaganda has shared around the world that patients with ME have a fear of exercise. Of course this has been fueled by the british psychiatrists who have just published another paper on that regards. This is once more propaganda. many of us who are sick with ME were athletes and highly functioning, highly active people before being ripped from our lives with ME. Mild stretching as treatment recommendation is not going to be beneficial to patients lives just as much as mild stretching would not be recommended as first line of treatment for HIV-AIDs. Behavioral research needs to be de-emphacized and bio-medical research needs to be funded at the same if not more rate that MS is being funded.

Please stop emphacizing behavioral treatment in your report.

20) Line 142-143 "Many patients with ME/CFS are misdiagnosed and treated erroneously with potentially toxic therapies that may cause harm and diminish hope"

i am not sure I understand what you are meaning. When i was diagnosed, my dr told me that Me was treated with anti-depressants. This is absolutely wrong.

That said, being diagnosed with ME is in my eye worse than being diagnosed with cancer. (i was a chemo nurse before getting sick) because it means there are no treatments, that it is highly stigmatized in society and in medicine and that all of your symptoms are not important because it's just ME. i would like to add that physician experts who offer treatment options with anti-viral and immunomodulatory therapies provide hope to the patient.

21) Line 151 "Defining ME/CFS requires standard, validated tools and measures"
How about biomarkers, which would make diagnosis easier? How about further studies in functional MRI?

22) line 179 "ME/CFS is a chronic, complex condition of unknown cause and with no cure"

In my opinion, indeed there is no cure, as no one recovers from it. However science has not contributed in finding a cause and a cure. How can you say it is chronic if no one has found the cause? It is chronic because it is not treated. Maybe lifelyong years of grief, loss of employment and suffering can be prevented. We don't quite know what causes it. Maybe it's a pathogen. I really wish NIH was very curious about finding out what exactly is ME.

23) Line 200-201 "To accelerate the progress of ME/CFS treatment, we recommend the following overarching research strategies"

First and foremost, please recommend to fund ME research at the same rate as other

similar chronic conditions, such as MS or Parkinson's disease. Without investment of money, there cannot be further research. Adequate research cannot occur at a rate of 5 millions per year.

24) Line 215-216 and 273-276 "Studies investigating homeopathy, non-pharmacologic, complementary, and alternative medicine treatments are needed. Studies addressing biopsychosocial parameters (including the mind-body connection), function, and QOL should be encouraged"

we do not need assistance from complimentary medicine in order to perform research, as this would further the stigma in health care. We do not need to research the mind-body connection or biopsychosocial parameters. Bio-medical research, search for biomarkers and clinical trials are the most urgent needs right now and where the money should go.

25) Line 234-238 "Research is needed investigating the effect of the intestinal microbiome on ME/CFS using cutting-edge technologies such as high-throughput sequencing. In addition, further exploration of the effect, if any, of the environment and microbiome on ME/CFS development using neurocognitive tests and neuroimaging should be conducted."

World class Columbia University Virus Hunter Ian Lipkin has seen his NIH grant request to study microbiome in Me patient denied in 2013-2014, due to stigma of the disease by a grant reviewer which commented that Me was all in their heads, so why study the microbiome. There needs to be an internal review and public inquiry in this regards. Patients have suffered from this kind of attitude and research is being delayed over and over.

26) Line 301-306 "Provide training and education. Although many health care providers do not fully understand ME/CFS, primary care clinicians will be instrumental in ensuring that patients are treated or referred to appropriate specialists. We believe ME/CFS is a distinct disease that requires a multidisciplinary care team (e.g., physicians, nurses, case managers, social workers, psychologists) to optimize care. Thus, properly training that workforce is critical"

Most of all we need a medical specialty assigned to the disease. Family practice has no time (and often time no interest) in managing a patient with complex diseases. No family physician would be expected to manage an HIV patient. Most family GP does not know about NK cell function and are disbelieved that herpes viruses are implicated in pathogenesis of ME.

27) Line 315-316 "Patients—in addition to the medical therapies they are receiving, patients must become active participants in their overall treatment"

Interesting you mention that. Patients are doing the very best they can to advocate for change and research funding, often to the detriment of their own health. Patients are doing more than their own share in participating in their own treatments.

28) Line 339-343 "Conduct clinical trials. An ongoing need for participants in clinical trials was noted. The NIH should work with ME/CFS partners and stakeholders to create a website for patient and clinician educational materials as well as information regarding clinical trials. Opportunities to utilize the NIH Clinical Center for clinical trials and to fast-track new therapies should also be explored"

Another baffling comment. Very few patients are willing to move to Norway for clinical trials, where the Rituximab trials are taking place. otherwise very few drug trials are taking place. Patients have very limited amount of funds to travel for clinical trials, and for instance, the Ampligen trial requires the patient to move near the center in order to receive treatment, for at least a year if not more, and the Ampligen trial requires patients to purchase the drug.

I would also add that most patients are not willing to enroll in trials where the benefits are likely to be minimal (anti-depressants) or the risks of harm are high (stimulants, CBT, GET) . In general patients are well informed and well educated in their illness.

29) Line 344-352 "Improve treatment. Patients should be active participants in care and decision-making. Lessons can be learned from palliative care, such as compassion, communication, and symptom management to improve the quality of care. Studies examining the role of self- management techniques as part of a comprehensive treatment plan for patients with ME/CFS during and after clinical interventions should be explored. 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. Comparative effectiveness research is also needed. We recommend that the NIH and the FDA convene a meeting on the state of ME/CFS treatment."

Above all that has been mentioned, we need bio-medical research. We need biomarkers, we need drug trial to improve functionality and quality of life. Symptom management, self-management, multi- modal therapies, further CBT and GET studies are not only not needed, they are least desired by patients because we had no choice but try for ourselves and it hasn't worked. No physician would enroll an AIDS patient into a CBT or self-management program. Drug therapy is above all the most effective treatment in making the AIDS patient better. In the case of ME, governments have not believed in the disease, and have not funded biomedical research adequately. The most important clues have been left behind. Most if not all ME patient will tell you we need bio-medical research, not complimentary, not holistic, not bio-psycho-social, not multi-modal. Medical advances have made it possible to find cause and treatments for many diseases, and it is time that these advances are being used for this disease.

30) Line 353 "Conclusions"

The conclusions from this report should highlight the elephant in the room, the gross neglect in funding a disease and the fact that a whole disease has been left behind for 30 years, not discussing the lack of communications between patients and providers. At most, the providers have worn earplugs all this time because patients have tried to talk

about their symptoms. it has been interpreted as non-important, vague and insignificant for all these years.

The conclusion should be there is a pressing need for bio-medical research and earmarking hundreds of millions for biomedical research, not behavioral not psychiatry, not complimentary, not lifestyle, not self-management. This leaves gene expression, yes. Immunology, yes. Endocrinology yes. Advanced brain imaging, yes. Microbiome, yes. System biology, yes. Next generation sequencing, yes. Biomarkers leading to clear diagnostic tools, yes, and finally, clinical trials which reflect scientific findings, leading to treatment and improved quality of life.

the conclusion should discuss costs of this disease to society which once more is not 1billions, but up to 30 billions if not more.

Here is not the pace to please some of your workshop speakers who advocated for holistic care or for body/mind so called medicine. Here is not the place to discuss how restricted the budget is, because there is always money out there for defense or for emerging diseases like Ebola. The funds allocated to other diseases need to be re-evaluated and re-distributed.

Patients have been left behnd for 3 long decades and we are still waiting to see if this time governments will get it riht and communicate the pressing needs right. Please do not disappoint us.

31) Line 355-356 "Unfortunately, patient- and clinician-related barriers were identified (e.g., attitudes, perceptions, knowledge, communication styles, time constraints, stigma) that inhibit quality care."

What is inhibiting care is stigma, the fact that this disease belongs to no medical specialty, the lack of or erroneous medical education in regards to this disease, and the lack of research funding. Communication style, well it would certainly pertain to all diseases, not jst ME. i disagree with your conclusions. Clearly, and respectfully, you need to listen to what the patients have to say.

32) Line 357 "For example, patients do not want to be labeled as complainers and want their stories to be heard."

Where did that come from? i am speechless. And by negating this sentence, you are making us the patient sound like we are complainers.

33) Line 359-360 Patients and their advocates may benefit from education on how to effectively communicate their symptoms and concerns to clinicians

This is quite offensive.

34) Line 361-363 "We note that education alone cannot fix this problem, but will

facilitate a partnership in medical decision-making, thereby optimizing care"

What optimizes care in cancer, HIV and rheumatology for instances, is research and clinical trials. The knowledge accumulated over the years through research and clinical trials have directed physicians and patients to best practices. This is the path that needs to happen for ME. Not optimizing communication between provider, which is fine tuning. it is like telling a smoker with lung cancer to start eating an apple a day.

35) Line 363-366 "Furthermore, the multiple case definitions for ME/CFS have hindered progress. Specifically, continuing to use the Oxford definition may impair progress and cause harm. Thus, for needed progress to occur we recommend (1) that the Oxford definition be retired.

Yes at retiring Oxford. However the committee needs to reject all papers who have used Oxford, including PACE trial which continues to be used in very harmful way to this day.

36) Line 369 Attention should be focused on providing access to high-quality, multidisciplinary care

Multidisciplinary means immunologist, rheumatologist, internal medicine, infectious medicine, neurology, endocrinology. not psychiatrist, social work, complimentary medicine, and yoga teacher. Please be precise.

37) Line 370-371 "We believe there is a specific role for multimodal therapy"
Please define multimodal therapy. I suspect you still think patients still need rehab therapy that includes CBT and some form of physical therapy. Patients will tell you they do not have maladaptive behaviors to their illness, are not fearful or exercise and that exercise makes them sick. it is time that NIH believes the patients and believes the experts who have provided them with this evidence. (For instance Dr Christopher Snell)

38) Line 388-389 We hope our work has dignified ME/CFS and those affected, while providing expert guidance to the NIH and the broader research community

I think in general the patient population has been frankly doubtful of the judge and jury P2P process, because the papers retained for the purpose of reviewing have been the wrong papers, most of them pertaining to behavior, personality and graded exercise therapy. You have purposefully left behind papers by our experts, those who have cared for us for decades. The Rituximab and Valcyte trial paper has been left behind. You have invited pro-CBT guest speakers at your workshop and cut off Dr Jason during the workshop when he had a very important message to pass on.

The most important points to move forward are

1) Case definition matters a lot. it needs to include post-exertional relapse. Oxford needs to be retired, and the PACE trial should be retracted. Our own experts need to be consulted in case definition decisions.

2) Cost to society is closer to 30 billions if not more and not 1 billion as mentioned by Dr carmen Green

3) Research needs to be funded at the same level as similar diseases namely multiple sclerosis or Parkinson's disease. The focus of research needs to revolve around gene expression, immunology, endocrinology, pathogens and the like.

4) All NIH grant reviewers, researchers, physicians need to know that ME is not a disease of the mind, and efforts should be focused on breaking down the stigma in the medical world and in society. We are not tired people, we are sick.