Thank you for this opportunity to provide comments about the Institute of Medicine's provisional committee appointments for the Institute of Medicine committee to evaluate diagnostic criteria for ME/CFS, and for the attention to this devastating and little-noticed disease.

I noticed that about half the nominees were already working in the field of ME/CFS, and this was encouraging to see Dr. Bateman, Dr. Chu, Dr. Davies, Dr. Keller, Dr. Klimas, Dr. Lerner, Dr. Natelson, and Dr. Rowe listed. All of these are acceptable or even wonderful.

I also noticed that some of the other experts had relevant expertise: Dr. Cleeland works on biology of pain and effective pain treatment strategies and how to make pain treatment actually work for patients; Dr. Diamond studies B cells, antibodies, and cognition in autoimmune disease, and racial and economic disparities of chronic illness; and Dr. Shelanski studies cell biology, memory problems, abnormalities of gene expression, and the like, in neuro-immune disease. In a definition effort, I would have to say they are misplaced simply because it is not customary to use outside experts to define diseases (I will have more to say about that in a bit). However, if this were an effort which was, for example, identifying opportunities for funding and gaps in the research, I would be thrilled to have them on board, and I hope they retain their interest in ME and CFS.

Others such as Jennie Spotila have identified concerns with Dr. Alegria, Dr. Ganiats, and Dr. Mulrow and I agree with Jennie's request for careful investigation of these members for a bias which could prevent any of them from examining a biomedical model fairly, especially in a situation where the funding has been astoundingly poor and unbalanced with respect to how little goes to research of biomarkers and biopathology versus how comparatively much and from what status of organizations (though still in most years an amazingly small amount of) funding goes to CBT/GET, deconditioning or personality models, and the like. Also for careful investigation for any bias which would prevent them from critically examining methods errors in the psychosocial papers.

I think Dr. Clayton is the only person not yet mentioned. I can understand she was chosen because of her experience with policy standards and guidelines, which is related to what IOM normally does, and is interesting to ME and CFS because of her interest in genetics and in people who deal with prejudices (as you may be aware, the labels of CFS and ME typically bring a lot of stigma, as does undiagnosed fatigue, or multiple symptoms, or debility, when not connected to a major diagnosis with well-described medical pathology) but this is not standard experience recruited in definition efforts (not to bring this experience in from outside experts, and not as chairman: experience in the disease under consideration is considered more important). Clayton may also be misplaced on this committee because of a lack of relevant experience in ME/CFS.

I also agree with Jennis Spotila that the panel overall is lacking in expertise in specific areas.

There is only one infectious disease specialist on the panel, yet there are many theories of infectious disease in ME and CFS.

- A Martin Lerner is an excellent choice.
- Jose Montoya is another leader in the field and a very thoughtful and compassionate person.

- John Chia has a different theory, about enteoriviruses, and has some remarkable papers.
- Ian Lipkin and his CFS team are doing excellent work looking at yet other theories.
- Jonathan Kerr has produced some great papers, if you could find him and if he wanted to re-enter the field.

There are no cardiologists (aside from POTS specialist) on the panel; however, I am not sure any American cardiologists with expertise in ME and CFS exist. HHS should make it a priority to recruit some to the field.

There are no endocrinologists on the panel; however, I am not sure any with expertise in ME and CFS exist. HHS should make it a priority to recruit some to the field.

There are no autoimmune specialists with specific expertise in ME and CFS on the panel, and I am not sure there are any in America. Hopefully Dr. Diamond will talk to Dr. Jonathan Edwards (previously an RA doctor now studying ME in UK), Drs. Fluge and Mella (oncologists also studying ME in Norway), Drs. Klimas and Fletcher (immunologists in Miami), Dr. Sonya Marshall-Gradisnik and team (immunologists at Griffith U, Australia), and so on, and begin to study the disease herself and bring other autoimmune doctors along. Also DHHS should make it a priority to recruit more autoimmune specialists to the field. Maybe if it were known that funding were available (NIH tells us it is) and definitions were being examined, Eng Tan would return to the field. The autoimmune theory is an interesting one. There are some very old papers showing interesting things in small studies like tissue biopsy evidence of Sjogren's, but without any Sjogren's autoantibodies (small subset of the cohort in Calabrese, Davis, and Wilke, 1994, *Clin Infect Dis*). Also several studies have found positive ANA in Fukuda-CFS, with various prevalence rates (but Fukuda is a bit wobbly of a criteria in any case, so it's not surprising the rates vary from study to study).

There are no gastroenterologists on the panel; however, I am not sure any with expertise in ME and CFS exist. HHS should make it a priority to recruit some to the field. Digestive issues are a large problem in ME. A significant portion of patients are severely underweight.

There are no pulmonologists on the panel; however, I am not sure any with expertise in ME and CFS exist. HHS should make it a priority to recruit some to the field. Patients report findings (from their doctors) of COPD-like dysfunction or lung muscle weakness, each of which seems to be attributable to ME.

Other recommendations:

- Lenny Jason has experience writing definitions and has a very good grasp of all the literature.
- Marty Pall is a biochemist who I think also knows the literature.
- I would love to recommend Rich Van Konynenburg, a scientist who had a fairly novel theory which seems to be helping patients, and who knew all the literature, but he is now passed away, and I am not sure who could take his place.

- Derek Enlander has a thorough understanding of the disease and the panel is a little light on doctors with a comprehensive understanding (rather than having a specialty like infectious disease, POTS, or exercise science).
- Dan Peterson for the same reasons as Dr. Enlander (though their approaches do differ).
- I still think it would be fantastic to have a B and T cell ME specialist like Fluge, Mella, and/or Jonathan Edwards.
- If you could get anyone from the ME/CFS unit from PHANU at Griffith University, that would be amazing.

My main concerns are about the overall makeup and the overall process.

- In other diseases, it is customary for experts from the field, perhaps with patient input often in the form of a disease organization, to define diseases. Just a couple of examples:

    i. The Beighton criteria for Ehlers-Danlos Syndrome, joint hypermobility type (current version) was written by 5 EDS geneticists and 2 disease orgs; it is linked on the review article which is linked from the NIH page (http://rarediseases.info.nih.gov/gard/2081/ehlers-danlos-syndrome-hypermobility-type/resources/1).

    ii. The 2010 McDonald criteria revision was written overwhelmingly by neurologists. They did not add occupational therapists, pulmonologists, immunologists, etc., however logical that might have been, because these specialists do not typically specialize in MS.

- The process and rules of evidence for evaluating treatments will not automatically apply to writing definitions. This is not the fault of IOM, but it's possible the contract was badly placed. We have not seen the contract and we don't know what the rules of evidence are. Without that, it's impossible to support the process. IOM should not assume that writing definitions can be done in the same manner as treatment evaluations. In particular, treatments generally come after pathology is known. Definitions, when there is not a clear biomarker (for example, the disease, like H1N1, follows Koch's postulates for a single, active infection which can readily be identified in the blood, but even then they follow the same pattern, just with much less time spent in the first two steps), follow a clear typical pattern (Ehlers-Danlos syndrome, again, for example, or Lupus or rheumatoid arthritis, etc.):

    1. Begin with an initial clinical definition identifying particular distinguishing features of the disease or syndrome (note that some of the CFS definitions fail entirely, as fatigue can be a feature of many diseases, and even most of the items from Fukuda can be featured in other diseases like Lupus or MDD).

    2. Conduct research using the specific clinical definition. Revise the definition as needed.

    3. The same doctors and researchers who have been using the definition in clinical practice and in research (often many of the same ones who wrote earlier definition(s)), commonly

together with other stakeholders such as patient orgs, and very occasionally with government sponsorship, revise the definition based on the research results.

Although the purpose of IOM is to do #3 with a different composition than is customarily used, we have not actually gotten to that step yet:

a. The definitions in most active use range from so broad as to be useless (e.g. Oxford) to somewhat useful but still too broad to be quite sure what is being studied or how many patients have the disease which is trying to be studied (i.e. Fukuda, and previously, Holmes). See, for example:
http://www.ncbi.nlm.nih.gov/pubmed/11958593
http://thescipub.com/html/10.3844/ajbbsp.2010.120.135
http://evaluatingpace.phoenixrising.me/aps1more.html
http://www.meresearch.org.uk/information/publications/misdiagnosis-on-a-grand-scale/

b. Although some studies are lately being done with more specific criteria like the Canadian Consensus Criteria and the International Consensus Criteria, this has only just begun. Interesting studies like the biomarker study from Columbia University with Ian Lipkin and others are due out shortly. And much more research is needed. Yet funding is practically non-existent (see next point).

- The process and rules of evidence which would normally be used in a standard funding environment may not apply in this situation.

c. Funding is devastatingly poor (and has always been). COPD is considered badly underfunded at 613M (in 2006), while they have a 10% prevalence. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044706/ We have a prevalence of .47 to 1%, but we don't get 1/10, 1/20, or even many years 1/100th of that kind of funding. And that's compared to the worst underfunded disease in the study. One may be able to make a case that the average ME patient has worse debility than the average COPD patient, but a reasonably well-informed person cannot argue that ME/CFS has less debility (CDC: "CDC studies show that CFS can be as disabling as multiple sclerosis, lupus, rheumatoid arthritis, heart disease, end-stage renal disease, chronic obstructive pulmonary disease (COPD), and similar chronic conditions."). (http://evaluatingpace.phoenixrising.me/sixminwalk.html ; the ME/CFS patients here were Oxford-defined [prior to subgrouping by other definitions] and it is known that less inclusive definitions like this select patients with a better prognosis, less symptomology, and less debility). See also:
http://www.cortjohnson.org/blog/2013/12/22/unfulfilled-commitments-broken-promises-nih-chronic-fatigue-syndrome-twenty-five-years/

d. What funding there is, a disproportionate amount goes to psychosocial studies rather than to more practical studies on biomarkers and pathology:
http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/

> > This disease is not classified as psychiatric and has no additional rates of psychiatric problems or depression as compared to any other chronic disease, e.g.:
> > http://www.ncbi.nlm.nih.gov/pubmed/15669445
> > http://sacfs.asn.au/download/guidelines_psychiatrists.pdf
>
> This would not leave a great deal of evidence, particularly evidence of biomarkers and pathology, with which to produce a robust research-based definition which will produce valuable evidence such as useful treatments. Low NK cell function is well replicated (though not specific to the disease). If carefully defined, post-exertional relapse may be specific. So it's possible to compose a useful definition using some research evidence and some clinical expertise, but it may not follow the exact rules of evidence used for evaluating treatments, and again, it would leave out whatever the Lipkin team finds.

So that all explains why it may be premature to be writing a new definition now as we are expecting new biomarkers coming out; IOM may not be best placed to write it in any case simply because IOM is not organized to write definitions and has not shown a willingness to write new rules for definitions; it's currently the time for clinical evidence, not research-based evidence as we have not yet accumulated much of that due to funding and related problems; and only those experts already working in ME/CFS should be involved in any definition efforts for ME/CFS, as is customary for definitions.

Thank you for your careful consideration of these issues.

All the best,
JW
patient and patient advocate