

Comments by Denise Lopez-Majano
on the draft report
National Institutes of Health Pathways to Prevention Workshop:
Advancing the Research on Myalgic Encephalomyelitis/chronic fatigue syndrome
December 9-10, 2014
Draft Executive Summary

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

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

I also appreciate the panel's concern and recommendations regarding patient care, stigma, etc. I hope however that the panel will strengthen its research recommendations which I understand to be the focus of the [workshop](#). The soon-to-be-released IOM report on "[Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome](#)" may recommend better and more appropriate care for patients.

I believe your entire report will be strengthened by the inclusion of references, including references to comments submitted regarding the draft report.

I believe your report will be further strengthened by your prioritization of your research recommendations with emphasis on biomedical research (from basic laboratory science to clinical research). As Dr. Anderson indicated in his opening remarks on 10 Dec. 2014 "Ultimately we should remember that it's the voices of the patients who will help advance the future of research on ME/cfs. ... Those affected are seeking the best possible research on the cause, development of treatments and a cure for ME/cfs." (at about minute 4:55 <http://videocast.nih.gov/summary.asp?Live=14723&bhcp=1>)

In addition your report will be strengthened by stipulating an implementation time-line for your recommendations.

Your openness to listening and learning, and your diligent work in developing this report, leads me to urge you to remain engaged and help us monitor progress on the implementation of your recommendations.

You (the panel) managed to grasp many concerns despite having been given an incomplete picture of the complexity of this illness. Some of the missing pieces not provided to you include findings in pediatrics, neurological findings, autonomic nervous system dysfunction. (Those missing pieces however, are significant and need to be detailed in your report.)

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

- this illness results in severe disability for a very large population
- research and the medical community have frustrated patients because of their failure to accurately assess and treat patients
- stigma, disdain, disrespect are widespread and unfounded
- this is a physiological illness through and through
- for over 20 years scant progress has been made on successful treatments, etiology, prevalence, incidence, longitudinal, epidemiological, studies, etc
- funding is needed
- outcomes that are meaningful to patients must be taken into account
- healthcare professionals need appropriate education.

During the course of the workshop, it seemed that very little information was presented about post-exertional malaise (PEM). PEM is not fatigue. Additional information about PEM is available [here](#). The video at this [link](#) includes descriptions of the devastating impact of post-exertional malaise (collapses/crashes) as experienced by one of my sons. Episodes of PEM can be brought on by minimal physical or mental exertion and episodes vary in triggers, symptoms, severity and duration.

Lines 3, 58, 95,106 - "fatigue" It feels that the term "fatigue" is overused/overemphasized in the report and in the term

“chronic fatigue syndrome” as its applicability to this population is limited. And research focusing on fatigue alone does *not* accurately identify ME – it does however identify fatigue which occurs in many illnesses – chronic and acute. For many patients with ME, fatigue is not their most debilitating or primary complaint. Patients with ME describe a feeling of pathological exhaustion but this exhaustion is magnitudes more intense than what is understood by the term fatigue. Instead it is symptoms such as PEM, cognitive dysfunction, autonomic nervous system dysfunction, neurological and immunological symptoms that patients often describe as those of greatest impact on their lives.

Line 6-7 - “... economic burden is estimated to be greater than \$1 billion...” is more specifically :

“...the direct and indirect cost of ME/CFS to society was estimated to be \$18,677,912,000 for the community sample and \$23,972,300,000 for the tertiary sample.” (in 2008 dollars) <http://www.dynamic-med.com/content/7/1/6>

Lines 8, 10, 63, 108, 158-9, 161-77, 182, 184, 186, 201, 204, 213 (NOTE – the term INVEST is critically important), 219, 236, 244, 291-2, 329, 334, 390-1, 399-401 - Funding increases for biomedical research must be clearly understood and agreed to be long term increases. In other words, as you say, this requires investment in biomedical research funding, not just temporary funding spikes. This investment must be commensurate with the burden and severity of the illness. NIH's current allocation of \$5 million/year is nowhere near enough for an illness whose economic impact is at least \$20 billion/year and funding increases must be sufficient to appropriately fund biomedical research as well as the biobank/repository/registry and COE's recommended by the panel.

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

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

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

Lines 58, 107, 265 – in addition to neurocognitive symptoms and PEM, etc., autonomic dysfunction *must* also be included.

Line 60 - “... children with similar symptoms.” This illness affects people of all races, genders, socioeconomic status, educational background and all ages. It therefore affects pediatric patients. *Please* make sure your report speaks to the necessity of biomedical research on ME in pediatric patients.

Your report mentions that young people have similar symptoms – does this imply that my sons don't have ME, but instead have something that has similar symptoms? Clarification would be appreciated.

The evidence review asserts that young people have better outcomes. It is true that some do. There can be many reasons for those who do. If they have an advocate (parent/other) who perseveres, quickly gets the patient to a specialist, and if the patient responds to treatment, their function and QOL may well improve. Early intervention likely also plays a role in degree of improvement as is the case with many illnesses. Early intervention is more likely when one has an advocate/parent “breaking down doors” to try to help their child. BUT, “improvement” could be a perception of improvement because the young person makes adjustments to the illness-imposed limitations and stays within the boundaries of their resources as Bell, Jason et al. [found](#). OR, they may not improve at all or even get worse, even *with* strong advocates, treatment and specialist care.

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

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

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

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

More accurate diagnosis also means less likelihood of misdiagnosis.

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

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

ME, best described by the 2003 Canadian Consensus Criteriaⁱ and the 2011 ME International Consensus Criteriaⁱⁱ, is a complex, disabling disease characterized by unrefreshing sleep, flu-like symptoms, impairment of memory and other cognitive issues, orthostatic intolerance, debilitating weakness, pain, fever and the hallmark symptom of post-exertional malaise (post-exertional neuroimmune exhaustion).ⁱⁱⁱ It has been shown to cause dysfunction of the neurological, immune, endocrine and energy production systems.^{iv} (Mary Dimmock et al letter to 2013 appended)

Lines 211, 218, 220, 322, 334, 387-9, 400 - During (at least) the past 2 decades progress towards successful treatment and/or cure of this illness has been imperceptible because of lack of funds, stigma, lack of commitment, etc. There is a history of lack of openness and transparency by HHS and its agencies regarding this illness. HHS developed and implemented the contract for the IOM project in total secrecy. An advocate found the signed contract by accident. You likely are not aware that the patient/advocate community has tried many times, in many ways, to engage with HHS and its agencies. Among other efforts we asked HHS to work with us to develop a comprehensive, strategic plan for ME yet HHS rebuffed us (yet again).

Because the current system has failed for decades, perhaps the system needs to be revamped to appropriately address this illness. And because neither (HHS') OWH or (NIH's) ORWH are disease specific researching entities they are not suitable NIH/HHS homes for ME.

This illness needs a home that fosters biomedical research.

WHO categorizes ME as a neurological illness. (p.233 G93.3 includes: benign myalgic encephomyelitis) So a more suitable home is NINDS, or perhaps NIAIDS. It is hoped that moving ME to a suitable NIH home, will result in the elimination of the institutional barriers and bias, funding difficulties and stigma, while attracting additional researchers to conduct biomedical research to help patients with ME.

ANY/ALL detailed plans for ME must be developed collaboratively and openly with the community and experts on a level playing field with NIH, etc. and with frequent input and feedback from the community and experts.

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

Lines 116, 130, 132, 134, 137, 283, 314, 360, 363, 364, 383, 385 - refer to multi-modal, self-management, multidisciplinary, biopsychosocial and mind-body connections. While the mind-body connection can be of intellectual interest, one does not suggest that patients with for example cancer or MS can be cured by means of changed illness beliefs. Because of the often inappropriate referral of patients with ME to psychosocial specialties, the above-mentioned terms are viewed with skepticism by patients as all too often patients are dealt with as though this illness is just a question of false illness beliefs that CBT (or similar) can cure them of.

Given that ME is a severely debilitating physiological illness, there is great need for specialty care for patients with ME. It must be biomedical specialty care provided by neurologists, rheumatologists, immunologists, endocrinologists, specialists in

infectious disease, cardiologists, pediatricians, as well as other biomedical specialties. These are the sorts of specialties that treatment teams should be comprised of in order to provide the quality care that patients need and deserve.

Lines 79-81, 311 – 327, 354, 374-5 - Medical professionals definitely need much more education about this illness. They also need to be active listeners and they need to be supportive of patients. Currently, patients often have more knowledge about this illness than healthcare professionals.

Line 173 - "... Does mononucleosis lead to ME/CFS in adolescents?" It is worth noting that several studies about mononucleosis and ME have been done (including Katz BZ, Jason LA. Chronic fatigue syndrome following infections in adolescents. *Curr Opin Pediatr.* Feb 2013;25(1):95-102. [[Medline](#)], <http://www.tandfonline.com/doi/pdf/10.1080/21642850.2013.869176>) and at least one is currently underway as Doctor Jason mentioned during the workshop.

However, ME is not confined to sudden onset and only suggesting that mononucleosis be looked into as a trigger overlooks many other things that seem to be triggers – giardia (<http://www.biomedcentral.com/1471-230X/12/13>), Parvo B19 (for instance <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4238837/>) among others.

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

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

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

The final evidence review says:

Different complementary and alternative (CAM) therapies have been studied only in small pilot trials with methodological limitations, and although homeopathy, pollen extracts, and carnitine preparations showed some benefit, the results have been inconsistent across different measurement tools precluding any determination of potential effectiveness. (p.97 <http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2004>)

and concludes that there is insufficient evidence of benefit.

The [NHMRC study conclusion](#) (evidence review conducted in 2014) that "...the assessment of the evidence from research in humans does not show that homeopathy is effective for treating the range of health conditions considered" cannot be ignored or dismissed.

The NHMRC study also noted (on page 14):

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

"Conclusion

For each condition, although some studies reported that homeopathy was more effective than placebo, these studies were not reliable. They were not good quality (well designed and well done), or they had too few participants to give a meaningful result, or both."

<http://consultations.nhmrc.gov.au/files/consultations/drafts/nhmrcdrafthomeopathyinformationpaper140408.pdf>

Line 294 - there is a PROMIS scale that can assess fatigue, but I find no PROMIS scale that can assess PEM, its triggers, symptoms or severity. Because PEM is not fatigue, in order to be applicable, the PROMIS fatigue (or other) scale does require significant alteration (and validation) by ME experts to accurately assess PEM.

Line 365 – NIH and FDA meeting – The report calls for an FDA meeting with NIH regarding the state of ME/cfs treatment. Please note that there was an [FDA meeting 2013 on drug development for ME\(cfs\)](#). If the panel feels another meeting is appropriate, the report should provide greater detail about such a meeting.

I know that the comments of others have better, more in-depth and more valid arguments than mine. I trust though that you will take all comments into account as you strengthen your report.

Thank you for your time and attention.

Denise Lopez-Majano

i

CCC: Carruthers, B., et al Jain, A., De Meirleir, K., Peterson, D., Klimas, N., Lerner, M., Bsted, A., Flor-Henry, P., Joshi, P., Powles, A., Sherkey, J., van de Sande, M. Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome, Vol. 11(1) 2003.
<http://mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Document.pdf>

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ME-ICC: Carruthers, B., van de Sande, M., De Meirleir, K., Klimas, K., Broderick, G., Mitchell, T., Staines, D., Powles, A., Speight, N., Vallings, R., Bateman, L., Baumgarten-Austrheim, B., Bell, D., Carlo-Stella, N., Chia, J., Darragh, A., Jo, D., Lewis, D., Light, A., Marshall-Gradisbik, S., Mena, I., Mikovits, J., Miwa, K., Murovska, M., Pall, M., Stevens, S. Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine. [Volume 270, Issue 4](#), pages 327–338, October 2011.
<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full>

iii

The Canadian Consensus Criteria (CCC) uses the term post-exertional malaise (PEM) and the ME International Consensus Criteria (ME-ICC) uses the term post-exertional neuroimmune exhaustion (PENE) to refer to post-exertional fatigability.

iv

There are numerous peer-reviewed articles that characterize this disease and the associated dysfunctions. Selected examples of these references include the following:

- Freeman, R. Komaroff, A. Does the chronic fatigue syndrome involve the autonomic nervous system? The American Journal of Medicine 1997;102:357364 <http://www.ncbi.nlm.nih.gov/pubmed/9217617>
- Komaroff AL, Cho TA. Role of infection and neurologic dysfunction in chronic fatigue syndrome. Semin Neurol. Epub 2011 Sep 30 <http://www.ncbi.nlm.nih.gov/pubmed/21964849>
- Light AR, White AT, Hughen RW, Light KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. J Pain. 2009 Oct;10(10):1099-112.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757484/?tool=pubmed>
- VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Post-exertional malaise in women with chronic fatigue syndrome. J Womens Health (Larchmt). 2010 Feb;19(2):239-44. <http://www.ncbi.nlm.nih.gov/pubmed/20095909>
- Carruthers, B., van de Sande, M., De Meirleir, K., Klimas, K., Broderick, G., Mitchell, T., Staines, D., Powles, A., Speight, N., Vallings, R., Bateman, L., Baumgarten-Austrheim, B., Bell, D., Carlo-Stella, N., Chia, J., Darragh, A., Jo, D., Lewis, D., Light, A., Marshall-Gradisbik, S., Mena, I., Mikovits, J., Miwa, K., Murovska, M., Pall, M., Stevens, S. Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine. [Volume 270, Issue 4](#), pages 327–338, October 2011.
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- Lange G, Streffner J, Cook D, Bly B, Christodoulou C, Liu W, Deluca J, Natelson BH. Objective evidence of cognitive complaints in chronic fatigue syndrome: A BOLD fMRI study of verbal working memory. NeuroImage 2005;26:513-524.
<http://www.ncbi.nlm.nih.gov/pubmed/15907308>
- Papanicolaou DA, Amsterdam JD, Levine S, McCann SM, Moore RC, Newbrand CH, Allen G, Nisenbaum R, Pfaff DW, Tsokos GC, Vgontzas AN, Kales A. Neuroendocrine aspects of chronic fatigue syndrome. Neuroimmunomodulation 2004;11(2):65-74. <http://www.ncbi.nlm.nih.gov/pubmed/14758052>

Mary Dimmock et al letter to 2013

To: Dr. Janet Woodcock, Director Center for Drug Evaluation and Research, Deputy Director Dr. Sandra Kweder, Office of New Drugs, Dr. Theresa Michele, Team Leader

CC: Dr. Margaret Hamburg, Commissioner Food and Drug Administration,

Date: March 18, 2013

Subject: FDA Stakeholder Workshop for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

The FDA will be holding a stakeholder workshop on April 25-26, 2013 to discuss the development of drugs for myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). Given the confusion and controversy in the scientific and medical community around the nature of ME and CFS, we are asking for assurance that this workshop will focus on ME as characterized below and not on the vaguely defined, overly broad “CFS”. We believe that this will help ensure the success of this important workshop.

ME, best described by the 2003 Canadian Consensus Criteria^v and the 2011 ME International Consensus Criteria^{vi}, is a complex, disabling disease characterized by unrefreshing sleep, flu-like symptoms, impairment of memory and other cognitive issues, orthostatic intolerance, debilitating weakness, pain, fever and the hallmark symptom of post-exertional malaise (post-exertional neuroimmune exhaustion).^{vii} It has been shown to cause dysfunction of the neurological, immune, endocrine and energy production systems.^{viii}

CDC has inappropriately lumped this disease into an umbrella of fatiguing illnesses called chronic fatigue syndrome and has said that CFS is defined by any of five disparate definitions.^{ix} Three of these definitions describe the essential and hallmark criteria of ME: the Canadian Consensus Criteria, the ME International Consensus Criteria and the 2006 IACFS/ME Pediatric Case Definition.^x

Unfortunately, two of the most commonly used CFS definitions, Oxford^{xi} and Fukuda^{xii}, are overly broad and fatigue-focused, do not require the hallmark symptoms of ME and allow primary psychiatric illness. In fact, Oxford only requires 6 months of medically unexplained debilitating fatigue. As a result, CFS – and ME by extension – have become associated with a diverse set of unrelated fatiguing conditions including depression, deconditioning and, in the minds of some, “false illness beliefs”.^{xiii}

For the past twenty-five years, the use of these overly-broad, non-specific definitions has confounded ME research with conflicting results, stalled ME drug development, corrupted prevalence estimates, confused the scientific and medical communities about the nature of ME and severely impacted the quality of care that ME patients receive.

Clinical trials on treatments for cancer and multiple sclerosis do not use patient cohorts that include patients who do not have the disease and whose only symptom is 6 months of fatigue. Similarly, we will not identify ME treatments until we stop mixing ME criteria with non-specific fatigue-based criteria. We must start studying ME for the disease that it is, using disease appropriate criteria like those seen in the 2003 Canadian Consensus Criteria, which has been used both in research and clinically for years.

As patients, we cannot accept the continued mixing of ME with unrelated fatiguing conditions. We also believe it is critical to avoid confusion among the FDA workshop participants about the nature of ME. Therefore, we ask for your assurance on four key points:

- The FDA stakeholder workshop will focus on ME as characterized above and will not also focus on conditions or patient populations that do not meet the kind of criteria laid out in the Canadian Consensus Criteria. If a stakeholder workshop is needed for these other conditions, that should be done separately.
- Workshop panels will include ME patients and recognized ME clinician and researcher experts – experts like Drs. Klimas, Rowe, Montoya, Peterson, Chia and Bateman.
- The FDA stakeholder workshop will address potential misperceptions by launching the workshop with a very brief overview of the biology of ME that includes the characteristic symptoms and what is known about the multi-system dysfunction, biomarkers, subtypes and levels of severity of ME.
- The FDA will encourage researchers and drug sponsors to use disease appropriate clinical trial inclusion criteria, like those seen in the Canadian Consensus Criteria, to avoid the overly broad patient cohorts that have stalled progress in the past.

We greatly appreciate FDA’s sponsorship of this critical workshop and are committed to its success. We believe that addressing these points will lay the foundation necessary for researchers and clinicians to gain insight into potential mechanisms to modify the course of this disease, best understand how to stratify patients for successful clinical trials and

identify effective approaches for measuring the outcomes of trials.

Thank you for your consideration of our concerns. We do appreciate feedback on these points by April 2. If you need clarification or additional information, please do not hesitate to contact Mary Dimmock. Signed

Patient Support Organizations

MAME (Mothers Against Myalgic Encephalomyelitis)

[Massachusetts CFIDS/ME and FM Association, Inc.](#)

[PANDORA \(a.k.a. CFS Solutions of West Michigan\)](#)

[Phoenix Rising](#)

[The Fibromyalgia - ME/CFS](#)

[Support Center, Inc.](#)

[Rocky Mountain CFS/ME and FM Association](#)

[Speak Up About ME](#)

[Wisconsin ME/CFS Association, Inc.](#)

Patient Advocates

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Rivka Solomon

Tamara Staples

Charlotte von Salis, J.D.

Michael Walzer

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- Komaroff AL, Cho TA. Role of infection and neurologic dysfunction in chronic fatigue syndrome. Semin Neurol. Epub 2011 Sep 30 <http://www.ncbi.nlm.nih.gov/pubmed/21964849>
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- VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Post-exertional malaise in women with chronic fatigue syndrome. *J Womens Health (Larchmt)*. 2010 Feb;19(2):239-44. <http://www.ncbi.nlm.nih.gov/pubmed/20095909>
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- Lange G, Streffner J, Cook D, Bly B, Christodoulou C, Liu W, Deluca J, Natelson BH. Objective evidence of cognitive complaints in chronic fatigue syndrome: A BOLD fMRI study of verbal working memory. *NeuroImage* 2005;26:513-524. <http://www.ncbi.nlm.nih.gov/pubmed/15907308>
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CDC CME “Diagnosis and Management of Chronic Fatigue Syndrome” states that Fukuda, Oxford, Canadian Consensus, ME International Criteria and Jason/IACFS/ME pediatric criteria are all different definitions for CFS.

<http://www.cdc.gov/cfs/education/diagnosis/index.html> page 3-9.

x

Jason L, Jordan K, Miike T, Bell DS, Lapp C, Torres-Harding S., Rowe, K., Gurwitt, A., DeMeirleir, K., Van Hoof, E. A Pediatric Case Definition for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. *J Chronic Fatigue Syndr*. 2006 13: 1-44

<http://www.cfids-cab.org/MESA/Jason-1a.pdf>

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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293107/>

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Fukuda K, et al Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953-9. http://www.ncf-net.org/patents/pdf/Fukuda_Definition.pdf

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White, P., et al, Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet* - 5 March 2011 (Vol. 377, Issue 9768, Pages 823-836) [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(11\)60096-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext). *The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which were used “on the basis of the fear avoidance theory of chronic fatigue syndrome” that “assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity.” The theory underlying CBT is often described as “false illness beliefs”. The CDC references this trial among others to support CBT as a treatment recommendation for CFS patients*