The Chronic Fatigue Syndrome Advisory Committee (CFSAC) provides advice and recommendations to the Secretary of Health and Human Services (HHS) through the Assistant Secretary for Health on issues related to Myalgic Encephalomyelitis and Chronic Fatigue Syndrome (ME/CFS).

January 2015

Comments

from the

HHS Chronic Fatigue Syndrome ADVISORY COMMITTEE

Subject: Draft Report Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Co-Sponsored by: NIH Office of Disease Prevention And the Trans-NIH Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) Research Working Group

The Chronic Fatigue Syndrome Advisory Committee (CFSAC) is authorized under 42 U.S.C. 217a, Section 222 of the Public Health Service Act, as amended. The Committee is governed by the provisions of the Federal Advisory Committee Act, as amended (5 U.S.C., App.), which sets forth standards for the formation and use of advisory committees.

Chronic Fatigue Syndrome Advisory Committee Roster

The Chronic Fatigue Syndrome Advisory Committee consists of eleven (11) members, each appointed by the Secretary and classified as a special government employee. Of the eleven members, seven (7) are research scientists with demonstrated expertise in biomedical research applicable to ME/CFS; and four (4) are individuals with expertise in health care delivery, private health care services or insurers, or voluntary organizations concerned with the problems of individuals with ME/CFS.

The Committee also includes seven (7) non-voting ex officio members who inform discussions of the Committee as recommendations are developed. The ex-officio membership is comprised of representation from the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Centers for Medicare and Medicaid Services (CMS), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), National Institutes of Health (NIH), and Social Security Administration (SSA). There are three (3) non-voting liaison positions selected by the DFO or designee, each filled by an individual who represents an organization concerned with the disease as well.

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Preface

Advancing the Research on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

Since 2002, the Chronic Fatigue Syndrome Advisory Committee (CFSAC) has provided advice and recommendations to the Secretary of the Department of Health and Human Services on issues that affect access and care for persons with myalgic encephalomyelitis and chronic fatigue syndrome (ME/CFS); the science and definition of ME/CFS; and broader public health, clinical, research and educational issues related to ME/CFS.

This document contains the comments of the CFSAC on the 389 line version of the Draft Executive Summary for the December 2014 Pathways to Prevention (P2P) Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

The CFSAC recognizes the challenge faced by the Pathway to Prevention Panel and wholly appreciates the astute observations that have informed the draft executive summary. It is clear that the Panel thoroughly digested the literature provided, absorbed the thoughtful comments made by the public, and listened carefully to each informative presentation. The Panel's enthusiasm and dedication were evident during the Workshop, and its commitment to professionalism is evident in the draft summary generated in such a short period of time.

Many of the observations highlighted in the draft executive summary support recommendations made to the Secretary by this Committee. (See Appendix A).These observations have also been made by stakeholders and ME/CFS experts who recommend use of the 2003 Canadian Consensus Criteria to define the disease until further research warrants modification.

The CFSAC is extremely pleased to have the opportunity to offer its experience and expertise to the Panel as you finalize this important document. We sincerely hope our comments will be of value.

During our review, the Committee identified several important areas that should be addressed. Those areas are reflected in the "Comments" section of this document.

Additionally, if the Panel did not review *The Voice of the Patient*[1] series of reports published in September 2013 following the U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis, we encourage you to do so.

"Post-exertional malaise is a signature symptom of ME/CFS."

We also ask that you review the Report from the National Institutes of Health (NIH) State of Knowledge Workshop during which researchers and stakeholders reached consensus on a number of key issues. Some of these issues may be of importance to the P2P Panel during the revision process:

- *"Post-exertional malaise is a signature symptom of ME/CFS."*
- *"If the rules for identifying who is a patient and who is not differ, then problems will occur, not only for a patient seeking an accurate diagnosis, but for the entire scientific enterprise."*
- *"There is a lack of longitudinal, natural history, early detection, pediatric-versus adult-onset, and animal model studies. In addition, few studies look at comorbid conditions, biomarkers, or genetics. Moreover, study designs needed for clinical*

trials require further refinement. Improved and more extensive data from patient-derived and reported outcomes will better define the successes or failures of treatment interventions. To capture the extensive information from such studies, a centralized interactive database, using common data elements and accessible to everyone, is sorely needed to collect, aggregate, store, and analyze results.

- *"While some major questions are currently being raised in the biomedical field as to what makes a biomarker and how to identify one, for ME/CFS, there is movement toward this research, with suggestions from Workshop participants to stratify biomarkers into four broad categories:*
  (1) diagnostics,
  (2) predictive and preventive,
  (3) metabolism biomarkers to determine how a patient metabolizes a particular medication and to help with dosing and schedule,
  (4) outcome biomarkers to forecast the disease response itself."
- *"Keeping in mind that these are lean budgetary times, the panel called for more coordination and leadership by NIH and commended the Office of Research on Women's Health as a driving force behind the transparency used in planning and execution of the Workshop and providing a home for ME/CFS research. The Trans-NIH ME/CFS Research Working Group will use the information from the Workshop to help NIH understand the complexity of this illness, and look for ways to further research on this devastating illness to conduct epidemiologic and clinical studies."*[2]

These reports contain important information that will help inform your deliberations. We ask that you review these important resources and consider them prior to finalizing the executive summary.

We also ask that you take note of the fact that among the 234 disease categories supported by NIH in 2014, chronic fatigue syndrome ranked 228th with an estimated $5 million in funding.

In order to move forward, it is vital that this issue be addressed.

We ask that the Panel explicitly address the urgent need for government funding in order to advance the research for ME/CFS.

Regarding the areas of review, the CFSAC agrees with many of the Panel's observations. We therefore ask the Panel to address the need for increase funding to accomplish those goals and advance the research for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Without a substantial change in funding at the national level, CFSAC believes it will be virtually impossible to address the comprehensive list of recommendations outlined in the Panel's Draft Executive Summary.

Comments

Introduction

Lines 2-7: "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by extreme fatigue and other symptoms that are not improved by rest. The etiology and pathogenesis remain unknown; there are no laboratory diagnostic tests; and there are no known cures. An estimated one million people, mostly women, are affected. ME/CFS is an unmet public health need with an economic burden estimated to be greater than $1 billion. ME/CFS results in major disability for a large proportion of the people affected. Limited knowledge and research funding creates an additional burden for patients and health care providers."

Revision Requested: *"Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by hallmark symptoms of neurological dysfunction, sleep disturbances, and post exertional malaise with predominant symptoms of immunological and endocrinological dysfunction. Post exertional malaise is defined as "an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period–usually 24 hours or longer.*[3]

The etiology and pathogenesis of ME/CFS remains unknown and there are no known cures. There is no single diagnostic test or standard set of tests being used to diagnose ME/CFS in the clinic at this time. However, a number of common biomarkers are being used by experts in the field to aid diagnosis, to strategize treatment, to define comorbid states and for research. Strong evidence indicates immunologic and inflammatory pathologies, neuroendocrine findings, and abnormalities in gene expression of energy and other related proteins post-exertionally in ME/CFS patients which differ from findings among age and sex matched normal control populations. Additionally, there is reproducible evidence of abnormalities in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies.[4]

Research has clearly shown that ME/CFS is not a psychiatric or a psychological disease. ME/CFS is a distinct pathological entity that can affect both sexes and all racial, age, and socioeconomic groups regardless of education, financial security, or social standing. The U.S. Centers for Disease Control and Prevention (CDC) reports over 1 million adults with ME/CFS in the United States, and recent evidence has shown a higher prevalence in females compared to males. Certain racial/ethnic groups have also been found to be at an increased risk for ME/CFS; most notably Native American and African American populations.[5]

The economic burden of ME/CFS in the U.S., including annual health care costs, is estimated to be between $1.9 billion and $7.2 billion.[6] *When considering indirect costs to society as a whole, the annual estimate jumps to between $18.7 and $23 billion in the U.S. alone.*[7]

ME/CFS results in major disability for a large proportion of patients and in its most severe form, can lead to individuals becoming housebound, dependent on wheelchairs, or bedbound and forced to turn to caregivers for all basic activities of daily living. Limited knowledge and research funding creates an additional burden for patients and health care providers.

Rationale: To clearly identify the hallmark symptoms of the disease and the important findings of the Panel, to improve the accuracy of the disease description and its economic burden, and to identify who is affected by the disease, CFSAC believes it is important to use this language to correct the false belief that ME/CFS is primarily a women's illness, generally about fatigue, and possibly psychological in nature. Studies show the economic burden to be much higher than $1 billion and the statement that "there are no laboratory diagnostic tests" is inaccurate. Recognition of the impact of ME/CFS on the most severely affected is important as well.

What is the incidence and prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and whom does it affect?

Lines 32-34: "ME/CFS exists. Despite the absence of a clear definition, an estimated million people have ME/CFS, and it overlaps with many other diseases (e.g., fibromyalgia, major depressive disorder, chronic pain)."

Revision Requested: *"ME/CFS exists. Despite the absence of a clear definition, an estimated one million Americans have the disease and it often presents with co-morbidities (e.g. allergies, fibromyalgia and other pain conditions, depression, interstitial cystitis, multiple chemical sensitivities)."*

Rationale: The diseases listed as examples are co-morbidities. A more detailed list of comorbidities is provided by the 2003 Canadian Consensus Criteria: "Co-Morbid Entities: Fibromyalgia Syndrome, Myofascial Pain Syndrome, Temporomandibular Joint Syndrome, Irritable Bowel Syndrome, Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities, Hashimoto's thyroiditis, and Sicca Syndrome. Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome."[8]

Lines 34-35: "There is no agreement from the research community on what needs to be studied…"

Deletion Requested: The CFSAC recommends that this statement be deleted from the report.

Rationale: It is the opinion of this Committee that the researchers who have dedicated much of their lives to this disease will disagree with this statement. The scientific community is in agreement that the pathophysiology, epidemiology, and evolving definition of the disease needs to be studied. Like any other illness, scientists with varying expertise have approached the problem from their "trained" perspective, however, there is no disagreement regarding the important areas of research for ME/CFS.

Lines 40-43: "The lack of a consistent, specific, sensitive diagnostic test and set of criteria has hampered all downstream research on pathogenesis and treatment, causing harm and preventing ME/CFS from being considered as a distinct pathologic entity."

Revision Requested: *"The lack of a universally accepted set of criteria has hampered some, but not all, downstream research on pathogenesis and treatment, causing harm."*

Rationale: Recent research studies show that laboratory testing can reveal important aspects of ME/CFS, define subsets, and direct treatment.[9] [10] [11] [12] The vast majority of the scientific community agrees that ME/CFS is a "real" pathologic entity and the Committee is justifiably concerned that the original statement, along with the implication that ME/CFS is not "considered as a distinct pathologic entity" is counter-productive to the Panel's intent to further the research for this disease. Additionally, the Committee does not agree that the lack of a diagnostic test has hampered all downstream research and requests that this statement be removed. There are many recognized pathologic entities, several of them multi-system/symptom disorders, which do not have definitive evidence regarding etiology and/or do not have a consistent, specific, sensitive diagnostic test.

Lines 48-49: "Studies of ME/CFS are fraught with methodological problems, preventing a clear understanding of who is affected by ME/CFS: there are no agreed-upon parameters for defining ME/CFS."

Revision Requested: *"Although dedicated researchers have identified parameters for defining ME/CFS, those parameters have not been universally adopted. As a result, studies of ME/CFS are fraught with methodological problems, preventing a clear understanding of who is affected by the disease."*

Rationale: It is important to acknowledge that a majority of experts in the field have agreed upon parameters for defining ME/CFS.

Lines 50-51: "…and 163 symptoms have been associated with ME/CFS."

Revision Requested: *"… and a multitude of symptoms have been associated with ME/CFS."*

Rationale: The "163" figure offered by Dr. Nacul during his presentation did not refer to symptoms, but rather to the combinations of symptoms that could occur using the Fukuda definition. It appears to this Committee that Dr. Nacul was making a point: the Fukuda definition is overly broad and non-specific. Transcript: *"If we use the Fukuda criteria, CDC 1994, which is probably the most widely used criteria, it's quite non-specific. It's a negative criteria. It mentions in this criteria not explained by disease, not relieved by rest, not due to exertion and so on. And also, it lists four, the need for four out of eight symptoms to be present so that definition is met. And this means 163 combinations of symptoms or possible combinations of symptoms that patients may have to be classified as having CFS. If for example we added post-exertional malaise as one of the criteria, a compulsory criteria, then the number of combinations of symptoms that make a diagnosis would drop to about thirty-five. So it seems that there may be an advantage of having more restrictive criteria."*

Lines 51-52: "Small sample sizes, the inclusion of participants with differing symptoms across studies, and the lack of inclusion of the homebound, rural residents, and a research focus on men limits the applicability of current studies."

Revision Requested: *"Small sample sizes, the inclusion of participants with differing symptoms across studies, and the lack of inclusion of the homebound, rural residents, and children and adolescents limits the applicability of current studies."*

Rationale: It is also important to note the lack of inclusion of children and adolescents. The statement about "a research focus on men" should either be removed or clarified. Is the intent to indicate that most studies of this disease focus on men?

Lines 54-55: "Many instruments used to evaluate ME/CFS are not validated, are inappropriate, and may be misleading."

Clarification Requested: It would be helpful if the Panel would provide further detail and support for this statement. It is unclear if the comment refers to various scales/questionnaires, routine blood tests, instruments to evaluate prevalence, or something else?

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

Revision Requested: *"Fatigue has been a focus of some recent research, but many other symptoms need to be explored further including neurocognitive deficit ("brain fog"), post-exertional malaise, pain, non-restorative sleep, orthostatic intolerance,[13] metabolic basis of energy production, and endocrine and immunological changes."*

Rationale: Although absent from the AHRQ Evidence Review, many small but promising studies have explored neurocognitive deficit, post-exertional malaise, and other symptoms as indicated.

Line 59-60: "Most ME/CFS studies focus on adults, excluding children with similar symptoms."

Revision Requested: *"Most ME/CFS studies focus on adults. The Panel's charge did not include a review of evidence related to children and youth with ME/CFS; however, such a review should be done. ME/CFS in children and youth often presents somewhat differently from that in adults. Symptoms more prominent in children include gastrointestinal upset, orthostatic intolerance, and headaches, among others."*[14]

Rationale: The section of the statement that is not completely accurate is that children often present with somewhat different symptoms than adults. Given that ME/CFS in children and youth was not addressed in the P2P study, a review of the state of science for this demographic would be appropriate as well.

Given the unique challenges to ME/CFS, how can we foster innovative research to enhance the development of treatments for patients?

Lines 80-81: "The scientific community also has a responsibility to address issues that are meaningful to patients."

Revision Requested: *"The Department of Health and Human Services and other government agencies, as well as the scientific community, have a responsibility to address issues that are meaningful to patients."*

Rationale: It is the opinion of this Committee that both the scientific community and the private sector have a great desire to address issues that are meaningful to patients but lack the resources to do so.

Lines 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)."

Revision Requested: *"A multitude of symptoms are associated with ME/CFS, as are a number of co-morbidities (e.g. allergies, fibromyalgia and other pain conditions, interstitial cystitis, multiple chemical sensitivities)."*

Rationale: The phrase "substantial overlap" is incorrect and should be removed. A more detailed list of co-morbidities is provided in the comment for Lines 32-34.

Lines 95-97: "Focusing on fatigue alone may identify many ME/CFS cases. However, this symptom taken in isolation fails to capture the essence of this complex condition."

Revision Requested: *"Focusing on fatigue alone may identify many ME/CFS cases but may also capture many individuals who do not have ME/CFS. This symptom, taken in isolation, fails to capture the essence of this complex multi-systemic disease and the hallmark symptoms of post-exertional malaise and neurocognitive deficits.*

Rationale: Although the intent of this statement is clear to the Committee, the wording has raised concerns in the community. It is hoped that a clarification will ease those concerns.

Lines 106-107: "We noted a consistent constellation of symptoms: fatigue, post-exertional malaise, neurocognitive deficit, and pain."

Revision Requested: *"We noted a consistent constellation of symptoms: fatigue, post-exertional malaise, neurocognitive deficit, sleep disorders, and pain."*

Rationale: During the P2P Workshop, sleep disorders were consistently mentioned as part of the constellation of symptoms for ME/CFS. Therefore, we request that sleep disorders be added to this list.

Lines 111-112: "Future studies must be collaborative, multicenter efforts and must include large, diverse samples across the lifespan."

Addition Requested: *(After Line 112) "In addition to supporting clinical trials on diverse but well defined subgroups of patients with ME/CFS over a lengthy period of time, this disease should be compared, not only to age and sex matched normal controls, but to other groups of chronically ill patients in addition to healthy controls. Biological models which can measure changes in the Hypothalamic Pituitary Axis (HPA) concomitant*

with changes in immune function pre- and post-exercise and their homeostatic regulatory mechanisms should be developed."

Rationale: In order to determine whether the phenotypic presentation and underlying biological mechanisms of ME/CFS patients are unique to their disease or whether there is overlap with other diseases with shared clinical features (such as Gulf War Syndrome and patients with inflammatory arthritis, to whom they have been compared) it is necessary to include patients who are impaired from other disorders among our control groups. Comparison of age and sex matched normal controls with ME/CFS patients is not sufficient to provide more detailed data and will not reveal overlapping features with patients with other chronic disease entities.

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."

Revision Requested: *"Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy [GET]) demonstrate modest improvement, but this has not translated to improvements in quality of life (QOL). Thus, they are not primary treatment strategies. When appropriate, pharmaceuticals and other clinical treatments should first be employed to address underlying pathologies and manage symptoms to the extent possible. CBT might then be suggested in order to help patients adjust and learn to cope with the realities of a chronic disease. Exercise therapy should only be considered if and when appropriately trained professionals are involved and fully understand how to ensure that the exercise does not induce post-exertional malaise or cause other physical harm."*

Rationale: Although the Panel has indicated that CBT and GET should *not* be used as primary treatment strategies, the recommendation to include them as a component of multimodal therapy should be carefully clarified. Far too many patients have been subjected to these treatments by uneducated or misinformed clinicians, only to result in further debility. Additionally, while small studies have shown modest improvements, the PACE ("Pacing, graded Activity and Cognitive behavioral therapy: a randomized Evaluation") study, which purports to demonstrate "measurable improvement," used the Oxford Criteria for subject selection. We agree with the Panel's assessment that *"continuing to use the Oxford definition may impair progress and cause harm"* and also that the Oxford Criteria should be retired. We, therefore, encourage the Panel to rethink referencing the PACE trial since the Oxford Criteria were used to identify patients for this study.

Lines 116-117: "Overall, agreeing on a case definition and clarifying comorbidities could launch bench-to-bedside science."

Revision Requested: *"Overall, agreeing on a case definition and clarifying comorbidities and subgroups could launch bench-to-bedside science."*

Rationale: Clarification of subgroups is equally important in launching bench-to-bedside science.

What does research on ME/CFS tell us about the presentation and diagnosis of ME/CFS in the clinic?

Lines 120-121: "Limited time during the clinical encounter has impaired patient/clinician communication and quality of care for patients with ME/CFS."

Addition Requested: *(after Line 121) "Time constraints that prevent the clinician from obtaining an adequate medical history, the number of symptoms which need to be reported and discussed, and patients struggling with neurocognitive dysfunction are other factors that impair the diagnosis and treatment of this complex condition."*

Rationale: Limited time during the clinical encounter is indeed an obstacle for effective patient/clinician communication, but there are other factors as well.

Lines 121-122: "Patients experience stigma from the diagnosis of ME/CFS, including social isolation and judgment."

Revision Requested: *"Patients experience stigma from the negative attitudes, psychological connotations, and misinformation associated with the diagnosis of CFS and ME/CFS, including social isolation and judgement."*

Rationale: The negative stigma associated with "CFS" may be partially due to the trivializing name[15] that was given to this disorder in 1988. Many patient groups believe that changing the name from Myalgic Encephalomyelitis to CFS was a major contributing factor to the stigmatization of this disease. A name change to Myalgic Encephalomyelitis, classified by the World Health Organization as a neurological disease with proper ICD-9 reimbursement codes, could help alleviate this stigma.

Lines 135-138: "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)."

Addition Requested: *(after Line 138) "While self-management may empower some patients with ME/CFS, more severely affected individuals may be harmed by this process. It is essential that clinicians who follow patients with ME/CFS keep abreast of the literature, participate in clinical trials, communicate with the patient's caregivers and primary care doctor, and assess any changes in clinical presentation at each patient encounter."*

Rationale: Because clinical presentation among ME/CFS patients varies with some patients being less impaired than others, it is necessary to tailor exercise and other proposed regimens involving physical activity to the individual to avoid imposing harm.

What tools, measures, and approaches help define individuals with ME/CFS? How are tools and measures used to distinguish subsets of patients with ME/CFS?

Lines 166-167: "The symptoms patients consider clinically meaningful are not in the scientific literature; this discordance must be rectified."

Clarification Requested: There is research and evidence for post-exertional malaise in ME/CFS and neurocognitive symptoms have been demonstrated for decades in this patient population. Therefore, further clarification of this statement would be helpful since epidemiological literature does list the most common symptoms reported by patients.10

Future Directions and Recommendations

Lines 183-185: "The subjective nature of ME/CFS, associated stigma, and the lack of a standard case definition has stifled progress. Patients must be at the center of the research efforts, and their engagement is critical, as is outreach to underserved and vulnerable populations."

Revision Requested: *"The methods of quantitatively and qualitatively characterizing the severity of disease remain subjective in nature at this time. The failure to universally adopt the Canadian Consensus Criteria has stifled progress. Patients must be at the center of the research efforts. Their engagement is critical, as is outreach to underserved and vulnerable populations."*

Rationale: There is published objective data about ME/CFS and the disease itself is *not* subjective in nature. The CFSAC fully expects that the pathophysiology of this disease will eventually be unveiled.

Lines 191-192: "The dissemination of diagnostic and therapeutic recommendations should focus on primary care providers."

***Revision Requested*:** *"The dissemination of diagnostic and therapeutic recommendations should focus on primary care providers and all other health care providers dealing with symptoms specific to this disease, including but not limited to cardiologists, endocrinologists, neurologists, rheumatologists, psychiatrists, clinical immunologists, and infectious disease specialists."*

Rationale: Although the education of primary care providers is vital, the multi-systemic nature of the disease requires that patients see multiple specialists as well.

DEFINE DISEASE PARAMETERS

Lines 202-205: "Assemble a team of stakeholders (e.g., patients, clinicians, researchers, federal agencies) to reach consensus on the definition and parameters of ME/CFS. A national and international research network should be developed to clarify the case definition and to advance the field."

Revision Requested: *"Assemble a team of stakeholders (e.g., patients, clinicians, researchers, federal agencies) to review the results of the study by the Institute of Medicine and reach consensus on a path forward. HHS should adopt a universal case definition to help advance the field."*

Rationale: HHS agencies have contracted with the Institute of Medicine to develop clinical diagnostic criteria for the disease. Therefore, it is recommended that this statement be revised to identify and incorporate the need for stakeholders (e.g., patients, clinicians, researchers, federal agencies) to review, analyze, and/or reject the IOM recommendation on this matter.

CREATE NEW KNOWLEDGE

Lines 220: Specific activities should focus on…"

Addition Requested: *(after Line 220) "Developing a list (or set) of diagnostic tests or indicators which could be used by health care providers."*

Rationale: Since standard laboratory tests are often within normal ranges in these very sick patients, proper diagnosis is vital to further knowledge.

Lines 228-230: fMRI and imaging technologies should be further studied as diagnostic tools and as methods to better understand the neurologic dysfunction of ME/CFS.

Revision Requested: *"fMRI, imaging technologies, and 2-day Cardiovascular Exercise Testing (CPET) with gas exchange should be further studied as diagnostic tools and as methods to better understand the neurologic and autonomic dysfunction of ME/CFS."*

Rationale: 2-day Cardiovascular Exercise Testing (CPET) with gas exchange is an important physiological marker for the hallmark symptom known as post-exertional malaise.

Lines 231-234: "Biologic samples—which may include serum and saliva, RNA, DNA, whole blood or peripheral blood mononuclear cell, and tissues—as well as de-identified survey data—should be linked in a registry/repository for studies of pathogenesis, prognosis, and biomarker discovery.

Addition Requested*: (after Line 234) "The NIH should adapt the architecture of the National Autism Research Database (NDAR) to setup and provide ongoing support for a data and bio-bank sharing platform for ME/CFS research. This platform should allow for both phenotype and biologic data."*

Rationale: The National Autism Research Database (NDAR) is an NIH-funded research data repository that aims to accelerate progress in autism spectrum disorders (ASD) research through data sharing, data harmonization, and the reporting of research results. NDAR also serves as a scientific community platform and portal to multiple other research repositories, allowing for aggregation and secondary analysis of data. NDAR is an extensible, scalable informatics platform for ASD relevant data at all levels of biological and behavioral organization (molecules, genes, neural tissue, behavioral, social and environmental interactions) and for all data types (text, numeric, image, time series, etc.). NDAR was developed to "share data" across the entire ASD field and to facilitate collaboration across laboratories, as well as interconnectivity with other informatics platforms. A similar database is needed to advance ME/CFS research.

Lines 241-242: "Researchers should be encouraged to develop a repository for qualitative and quantitative work."

Addition Requested: *(after Line 242) "Inventorying and describing existing registries/repositories to identify gaps and establish opportunities for sharing would be a first step."*

Rationale: In a field with limited resources, it is important to collaborate and share resources whenever possible.

Lines 246-248: "For instance, drugs therapies used for fibromyalgia or other pain-related syndromes and disorders should be examined for their effectiveness in those with ME/CFS, and existing registries should be leveraged."

Revision Requested: *"For instance, using well characterized ME/CFS patients from existing practices as well as tissue samples from existing registries for this disease, drugs previously targeted only for autoimmune,[16] [17]neurodegenerative and viral diseases[18] should be examined for their effectiveness in patients with ME/CFS. Pharmacological treatments that address the symptoms of autonomic, immunologic and endocrine dysfunction should be explored as well."*

Rationale: Citing drugs for fibromyalgia and pain-related syndromes may give an incorrect impression of the nature of this disease. Based on promising research, the requested revision is a more appropriate statement.

IMPROVE METHODS AND MEASURES

Line 270 - 271: "How patients' background medications (including psychiatric drugs) affect function and outcome should be explored."

Revision Requested: *"How patients' background medications (including statins, anti-inflammatories, psychiatric drugs, sleep and pain medications) affect function and outcome should be explored."*

Rationale: Inclusion of additional medications is needed so as not to imply that ME/CFS is a psychiatric or psychological illness.

Lines 275-276: "Studies addressing biopsychosocial parameters (including the mind-body connection), function, and QOL should be encouraged."

Revision Requested: *"Use of outcome measures such as QOL and function should be encouraged in studies of immunological, neurologic and genomic factors as well as the other valuable studies outlined in the 'Create New Knowledge' section of this Workshop Report."*

Rationale: CFSAC has heard repeated public testimony from advocates objecting to a perceived emphasis on research that is focused on psychosocial factors as possible contributors to ME/CFS or the use of psychological/social/behavioral interventions. Based on the history of research funding for ME/CFS, the CFSAC is concerned that the study of biopsychosocial parameters will divert research funding from higher

priority studies of pathogenesis, prognosis, biomarker, drug repurposing and other discovery. The proposed edit would encourage biologically-focused studies that incorporate outcome measures such as function and QOL.

FINDING NEW FUNDING SOURCES

Lines 322-327: Opportunities exist within HHS to engage new ME/CFS working group members, to create efficiency, and to co-fund research that will promote diversity in the pipeline, eliminate disparities, and enhance the quality of the science (e.g., the National Institute on Minority Health and Health Disparities [NIMHD], the National Cancer Institute [NCI], the Department of Education's National Center for Medical Rehabilitation Research, [NCMRR], the Department of Defense [DoD]).

Addition Requested: *(after Line 327) "Since ME/CFS is a multi-systemic disease, there are also opportunities for other Institutes to add ME/CFS to their research portfolio. These opportunities will help advance ME/CFS on multiple fronts."*

Rationale: Again, we urge the Panel to address the need for funding to accomplish the goals outlined in this draft and to advance the research for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Lines 328-336: "Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences. These centers will be charged with determining the biomarkers associated with diagnosis and prognosis, epidemiology (e.g., health care utilization), functional status and disability, patient-centered QOL outcomes, cost-effectiveness of treatment studies, and the role of comorbidities in clinical and real-life settings. The centers should provide a complete characterization of control populations, as well as those who recover from ME/CFS. Ideally, these collaborative studies will recruit from the broad spectrum of Americans and will use measures that are reproducible."

Comment: The CFSAC wholeheartedly endorses this recommendation. A CFSAC Working Group is currently meeting to define the components of a ME/CFS Centers of Excellence. However, we caution the NIH to refrain from tagging ME/CFS onto the existing Interstitial Cystitis (IC) program. While IC can occur in ME/CFS, it is not a common co-morbidity, and studies using this population would introduce a bias that would not translate to the larger group. However, it should be noted that the IC MAPP (Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain) program could serve as a model to link and coordinate a research portfolio that would truly deliver the key needs: biomarkers, translational trials, and phase 2 and 3 clinical trials for ME/CFS.

CONDUCT CLINICAL TRIALS

Lines 339-343: 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.

Addition Requested: *"High quality clinical trials to facilitate the development of effective drugs for ME/CFS is recommended.*

Rationale: There are currently no FDA-approved drug therapies for ME/CFS; this gap should be specifically addressed.

CONCLUSIONS

Lines 359-361: "Patients and their advocates may benefit from education on how to effectively communicate their symptoms and concerns to clinicians, while health care providers could benefit from enhanced active listening skills and increased education."

Revision Requested: *"However, patients and their advocates should continue to communicate their symptoms and concerns to clinicians to the best of their ability. Health care providers will benefit from increased education about the realities of this disease."*

Rationale: Very few doctors are appropriately educated and informed about ME/CFS, educational efforts focusing on the medical community are necessary to ensure that patients receive the support and care they need. Although excellent "primers" for physicians exist, it is difficult for busy physicians to accept and absorb new materials. Therefore, strong, clear statements about the nature of the disease from respected groups such as this Panel may be helpful in encouraging the medical community to learn more about ME/CFS to improve the care provided to their patients.

Lines 365-368: "Thus, for needed progress to occur we recommend (1) that the Oxford definition be retired, (2) that the ME/CFS community agree on a single case definition (even if it is not perfect), and (3) that patients, clinicians, and researchers agree on a definition for meaningful recovery."

Revision Requested: *"Thus, for needed progress to occur we recommend (1) that the Oxford definition be retired and that studies using the Oxford definition not be used to inform treatment recommendations for ME/CFS, (2) that the Canadian Consensus Criteria be universally adopted until such time that updated criteria are accepted, (3) that the ME/CFS community review the clinical diagnostic criteria recommendation produced by the Institute of Medicine and then agree on a single clinical diagnostic case definition (even if it is not perfect) for use by all health care providers caring for patients with ME/CFS, (4) that this single clinical diagnostic case definition be followed by development of a research case definition for use by all conducting research on ME/CFS, and (5) that patients, clinicians, and researchers agree on a definition for meaningful recovery."*

Rationale: The CFSAC endorses universal acceptance of the Canadian Consensus Criteria at this time. A single case definition is needed to conduct reproducible research and appropriate treatment strategies.

Closing Remarks

The CFSAC appreciates the opportunity to provide expert advice and guidance regarding the executive draft summary. Our goal in preparing these comments is to assist you in developing a final Executive Summary that accurately reflects the concerns the Committee has heard from the ME/CFS community and ME/CFS experts caring for patients and conducting research in this area.

The P2P Panel is in a unique position to help advance research and care for individuals with ME/CFS. We appeal to you to leverage this opportunity to make comprehensive, concise targeted recommendations to the National Institutes of Health that will result in major efforts to "Advance the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome."

We commend you for undertaking the effort to address clarify and make recommendations to resolve key issues relating to this challenging disease. It is hoped that the final P2P report will possess the power to move federal agencies forward with funding and action.

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APPENDIX A

Historical CFSAC Recommendations Supportive of P2P Draft Executive Summary

CASE DEFINITION

October 2009: Multiple case definitions currently are used for CFS. The CFSAC rejects the empirical case definition and the terminology of "chronic un-wellness", both of which are endorsed by the CDC, and recommends that DHHS recognize a need for and commit to support a national effort to arrive at a consensus definition of CFS that is accurate, standardized, and reflective of the true disease.

October 2012: CFSAC recommends that you will promptly convene (by 12/31/12 or as soon as possible thereafter) at least one stakeholders' (ME/CFS experts, patients, advocates) workshop in consultation with CFSAC members to reach a consensus for a case definition useful for research, diagnosis and treatment of ME/CFS beginning with the 2003 Canadian Consensus Definition for discussion purposes.

March 2014: The Chronic Fatigue Syndrome Advisory Committee (CFSAC) unanimously stipulated that all references to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in these recommendations are defined by the 2003 Canadian Consensus Criteria.

RESEARCH/FUNDING

September 2004, August 2005: Promote, encourage, and fund research directed toward the diagnosis, epidemiology, and treatment of CFS in children and adolescents.

November 2006: Recommend the FY 08 and 09 budgets of the CDC for research be restored to or increased beyond the FY 05 level in order to sustain the CDC's remarkable momentum including the ability to finish the Georgia Study (especially the longitudinal portions).

November 2006: Based on the positive response to the NIH's Request for Applications issued in July 2005 (funded in 2006), the Committee recommends equivalent funding for a second RFA.

November 2006: The FY 08 and 09 budgets of the CDC for CFS public awareness education [should] be restored to or increased beyond the FY06 level based on the positive initial response to the November 2006 campaign launch.

May 2009: Provide adequate funding to CDC to effectively carry out a detailed 5-year plan. This should include, but not be limited to, immediate progress in these priority

areas: a) Identification of biomarkers and etiology of CFS; b) Creation of guidelines for adult and pediatric CFS management in full partnership with organizations representing CFS scientific and clinical expertise; c) Provision of web-based guidelines for CFS management given our current state of knowledge and expert opinion, again in full partnership with organizations representing CFS clinical and scientific expertise; and d) provision of comprehensive information about CFS in partnership with CFS experts to the scientific community, medical and mental health providers, educational institutions and the public for both adult and pediatric CFS through DHHS resources.

October 2009: Resubmission of the May 2009 recommendation with a modification to priority area a.) Identification of biomarkers, *with increasing efforts in viral etiology of CFS.*

May 2011: ME/CFS is an illness with enormous economic and human costs. The April 2011 NIH State of Knowledge Workshop identified a number of gaps in what is known about the illness. To address these gaps warrants an interagency effort comprising, but not limited to, NIH, CDC, and AHRQ. Further, the focus should be on interdisciplinary discovery and translational research involving interacting networks of clinical and basic science researchers. Areas to be examined would include the following: identification of patient subsets for detailed phenotyping and targeted therapeutic interventions, biomarker discovery, systems biology approaches and disability assessment. To facilitate the above goal, CFSAC recommends that ME/CFS research receive funding commensurate with the magnitude of the problem and that the NIH (and/or other appropriate agencies) issue and RFA specifically for ME/CFS.

November 2011: CFSAC recommends to the Secretary that the NIH or other appropriate agency issue a Request for Applications (RFA) for clinical trials research on chronic fatigue syndrome/Myalgic encephalomyelitis.

October 2012: CFSAC recommends that you instruct the NIH to issue an RFA (funded at the $7-10 million range) for projects to establish outcomes measures for ME/CFS diagnosis, prognosis and treatment which would include but not be limited to biomarker discovery and validation in patients with ME/CFS. CFSAC recommends that you allocate specific funds to study patients with ME/CFS from past cluster outbreaks. CFSAC recommends that you allocate funds to study the epidemiology of patients with severe ME/CFS.

May 2013: ME/CFS is an illness with enormous economic and human costs. The April 2011 NIH State of Knowledge Workshop identified a number of gaps in what is known about the illness. To address these gaps warrants an interagency effort comprising, but not limited to, NIH, CDC, and AHRQ. Further, the focus should be on interdisciplinary discovery and translational research involving interacting networks of clinical and basic science researchers. Areas to be examined would include the following: identification of patient subsets for detailed phenotyping and targeted therapeutic interventions, biomarker discovery, systems biology approaches and disability assessment. To accomplish this, specific issues would include:

- Fund specific research for identification of biomarkers and etiology of CFS
- NIH or other appropriate agency should issue a Request for Applications (RFA) for specific clinical trials research on chronic fatigue syndrome/Myalgic encephalomyelitis.

March 2014: CFSAC recommends that the Secretary fund ME/CFS commensurate with the epidemiologic prevalence and economic burden that this disease imposes on American society.

June 2014: CFSAC recommends that the NIH issue a Request for Applications (RFA) for ME/CFS by November 1st, 2014, or as soon as feasible, to address the gaps in ME/CFS knowledge and research. The RFA should consider current known gaps in knowledge for the following areas:

- Provocation designs where symptoms are triggered through standardized challenges involving exercise, cognitive tasks, and mental stressors. These designs appear to be more likely to identify symptom to biology relationships in comparison to assessments done in resting states.
- Ambulatory monitoring of symptoms, activities, behaviors, and physiological states that identify associations between biological and behavioral measures, e.g., daily fatigue ratings and cytokine fluctuations.
- Network analysis of dysregulation of multiple bodily systems, such as the neuroendocrine system, the central nervous system, the autonomic nervous system and the immune system.
- Natural history studies aimed at identifying the genetic triggers and causal factors of ME/CFS.
- Treatment trials that address both clinical and biologic outcomes.

This RFA may also be informed by the gaps identified in the 2011 NIH State of the Knowledge Workshop, the Pathways to Prevention Program for ME/CFS research panel report or any relevant source, including but not limited to, the IACFS meeting summary.

CENTERS OF EXCELLENCE

September 2004, August 2005: Direct the NIH to establish five Centers of Excellence within the United States that would effectively utilize state of the art knowledge concerning the diagnosis, clinical management, treatment, and clinical research of persons with CFS with funding in the range of $1.5 million per year for five years.

May 2007: Recommend that HHS establish 5 regional clinical care, research, and education centers, centers which will provide care to this critically underserved population, educate providers, outreach to the community, and provide effective basic science, translational, and clinical research on CFS.

October 2009: Establish Regional Centers funded by DHHS for clinical care, research, and education on CFS.

May 2009: Establish Regional Centers funded by DHHS for clinical care, research, and education on CFS to provide care to this critically underserved population, educate providers, outreach to the community, and provide effective basic science, translational, and clinical research on CFS.

October 2009: Establish Regional Centers funded by DHHS for clinical care, research, and education on CFS.

November 2011, May 2013: CFSAC would like to encourage and support the creation of the DHHS Interagency Working Group on Chronic Fatigue Syndrome and ask this group to

work together to pool resources that would put into place the "Centers of Excellence" concept that has been recommended repeatedly by this advisory committee. Specifically, CFSAC encourages utilizing HHS agency programs and demonstration projects, available through the various agencies, to develop and coordinate an effort supporting innovative platforms that facilitate evaluation and treatment, research, and public and provider education. These could take the form of appropriately staffed physical locations, or be virtual networks comprising groups of qualified individuals who interact through a variety of electronic media. Outreach and availability to underserved populations, including people who do not have access to expert care, should be a priority in this effort.

COLLABORATION AND NETWORKING

September 2004: DHHS should provide funds to develop an international Network of Collaborators that would allow for multidisciplinary CFS-related research using standardized criteria accepted by the international CFS research community.

October 2010: Develop a national research and clinical network for ME/CFS (myalgic encephalomyelitis/CFS) using regional hubs to link multidisciplinary resources in expert patient care, disability assessment, educational initiatives, research and clinical trials. The network would be a resource for experts for health care policy related to ME/CFS

March 2014: CFSAC recommends that HHS provide funding to gather requisite data (prevalence rate/provider attitudes and knowledge, etc.) regarding ME/CFS patients as defined by the 2003 Canadian Consensus Criteria through established primary care associations such as the American Academy of Pediatrics; the American Academy of Family Practice; the American College of Physicians; the American Board of Family Practice; and the American College of Obstetrics and Gynecology.

June 2014: CFSAC recommends that the NIH adapt the architecture of the National Autism Research Database (NDAR) to setup and provide ongoing support for a data and bio-bank sharing platform for ME/CFS research. This platform should allow for both phenotype and biologic data.

EDUCATION AND CARE

September 2004, August 2005: Pursue making CFS a topic of training for health care providers, wherever appropriate at regional and national conferences sponsored by the Department.

May 2008: Direct the Administrator of HRSA to communicate with each Area Health Education Center regarding the critical need for provider education of CFS. HRSA has the potential to disseminate information on CFS to a wide range of providers, communities and educational institutions. HRSA should inform these groups that persons with CFS represent an underserved population and that there is a dramatic need for healthcare practitioners who can provide medical services to CFS patients. HRSA should further inform these groups that the CDC offers a web based CME program on CFS, and encourage AHEC providers to participate in this CME program.

October 2009: AHRQ is expected to complete a review of CFS for the NIH State of the Knowledge Workshop. After this process, we recommend that the findings be communicated immediately to key medical education, accreditation, licensing, specialty,

and certification boards and organizations. In addition, we recommend a Surgeon General's letter be disseminated to inform clinicians and other health professionals throughout the US and its territories on the impact of CFS on the health of US adults and children.

May 2010: The Secretary should recognize the special challenges of ensuring that CFS is part of any efforts to train or educate health care providers under health reform.

June 2012: CFSAC asks that HHS partner with Committee members and the Department of Education to educate educators and school nurses on ME/CFS affecting children and adolescents.

June 2012: CFSAC asks that a link be added to the CFSAC website for the Department of Education-supported Parent Technical Assistance Center Network.

March 2014: CFSAC recommends that HHS provide opportunities for dissemination of information through the development of a curriculum at all U.S.-based medical schools providing the tools needed for physicians and other medical professionals to recognize ME/CFS as defined solely by the 2003 Canadian Consensus Criteria and to make appropriate referrals. CFSAC recommends that funding be allotted to the appropriate agencies that can best develop teaching modules featuring ME/CFS patients with complex presentations as defined by the 2003 Canadian Consensus Criteria. CFSAC recommends that HHS provide funding through Health Resources and Services Administration (HRSA) and other agencies to support integrative medicine programs featuring learning about ME/CFS patients as defined by the 2003 Canadian Consensus Criteria.

March 2014: CFSAC recommends that HHS fund through appropriate agencies novel programs such as "Project Echo" comprised of experts and/or multidisciplinary teams with expertise in ME/CFS that reach areas where patients do not have access to adequate clinical care for ME/CFS as defined by the 2003 Canadian Consensus Criteria.

Annotated Bibliography

[1] Voice of the Patient: http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf
[2] 2011 State of Knowledge Workshop Report: http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf
[3] Journal of Chronic Fatigue Syndrome Volume 11 Number 1 2003
[4] NIH ODP P2P Workshop Draft Report: https://prevention.nih.gov/docs/programs/mecfs/ODP-MECFS-DraftReport.pdf
[5] Background statement NIH ODP P2P Workshop: https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs
[6] Background statement NIH ODP P2P Workshop: https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs
[7] Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The economic impact of ME/CFS: individual and societal costs. Dyn Med. 2008 Apr 8;7:6. PMID: 18397528
[8] Carruthers, van de Sande A Clinical Case Definition and Guidelines for Medical Practitioners http://sacfs.asn.au/download/consensus_overview_me_cfs.pdf
[9] Light KC, Agarwal N, Iacob E, White AT, Kinney AY, VanHaitsma TA, Aizad H, Hughen RW, Bateman L, Light AR. Differing leukocyte gene expression profiles associated with fatigue in patients with prostate cancer versus chronic fatigue syndrome. Psychoneuroendocrinology. 2013 Dec;38(12):2983-95. doi: 10.1016/j.psyneuen.2013.08.008. Epub 2013 Sep 6.

[10] Booth NE, Myhill S, McLaren-Howard J. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Int J Clin Exp Med. 2012;5(3):208-20. Epub 2012 Jun 15.

[11] de Vega WC, Vernon SD, McGowan PO.DNA methylation modifications associated with chronic fatigue syndrome. PLoS One. 2014 Aug 11;9(8):e104757. doi: 10.1371/journal.pone.0104757. eCollection 2014.

[12] Smylie AL, Broderick G, Fernandes H, Razdan S, Barnes Z, Collado F, Sol C, Fletcher MA, Klimas N. A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome. BMC Immunol. 2013 Jun 25;14:29. doi: 10.1186/1471-2172-14-

[13] Naschitz J. Midodrine treatment for chronic fatigue syndrome. Postgrad Med J 2004 April; 80(941): 230-232.
[14] Burley L, Cox DL, Findley LJ. Br J Occup Ther 2007;70:339–44]
[15] The 8th INTERNATIONAL IACFS CONFERENCE, January 10-14, 2007 Jason, et al http://www.iacfsme.org/WhytheNameofAnIllnessisofImportance/tabid/100/Default.aspx
[16] Strayer D. A double-blind placebo-controlled, randomized clinical trial of the TLR-3 against rintatolimod in severe cases of chronic fatigue syndrome. PLoS One. 2012; 7(3):e31334.

[17] Oystein Fluge, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome: a double –blind placebo controlled study. PLoS One.2011; 6(10)
[18] A.Martin Lerner, et al. Antibody to Epstein Barr Virus Deoxyuridine Nucleotidohydrolase Triphosphate and Deoxyribonucleotide polymerase in a chronic fatigue syndrome subset. PLoS One 2012; 7(11):e47891.
[19] Goudsmit EM, Nijis J, Jason LA, et al. Pacing as a Strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome:a consensus document. Disabil Rehavil; 2012 34 (13): 1140-7.