

Chronic Fatigue Syndrome Advisory Committee

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).

August 2015

Recommendations

From the

HHS Chronic Fatigue Syndrome ADVISORY COMMITTEE

Following Publication of:

INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES BEYOND MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME: Redefining an Illness

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Sponsored by the U.S. Department of Health and Human Services Office on Women's Health, the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Agency for Healthcare Research and Quality, and the Social Security Administration

and

NATIONAL INSTITUTES OF HEALTH Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

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

Note: The term "ME/CFS" is used herein to correspond with terminology used in both reports.

Executive Summary

The H.H.S. Chronic Fatigue Syndrome Advisory Committee (CFSAC) acknowledges the positive intent underlying the commission of reports from the Institute of Medicine (IOM) and the NIH Pathways to Prevention Workshop (P2P) and appreciates this opportunity to provide advice and recommendations to the Secretary of Health and Human Services (HHS) through the Assistant Secretary for Health (ASH).

The involvement of the Institute of Medicine confers a legitimacy to the science that has not been heretofore acknowledged by the medical community. We hold the Institute in high regard and respect the dedication, effort and enthusiasm displayed by the members of the Committee during their appointment. It is clear that both disease experts and non-experts recognized the debilitating nature of the disease and the urgent need for scientific research, medical education, and improved patient care.

It is also clear that the members of the P2P Panel brought open minds and compassionate hearts to their work. Their identification of numerous research gaps, unique challenges, and methodological and scientific weaknesses has reinforced prior CFSAC recommendations and should serve as a key resource for moving the science forward.

As substantiated by the P2P panel, ME/CFS is *"an unmet public health need"* with *"tremendous impact at the individual, family, and societal level."* The IOM Committee has concurred, stating that the disease causes *"significant impairment and disability that have negative economic consequences at both the individual and the societal level"* and emphasizing an *"urgent need for more research."*

Although a long history of minimal federal funding has impacted scientific research for this disease at every level, rapid scientific discovery is within reach. During the past decade alone, a number of privately-funded studies have used existing and emerging technologies to identify potential biomarkers that could enhance understanding of the biological factors involved in both onset and progression. Additionally, small clinical trials of Rituxan (an FDA-approved monoclonal antibody) have demonstrated substantial improvement in a significant percentage of patients. A commitment of resources by HHS agencies at this time will enable scientists to reproduce important research, address identified gaps, accelerate progress, and better understand this debilitating disease.

This document provides actionable recommendations to the Secretary which are supported by the IOM and P2P reports. Additional statements from the AHRQ Evidence Review, the FDA Voice of the Patient, and the NIH State of the Knowledge Workshop Report serve as reinforcement of recommendations as appropriate. Areas of consideration are as follows:

- ❖ **Research Direction, Funding and Goals**
- ❖ **Diagnostic Criteria: A Path for Moving Forward**
- ❖ **Medical Education and Guidelines**
- ❖ **Acknowledgement and Identification of the Disease**

The publication of the IOM and P2P reports signifies a potential turning point in the history of this disease. Failure to acknowledge and follow through on the numerous recommendations provided in these reports would be an injustice to all concerned.

Research Direction, Funding, and Goals

ME/CFS is a serious multi-systemic disease that imposes a burden of illness on millions of people in the United States and around the world. As acknowledged by the Institute of Medicine, ***“In its most severe form, this disease can consume the lives of those whom it afflicts.”***

Despite the monumental toll on human lives and the estimated cost to U.S. society of \$17 to \$24 billion annually, research funding for this disease has been woefully inadequate. In fact, every recent federally-sponsored report has underscored the need for substantial research and a sustained commitment from the Department of Health and Human Services in order to understand and find treatments for the disease.

- Institute of Medicine (2015): *“... the committee was struck by the relative paucity of research on ME/CFS conducted to date. Remarkably little research funding has been made available to study the etiology, pathophysiology, and effective treatment of this disease, especially given the number of people afflicted. Thus, the committee was unable to define subgroups of patients or even to clearly define the natural history of the disease. More research is essential.”*
- NIH Pathways to Prevention (2015): *“Overall, there has been a failure to implement what we already know for ME/CFS patients while the disease steals their health and well-being. Scientifically rigorous research is needed to improve this situation... There are few disease-specific clinical trials; a disconnect on ways patients, clinicians, and researchers define meaningful outcomes; a lack of well-controlled, multifaceted studies using large, diverse samples; and limited public and private research dollars directed at ME/CFS... The public, provider, and research communities are frustrated with the minimal progress to improve the state of science for ME/CFS over the last 20 years.”*
- AHRQ Evidence Review (2014): ***“More definitive studies are needed to fill the many research gaps in diagnosing and treating ME/CFS... Given the prevalence and health impacts of ME/CFS, future research is necessary in several areas...”***
- FDA Patient-Focused Drug Development Initiative Voice of the Patient (2014): ***“A significant unmet medical need exists for patients with CFS and ME... Patients are desperate for research and development of treatments that can: (a) better relieve their most significant symptoms and (b) address the underlying cause(s) of their disease.”***

In response to a June 2014 CFSAC Recommendation for RFA's, the NIH advised: "Unfortunately there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment for ME/CFS.... RFAs generally encourage a narrowly defined research area that addresses more specific gaps in scientific knowledge. RFAs are designed to build upon recommendations that have been identified through cutting-edge research findings in the extant literature, address unmet NIH Institute mission-specific objectives, as well as incorporate findings from workshops and conferences on specific topics."

Since that time, both the IOM and P2P reports have identified definitive evidence of biological impairment; acknowledged cutting-edge research findings; specified numerous gaps in knowledge; and emphasized the urgent need for research. Accordingly, **the H.H.S. Chronic Fatigue Syndrome Advisory Committee urges the Secretary to facilitate allocation of the funding and resources necessary to advance the following recommendations regarding research direction, funding and goals.**

1. **PRIORITIZE DEVELOPMENT OF BIOMARKERS AND OBJECTIVE DIAGNOSTIC TESTS:** CFSAC recommends that targeted Requests for Applications (RFAs), which clearly prioritize the identification and validation of distinct biomarkers and objective diagnostic tests and give preference to collaborative network initiatives, be issued as soon as possible. RFAs should advance the study of fMRI, positron emission tomography (PET) and other imaging technologies; 2-day cardiopulmonary function/recovery with gas exchange; cytokine abnormalities; gene expression, protein, or metabolite signatures; natural killer (NK) cell function; and other promising markers for diagnostic or therapeutic use. CFSAC believes that **time is of the essence** regarding this urgent recommendation.

Rationale: The decades-long debate regarding Diagnostic Criteria will end with development of a sufficiently accurate set of diagnostic biomarkers and objective diagnostic tests for clinical use. Biomarkers related to therapeutic response will encourage drug development. Research will be most effective if conducted through collaborative network initiatives, including, but not limited to, multi-site studies or networks of investigators. As substantiated by both the Institute of Medicine and the NIH Pathways to Prevention panel, **biomarker research is an urgent priority.**

- Institute of Medicine (2015): *“There is an urgent need for more research to discover what causes ME/CFS, understand the mechanisms associated with the development and progression of the disease, and develop effective diagnostic markers and treatments... Few attempts have been made to follow up on or replicate intriguing findings in the literature... More research is needed to address cytokine abnormalities and their potential use as biomarkers of possibly distinct subgroups of ME/CFS... Further studies confirming the different expression of genes and immune biomarkers in patients with ME/CFS in response to physical exertion may help us to better understanding the pathophysiology of PEM... Deficits in patients may lead to poor activation or reduced connectivity of the anterior cingulate cortex. Exploring this possibility could further the effort to identify biomarkers of the disorder.”*
- NIH Pathways to Prevention (2015): *“A priority should be placed on developing biomarkers and diagnostic tests... The field could be energized and diversified by creating opportunities for junior and new investigators to be involved... Current research has neglected many of the biological factors underlying ME/CFS onset and progression. Research priorities should be shifted to include basic science and mechanistic work that will contribute to the development of tools and measures such as biomarker or therapeutics discovery... Determining the most important physiologic measures and pathophysiology, as well as genome-wide association studies (GWAS) and phenotyping, is essential for stratifying patients. Specific activities should focus on: Developing valid prognostic tests that can guide treatment strategies using genomic, epigenomic, proteomic, and metabolomic strategies to identify critical biomarkers that will be clinically applicable. Gene expression, protein, or metabolite signatures that can correctly diagnose ME/CFS and distinguish it from other chronic conditions, while predicting disease severity and clinical outcomes, are needed... fMRI and imaging technologies should be further studied as diagnostic tools ...”*
- AHRO Evidence Review (2014): *Much research in this field focuses on discovering etiologies rather than testing diagnostic strategies... studies on serum biomarkers and cardiopulmonary function/recovery that did meet the inclusion criteria were not adequately tested in a broad spectrum of patients to determine utility for distinguishing patients ... Further studies are needed to determine the utility of 2-day cardiopulmonary exercise testing to identify or monitor symptoms of post-exertional malaise.*

- NIH State of Knowledge (2011): “A number of biomarkers have been described but need to be validated in ME/CFS patients, including natural killer (NK) cell function, perforin, cell membrane dipeptidyl peptidase-4 (CD26 antigen), and levels of various individual cytokines... **Biomarkers, quantifiable outcomes or end points, and a deeper understanding of patient genomics are critical needs for developing diagnostics and effective interventions.**”

2. **ADDRESS GAPS IN BASIC, TRANSLATIONAL, CLINICAL AND EPIDEMIOLOGICAL RESEARCH:**

CFSAC recommends that the NIH issue Requests for Applications (RFAs), and the CDC allocate targeted funding, to address the gaps in basic, translational, clinical and epidemiological research as identified in the *NIH Pathways to Prevention Workshop Report*, the IOM’s *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*, the AHRQ Evidence Report *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*, and the 2011 *NIH State of the Knowledge Workshop Report*. Such RFAs should be issued as soon as feasible. As was made clear by the NIH P2P panel, **“Innovative biomedical research is urgently needed.”**

Rationale: Each and every federally-sponsored report published in the past several years has indicated that ME/CFS results in enormous economic and human costs and merits substantial biomedical research. Areas identified in these reports include but are not limited to the following:

- Institute of Medicine (2015): “Almost all the studies conducted to date have compared patients with ME/CFS with healthy controls rather than with patients with these other fatiguing disorders. As a result, **there is a paucity of data to guide clinicians in distinguishing among these disorders, a gap that urgently needs to be filled... Finding the cause of and cure for ME/CFS may require research that enlists large numbers of patients** with this disorder from which important subsets can be identified in terms of disease symptomatology, responses to physical and cognitive stressors, brain imaging, the microbiome, virology, immune function, and gene expression. Integrative approaches using systems biology may be useful in unraveling illness triggers. Studies aimed at assessing the natural history of the disease and its temporal characteristics (onset, duration, severity, recovery, and functional deficits) are essential...”
- NIH Pathways to Prevention (2015): **“Innovative biomedical research is urgently needed... An integrated, systems-level approach should be followed to understand how immunologic, neurologic, and metagenomic factors may contribute to ME/CFS. Immunologic mechanisms of ME/CFS and pathways associated with disease progression must be defined and characterized.... Gene expression, protein, or metabolite signatures that can correctly diagnose ME/CFS and distinguish it from other chronic conditions, while predicting disease severity and clinical outcomes, are needed. Determining the most important physiologic measures and pathophysiology, as well as genome-wide association studies (GWAS) and phenotyping, is essential... fMRI and imaging technologies should be further studied as diagnostic tools and as methods to better understand the neurologic dysfunction. Further exploration is needed of the intestinal microbiome, and the effect, if any, of the environment and microbiome on ME/CFS development using cutting-edge technologies (e.g., high-throughput sequencing), neurocognitive tests, and neuroimaging.... Investing in bench-to-bedside research for ME/CFS is recommended... Longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction in ME/CFS remain important... Epidemiological studies of ME/CFS, including incidence and prevalence, who is at high risk, risk factors, geographical distribution, and the identification of potential health care disparities are critical.”**
- AHRQ Evidence Review (2014): **“... diagnosing and treating specific symptoms such as PEM or orthostasis, and synthesizing this literature and evaluating its utility in diagnosing the syndrome of ME/CFS or subsets of the population is needed.”**

- NIH State of Knowledge (2011): “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.**”
3. **ADVANCE TREATMENTS AND THERAPEUTICS**: CFSAC recommends that the NIH make use of resources such as the NIH Clinical Center as well as other public and private options as soon as feasible for clinical trials and fast-track testing of new or repurposed therapies. High quality multi-site clinical trials using well-characterized patients (as defined in the recommendation that follows) are considered essential to facilitate the approval of effective drugs, address both biological and clinical outcomes, and establish outcome measures for treatment and prognosis.

Rationale: There are no FDA-approved drug therapies for ME/CFS and no agreement on how to assess treatment response, two important gaps that urgently need to be filled. Opportunities exist for repurposing of approved drugs previously targeted for autoimmune, neurodegenerative, viral and other diseases as evidenced by the recent Valganciclovir study in the U.S. and the Rituxan studies performed in Norway. However, public-private partnership is needed. Initial investment by the NIH will catalyze pharmaceutical interest, something which is critical in an area with minimal pharmaceutical investment to date.

- NIH Pathways to Prevention (2015): “**There is a need for “omics”-based drug repurposing and neurobiology studies...** New knowledge might include an understanding of molecular mechanisms underlying ME/CFS, new ways to perform pathway analyses, and/or new pharmacogenomic drug discovery or repurposing... New technologies to address underserved populations and unmet needs (e.g., mobile technology, online tracking tools) should be developed and employed... Previously collected research data should be analyzed to advance knowledge and inform trial development and design and facilitate necessary clinical trials. **Opportunities to utilize the NIH Clinical Center for clinical trials and to fast-track testing of new therapies should also be explored.**”
- AHRQ Evidence Review (2014): “... **interventions should be in multiple sites, use multicomponent treatments, larger sample sizes based on power calculations for key outcomes, and more rigorous adherence to methodological standards for clinical research.** Given the fluctuating nature of the condition, follow-up periods greater than 1 year would be optimal to determine effectiveness over time... Reporting of information about co-interventions, the timing of studied interventions in relation to other interventions, and adherence to interventions would improve the applicability of study findings. Similarly, stratification of findings by patient characteristics (e.g., baseline severity, comorbidities, demographics, symptom sets) would help determine the applicability of different interventions for specific patients and situations.”
- NIH State of Knowledge (2011): **Treatment Research: Studies suggest immune abnormalities consistent with chronic viral infection... Some of these studies point to reasonable biomarkers for disease presence and severity, possibly leading to future therapeutics.**”
- FDA Voice of the Patient: “**A significant unmet medical need exists for patients with CFS and ME... Currently, there are no approved therapies indicated to treat CFS and ME... Patients are desperate for treatments that target the underlying cause of the disease.**”

4. **STANDARDIZE ASSESSMENT METHODS AND MEASURES:** As both the IOM and P2P reports have emphasized the need for improved methods and standards for both research and clinical care, CFSAC recommends the following strategy to advance those goals:

- a) CFSAC recommends that federally-funded research specify use of the 2003 Canadian Consensus Criteria as a research case definition for patient selection (in addition to other requirements established for specific research purposes) using standardized and uniform assessment methods and measures for applying the definition.
- b) CFSAC recommends timely formation of a methodological workgroup comprised of disease experts and stakeholders to establish uniform assessment methods, measures and data standards for federally-funded research; define and standardize disease terminology; operationalize symptom assessment methods in clinical care; and advance clinical guidelines and validated tools for diagnosis and treatment.

Rationale: Reproducible research requires well-characterized patients. The NIH Pathways to Prevention panel has recommended a methodological workgroup to improve methods and measures for research, and the IOM has affirmed that the development of validated clinical and research tools is an urgent priority. It is the opinion of the HHS CFSAC that a methodological workgroup could address clinical methods and measures as well, and that Centers of Excellence could also have a substantial impact on the development of uniform assessment standards and guidelines.

Additionally, until such time that distinct biomarkers have been developed and disease subtyping is achieved, it is critical that researchers use a single, consistent, and universally-accepted research criterion with uniform assessment methods and measures for patient selection. CFSAC recognizes that the IOM definition is for clinical diagnostic purposes only and agrees that consensus is needed on a research case definition. CFSAC believes that the criterion most likely to achieve universal consensus for research purposes at this time is the 2003 Canadian Consensus Criteria (CCC), which have been identified by the Institute of Medicine as being "quite similar" to the proposed Diagnostic Criteria and have been a recognized standard in the research community for years. The 2003 Canadian Consensus Criteria (CCC) have been formally endorsed by 50 international experts and currently serves as an important standard for researchers in the U.S. and abroad. The CCC is translated into several languages, is accompanied by overview documents, and as reflected in the IOM report, "*The proposed criteria are quite similar to the Canadian Consensus Criteria (CCC) (Carruthers et al., 2003).*" Further, the IOM has made it clear that the Fukuda Criteria will capture different cohorts: "*The committee recognizes that some patients diagnosed by other criteria, such as the Fukuda definition (Fukuda et al., 1994), will not fulfill all of the criteria proposed here...*"

- Institute of Medicine (2015): "*Studies on ME/CFS used different inclusion criteria... creating an unclear picture... the use of different diagnostic criteria for patient selection limits comparisons across studies... contradictory findings may also be due to the use of various scales, instruments, and measures for symptoms, some of which are imprecise, not comprehensive, or not validated. The development of clinical questionnaire or history tools that are valid across populations of patients should be an urgent priority... Use of a standardized instrument is critical to measuring PEM accurately.*"
- NIH Pathways to Prevention (2015): "*...The lack of a specific and sensitive diagnostic test and clearly defined diagnostic criteria has hampered research on pathogenesis, treatment, and conceptualization of ME/CFS as a distinct entity... multiple case definitions for ME/CFS have hindered progress... Agreeing on a case definition and clarifying comorbidities could launch bench-to-bedside science... instruments used to evaluate ME/CFS are not validated, are inappropriate, and may be misleading...*"

*Small clinical trials, most with methodological limitations and all constrained by the lack of a gold standard for diagnosis of ME/CFS, have led to confusion... participant variability at different study centers may, in part, be responsible for conflicting results... Without a diagnostic test, stratification must occur to reduce and comprehend variability (e.g., onset, time course, comorbid conditions), and to identify clearly defined endpoints for treatment trials and interventions. **The NIH should develop an ME/CFS methodological workgroup.***

- AHRO Evidence Review (2014): ***“Consensus about which case definition is appropriate to use as the gold standard will further advance the study of diagnostic methods for ME/CFS. None of the current diagnostic methods have been adequately tested to identify patients with ME/CFS when diagnostic uncertainty exists... Future studies evaluating the diagnostic capability of instruments for the identification of ME/CFS should include populations that include a broad range of people with relevant conditions that require clinical distinction from ME/CFS.”***
- NIH State of Knowledge (2011): ***“... the lack of consistency in using one definition across the world is a major impediment to replicating findings in research and makes it exceedingly difficult to identify biomarkers for the disease... Throughout the Workshop, participants identified opportunities for advancement in the current research paradigm for ME/CFS, beginning with a need to define and standardize the terminology and case definitions... 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.”***

5. ASSIGN THE DISEASE TO AN INSTITUTE: Given the clear involvement of neurological dysfunction in ME/CFS, CFSAC recommends that the disease be assigned to the National Institute of Neurological Disorders and Stroke (NINDS). CFSAC supports a continuing role for the Trans-NIH ME/CFS Working Group but recommends that leadership of the group be held jointly by the National Institute of Neurological Disorders and Stroke (NINDS) and by the National Institute of Allergy and Infectious Diseases (NIAID).

Rationale: Although ME/CFS is a multi-systemic disease that requires study in several fields, there is a pressing need for manifest leadership and resolute commitment within the National Institutes of Health. Substantial gaps in research warrant assignment to an Institute with the expertise, authority and resources needed to fund, facilitate, coordinate, and monitor the considerable work that is needed and to ensure that the disease is a part of the NIH-Wide Strategic Plan. . The NINDS possesses the resources, expertise, and influence needed to engage intramural and extramural researchers, provide and facilitate research funding, advocate for involvement of other institutes, and resolve barriers that impede progress. The NINDS supports research for diseases which present similarly to ME/CFS and may be important controls for research (e.g. multiple sclerosis, systemic lupus, neurological sequelae in Lyme disease). The NINDS is currently associated with a Phase II Rituximab Trial for Myasthenia Gravis through the NIH Network for Excellence in Clinical Trials. A number of areas of NINDS study relate closely to ME/CFS, e.g. aphasia; ataxia; orthostatic intolerance; chronic pain syndromes; cytomegalovirus; dysautonomia; hypersomnia and other sleep disorders; encephalopathy and encephalitis; inflammatory and mitochondrial myopathies; neuromuscular disease; neurotoxicity; and post-polio syndrome. Due to the role of immune dysfunction and evidence of infection as a possible trigger for the disease, it is anticipated that the NIAID will play a more active role in advancing the research moving forward. CFSAC therefore suggests that leadership of the Working Group be held jointly by the NINDS and the NIAID.

- NIH Pathways to Prevention (2015): *"The NIH Institutes and Centers... and other U.S. Department of Health and Human Services (HHS) agencies should coordinate research efforts to promote efficiency and effectiveness, while using public/private partnerships to leverage existing NIH infrastructure and dollars..."*

there is a need for partnerships across institutions to advance the research and develop new scientists... New collaborative models, investigator-initiated studies, career development, and small grant mechanisms with specific attention to developing a cadre of junior investigators, including women and minorities who may offer innovative new approaches, are needed."

6. APPOINT A CROSS-AGENCY LEADER: To address the breadth and magnitude of needs raised by the IOM and P2P reports, CFSAC recommends that the HHS appoint a senior-level cross-agency leader ("czar") with the authority, position and fiscal responsibility required to coordinate, develop, implement, and monitor a broad strategic cross-agency response to this disease through open and collaborative engagement of both internal and external stakeholders. At minimum, the strategic cross-agency plan should address the critical need for research, drug development, epidemiology, medical education, medical care and public awareness. It is recommended that this cross-agency leader serve as Designated Federal Official (DFO) to the CFSAC and be required to provide a comprehensive biannual report regarding progress and goals.

Rationale: The Institute of Medicine has recommended appointment of a "czar" to oversee the dissemination of diagnostic guidelines to healthcare professionals nationwide as outlined in the IOM report. To facilitate rapid progress and address the critical gaps identified in the IOM, P2P and AHRQ reports, such a position could be expanded to include cross-agency leadership and development of a strategy designed to ensure forward progress regarding the numerous needs outlined in the IOM and P2P reports including, but not limited to, scientific research, epidemiology, medical education, public awareness, treatment and care. Given the expectation that CFSAC will continue to provide a primary mechanism for community engagement, it is recommended that this leader also fill the role of Designated Federal Official (DFO) to the CFSAC.

- Institute of Medicine (2015): *"Designation of an HHS Point Person - HHS should consider appointing an individual to oversee the dissemination of the new diagnostic criteria nationwide to health care professionals (i.e., a "SEID czar" within the department). This person should have access to the necessary resources and the authority to implement the dissemination plans for the new criteria and address any questions or concerns that arise. Having such an individual in place will also help demonstrate HHS's responsiveness to this issue."*
- NIH Pathways to Prevention (2015): *"...we strongly encourage engaging with: Health professional licensing and accreditation agencies to ensure a curriculum that facilitates ME/CFS knowledge acquisition; Health Resources and Services Administration (HRSA) to facilitate training; Professional societies and patient organizations to facilitate a public-private partnership, as well as training and funding of health care professionals; Clinicians and researchers, who have a responsibility to encourage and track progress... Federal agencies (e.g., AHRQ, the U.S. Department of Veterans Affairs [VA]) and professional societies should work together to create quality metrics and a standard of care."*

7. PROVIDE RESEARCH FUNDING COMMENSURATE WITH THE BURDEN OF DISEASE: To facilitate the above goals, CFSAC recommends that the Secretary work with HHS agencies to ensure that total research funding is commensurate with the epidemiologic prevalence and economic burden imposed by this disease. Based on disease prevalence, equitable funding is estimated to be \$250,000,000 per year.

Rationale: In the absence of appropriate funding for needed research, meaningful advancement will not occur. NIH funding averages a mere \$5 per patient, compared with \$255 per multiple sclerosis patient and \$2,482 per HIV/AIDS patient.

Based on the findings of the IOM and NIH P2P, the disparity of federal resources, and the huge economic burden of ME/CFS, funding that is commensurate with economic burden is well-justified to reverse the decades long trend of misunderstanding and inappropriate treatment of patients and reduce the overall economic burden imposed on individuals and society.

Diagnostic Criteria: A Path for Moving Forward

In the IOM report preface, Dr. Ellen Wright Clayton wrote *“The committee’s goal in addressing this task was to ensure that these patients receive the diagnoses and treatment they require and deserve. It is to them and to their return to health that this work is dedicated.”*

The members of the CFSAC are dedicated to that goal as well. Accordingly, we submit the following Recommendations related to the Diagnostic Criteria.

8. USE INFORMATION FROM THE IOM REPORT TO DETAIL AND CLARIFY THE CRITERIA:

a) CFSAC recommends that a brief disease overview be provided with the Diagnostic Criteria in order to advance understanding of the complex, multi-systemic nature of the disease; emphasize the IOM findings of systemic exertion intolerance, immune and neurological impairment and other physiological dysfunction; reflect the range of debilitating symptoms that are commonly experienced by patients; and begin to "change the narrative" regarding the disease.

b) CFSAC recommends that each category of Core Criteria be described, using language provided in the IOM report, in order to facilitate understanding of the distinct presentation of symptoms required for diagnosis. CFSAC recommends that objective testing identified by the IOM (for cases of diagnostic uncertainty or other reasons) be included as well.

c) CFSAC recommends that the phrase "Unrefreshing Sleep" be changed to "Sleep Abnormalities" to more accurately reflect the myriad sleep-related problems associated with the disease.

d) CFSAC recommends that "Important and Frequently-reported Symptoms that Support Diagnosis" (as identified by the IOM) be consistently reflected in conjunction with Core Criteria in all materials developed, specifically immune and neurological impairment, pain, and other common symptoms/ manifestations.

e) CFSAC recommends sole use of an expanded version of the Criteria as reflected herein (Box 1) rather than the simplified version (IOM Box S) and algorithm (IOM Fig S-1) which do not convey the full nature of the disease or the important symptoms that support diagnosis.

Rationale: For more than two decades, inadequate clinical education has resulted in confusion regarding the nature of the disease and delayed diagnosis or misdiagnosis for hundreds of thousands of Americans and millions around the world. As reported by the IOM, *“Less than one-third of medical schools include ME/CFS-specific information in the curriculum, and only 40 percent of medical textbooks include information on the disorder... Seeking and receiving a diagnosis can be a frustrating process for several reasons, including skepticism of health care providers about the serious nature of ME/CFS and the misconception that it is a psychogenic illness or even a figment of the patient’s imagination.”*

Providing more detail in the proposed criteria will better inform and educate clinicians regarding diagnosis of this disease. Inclusion of IOM-source descriptions will better educate the medical

community and may help curtail the misrepresentation perpetuated by those who have not read or understood the IOM report. There is a need to detail the symptoms attributed to PEM which, as confirmed by the IOM, *"is a primary feature that helps distinguish ME/CFS from other conditions."* There is also a need to educate clinicians about other common symptoms, some of which are experienced by patients during early onset or at different stages of disease, and others which are undeniably debilitating in the most severely ill. The inclusion of objective testing, whether required for cases of diagnostic uncertainty or not, serves to further educate clinicians and underscore the IOM finding that the disease is biological in nature and is clearly not a *"psychogenic illness"* or a *"figment of the patient's imagination."*

ME/CFS is an acquired, chronic multi-systemic disease characterized by significant relapse after physical, cognitive, or emotional exertion of any sort. The disease includes immune, neurological and cognitive impairment, sleep abnormalities, and autonomic dysfunction, resulting in significant functional impairment accompanied by a pathological level of fatigue. The cause of the disease remains unknown, although in many cases symptoms may have been triggered by an infection or other prodromal event.

Diagnosis requires that the patient have the following symptoms:

A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.

Post-exertional malaise* due to systemic exertion intolerance, manifested as an exacerbation of some or all of an individual's symptoms after seemingly minor physical or cognitive exertion or activity. PEM may result in flu-like symptoms; pain; cognitive dysfunction; nausea/gastrointestinal discomfort; weakness/instability; lightheadedness/vertigo; sensory changes; depression/anxiety; sleep disturbances; and difficulty recovering capacity. PEM may be delayed and is unpredictable in duration, potentially lasting hours, days, weeks, and even months. Subjective reports of PEM can be supported by failure to normally reproduce exercise test results (2-day CPET) and impaired cognitive function. However, this test may induce severe exacerbation of symptoms and is not required for diagnosis.

Sleep Abnormalities* which may include insomnia, sleep disturbances, daytime sleepiness, unrefreshing sleep, and nonrestorative sleep. Unrefreshing sleep is among the most common symptoms reported by patients.

At least one of the two following manifestations:

Cognitive Impairment* which may include short-term memory problems, inability to concentrate, difficulty expressing thoughts, confusion, disorientation, and difficulty performing simple activities such as watching television. Slowed information processing is common and may play a role in overall neurocognitive impairment. Neuropsychological testing is not necessary for diagnosis, however, it can be used to observe slowed information processing, memory impairments, reduced attention, and impaired psychomotor function.

Orthostatic Intolerance measured by objective heart rate and blood pressure abnormalities and physical findings during standing, bedside orthostatic vital signs, head-up tilt testing, or by patient-reported exacerbation of orthostatic symptoms with standing in day-to-day life.

Important and Frequently-reported Symptoms that Support Diagnosis:

Immune impairment: Acute, infection-like onset; Susceptibility to infection; perpetual flu-like symptoms; sore throat; tender lymph nodes; fever; new or worsened sensitivities to certain substances (e.g. foods, odors, medications, chemicals). Poor NK cell cytotoxicity (NK cell function, not number) correlates with illness severity in patients and could serve as a biomarker for the severity of the disease.

Neurological impairment: Impaired psychomotor function; muscle weakness; twitching; instability; spatial disorientation; ataxia; sensory changes (e.g. sensitivity or intolerance to light, noise and touch).

Pain: Headaches; arthralgia; myalgia; other pain symptoms (all highly variable in presence, nature and severity).

Other: Gastrointestinal impairments; genitourinary impairment; neuroendocrine manifestations (e.g. cold extremities, weight change, excessive sweating, high/low temperature, chills/shivers, loss of appetite, alcohol intolerance).

9. **VALIDATE AND REFINE THE PROPOSED CRITERIA WITHIN TWO YEARS**: CFSAC recommends that the proposed Diagnostic Criteria be validated, and refined if needed, within two years by disease experts and/or by the methodological workgroup recommended herein for sensitivity and specificity during different stages of disease and different levels of severity.

Rationale: In order to facilitate diagnostic accuracy and achieve acceptance as recommended in virtually all of the recent HHS reports, validation and review and/or testing is recommended within two years of implementation.

The IOM took on a monumental challenge when asked to develop evidence-based diagnostic criteria for a disease which has been so poorly funded. As indicated in the report, the Committee was required to "...glean evidence of symptoms, signs, and objective measures" from an evidence base fraught with "methodological limitations" and "issues related to external and internal validity..." Additionally, "Almost all of the studies conducted to date have compared patients with ME/CFS with healthy controls rather than with patients with these other fatiguing disorders. As a result, there is a paucity of data to guide clinicians in distinguishing among these disorders, a gap that urgently needs to be filled."

As a result, concerns regarding the proposed criteria have been raised by disease experts, international organizations, advocates and other stakeholders, specifically that the criteria may be too broad given the lack of objective biomarkers; that cognitive impairment should be required rather than optional; that pain and/or immune impairment should be core symptoms; and that neurological symptoms should be included.

There is also concern about the lack of early onset symptoms in the Criteria, particularly since opportunities for intervention may be transient. CFSAC has been asked to consider a 1996 NIH-supported study which concluded: "In any future revisions of the case definition we would recommend preserving the major criteria and all of the infectious-type minor criteria (i.e., fever/chills, sore throat, swollen neck and arm glands), as well as myalgias, post exertional malaise, and headaches" as these symptoms were found to be the most successful discriminators when compared to patients with Multiple Sclerosis and major depression."^{*}

Despite the challenges involved, the Committee was able to draw a number of important conclusions that may help change the narrative for this disease for years to come.

However, as recognized by the IOM, "...**diagnostic criteria should be updated when evidence supports a change in order to improve the identification and care of affected individuals.**"

Testing or validation will help determine if modification may be warranted in order to achieve this mutual goal – to improve the identification and care of affected individuals with this debilitating but under-recognized disease.

* An Examination of the Working Case Definition of Chronic Fatigue Syndrome, American Journal of Medicine, Jan. 1996, Komaroff et al.

Medical Education and Guidelines

10. **PROVIDE DISEASE GUIDANCE WITH THE CRITERIA:** In order to improve diagnostic accuracy while appropriate tools are developed and validated, CFSAC recommends development of clinical guidelines for the assessment of post-exertional malaise (PEM) along with a brief guidance document designed to accompany and supplement the Criteria in all dissemination efforts. Disease guidance should include the following key information:
 - a. **Disease Overview:** Identification of ME/CFS as an acquired, chronic multi-systemic disease characterized by "*systemic exertion intolerance*" resulting in significant relapse after exertion of any sort; A statement that the disease includes immune, neurological and cognitive impairment, sleep abnormalities, and autonomic dysfunction resulting in significant functional impairment accompanied by a pathological level of fatigue; Clear indication that the disease is not a psychiatric or somatoform disorder and that it is not synonymous with "chronic fatigue," "idiopathic fatigue" or "fatigue syndrome."
 - b. **Diagnostic Techniques and Procedures:** Appropriate guidance on "Operationalizing the Diagnosis" (*pp 11-12 of the IOM Guide for Clinicians*) along with the recommended clinical guideline for assessing PEM; Information about early onset signs; A list of interim diagnostic tools (*from pp 13-14 of the IOM Guide for Clinicians*) with instructions and scoring criteria for assessment of PEM, impaired function, and other symptoms if/when diagnosis is in question.
 - c. **Differential Diagnosis:** A list of conditions that share common symptoms and might be missed, including but not limited to Addison's disease; B12 deficiency; chronic hepatitis; celiac disease; Cushing's Syndrome; diabetes mellitus; heart disease; HIV related illness; iron deficiency or overload syndrome; lupus; Lyme disease; malignancy; myasthenia gravis; multiple sclerosis; rheumatoid arthritis; sleep disorders; thyroid imbalance or disease; tuberculosis. Additionally, guidance should be included regarding differentiation of primary psychiatric disorders (particularly depression, somatoform disorder, somatic symptom disorder, neurasthenia and similar conditions), substance abuse, and "school phobia" in pediatric patients.
 - d. **Comorbidities:** Indication that diagnosis and treatment of co-morbid conditions are necessary when caring for patients and that clinicians may wish to consider (among others): allergies, central or obstructive sleep apnea, depression, fibromyalgia, interstitial cystitis, irritable bladder syndrome, irritable bowel syndrome, migraine, multiple chemical sensitivities, myofascial pain syndrome, prolapsed mitral valve, Raynaud's phenomenon, reactive depression or anxiety, Sicca syndrome, and temporomandibular joint syndrome.
 - e. **Treatment and Care:** Basic information regarding symptom-based treatment using pharmaceuticals and other clinical treatments when appropriate to address underlying pathologies and manage symptoms to the extent possible; Information regarding management of PEM; Clarification that counseling therapies are not treatments but may be helpful coping mechanisms; Declaration that the disease is not the result of fear-based avoidance of activity and that cognitive behavioral therapy (CBT) and graded exercise therapy (GET) for this purpose are inappropriate; Clear warning about the potential harms of graded exercise therapy and a statement that exercise therapy of any kind should only be considered if and when appropriately trained professionals are involved and measures are taken to ensure that the exercise does not induce post-exertional malaise or cause other physical harm. Further, treatment recommendations and clinical findings based on Oxford or Reeves definitions should no longer be applied to these patients.
 - f. **Resources:** Links to the IOM report, the IACFS/ME primer on guidelines.gov, and other appropriate resources.

Rationale: It is expected that full operationalization and validation of diagnostic tools and criteria will require additional study. However, the IOM has made it clear that Post-exertional malaise *"is a primary feature that helps distinguish ME/CFS from other conditions..."* and that the *"Use of a standardized instrument is critical to measuring PEM accurately..."* Until the necessary studies occur, clinicians need information about the nature of the disease, guidelines for identifying the core symptoms required for diagnosis, information regarding the importance of differential diagnosis, testing methods when diagnosis is unclear, and guidance regarding symptom-based therapies for treatment and care. As indicated previously, CFSAC does not recommend use of the IOM's proposed algorithm (Fig. S-1 on p. 30 of the IOM report). Patients do not always present with fatigue or have substantial impairment in function early in the disease.

11. DEVELOP DIAGNOSTIC TOOLS and CLINICAL PRACTICE GUIDELINES: CFSAC recommends that disease-specific diagnostic tools be developed and validated in collaboration with disease experts and also that comprehensive Clinical Practice Guidelines be developed in accordance with the IOM's *Standards for Developing Trustworthy Clinical Practice Guidelines*.

Rationale: As indicated by the IOM, new diagnostic tools should include *"clinical questionnaire or history tools that are valid across populations of patients... brief in-office tests for detecting PEM and orthostatic intolerance... a brief set of neuropsychology tests targeting the information processing problems that affect patients... Identification of a set of distinctive biomarkers for this disorder should also be a priority. Finally, all of the above tools should be evaluated to determine how well they distinguish ME/CFS from other complex, multisystem, and fatiguing disorders."*

A comprehensive Clinical Practice Guideline that provides expanded and up-to-date information on the science and the nature of the disease, the range of symptoms/manifestations across time and severity (even if not strictly used diagnostically), appropriate diagnostic testing, therapeutics and treatment options, and other disease-specific information will advance clinical understanding, treatment and care.

12. PROMOTE MEDICAL EDUCATION and AWARENESS: CFSAC recommends that HHS promote inclusion of the disease on the United States Medical Licensing Examination (USMLE). CFSAC endorses recommendations provided in the IOM and P2P reports regarding engagement of health professional licensing and accreditation agencies, involvement of HRSA to promote training, and formation of public-private partnerships to further education and awareness regarding the disease. Additionally, CFSAC endorses the recommendation of the IOM to update all websites and materials of HHS and its agencies using consistent messaging and standard terminology based on the recommendations in this report, and to communicate with third party health information provider websites and federally supported provider networks as well.

Rationale: The IOM and P2P reports have laid out clear rationales regarding the need for appropriate medical education, consistent messaging, and accurate health information on provider websites.

13. IDENTIFY ICD CODING: CFSAC recommends G93.3 as the recommended ICD-10-CM code for this disease unless and until such time that robust research justifies reclassification and a new code is created.

Rationale: According to the IOM, *"a new code should be assigned to this disorder in the International Classification of Diseases, Tenth Revision (ICD-10), that is not linked to "chronic fatigue" or "neurasthenia."* CFSAC believes that the US should follow the international convention by using G93.3 for this disease until such time that robust research justifies reclassification and creation of a new code.

Acknowledgement and Identification of the Disease

As reflected in the NIH P2P report, "*Clinicians have a poor understanding of the condition, and patients are typically underserved... They are often treated with skepticism, uncertainty, and apprehension and labeled as deconditioned or having a primary psychological disorder.*" The IOM concurred, stating "*Indeed, the main barriers to appropriate and timely diagnosis of ME/CFS appear to be primarily attitudinal rather than knowledge based...*" Tragically, the IOM also found that "*The stigma and social effects of pediatric ME/CFS include the loss of normal childhood activities and, in some extreme instances, inappropriate forcible separation of children from their parents.*"

Armed with the findings of the IOM and the P2P, we are in a position to change this situation. A cross-agency strategy to facilitate recognition and acknowledgement of this disease is greatly needed. Accordingly, CFSAC submits the following recommendations.

14. **ACKNOWLEDGE THE DISTINCT DISEASE IDENTIFIED BY THE IOM:** The IOM has acknowledged and identified a distinct medical condition involving systemic exertion intolerance with PEM and universal core criteria. CFSAC recommends that the disease identified by the IOM be clearly distinguished from other causes of chronic fatigue, such as conditions described by Fukuda et al, 2005 Reeves, Oxford and other forms of chronic fatigue which include patients that do not meet the IOM core criteria.

Rationale: Fukuda CFS is an exclusionary criteria based on "clinically evaluated, unexplained chronic fatigue" and polythetic criteria. Other CFS definitions are primarily based on "medically unexplained" chronic fatigue. The IOM has formally acknowledged a distinct, identifiable disease that includes a pathological level of fatigue explained by systemic exertion intolerance and/or multi-systemic dysfunction, and the NIH P2P Workshop Report has agreed. Additionally, the IOM, P2P and AHRQ reports all acknowledge that findings and recommendations from some CFS definition studies included patients who do not have the disease. The disease is now considered "a diagnosis to be made" and should therefore be excluded from the CFS umbrella.

- NIH Pathways to Prevention (2015): "***We believe ME/CFS is a distinct disease...***"
- Institute of Medicine (2015): "*The central point is that ME/CFS is **a diagnosis to be made...** A new code should be assigned to this disorder in the International Classification of Diseases, Tenth Revision (ICD-10), that is not linked to 'chronic fatigue' or 'neurasthenia'... a diagnosis of CFS is not equivalent to a diagnosis of ME... A study suggesting a role for childhood trauma in ME/CFS used the broad empirical definition of ME/CFS, which resulted in a biased sample with overrepresentation of individuals with depression and posttraumatic stress disorder (PTSD) (Heim et al., 2009). The unusually high proportion of subjects with serious psychiatric problems likely explains the study finding of an association between ME/CFS and adverse childhood experiences. No other studies have suggested a higher rate of childhood trauma in those with confirmed ME/CFS as opposed to nonspecific chronic fatigue... The committee recognizes that some patients diagnosed by other criteria, such as the Fukuda definition (Fukuda et al., 1994), will not fulfill all of the criteria proposed here... **the most commonly used case definition (Fukuda et al., 1994) identifies a more broadly defined patient population in which PEM, arguably a hallmark of ME/CFS, is not required for diagnosis...***"
- AHRQ Evidence Review (2014): "... "*Most of the intervention trials used the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions for inclusion and the results may not be applicable to patients meeting case definitions for ME.*" "*The case definitions overlap but vary greatly in their symptom set, leading to concern that they do not all represent the same disease or identify the same cohort of patients.*"

15. **CHANGE THE NARRATIVE:** CFSAC recommends a coordinated cross-agency effort to change the narrative – from "unexplained fatigue" to an understanding of the multi-systemic nature of this disease – through the use of consistent messaging provided by the IOM and P2P reports as highlighted below.

Rationale: The IOM advised that *"Effective messaging informs, persuades, and moves a target audience to action"* and suggested that certain messages *"serve as a framework for use in conjunction with all dissemination activities."* The IOM also stated that *"successful dissemination of the committee's new clinical diagnostic criteria will entail not only educating clinicians about the content of the criteria but also addressing the attitudes and beliefs that could hinder the criteria's acceptance."* Use of the following messaging will help to accomplish this goal:

- **ME/CFS is an acquired, chronic multi-systemic disease characterized by "systemic exertion intolerance" resulting in significant relapse after exertion of any sort. The disease includes immune, neurological and cognitive impairment, sleep abnormalities, and autonomic dysfunction, resulting in significant functional impairment accompanied by a pathological level of fatigue. The cause of the disease remains unknown, although in many cases symptoms may have been triggered by an infection or other prodromal event.**
- **The disease is not psychiatric in nature and should not be equated with neurasthenia, somatic symptom disorder, or functional somatic syndrome.**
- **ME/CFS has been reported in patients younger than age 10 and older than age 70.**
- **There is strong scientific evidence of immunologic and inflammatory pathologies, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities in the disease.**
- **PEM is a primary feature that helps distinguish ME/CFS from other conditions and manifests as muscular or cognitive fatigability and exacerbation of some or all of an individual's symptoms after seemingly minor physical or cognitive exertion or activity. PEM may be delayed and is unpredictable in duration.**
- **At least one-quarter of ME/CFS patients are bedbound or housebound at some point in the illness and most patients never regain their pre-disease level of functioning.**
- **ME/CFS patients have been found to be more functionally impaired than those with other disabling illnesses including type 2 diabetes mellitus, congestive heart failure, hypertension, depression, multiple sclerosis, and end-stage renal disease.**
- **Pediatric ME/CFS can follow acute infectious mononucleosis and EBV. Orthostatic intolerance and autonomic dysfunction are common in pediatric patients; neurocognitive abnormalities emerge when pediatric patients are tested under conditions of orthostatic stress or distraction; there is a high prevalence of profound fatigue, unrefreshing sleep, and post-exertional exacerbation of symptoms.**
- **The disease is not synonymous with "chronic fatigue," "idiopathic fatigue" or "fatigue syndrome."**

Closing Remarks

As documented in both the Institute of Medicine and the NIH Pathways to Prevention Workshop reports, ME/CFS is an unmet public health need which imposes a burden of illness on millions of people in the United States and around the world.

A meaningful and sustained commitment by the Department of Health and Human Services is needed at this time to identify biomarkers, reproduce important research, address identified gaps, overcome institutional barriers, promote accurate medical education, and offer hope to patients and their loved ones through better diagnosis, treatments, and access to care from knowledgeable providers.

It is our fervent hope that these recommendations, painstakingly developed together with stakeholders using our collective experience and expertise, will guide the Secretary as she works to move our federal agencies forward with funding, resources and action.

CFSAC "IOM/P2P" Recommendations #1-15

August 2015

RESEARCH DIRECTION, FUNDING, AND GOALS (#1-7)

1. **PRIORITIZE DEVELOPMENT OF BIOMARKERS AND OBJECTIVE DIAGNOSTIC TESTS:** CFSAC recommends that targeted Requests for Applications (RFAs), which clearly prioritize the identification and validation of distinct biomarkers and objective diagnostic tests and give preference to collaborative network initiatives, be issued as soon as possible. RFAs should advance the study of fMRI, positron emission tomography (PET) and other imaging technologies; 2-day cardiopulmonary function/recovery with gas exchange; cytokine abnormalities; gene expression, protein, or metabolite signatures; natural killer (NK) cell function; and other promising markers for diagnostic or therapeutic use. CFSAC believes that time is of the essence regarding this urgent recommendation.
2. **ADDRESS GAPS IN BASIC, TRANSLATIONAL, CLINICAL AND EPIDEMIOLOGICAL RESEARCH:** CFSAC recommends that the NIH issue Requests for Applications (RFAs), and the CDC allocate targeted funding, to address the gaps in basic, translational, clinical and epidemiological research as identified in the *NIH Pathways to Prevention Workshop Report*, the IOM's *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*, the AHRQ Evidence Report *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*, and the 2011 *NIH State of the Knowledge Workshop Report*. Such RFAs should be issued as soon as feasible. As was made clear by the NIH P2P panel, "Innovative biomedical research is urgently needed."
3. **ADVANCE TREATMENTS AND THERAPEUTICS:** CFSAC recommends that the NIH make use of resources such as the NIH Clinical Center as well as other public and private options as soon as feasible for clinical trials and fast-track testing of new or repurposed therapies. High quality multi-site clinical trials using well-characterized patients (as defined in the recommendation that follows) are considered essential to facilitate the approval of effective drugs, address both biologic and clinical outcomes, and establish outcome measures for treatment and prognosis.
4. **STANDARDIZE ASSESSMENT METHODS AND MEASURES:** As both the IOM and P2P reports have emphasized the need for improved methods and standards for both research and clinical care, CFSAC recommends the following strategy to advance those goals:
 - a. CFSAC recommends that federally-funded research specify use of the 2003 Canadian Consensus Criteria as a research case definition for patient selection (in addition to other requirements established for specific research purposes) using standardized and uniform assessment methods and measures for applying the definition.
 - b. CFSAC recommends timely formation of a methodological workgroup comprised of disease experts and stakeholders to establish uniform assessment methods, measures and data standards for federally-funded research; define and standardize disease terminology; operationalize symptom assessment methods in clinical care; and advance clinical guidelines and validated tools for diagnosis and treatment.
5. **ASSIGN THE DISEASE TO AN INSTITUTE:** Given the clear involvement of neurological dysfunction in ME/CFS, CFSAC recommends that the disease be assigned to the National Institute of Neurological Disorders and Stroke (NINDS). CFSAC supports a continuing role for the Trans-NIH ME/CFS Working Group but recommends that leadership of the group be held jointly by the National Institute of Neurological Disorders and Stroke (NINDS) and by the National Institute of Allergy and Infectious Diseases (NIAID).
6. **APPOINT A CROSS-AGENCY LEADER:** To address the breadth and magnitude of needs raised by the IOM and P2P reports, CFSAC recommends that the HHS appoint a senior-level cross-agency leader ("czar")

with the authority, position and fiscal responsibility required to coordinate, develop, implement, and monitor a broad strategic cross-agency response to this disease through open and collaborative engagement of both internal and external stakeholders. At minimum, the strategic cross-agency plan should address the critical need for research, drug development, epidemiology, medical education, medical care and public awareness. It is recommended that this cross-agency leader serve as Designated Federal Official (DFO) to the CFSAC and be required to provide a comprehensive biannual report regarding progress and goals.

7. PROVIDE RESEARCH FUNDING COMMENSURATE WITH THE BURDEN OF DISEASE: To facilitate the above goals, CFSAC recommends that the Secretary work with HHS agencies to ensure that total research funding is commensurate with the epidemiologic prevalence and economic burden imposed by this disease. Based on disease prevalence, equitable funding is estimated to be \$250,000,000 per year.

DIAGNOSTIC CRITERIA: A PATH FOR MOVING FORWARD (#8-9)

8. USE INFORMATION FROM THE IOM REPORT TO DETAIL AND CLARIFY THE CRITERIA:

- a. CFSAC recommends that a brief disease overview be provided with the Diagnostic Criteria in order to advance understanding of the complex, multi-systemic nature of the disease; emphasize the IOM findings of systemic exertion intolerance, immune and neurological impairment and other physiological dysfunction; reflect the range of debilitating symptoms that are commonly experienced by patients; and begin to "change the narrative" regarding the disease.
- b. CFSAC recommends that each category of Core Criteria be described, using language provided in the IOM report, in order to facilitate understanding of the distinct presentation of symptoms required for diagnosis. CFSAC recommends that objective testing identified by the IOM (for cases of diagnostic uncertainty or other reasons) be included as well.
- c. CFSAC recommends that the phrase "Unrefreshing Sleep" be changed to "Sleep Abnormalities" to more accurately reflect the myriad sleep-related problems associated with the disease.
- d. CFSAC recommends that "Important and Frequently-reported Symptoms that Support Diagnosis" (as identified by the IOM) be consistently reflected in conjunction with Core Criteria in all materials developed, specifically immune and neurological impairment, pain, and other common symptoms/manifestations.
- e. CFSAC recommends sole use of an expanded version of the Criteria as reflected herein (Box 1) rather than the simplified version (IOM Box S) and algorithm (IOM Fig S-1) which do not convey the full nature of the disease or the important symptoms that support diagnosis.

9. VALIDATE AND REFINE THE PROPOSED CRITERIA WITHIN TWO YEARS: CFSAC recommends that the proposed Diagnostic Criteria be validated, and refined if needed, within two years by disease experts and/or by the methodological workgroup recommended herein for sensitivity and specificity during different stages of disease and different levels of severity.

MEDICAL EDUCATION AND GUIDELINES (#10-13)

10. PROVIDE DISEASE GUIDANCE WITH THE CRITERIA: In order to improve diagnostic accuracy while appropriate tools are developed and validated, CFSAC recommends development of clinical guidelines for the assessment of post-exertional malaise (PEM) along with a brief guidance document designed to accompany and supplement the Criteria in all dissemination efforts. Disease guidance should include the following key information:

- a. Disease Overview: Identification of ME/CFS as an acquired, chronic multi-systemic disease characterized by "systemic exertion intolerance" resulting in significant relapse after exertion of any

sort; A statement that the disease includes immune, neurological and cognitive impairment, sleep abnormalities, and autonomic dysfunction resulting in significant functional impairment accompanied by a pathological level of fatigue; Clear indication that the disease is not a psychiatric or somatoform disorder and that it is not synonymous with "chronic fatigue," "idiopathic fatigue" or "fatigue syndrome."

- b. Diagnostic Techniques and Procedures: Appropriate guidance on "Operationalizing the Diagnosis" (pp 11-12 of the IOM Guide for Clinicians) along with the recommended clinical guideline for assessing PEM; Information about early onset signs; A list of interim diagnostic tools (from pp 13-14 of the IOM Guide for Clinicians) with instructions and scoring criteria for assessment of PEM, impaired function, and other symptoms if/when diagnosis is in question.
- c. Differential Diagnosis: A list of conditions that share common symptoms and might be missed, including but not limited to Addison's disease; B₁₂ deficiency; chronic hepatitis; celiac disease; Cushing's Syndrome; diabetes mellitus; heart disease; HIV related illness; iron deficiency or overload syndrome; lupus; Lyme disease; malignancy; myasthenia gravis; multiple sclerosis; rheumatoid arthritis; sleep disorders; thyroid imbalance or disease; tuberculosis. Additionally, guidance should be included regarding differentiation of primary psychiatric disorders (particularly depression, somatoform disorder, somatic symptom disorder, neurasthenia and similar conditions), substance abuse, and "school phobia" in pediatric patients.
- d. Comorbidities: Indication that diagnosis and treatment of co-morbid conditions are necessary when caring for patients and that clinicians may wish to consider (among others): allergies, central or obstructive sleep apnea, depression, fibromyalgia, interstitial cystitis, irritable bladder syndrome, irritable bowel syndrome, migraine, multiple chemical sensitivities, myofascial pain syndrome, prolapsed mitral valve, Raynaud's phenomenon, reactive depression or anxiety, Sicca syndrome, and temporomandibular joint syndrome.
- e. Treatment and Care: Basic information regarding symptom-based treatment using pharmaceuticals and other clinical treatments when appropriate to address underlying pathologies and manage symptoms to the extent possible; Information regarding management of PEM; Clarification that counseling therapies are not treatments but may be helpful coping mechanisms; Declaration that the disease is not the result of fear-based avoidance of activity and that cognitive behavioral therapy (CBT) and graded exercise therapy (GET) for this purpose are inappropriate; Clear warning about the potential harms of graded exercise therapy and a statement that exercise therapy of any kind should only be considered if and when appropriately trained professionals are involved and measures are taken to ensure that the exercise does not induce post-exertional malaise or cause other physical harm. Further, treatment recommendations and clinical findings based on Oxford or Reeves definitions should no longer be applied to these patients.
- f. Resources: Links to the IOM report, the IACFS/ME primer on guidelines.gov, and other appropriate resources.

11. DEVELOP DIAGNOSTIC TOOLS and CLINICAL PRACTICE GUIDELINES: CFSAC recommends that disease-specific diagnostic tools be developed and validated in collaboration with disease experts and also that comprehensive Clinical Practice Guidelines be developed in accordance with the IOM's Standards for Developing Trustworthy Clinical Practice Guidelines.

12. PROMOTE MEDICAL EDUCATION and AWARENESS: CFSAC recommends that HHS promote inclusion of the disease on the United States Medical Licensing Examination (USMLE). CFSAC endorses recommendations provided in the IOM and P2P reports regarding engagement of health professional licensing and accreditation agencies, involvement of HRSA to promote training, and formation of public-private partnerships to further education and awareness regarding the disease. Additionally, CFSAC endorses the recommendation of the IOM to update all websites and materials of HHS and its agencies using consistent messaging and standard terminology based on the recommendations in this report, and to communicate with third party health information provider websites and federally supported provider networks as well.

13. **IDENTIFY ICD CODING:** CFSAC recommends G93.3 as the recommended ICD-10-CM code for this disease unless and until such time that robust research justifies reclassification and a new code is created.

ACKNOWLEDGEMENT/IDENTIFICATION OF THE DISEASE (#14-15)

14. **ACKNOWLEDGE THE DISTINCT DISEASE IDENTIFIED BY THE IOM:** The IOM has acknowledged and identified a distinct medical condition involving systemic exertion intolerance with PEM and universal core criteria. CFSAC recommends that the disease identified by the IOM be clearly distinguished from other causes of chronic fatigue, such as conditions described by Fukuda et al, 2005 Reeves, Oxford and other forms of chronic fatigue which include patients that do not meet the IOM core criteria.

15. **CHANGE THE NARRATIVE:** CFSAC recommends a coordinated cross-agency effort to change the narrative – from "unexplained fatigue" to an understanding of the multi-systemic nature of this disease – through the use of consistent messaging provided by the IOM and P2P reports as highlighted below.

- **ME/CFS is an acquired, chronic multi-systemic disease characterized by "systemic exertion intolerance" resulting in significant relapse after exertion of any sort. The disease includes immune, neurological and cognitive impairment, sleep abnormalities, and autonomic dysfunction, resulting in significant functional impairment accompanied by a pathological level of fatigue. The cause of the disease remains unknown, although in many cases symptoms may have been triggered by an infection or other prodromal event.**
- **The disease is not psychiatric in nature and should not be equated with neurasthenia, somatic symptom disorder, or functional somatic syndrome.**
- **ME/CFS has been reported in patients younger than age 10 and older than age 70.**
- **There is strong scientific evidence of immunologic and inflammatory pathologies, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities in the disease.**
- **PEM is a primary feature that helps distinguish ME/CFS from other conditions and manifests as muscular or cognitive fatigability and exacerbation of some or all of an individual's symptoms after seemingly minor physical or cognitive exertion or activity. PEM may be delayed and is unpredictable in duration.**
- **At least one-quarter of ME/CFS patients are bedbound or housebound at some point in the illness and most patients never regain their pre-disease level of functioning.**
- **ME/CFS patients have been found to be more functionally impaired than those with other disabling illnesses including type 2 diabetes mellitus, congestive heart failure, hypertension, depression, multiple sclerosis, and end-stage renal disease.**
- **Pediatric ME/CFS can follow acute infectious mononucleosis and EBV. Orthostatic intolerance and autonomic dysfunction are common in pediatric patients; neurocognitive abnormalities emerge when pediatric patients are tested under conditions of orthostatic stress or distraction; there is a high prevalence of profound fatigue, unrefreshing sleep, and post-exertional exacerbation of symptoms.**
- **The disease is not synonymous with "chronic fatigue," "idiopathic fatigue" or "fatigue syndrome."**