IOM/P2P WORKING GROUP

Follow-Up Recommendations, May 2016

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
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NIH National Institutes of Health
Office of Disease Prevention

NIH Pathways to Prevention Workshop:

Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

NEW! An independent panel shares their findings and recommendations.

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Final Report Now Available!

BEYOND MYALGIC ENCEPHALOMYELITIS/
CHRONIC FATIGUE SYNDROME:
Redefining an Illness ©

NIH Pathways to Prevention Workshop:
Advancing the Research on Myalgic Encephalomyelitis/
Chronic Fatigue Syndrome

We Acknowledge and Appreciate

- **NINDS** as initial leader for new Trans-NIH Working Group
- 3-Phase **Intramural study** expected to shed light on biomarkers, inform development of therapies, lead to expanded studies
  - Phase 1: Understand biology of the disease
  - Phase 2: Longitudinal study to identify biomarkers
  - Phase 3: Interventional study targeting identified biomarkers
- **Comprehensive research strategy** by Trans-NIH Working Group that acknowledges the need for biomarker research and **will include RFAs**; Mechanisms for community to provide input and feedback

- CDC multi-site study to continue; inclusion of pediatric and housebound patients; data collection regarding some gaps in research, specifically NK cell function testing, evaluating questionnaires most effective in measuring ME/CFS, and cognitive testing
- NIH exploring cost/feasibility of Data Coordinating Center; Working with CDC for development of Common Data Elements for all federally-funded research
- Investigators encouraged by NIH to submit grant applications focused on *"new approaches to study the disease"* and urged to review clinical treatment trial ideas with program staff prior to peer review

- Trans-NIH Working Group working to stimulate new research strategies to increase funding, expand training~~,~~ attract and interest new investigators e.g. Availability of Administrative Supplements, April 2016 “NIH is committed to supporting research to better understand ME/CFS. This notice is one component of this effort.”

- Federal Partners meeting regarding P2P Workshop Report

- HRSA obtained agreement of Arizona Center for Integrative Medicine in Primary Care (CIMPC) for ME/CFS case in curricula including diagnostics and treatment

- CDC Technical Development Workgroup (TDW) to provide advice regarding updated website and educational materials/toolkits to be developed; Includes advocates and organizations, and:

American Academy of Neurology
American Academy of Pediatrics
American College of Physicians
American Nurses Association
American Chronic Pain Association
American Osteopathic Association
Global Academy CME
Healthwise

American Academy of Nurse Practitioners
American Academy of Physician Assistants
American College of Osteopathic Family Physicians
American College of Obstetrics and Gynecology
Association of Schools and Programs of Public Health
American Association of Colleges of Nursing
National Association of Pediatric Nurse Practitioners
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Working Group Discussion - Priorities for "Follow-Up"

- HHS agreement that review and updating the IOM Diagnostic Criteria is important but no commitment or timeline provided
- Crucial CFSAC Recommendation regarding the need to detail the Criteria (sole source IOM) and provide brief disease guidance has been referred to CDC's TDW;
- No response regarding Recommendations to "Acknowledge the Distinct Identified by the IOM" (#14) and "Change the Narrative" (#15)

Working Group Discussion

IOM: "… reexamine the diagnostic criteria set forth in this report when firm evidence supports modification to improve the identification or care of affected individuals. Such a group should consider, in no more than 5 years, whether modification of the criteria is necessary."

- ➢ Funding will be needed
- ➢ Federal process is time-consuming:
  - ❖ 2012 CFSAC "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."
  - ❖ 2013 IOM Contract
  - ❖ 2015 IOM Report (February)
  - ❖ 2015 CFSAC Recommendations (August)
  - ❖ 2016 CDC Technical Development Workgroup
  - ❖ ? New Criteria on HHS websites and in educational materials

Proposed Recommendation #1:

INITIATE THE PROCESS FOR REVIEW OF THE IOM DIAGNOSTIC CRITERIA SO AS TO OCCUR NO LATER THAN MAY 2019:

CFSAC recommends that HHS initiate the federal processes required as soon as feasible such that a methodological and multidisciplinary workgroup can be convened in a timely fashion, and in no event later than May 2019, to reexamine and update the IOM diagnostic criteria. Further, CFSAC recommends that said workgroup be required to consider and incorporate new evidence to update and refine the criteria for sensitivity and specificity during different stages of disease and different levels of severity.

Working Group Discussion

Clinically evaluated, unexplained chronic fatigue cases can be classified as CFS if… severe chronic fatigue for 6 or more consecutive months that is not due to ongoing exertion or other medical conditions associated with fatigue… fatigue significantly interferes with daily activities and work… four or more of the following symptoms: post-exertion malaise lasting more than 24 hours; unrefreshing sleep; significant impairment of short-term memory or concentration; muscle pain; pain in the joints without swelling or redness; headaches of a new type, pattern, or severity; tender lymph nodes in the neck or armpit; a sore throat that is frequent or recurring

Conditions that Exclude a Diagnosis of CFS: Any active medical condition that may explain the presence of chronic fatigue…

CDC Website

Is this disease an active medical condition that may explain the presence of chronic fatigue?

NIH P2P: “We believe ME/CFS is a distinct disease…”

IOM: “The central point the committee wishes to emphasize is that ME/CFS is a diagnosis to be made **…** the most commonly used case definition (Fukuda et al, 1994) identifies a more broadly defined patient population …”

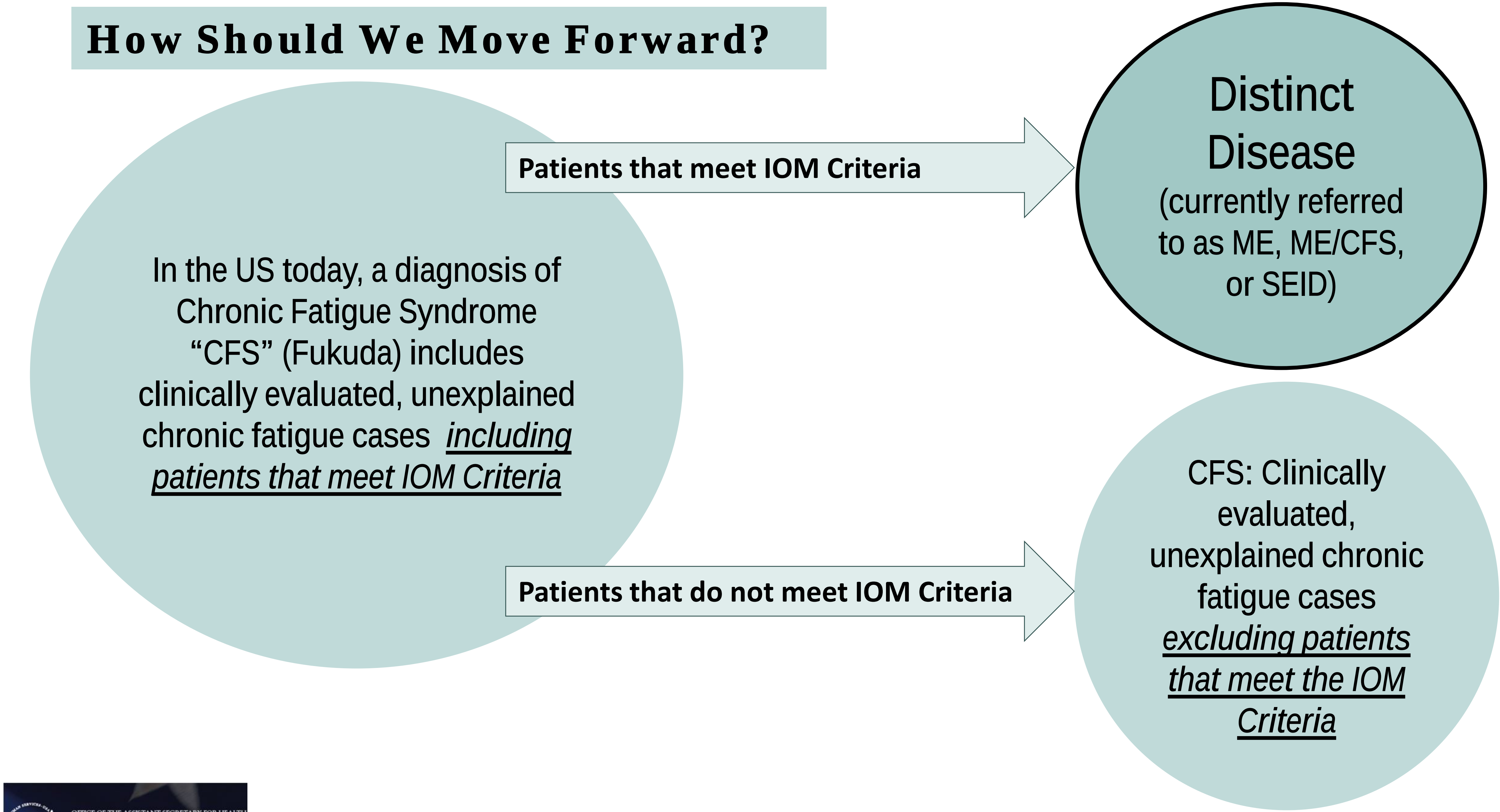
AHRQ: “Most of the intervention trials used the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions for inclusion and the results may not be applicable to patients meeting case definitions for ME…”

> *“Patients who do not meet the criteria for ME/CFS (SEID)* ***should continue to be diagnosed by other criteria*** *as their symptoms and evaluations dictate. These patients should also receive appropriate care.”*

Report Guide for Clinicians

Institute of Medicine of the National Academies

How Should We Move Forward?



In the US today, a diagnosis of Chronic Fatigue Syndrome "CFS" (Fukuda) includes clinically evaluated, unexplained chronic fatigue cases *including patients that meet IOM Criteria*

Patients that meet IOM Criteria

Distinct Disease

(currently referred to as ME, ME/CFS, or SEID)

Patients that do not meet IOM Criteria

CFS: Clinically evaluated, unexplained chronic fatigue cases *excluding patients that meet the IOM Criteria*

Proposed Recommendation #2:

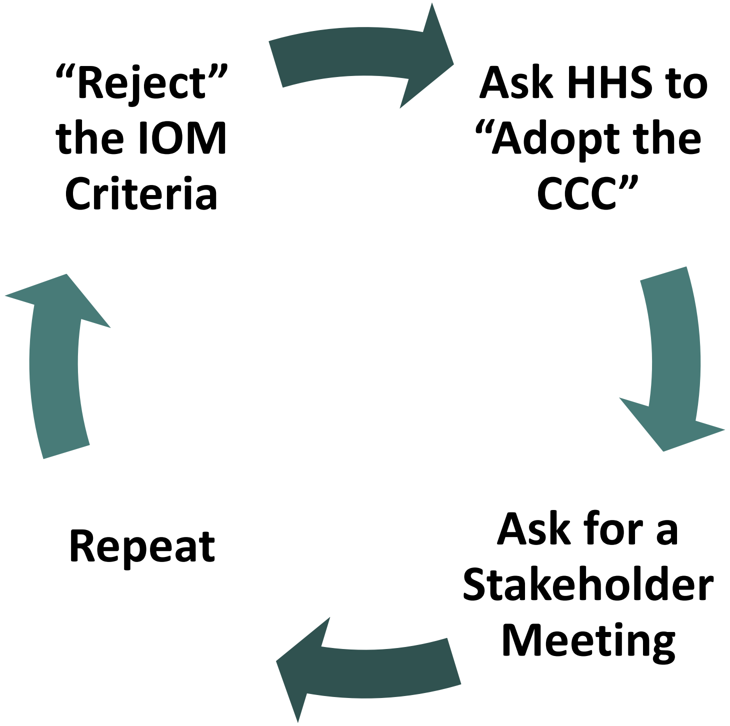
SEPARATE THE DISTINCT DISEASE ACKNOWLEDGED BY THE IOM (currently referred to as "ME," ME/CFS" or "SEID") FROM THE BROADER SET OF CONDITIONS DEFINED BY FUKUDA AND OXFORD:

CFSAC recommends that new clinical guidelines, new CDC webpages, a new name, and a new ICD code be established for the distinct disease identified and acknowledged by the Institute of Medicine, and that they be separate and clearly distinguished from the clinical guidelines, CDC webpages, name, and ICD code used for the remaining patients diagnosed with Chronic Fatigue Syndrome (CFS) as defined by Fukuda. Statements and treatment recommendations based on the Oxford definition should not be included in clinical guidelines for this disease. Until such time that a new ICD code is established, CFSAC again recommends that the G93.3 ICD code be used for this disease.

Prior Working Group Discussion

- The nature of the disease is not reflected by the Criteria.
- Common early onset symptoms are not reflected, possibly resulting in delayed diagnosis and missed opportunities for early intervention.
- PEM is not recognized or understood by clinicians as it applies to this disease.
- Immune impairment is recognized to be part of the disease but was excluded from Core criteria due to lack of diagnostic tests.
- Disabling neurological symptoms, including muscle weakness and sensitivity/ intolerance to light, noise and touch, are not reflected in the Core criteria.
- Pain is common but was excluded from Core criteria only because it is not specific to the disease.
- The lack of objective measures and diagnostic tools/tests will negatively impact diagnosis and care.

Prior Working Group Discussion

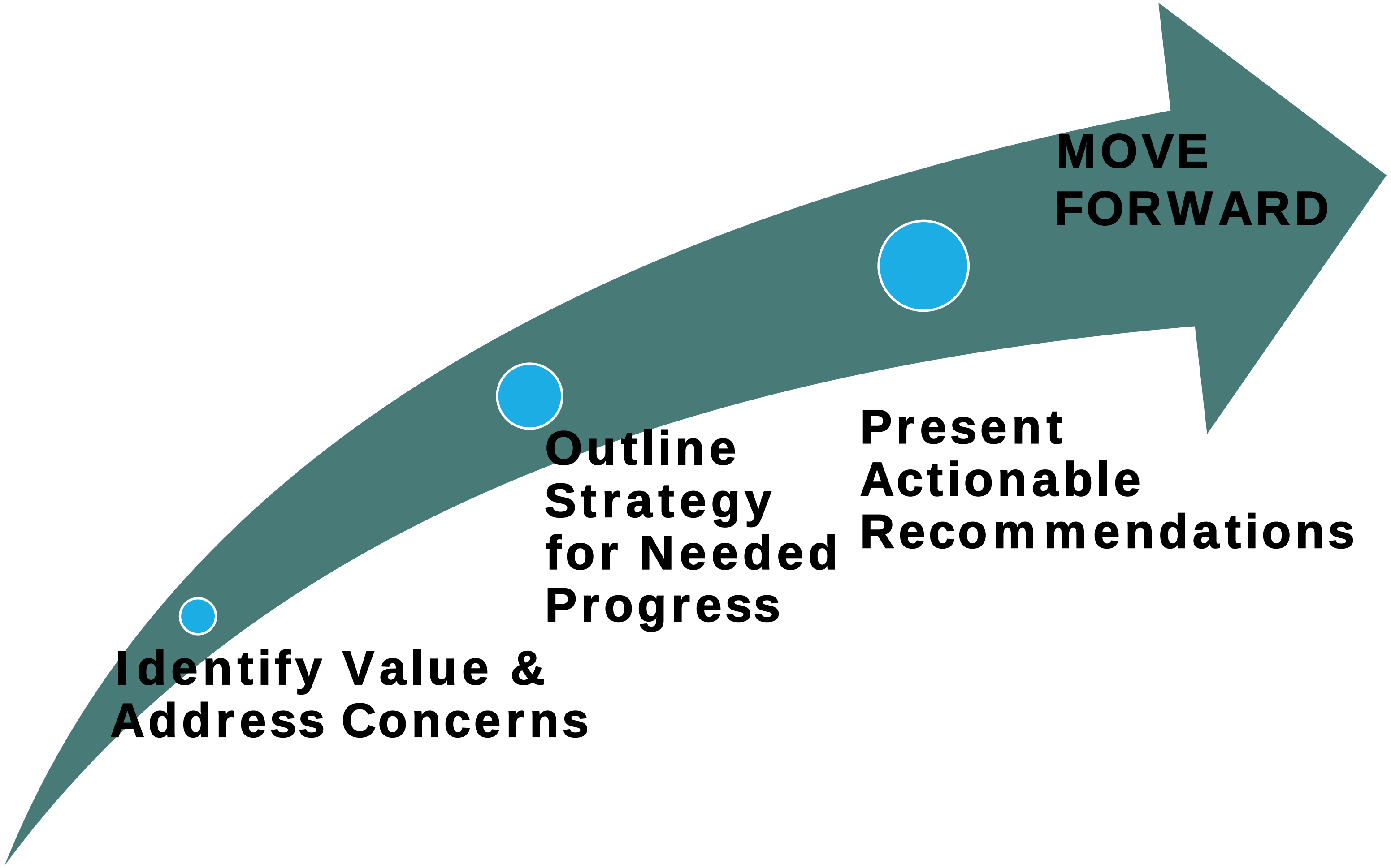


“Reject” the IOM Criteria

Ask HHS to “Adopt the CCC”

Ask for a Stakeholder Meeting

Repeat



Identify Value & Address Concerns

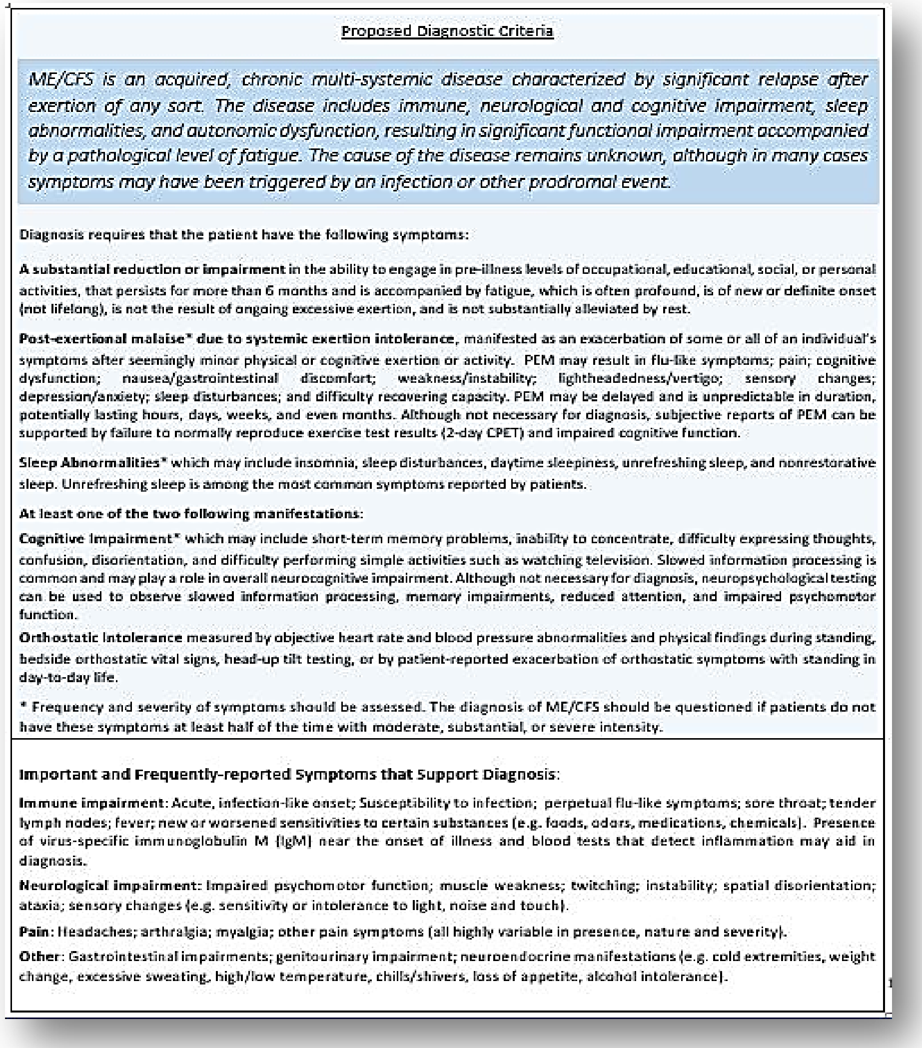
Outline Strategy for Needed Progress

Present Actionable Recommendations

MOVE FORWARD

Excerpt: August 2015 Recommendation

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.



Proposed Diagnostic Criteria

ME/CFS is an acquired, chronic multi-systemic disease characterized by 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.

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. Although not necessary for diagnosis, subjective reports of PEM can be supported by failure to normally reproduce exercise test results (2-day CPET) and impaired cognitive function.

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. Although not necessary for diagnosis, neuropsychological testing 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.

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

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). Presence of virus-specific immunoglobulin M (IgM) near the onset of illness and blood tests that detect inflammation may aid in diagnosis.

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).

Proposed Recommendation #3:

COLLABORATE WITH DISEASE EXPERTS AND STAKEHOLDERS REGARDING ALL EDUCATIONAL MATERIALS PRIOR TO RELEASE:

CFSAC recommends systematic collaboration with a workgroup or panel of recognized disease experts and stakeholders for review of all items of medical education produced by HHS agencies, Institutes and Centers prior to release. Additionally, CFSAC again recommends that the best way to move forward regarding the proposed Diagnostic Criteria was reflected in recommendations that were submitted to the Secretary in August 2015 (as attached), specifically: 8.) USE INFORMATION FROM THE IOM REPORT TO DETAIL AND CLARIFY THE CRITERIA; 10.) PROVIDE DISEASE GUIDANCE WITH THE CRITERIA; and 15.) CHANGE THE NARRATIVE.

Thank You

IOM/P2P Working Group

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