Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

Redefining an Illness

Committee on Diagnostic Criteria for ME/CFS
February 10th, 2015

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Committee on Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Outline

I. Background and context

II. Committee's statement of task and approach

III. Key messages and recommendation of the report
  - **Recommendation 1**: Diagnosing the illness
  - **Recommendation 2**: Toolkit for diagnosis
  - **Recommendation 3**: Reexamining the criteria
  - **Recommendation 4**: Renaming the illness

IV. Pediatrics

V. Comorbidities, future study, and dissemination of recommendations

Background

- Myalgic encephalomyelitis (ME)/ chronic fatigue syndrome (CFS) is a serious, debilitating condition that imposes a substantial burden of illness on millions of people in the United States and around the world. Somewhere between 836,000 and 2.5 million Americans are estimated to have this disorder.
- Over a period of decades, clinicians and researchers developed separate case definitions and diagnostic criteria for ME and CFS, although the terms denote conditions with similar symptoms.

Background

- Diagnosing ME/CFS in the clinical setting remains a challenge. Patients often struggle with their illness for years before receiving a diagnosis, and an estimated 84 to 91 percent of patients affected by ME/CFS are not yet diagnosed.
- 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.

Background

- ME/CFS can cause significant impairment and disability that have negative economic consequences at both the individual and societal levels. At least one-quarter of ME/CFS patients are house- or bedbound at some point in their lives.
- The direct and indirect economic costs of ME/CFS to society have been estimated at $17 to $24 billion annually.

Context

- The study was commissioned in response to a recommendation from HHS's Chronic Fatigue Syndrome Advisory Committee (CFSAC) to "promptly convene ... 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."

Charge to the Committee (abbreviated)

The Department of Human and Health Services and five other federal agencies asked the Institute of Medicine to convene a committee to:

- Develop **evidence-based diagnostic criteria for ME/CFS** to address the needs of health providers, patients and their caregivers, considering the various existing definitions and the unique diagnostic issues facing people with ME/CFS, specifically related to: gender, across the lifespan, and specific subgroups such as patients with substantial disability.
- Recommend whether **new terminology for ME/CFS** should be adopted.
- Develop an **outreach strategy** to disseminate the definition nationwide to health professionals, and a **plan for updating the new criteria**.

The IOM Study Process

Study Defined

Committee Selection and Approval

Committee Meetings, Information Gathering, Deliberations, and Drafting Report

Report Review and Approval

Report Released

Communication Strategy

Communication

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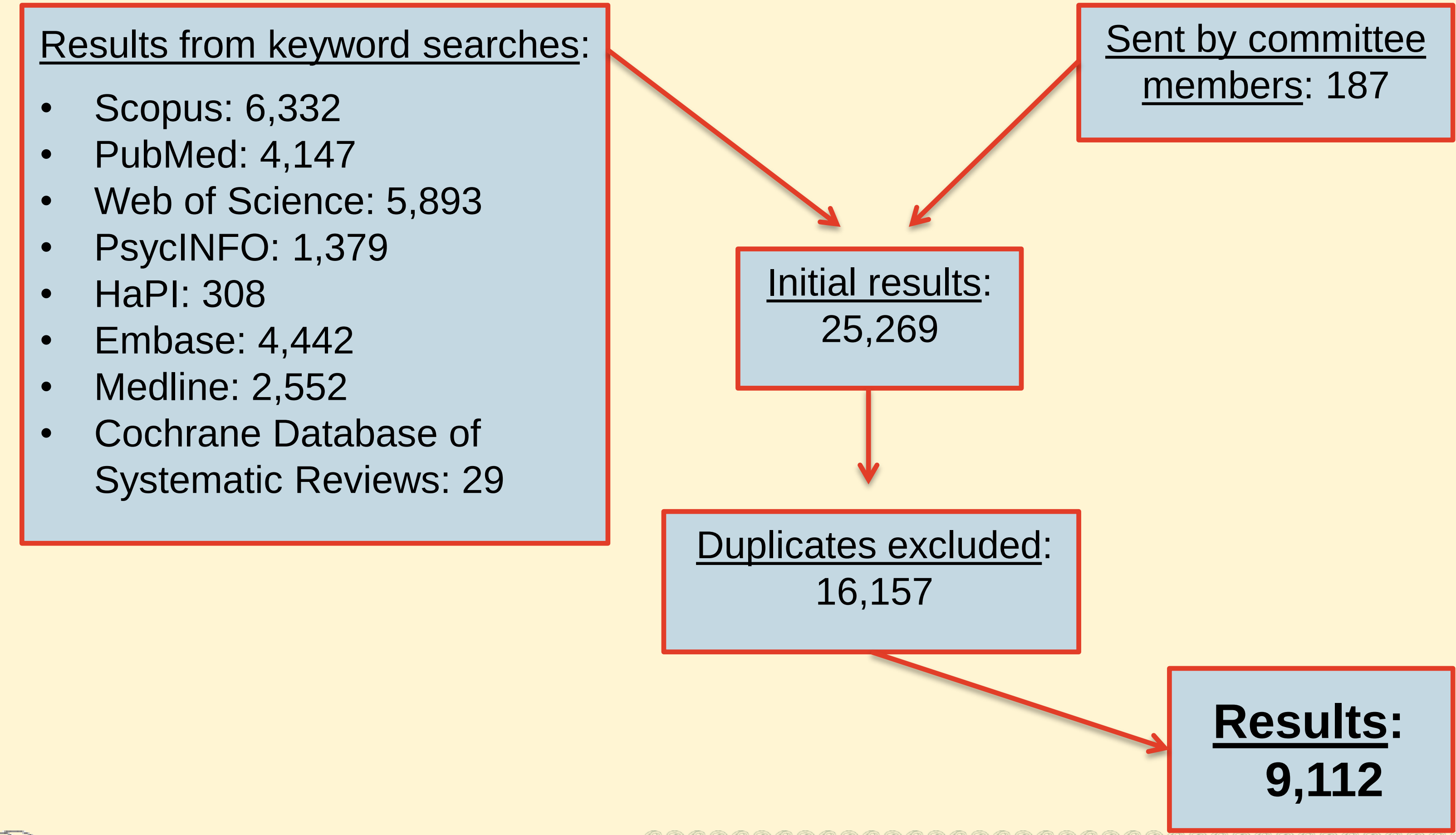
The Committee's Approach

The committee engaged in a number of activities to inform its work:

- Committee's deliberation and consensus process (five meetings: Jan, Mar, May, Jul, and Sep 2014)
- Two public sessions (testimony from patients and experts), and hundreds of public comments
- Input from CDC Multi-site Clinical Study of CFS, but lack of access to NIH P2P Workshop
- Consultants: (1) communications specialist with expertise in dissemination for health care professionals, and (2) statistician who summarized papers on symptom data from ME/CFS patients.
- Comprehensive literature review (January 1, 1950 - May 30, 2014)

Initial Literature Search



Results from keyword searches:

- Scopus: 6,332
- PubMed: 4,147
- Web of Science: 5,893
- PsycINFO: 1,379
- HaPI: 308
- Embase: 4,442
- Medline: 2,552
- Cochrane Database of Systematic Reviews: 29

Sent by committee members: 187

Initial results: 25,269

Duplicates excluded: 16,157

Results: 9,112

Literature Search

The committee reviewed literature on a number of symptoms in ME/CFS patients:

- **Post-exertional malaise**
- **Orthostatic intolerance and autonomic dysfunction**
- **Neurocognitive manifestations**
- **Sleep-related symptoms**
- **Symptom Constructs and Clusters**
- Immune impairment
- Neuroendocrine manifestations
- Fatigue
- Pain
- Infection

Targeted literature searches are in bold.

Targeted Literature Searches

- Priority research questions were developed.
- Search was conducted from Jan 1950 – May 2014
- Screening: Inclusion and exclusion criteria applied to identify articles addressing diagnosis, prognosis, and manifestations of subgroups.

	Search Results	Fulfilled Criteria	Deemed Relevant
Adults	2,298	359	319
Pediatrics	427	58	49

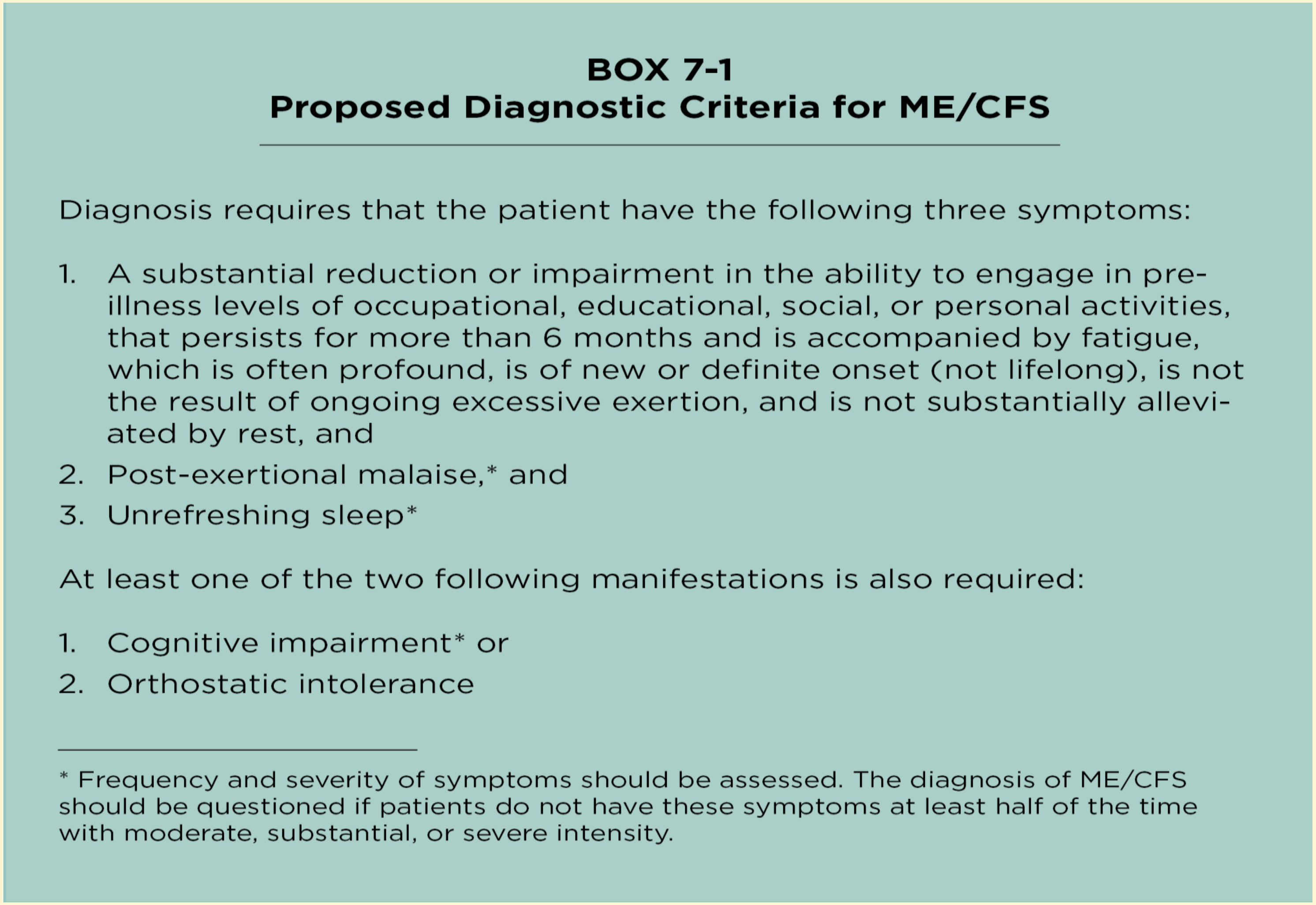
Additionally, the committee received a total of **1,291 articles from the public** and reviewed them all.

Key Messages

- ME/CFS is a serious, chronic, complex, multisystem disease that often can profoundly limit the health and activities of affected patients.
- A thorough history, physical examination, and targeted work-up are necessary to determine a differential diagnosis and often sufficient for diagnosis of ME/CFS.

Recommendation 1

Physicians should diagnose ME/CFS if diagnostic criteria are met following an appropriate history, physical examination, and medical work-up. A new code should be assigned to this disorder in the International Classification of Diseases, Tenth Edition (ICD-10) that is not linked to “chronic fatigue” or “neurasthenia.”



BOX 7-1
Proposed Diagnostic Criteria for ME/CFS

Diagnosis requires that the patient have the following three symptoms:

1. 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, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

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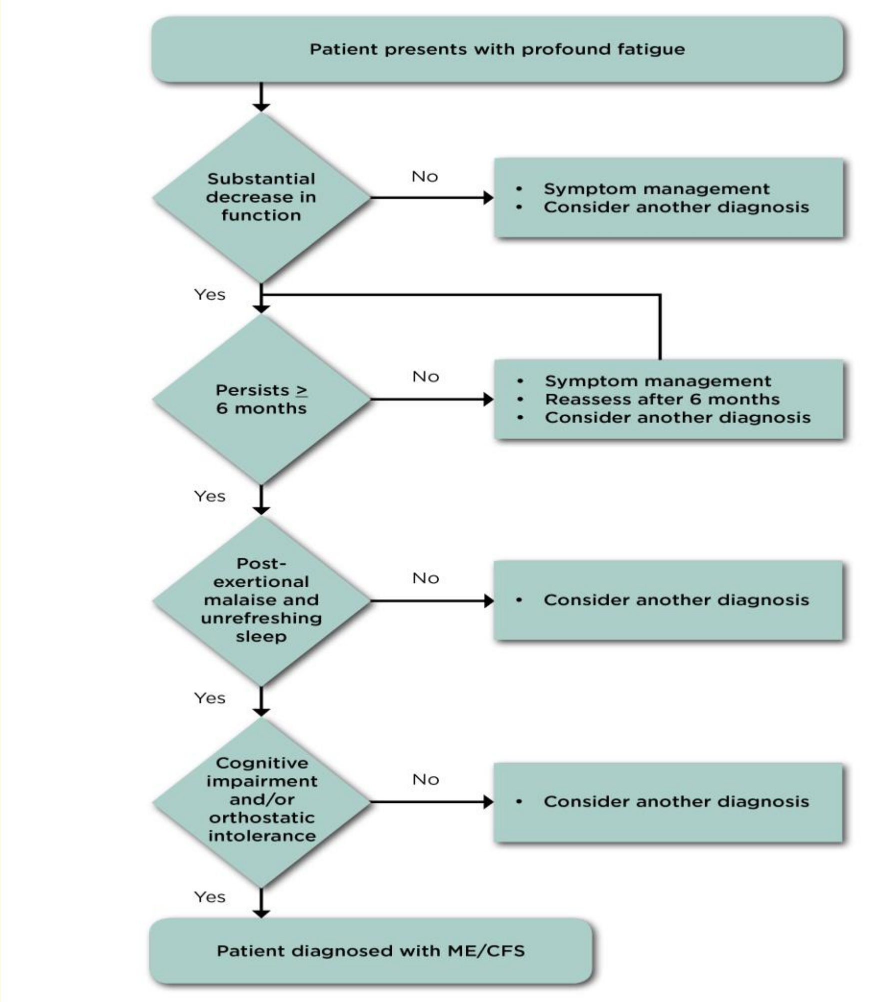
* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Diagnostic Algorithm for ME/CFS



Patient presents with profound fatigue

Substantial decrease in function

No

- Symptom management
- Consider another diagnosis

Yes

Persists ≥ 6 months

No

- Symptom management
- Reassess after 6 months
- Consider another diagnosis

Yes

Post-exertional malaise and unrefreshing sleep

No

- Consider another diagnosis

Yes

Cognitive impairment and/or orthostatic intolerance

No

- Consider another diagnosis

Yes

Patient diagnosed with ME/CFS

Severity and Frequency of Symptoms Duration of the Disease

- It is essential that clinicians assess the severity and duration of symptoms over the past month or more, not just on a few days. Chronic, frequent, and moderate or severe symptoms are required to distinguish ME/CFS from other illnesses.
- Regarding the duration of the illness, the proposed criteria require 6 months to make a diagnosis in light of evidence that most other causes of similar fatigue do not last beyond 6 months.

Other ME/CFS manifestations

- Pain – very common, but highly variable in presence, nature and severity.
- Certain infections may act as triggers
- Gastrointestinal and genitourinary problems
- Sore throat or scratchy throat
- Painful or tender axillary/cervical lymph nodes
- Sensitivity to external stimuli

Treating the Symptoms

Even if patients do not meet the criteria for this disorder, clinicians should address their symptoms and concerns. Patients who have not yet been symptomatic for 6 months should be followed over time to see whether they meet the criteria for ME/CFS at a later time.

What will these new criteria mean for clinicians?

- Educate about the disease. ME/CFS is a serious systemic disease.
- Recognize ME/CFS core symptoms and make a diagnosis.
- Improve care for ME/CFS patients:
  - Having a diagnosis
  - Treatment of the symptoms
  - Avoid the prescription of potentially harmful therapies

Recommendation 2

The Department of Health and Human Services should develop a toolkit appropriate for screening and diagnosing patients with ME/CFS in a wide array of clinical settings in which these patients are encountered, including primary care practices, emergency departments, mental/behavioral health clinics, physical/occupational therapy units, and medical subspecialty services (e.g., rheumatology, infectious diseases, neurology, cardiology).

Recommendation 3

A multidisciplinary group should 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 for this update effort should be provided by nonconflicted sources, such as the Agency for Healthcare Research and Quality, through its Evidence-based Practice Centers process, and foundations.

Recommendation 4

The committee recommends that this disorder be renamed “systemic exertion intolerance disease” (SEID). SEID should replace myalgic encephalomyelitis/ chronic fatigue syndrome for patients who meet the criteria set forth in this report.

The term “chronic fatigue syndrome” can result in stigmatization and trivialization and should no longer be used as the name of this illness.

Pediatrics—Background

- Estimates of the prevalence of pediatric ME/CFS vary widely from 0.03 to 1.29 percent.
- ME/CFS clearly hinders the social and educational development of pediatric patients.

  -School attendance is significantly reduced in a large percentage of patients. These patients are often misdiagnosed with labels of “school refusal” or “school phobia”.

Pediatrics—Evidence Base

The committee was struck by the paucity of the research conducted to date in children and adolescents.

Topic	Search Results	Fulfilled Criteria	Deemed Relevant
Autonomic manifestations	172	27	22
Neurocognitive manifestations	144	13	12
Post-exertional malaise (PEM)	43	8	7
Sleep	68	10	8

In addition to the limitations found in the adult ME/CFS literature, the committee found that numerous studies of children used a less restrictive definition of ME/CFS.

Pediatrics—Evidence Base

Conclusions:

There is sufficient evidence that:

- orthostatic intolerance and autonomic dysfunction are common in pediatric ME/CFS;
- that neurocognitive abnormalities emerge when pediatric ME/CFS patients are tested under conditions of orthostatic stress or distraction;
- that there is a high prevalence of profound fatigue, unrefreshing sleep, and post-exertional exacerbation of symptoms in these patients.
- and that pediatric ME/CFS can follow acute infectious mononucleosis and EBV.

Pediatrics—Diagnostic Criteria

- Based on the existing evidence to date, the committee concluded that the diagnostic criteria proposed in Chapter 7 should apply to the pediatric patient population.
- Though a symptom duration of 6 months is required, this criterion should not interfere with initiating appropriate symptom-based management long before 6 months has elapsed.

Comorbidities

The committee decided against developing a comprehensive list of potential comorbid conditions, but points to conditions that clinicians may wish to consider that have been identified by the ME-International Consensus Criteria (ME-ICC) and the CCC, including:

- fibromyalgia
- 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
- Sicca syndrome
- obstructive or central sleep apnea
- reactive depression or anxiety

Areas that Deserve Further Study

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.

Dissemination of Diagnostic Criteria - Audiences

- key decision makers (i.e., primary care providers [PCPs])
- other health care providers traditionally associated with the diagnosis and care of patients with ME/CFS
- audiences that can be engaged to help influence PCPs and other health care providers (school-based professionals, independent ME/CFS organizations, and professional societies)

Dissemination of Diagnostic Criteria - Activities

- Educational Material
- Presentations/exhibits at major medical meetings
- Online outreach
- Collaboration with professional societies
- Collaboration with large health care systems/medical groups, managed care organizations, and insurance providers
- Media outreach
- Social media outreach
- Outreach to opinion leaders
- Patient-directed interventions
- Educational Awareness Campaign
- Collaboration with Training and Examination Organizations
- Collaboration with Licensure and Certification Organizations
- Continuing Medical Education Opportunities
- Designation of an HHS Point Person

Thank you

- The Committee thanks HHS, AHRQ, CDC, FDA, NIH, and SSA for sponsoring the study.
- We also thank the speakers, consultants, and reviewers listed in the report who contributed to this project as well as all other researchers and clinicians who expressed interest in our study and attended our public meetings.
- We thank those involved in the FDA *Voice of the Patient* report.

Thank you

We thank the IOM project staff:

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Finally, we thank the patient community and advocates for their heroic effort to inform the committee throughout the study. This report would not exist without their knowledge and perspective.

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Supporting slides

Substantial decrease or impairment in function with profound fatigue

Patient Descriptions

- “flu-like fatigue/ exhaustion”
- “I feel like a battery that is never able to be recharged fully despite resting a lot and limiting my activities to only the bare essentials needed to get by”
- “Thinking takes a lot more work than it used to”
- “My arms, legs, body feel heavy and harder to move”
- severe limitations in personal and household management
- loss of job, medical insurance and career
- being predominantly housebound
- decreased social interaction and increased isolation

Substantial decrease or impairment in function with profound fatigue

Questions for Eliciting Medical History

How fatigued are you?

What helps your fatigue the most (resting, lying down, quiet situations, not exercising or avoiding exercise)?

What makes the fatigue worse?

What are you able to do now? How does it compare with what you were able to do before?

Think back to what you were able to do before you became sick. How much has this illness affected:

- your ability to work?
- your ability to take care of yourself/your family and to do chores?

What happens when you try to push through the fatigue?

Post exertional malaise (PEM)

PEM is a prolonged exacerbation of a patient’s baseline symptoms after physical/ cognitive/orthostatic exertion or stress. It may be delayed relative to the trigger.

Patient Descriptions

- “crash,” “relapse,” “collapse”
- mentally tired after the slightest effort
- physically drained or sick after mild activity
- the more demanding, prolonged or repeated the activity, the more severe and prolonged the payback

Post exertional malaise (PEM)

Questions for Eliciting Medical History

- What happens to you as you engage in normal physical or mental exertion? Or after?
- How long can you stand in place?
- How much activity does it take for you to feel ill?
- What symptoms develop from standing or exertion?
- How long does it take to recover from physical or mental effort?
- If you go beyond your limits, what are the later consequences?
- What types of activities do you avoid because of what will happen if you do them?

Consider asking patients to keep a diary for a week or two, documenting activities and symptoms

Unrefreshing Sleep

Patient Descriptions

- “feeling like I never slept”
- “cannot fall asleep or stay asleep”
- “After long or normal hours of sleep, I still don’t feel good in the morning”

Questions for Eliciting Medical History

- Do you have any problems getting to sleep or staying asleep?
- Do you feel rested in the morning or after you’ve slept?
- Tell me about the quality of your sleep.
- Do you need too much sleep?
- Do you need to take more naps than other people? (There may be other sleep disruptors as well)

Cognitive Impairments

Patient Descriptions

“brain fog”

“confusion”

“disorientation”

“hard to concentrate, can’t focus”

“inability to process information”

“can’t find the right words”

“inability to multi-task”

“problems with decision making”

“absent-minded/ forgetful”

Questions for Eliciting Medical History

Do you have problems doing the following activities: driving, watching a movie, reading a book/magazine, completing complex tasks under time constraints, following/participating in conversation, doing more than one thing at a time?

Compared with before your illness, how is your performance at work or school now?

Orthostatic intolerance

Symptoms worsen upon assuming and maintaining upright posture and are improved, though not necessarily abolished, by lying back down or elevating feet.

Patient Descriptions

- lightheadedness
- dizziness
- spatial disorientation or imbalance
- feeling unwell, dizzy, or lightheaded when sitting up or standing still for extended periods (note “extended” can mean a few minutes for the severely affected)

Orthostatic intolerance

Questions for Eliciting Medical History

How do you feel when you have been standing still for more than a few minutes?

What happens to you after you get up rapidly after lying down or sitting for a long time?

How long can you stand before feeling ill? For example, can you do the dishes? Can you stand in line for a bus or movie? Are you able to grocery shop or go to mall?

How does hot weather affect you?

Do you study or work lying down, in bed or recliner? Why?

Do you prefer to sit with knees to your chest or legs under you?

Observations during Clinical Visit

Fatigue	Observe for progressive fatigue (physical or mental), need for help or need to lie down during a prolonged exam.
Cognitive impairment	Observe for difficulties with thinking during the clinic visit—unusual trouble remembering medications, relating details of history or understanding questions/ recommendations, expressing self.
Orthostatic intolerance	Severely affected patients may need to lie down while they are being interviewed. Exam observations while standing: pallor, general discomfort, blue discoloration of extremities, cold hands and feet, diminished peripheral pulses, sway, efforts to compensate by moving around.

Objective Tests

When considered in the context of other symptoms, abnormal findings may support the diagnosis of ME/CFS. These tests are not routinely required, nor do negative results preclude the diagnosis.

PEM	Two cardiopulmonary exercise tests (CPETs) separated by 24 hours	Demonstrate marked inability to reproduce maximal or anaerobic threshold measures on the second day (note that this test may induce severe exacerbation of symptoms in these patients)
Cognitive impairment	Formal neuropsychological testing	Slowed information processing, memory impairments, reduced attention, impaired psychomotor function
Orthostatic intolerance	Standing test or tilt test	Evaluate for postural tachycardia syndrome, neurally mediated hypotension, and orthostatic hypotension

Pediatrics--Background

Several sets of diagnostic criteria for ME/CFS specific to children and adolescents have been proposed in the past.

The only main difference between adult and pediatric criteria has been the consideration of a shorter required duration of symptoms, from 6 months to 3 months.

- This has been put forth inconsistently, and research has shown that many children with infectious mononucleosis experience acute fatigue up to 6 months.

Pediatrics—Evidence Base

The committee reviewed literature on a number of symptoms in ME/CFS pediatric patients:

- Post-exertional malaise
- Orthostatic intolerance and autonomic dysfunction
- Neurocognitive manifestations
- Sleep-related symptoms
- Infection
- Immune impairment
- Neuroendocrine manifestations
- Fatigue
- Pain

*The committee also reviewed two studies that used factor analysis to attempt to define separate phenotypes.

GRADE Grid Template

	GRADE score				
	2	1	0	-1	-2
Balance between desirable and undesirable consequences of inclusion as a core or required symptom	Desirable clearly outweigh undesirable	Desirable probably outweigh undesirable	Trade-offs equally balanced or uncertain	Undesirable probably outweigh desirable	Undesirable clearly outweigh desirable
Assessment of quality of evidence	Strong: “definitely include as required”	Weak: “probably include as required”	No specific recommendation	Weak: “probably don’t include as required”	Strong: “definitely don’t include as required”
For each symptom or category of symptoms below, please mark with an “X” the cell that best corresponds to your assessment of the available evidence, in terms of benefits versus disadvantages for inclusion as a core or required symptom					
PEM (exacerbation of symptoms or fatigue triggered by physical or mental exertion and lasting > 24 hours after exercise)					
Sleep (unrefreshing sleep, sleep disturbance/dysfunction)					
Neurocognitive manifestations (mental fatigue, memory impairment, concentration difficulties, confusion)					
Autonomic manifestations (orthostatic intolerance, cardiovascular irregularities, gastro-intestinal impairments, genitourinary impairments)					
Immune manifestations (sore throat, tender lymph nodes)					
Neuroendocrine manifestations (loss of thermostatic stability, sweating episodes, intolerance of temperature extremes)					
Pain (headaches, muscle pain, joint pain)					

Diagnostic Criteria

The committee weighed several factors in reaching consensus on these diagnostic criteria:

- the frequency and severity with which these symptoms were experienced by patients,
- the strength of the scientific literature, and
- the availability of objective measures supporting the association of particular symptoms with the diagnosis.

Brief Symptom Descriptions

Post-exertional malaise (PEM): A prolonged exacerbation of a patient’s baseline symptoms after physical/ cognitive/orthostatic exertion or stress. It may be delayed relative to the trigger.

Unrefreshing sleep: Feeling unrefreshed after sleeping many hours.

Cognitive impairments: Problems with thinking exacerbated by exertion, effort, or stress or time pressure.

Orthostatic intolerance: Symptoms worsen upon assuming and maintaining upright posture and are improved, though not necessarily abolished, by lying back down or elevating feet.