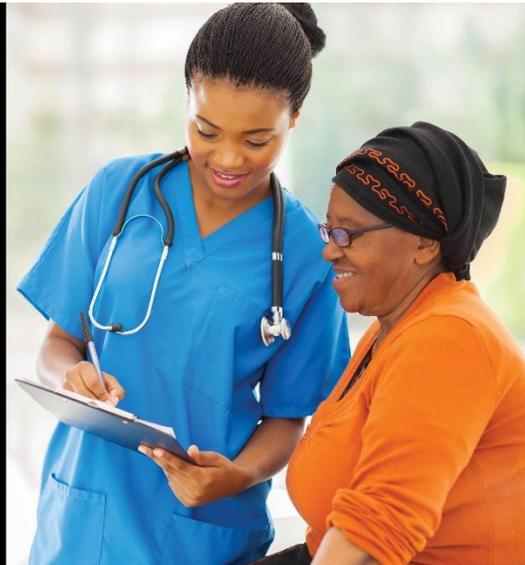
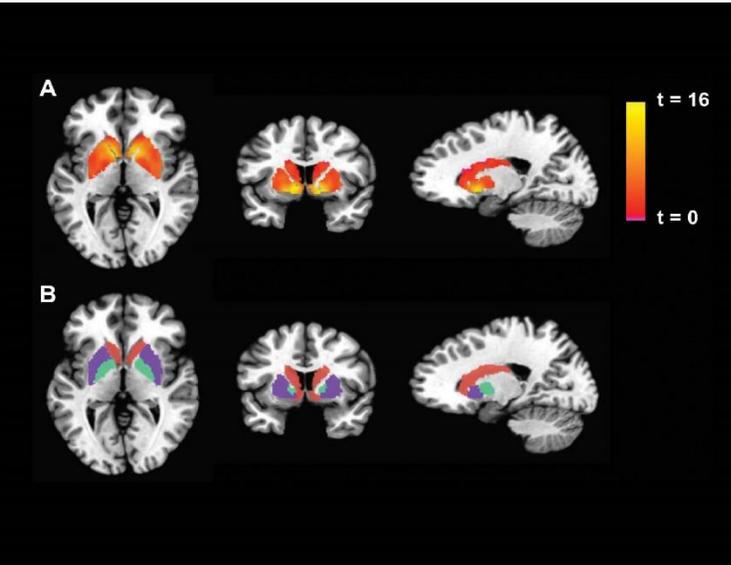


CDC PUBLIC HEALTH GRAND ROUNDS

Chronic Fatigue Syndrome: Advancing Research and Clinical Education



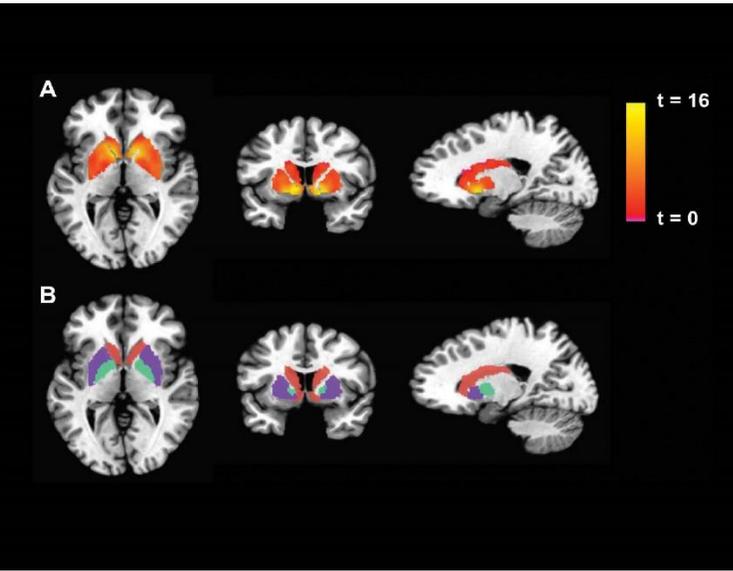
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February 16, 2016



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

Clinical Presentation of Chronic Fatigue Syndrome



Accessible version: <https://youtu.be/0SnJy5AOSd8>

Charles W. Lapp, MD

Medical Director

Hunter-Hopkins Center, P.A.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

The Disease of a Thousand Names

- **Royal Free Disease**
- **Iceland Disease**
- **Tapanui Flu**
- **“Yuppie Flu”**
- **Myalgic encephalomyelopathy**
- **Chronic Fatigue Immune Dysfunction Syndrome**
- **SEID, or Systemic Exertion Intolerance Disease**
 - Name recommended by Institute of Medicine, 2015

Clinical Case



theantiagingartist.com/wp-content/uploads/2010/04/Tired-Business-Woman.jpg

Clinical Case

- **Clinical case demonstrates all the key features of CFS:**
 - Exertion intolerance and debilitating fatigue
 - Post-exertion relapse and malaise
 - New onset of sleep problems
 - Cognitive difficulties
 - Orthostatic intolerance (such as dizziness, lightheadedness upon standing up)
 - Symptoms wax and wane
 - Whole body flu-like myalgias, arthralgias, or widespread body pain

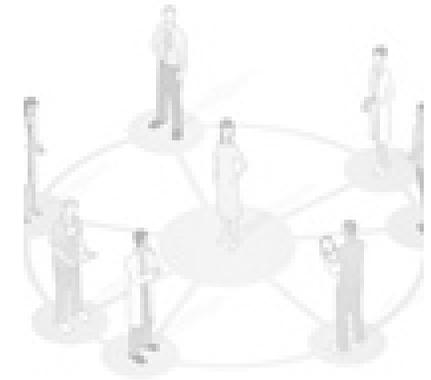
Precipitating Factors and Natural History of Illness

- **Symptoms develop acutely over hours to days**
- **Up to 85% of patients report a trigger:**
 - Bacterial or viral infection (72%)
 - Trauma (4.5%)
 - Surgery or childbirth (4.5%)
 - Allergic reactions (2.2%)
 - Stress, emotional trauma (1.7%)
- **Natural course of illness is to wax and wane**
- **Unpredictable onset and severity of relapses**
- **Most adults do not return to their pre-illness level of function**

Clinical Presentation

➤ Comorbidities

- Fibromyalgia
- Irritable bowel and bladder (up to 85%)
- Sjögren's syndrome (up to 85%)
- Joint hyperextensibility (Ehlers-Danlos syndrome) (12%–60%)
- Chemical sensitivities (up to 67%) or sensitivity to light, sound, temperature, touch,
- Gut motility disorder with dysphagia, early satiety, nausea, and/or constipation (58%)
- Celiac disease-like disorders with sensitivity to wheat, grains, or gluten
- Abdomino-pelvic pain
- Vasomotor (autonomic or non-allergic) rhinitis
- And many other conditions ...



Diagnostic Evaluation

➤ The essentials of evaluation include:

- Thorough medical history
- Thorough psychosocial history
- Complete physical exam
- Mental health assessment
 - Hospital Anxiety and Depression Scale (HADS)
 - Patient Health Questionnaire (PHQ8)
- Basic screening laboratory tests



Laboratory Evaluation

➤ Basic laboratory tests include:

- CBC with leukocyte differential
- Sodium/potassium, glucose, BUN, creatinine, LDH, AST, ALT, alkaline phosphatase, total protein, albumin, calcium, phosphorus, magnesium
- TSH, free T4 test
- Sedimentation rate and/or CRP (markers of systemic inflammation)
- Urinalysis

➤ Additional laboratory tests may be clinically indicated



Making the Diagnosis

- **Institute of Medicine recommends making diagnosis actively**
- **Recommended diagnostic criteria**
 - Institute of Medicine SEID Criteria
 - 1994 Research Case Definition
 - Canadian Consensus Criteria
- **Making diagnosis sooner helps patients by reducing uncertainty and anxiety, and by lowering costs**
 - Many CFS patients face substantial out-of-pocket costs

SEID: Systemic Exertion Intolerance Disease

iom.nationalacademies.org/reports/2015/me-cfs.aspx

Fukuda K, Straus SE, Hickie I, et al. *Ann Intern Med.* 1994 Dec 15; 121(12): 953-9.

Carruthers BM, van de Sande MI, De Meirleir KL, et al. *J Intern Med.* 2011; 270(4): 327-338.

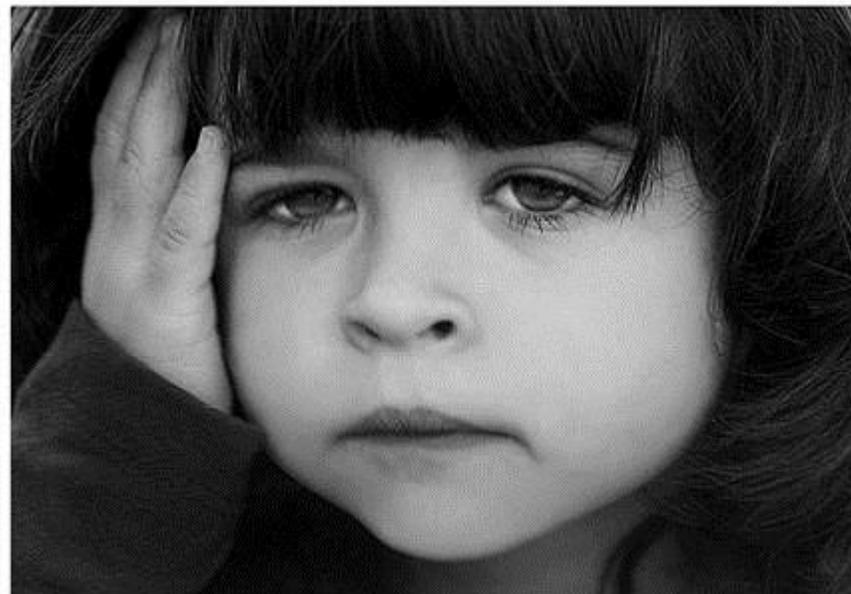
Prognosis

➤ Adults

- Up to 40% may improve
- Median full recovery is ~5%

➤ Children and adolescents

- 60%–88% improvement over time

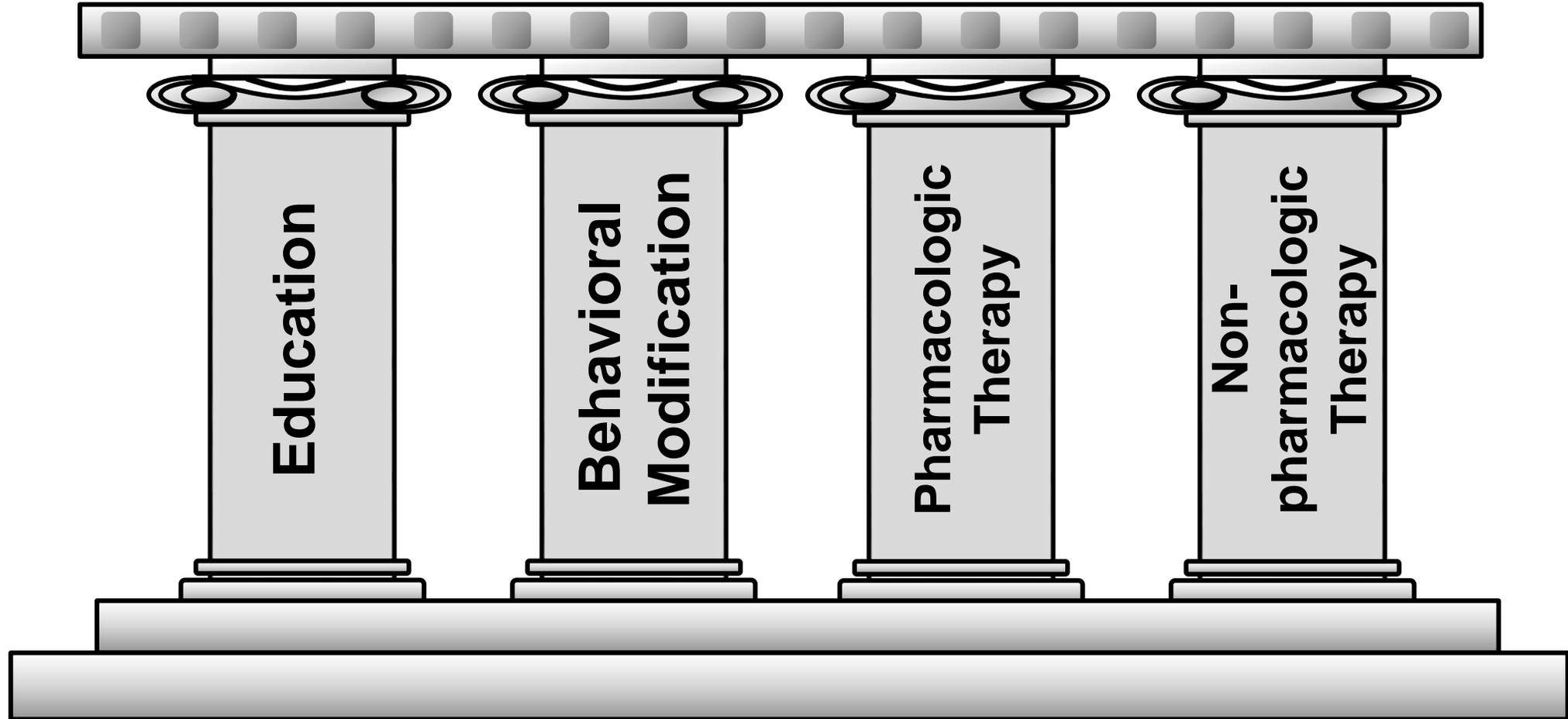


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Rowe K. IAME/CFS Scientific Conference in Ottawa, Canada. September 2011.

Brown MM, Bell DS, Jason LA, et al. *J Clin Psychol*, 2012 Sep; 68(9):1028-35.

Management



Pharmacologic and Non-Pharmacologic Therapy



➤ Pharmacologic therapy

- Manage sleep and pain
 - ▣ Avoid narcotic pain medications if possible
- Manage symptoms and comorbidities

➤ Non-pharmacologic therapy

- Physical therapies
 - ▣ Epsom soaks, hot or cold packs, liniments, massage, osteopathic manipulation, acupuncture

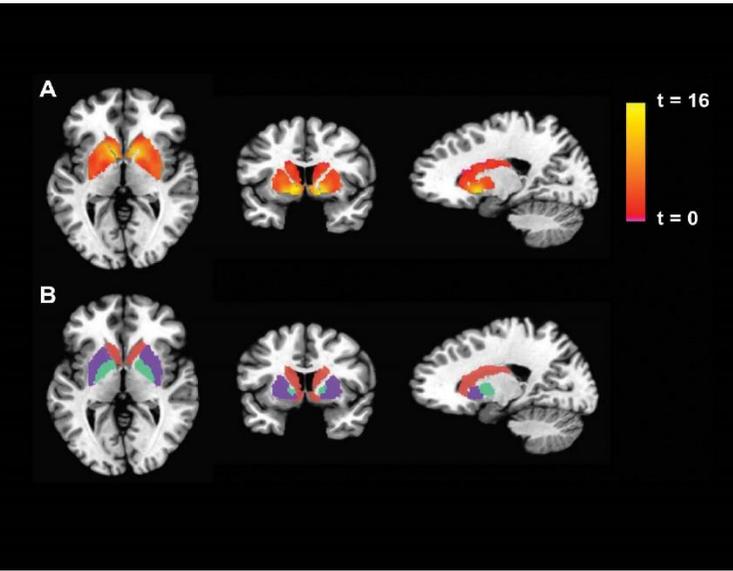
Stay Active, But Not Too Active

- **Begin with active stretching, range of motion**
- **Follow with simple resistance training (light weights, elastic bands)**
- **Advance to certain types of aerobic activities**
 - Tai chi, yoga, walking, bicycling, pool therapy
- **To avoid flares, encourage patients to limit activity by time (5 minutes/day to start) or limit the number of repetitions**
- **If patients experience excessive fatigue reduce the amount of time or number of repetitions**

ME/CFS: Clinical Summary

- **Can present in both pediatric and adult groups**
- **Typically has preceding medical event, often infection**
- **Patients benefit from earlier comprehensive evaluation and diagnosis**
- **Disease can have severe impact on quality of life, but improvement and recovery are possible**
- **No curative therapy, but graded exercise and some types of pharmacotherapy can be of benefit**

Public Health Approach to CFS



Elizabeth R. Unger PhD, MD

Chief, Chronic Viral Diseases Branch

Division of High-Consequence Pathogens and Pathology

National Center for Emerging and Zoonotic Infectious Diseases



Epidemiology of CFS

➤ How common is CFS?

- At least 1 million Americans have CFS (Prevalence 0.2%–0.7%, estimated from population survey)
 - ❑ Only about 20% have been diagnosed
 - ❑ Most have been ill longer than 5 years, but only about 50% continue to seek medical care

➤ Who has CFS?

- Three to four times more common in women than men
- All races and ethnicities affected
 - ❑ Suggestion of higher burden in minority and socioeconomically disadvantaged
- Broad age range
 - ❑ Highest prevalence in 40- to 50-year-olds
 - ❑ Children and adolescents are affected



Afari N and Buchwald D. *Am J Psychiatry*. 2003; 160:221-36.
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Reyes M, Nisenbaum R, Hoaglin DC, et al. *Arch Intern Med*. 2003; 163:1530-6.

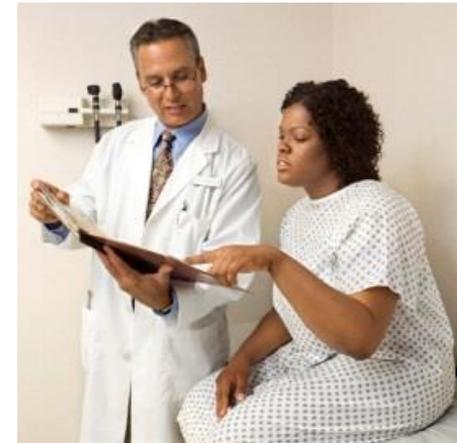
Economic Burden of CFS and Barriers to Healthcare Utilization

- **Patients, their families, employers, and society bear significant costs**
 - Estimated \$9–\$14 billion annually in direct medical costs in U.S.
 - Nearly one-quarter of these expenses are paid out of pocket
 - Estimated \$9–\$37 billion annually in lost productivity in U.S.
 - CFS patients less likely to be employed due to disability
 - Caregivers employment may be affected
 - Illness onset before age 25 frequently blocks full educational potential, limiting lifetime earnings



Patients Face Significant Barriers to Healthcare

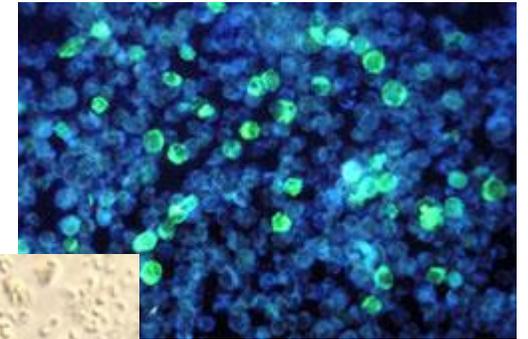
- **Survey in Georgia (2007–2009) found that 55% of those with CFS reported at least one barrier to healthcare**
 - Finances prevented 10% from seeking care (twofold greater than population average in 2005 National Health Interview Survey)



Infectious Risk Factors Associated with CFS

➤ Infections

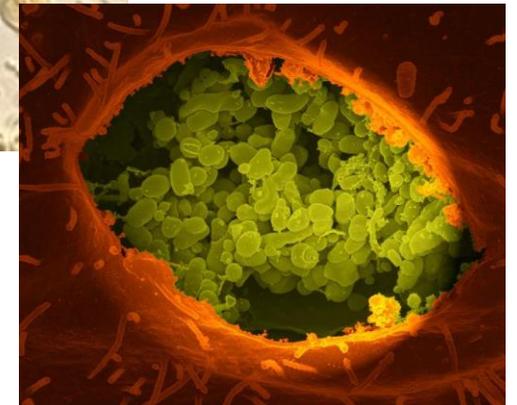
- No one pathogen implicated
- Viral and nonviral pathogens, e.g., Epstein-Barr Virus, Ross River Virus, Q fever (*Coxiella burnetti*), Giardia
- Severity of acute infection most predictive of subsequent CFS diagnosis



Epstein-Barr virus



Giardia



Coxiella burnetti

Afari N and Buchwald D. *Am J Psychiatry*. 2003;160:221-36.

Hickie I, Davenport T, Wakefield D, et al. *BMJ*. 2006;333(7568):575-575.

Naess H, Nyland M, Hauskeb T, et al. *BMC Gastroenterol*. 2012 Feb 8;12:13

Non-infectious Risk Factors Associated with CFS

➤ Stressors

- Physical trauma and adverse events
- Allostatic load—physiologic consequences of neuroendocrine response to chronic stress
- Metabolic syndrome

➤ Genetics

- Twin and family studies support additive genetic and environmental contributions

Afari N and Buchwald D. *Am J Psychiatry*. 2003;160:221-36.

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Heim C, Nater UM, Maloney E, et al. *Arch Gen Psychiatry*. 2009; 66:72.

Maloney EM, Boneva RS, Lin JS. *Metabolism* 2010; 59:1352.

Newton JL, Sheth A, Shin J, et al. *Psychosom Med*. 2009 Apr;71(3):361-5.

Multisite Clinical Assessment of ME/CFS (MCAM)

- **Heterogeneity of patients in research studies could confound results**
 - Duration of illness, symptom severity, co-morbid conditions, medications
 - Differences in case definitions and how they are applied
- **MCAM was designed to capitalize on the clinical expertise of physicians specializing in care and treatment of ME/CFS patients**
 - Enrollment based on clinical judgement rather than case definition criteria – providing evidence-based data to address case definition and CFS subgroups
 - Collect standardized data on the major illness domains using questionnaires to allow comparisons between clinics and to symptom severity in other conditions
 - Collect data on use of laboratory tests and medications

7 MCAM Clinics Funded Since 2011

Mount Sinai Beth Israel, New York City, NY (Benjamin Natelson, MD)

Institute for Neuro Immune Medicine, Miami, FL (Nancy Klimas, MD)

[Open Medicine Institute Consortium](#)

Bateman Horne Center, Salt Lake City, UT (Lucinda Bateman, MD)

Hunter-Hopkins Center, Charlotte, NC (Charles Lapp, MD)

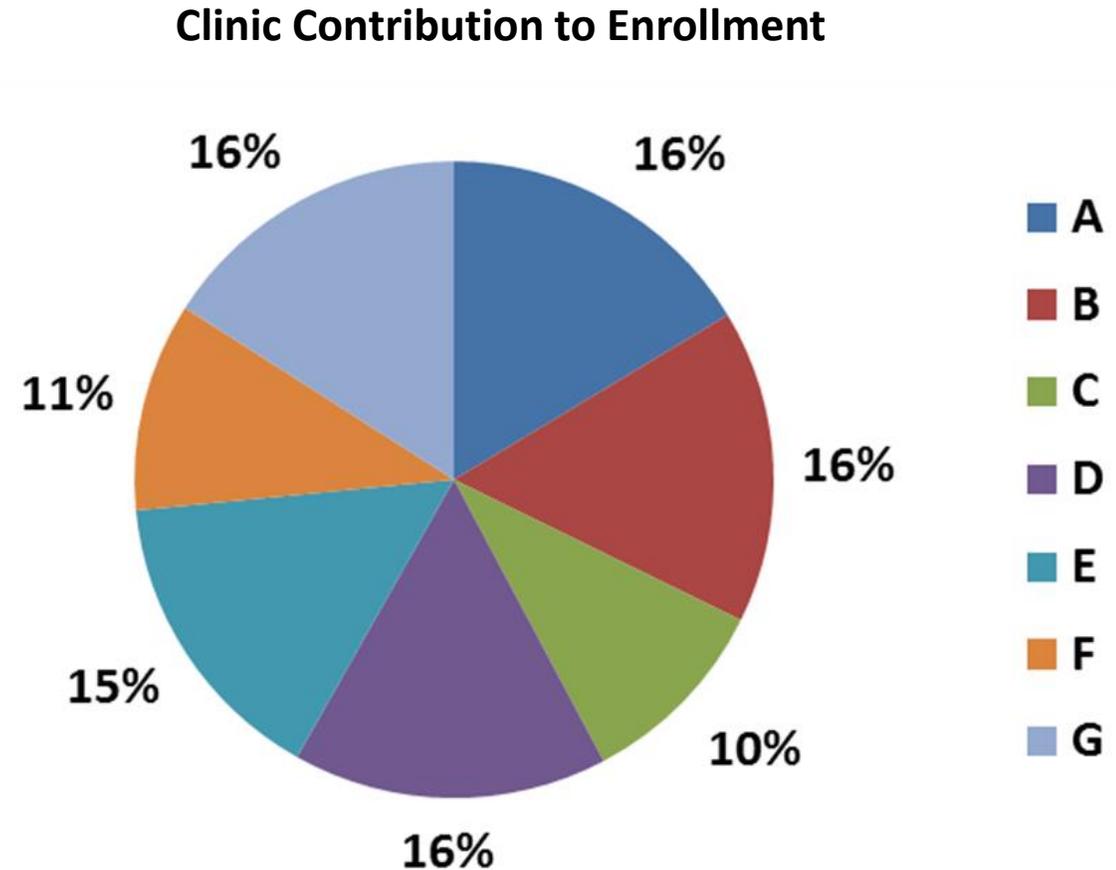
Open Medicine Clinic, Mountain View, CA (Andreas Kogelnik, MD)

Richard Podell Medical, Summit, NJ (Richard Podell, MD)

Sierra Internal Medicine, Incline Village, NV (Daniel Peterson, MD)

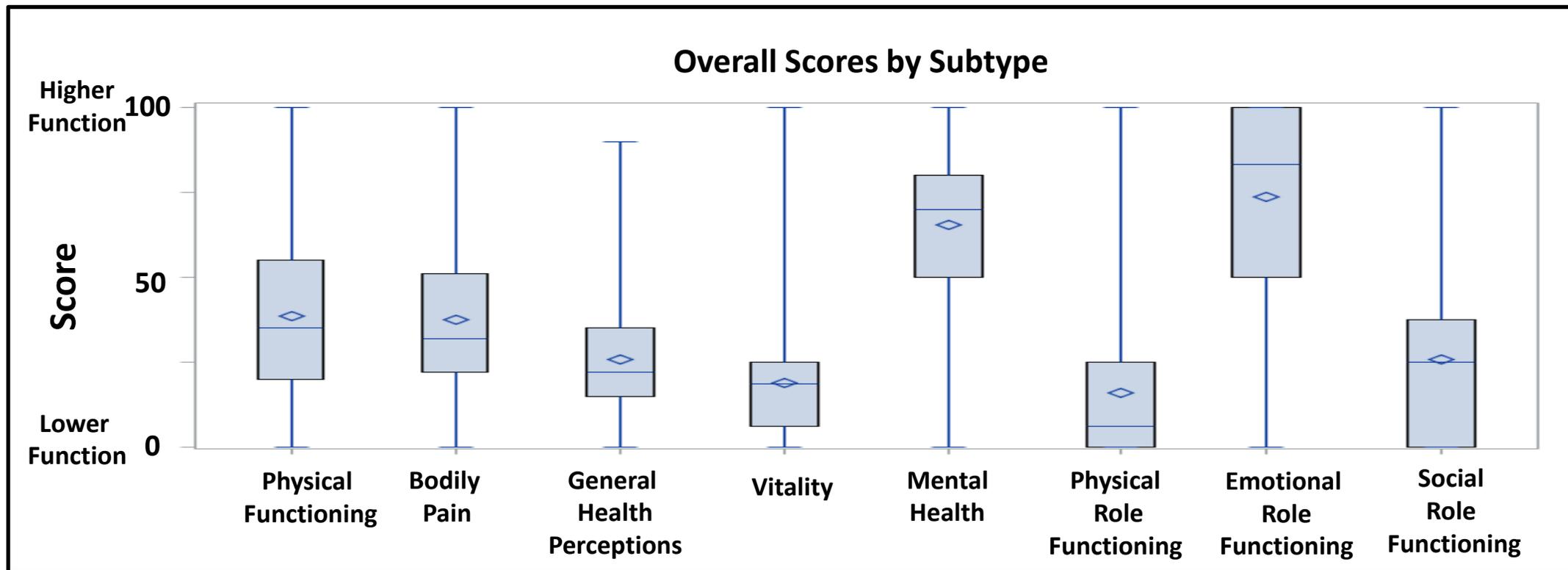
MCAM Study Sample – Baseline (471 patients)

- **Mean age at enrollment 48 years**
- **Mean age at onset 38 years**
 - Mean duration of illness – 14 years
 - 74% Female
 - 90% White
 - Mean BMI 26.6
 - 77% \geq College education
 - 94% Insured
 - 75% Not working
 - 14% Receiving unemployment benefits



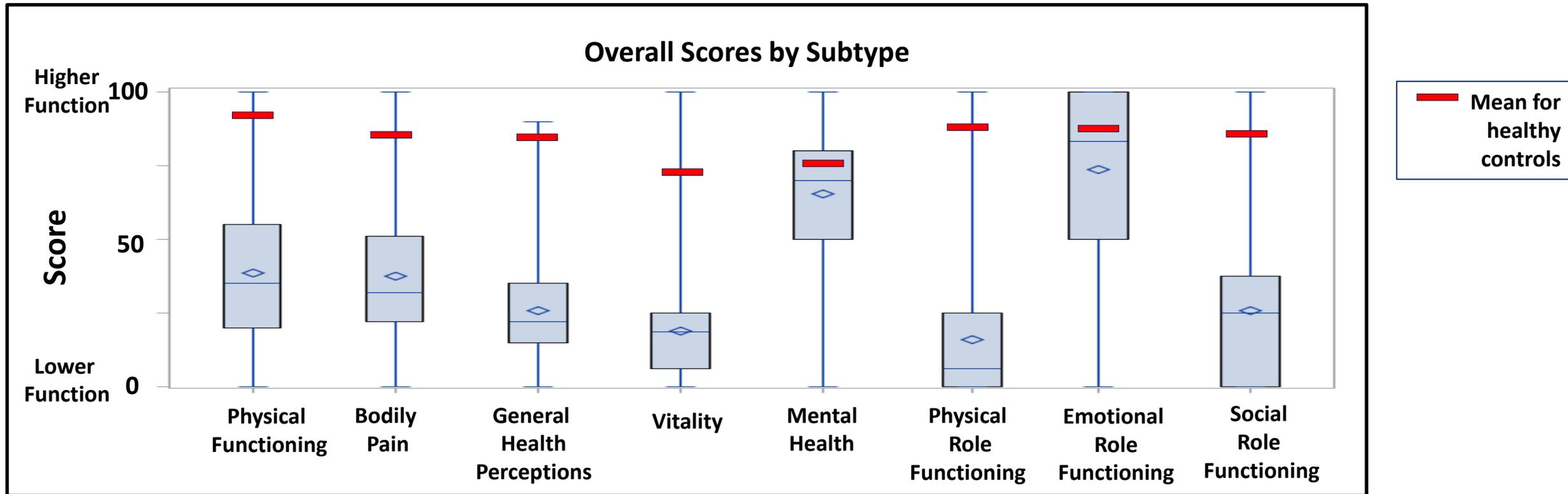
For Many Patients, Similar Symptoms But Severity Differs and Affects Functional Status

- Few differences in illness characteristics in patients between clinics
- Patients as a whole exhibit broad distribution in symptom severity



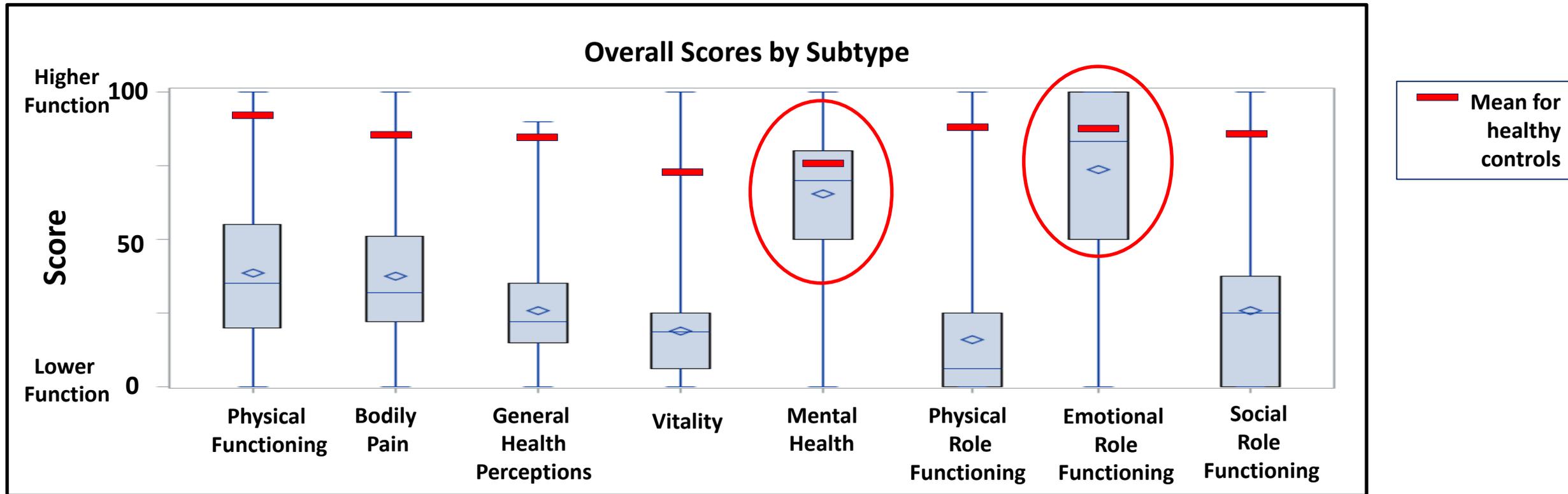
For Many Patients, Similar Symptoms But Severity Differs and Affects Functional Status

- Functional status is substantially impaired in comparison to healthy controls



For Many Patients, Similar Symptoms But Severity Differs and Affects Functional Status

- **Functional status is substantially impaired in comparison to healthy controls**
 - Exception is preservation of mental health and emotional function



MCAM Summary

- **Data confirm seriousness of illness and extent of impairment**
- **Analysis indicates heterogeneity of CFS population as a whole**
 - Patient variation between clinics does not appear to be significant
- **Study is ongoing**
 - Collect measures of illness characteristics over time
 - Enroll understudied groups of patients (pediatric, homebound, new-onset) and comparison groups (ill and healthy)
 - Collect biologic samples (blood and saliva) to measure potential biomarkers of illness
 - Use data to find patient subgroups that reflect different causes or responses to treatment
- **Population in specialized referral clinics is not representative of the CFS population**
 - Emphasizes the need for knowledge dissemination to medical community

Outreach to Clinicians: Continuing Medical Education Courses

- **Medscape roundtable discussions—combined audience ~22,000 physicians; 6,022 credits awarded**
 - Chronic Fatigue Syndrome: The Challenges in Primary Care (2012–2013)
 - A Case-Based Approach to Chronic Fatigue Syndrome (2013–2014)
- **Online continuing education courses available at CDC's CFS webpage until June 2016**
 - Diagnosis and Management of CFS (1,997 CE credits issued through February 2016)
 - Sleep Problems in CFS (1,867 CE credits issued through February 2016)
 - Accredited for physicians, nurses, health educators, and others for continuing education credit
- **Curriculum under review by MedEd portal**
 - Standardized patient videos and curriculum for use by medical school faculty

Communication with Advocacy Community

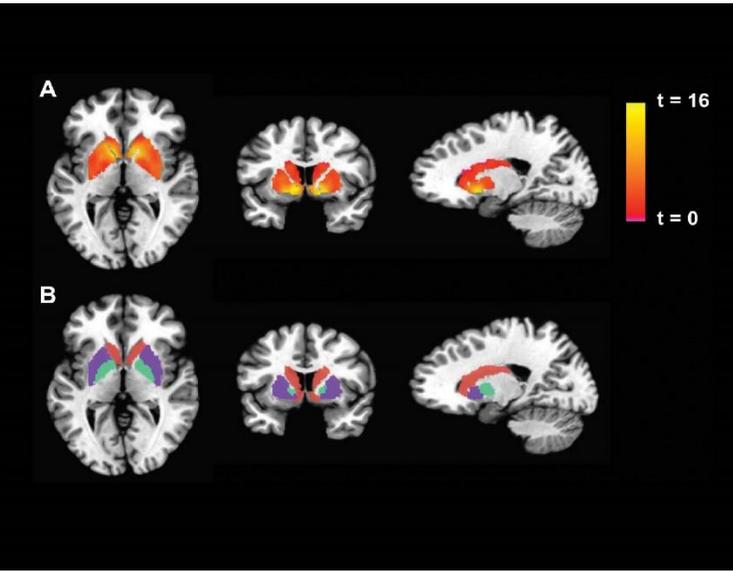
➤ **Patient-Centered Outreach and Communication calls (PCOCA calls)**

- Twice-annual calls initiated in 2012
- Update on CDC activities (10 minutes)
- Topics of interest to advocate community presented by outside experts (35–40 minutes)
- Answers to questions submitted via e-mail (10–15 minutes)
- Topics have included identifying patients for clinical studies, exercise, infection and immunity in CFS, CFS and cognitive function, sleep research and CFS, and self-management strategies in CFS

Developing Educational Materials with Broad Stakeholder Collaboration

- **Follows recommendation of Institute of Medicine report**
- **Includes patient advocates, medical professional organizations, expert clinicians, government**
- **One focus will be to widely disseminate the educational materials to the medical community at large**

Lessons from the Institute of Medicine and NIH Pathways to Prevention Reports



Anthony L. Komaroff, MD

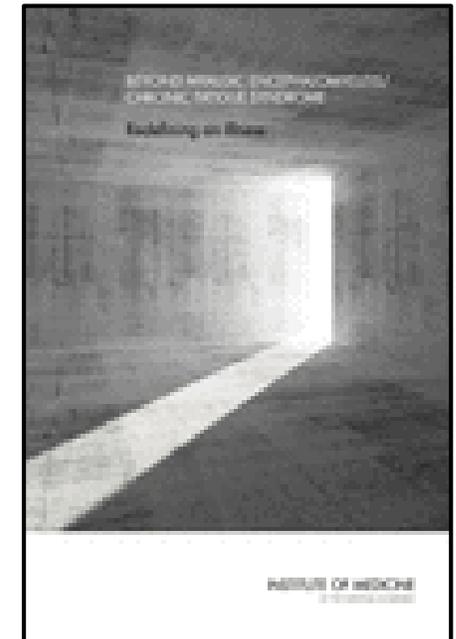
Simcox-Clifford-Higby Professor of Medicine, Harvard Medical School
Senior Physician, Brigham and Women's Hospital



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Recent Reports on ME/CFS From Authoritative Sources

- ***Institute of Medicine, National Academy of Sciences***
 - 300-page report reviewing all (9,000+ articles) of the published literature
 - Concludes ME/CFS is a biologically-based illness, proposes new case definition and new name (2015)
- ***National Institutes of Health Pathways to Prevention***
 - Conference and report
 - Also concludes ME/CFS is a biologically based illness (2015)
- ***Agency for Healthcare Research and Quality (AHRQ)***
 - Review of literature on diagnosis and treatments (2014)



Institute of Medicine Report: Scope and Seriousness of ME/CFS



- **836,000 to 2.5 million Americans have ME/CFS**
- **\$18 billion to \$51 billion annually, costs to society measured in medical expenses and lost productivity**
- **“ME/CFS is a serious, chronic, complex systemic disease that often can profoundly affect the lives of patients.”**
- **ME/CFS “... is not, as many clinicians believe, a psychological problem.”**

Institute of Medicine Report: Biology of ME/CFS

➤ The central question:

Given that ME/CFS is defined exclusively by *subjective* symptoms, are there underlying **objective biological abnormalities**?



Institute of Medicine Report: Neurobiology of ME/CFS

➤ Neurological abnormalities

- Slowed information processing on neuropsychological testing
- Problems with white matter integrity, as shown by MRI
- Neuroinflammation, as shown by positron emission tomography (PET) studies
- Impairment of working memory, as shown by functional MRI (fMRI)
- Hypothalamic-pituitary axis abnormalities
- Autonomic nervous system abnormalities: defective sympathetic and parasympathetic signaling, with orthostatic tachycardia and hypotension



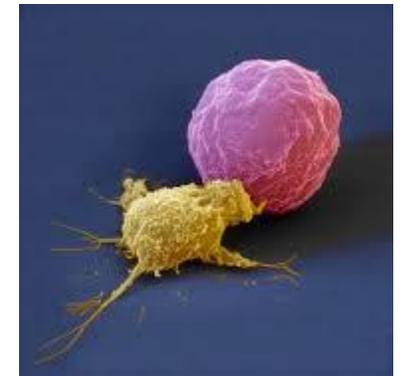
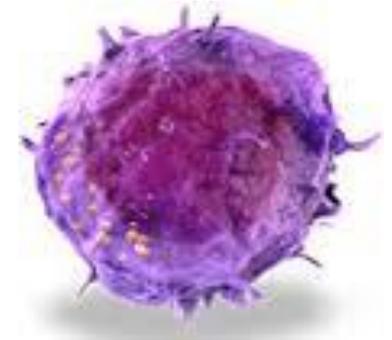
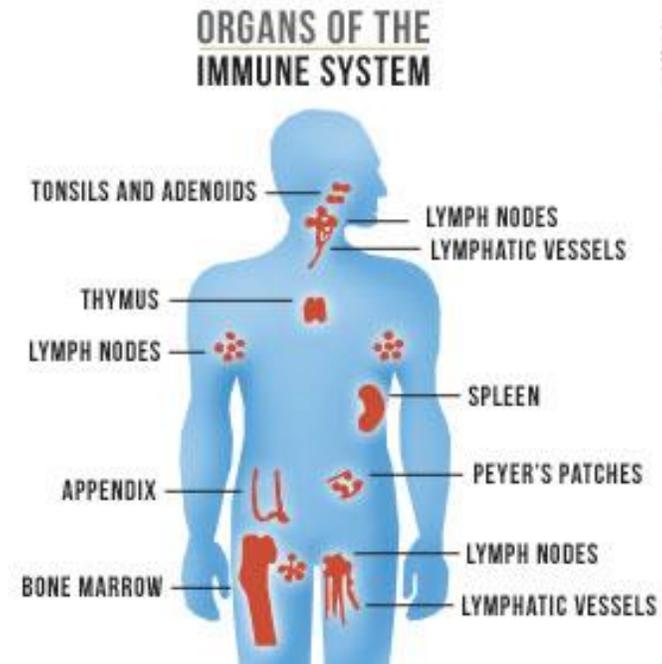
Neurons

➤ NIH report in general agreement with IOM on the underlying neurobiology

Institute of Medicine Report: Immunobiology of ME/CFS

➤ Immunological abnormalities

- Impaired natural killer cell function that correlates with illness severity
- Increased cytokine levels, suggesting a state of chronic immune system activation



Institute of Medicine Report: Biology of ME/CFS

➤ Patient history often suggests infection

- Many, but not all, patients report that the illness began suddenly, following an infectious-like illness characterized by fever, myalgias, respiratory, gastrointestinal and neurological symptoms, along with severe fatigue—an illness from which they feel they have never recovered
- Medical literature of the past 100 years includes many reports of “post-infectious fatigue syndromes” following different well-documented acute infections

➤ Institute of Medicine’s conclusions on possible role of infection, in some cases

- “Sufficient evidence suggesting that ME/CFS follows infection with EBV [Epstein–Barr virus] and possibly other specific infections—viral, bacterial and possibly protozoal.”
- NIH report calls for research on possible role of herpesviruses in ME/CFS, based on evidence of reactivation of herpesviruses in some ME/CFS patients, and the neurotropism of herpesviruses

Institute of Medicine Report: New Case Definition



➤ Proposed a new case definition that is:

- Simpler and shorter
- Easier to apply consistently
- Likely to result in fewer false negative and false positive classifications, leading to a more homogeneous patient group
- Likely to be a better predictor of response to therapy and a better predictor of prognosis

Key Elements of the IOM Case Definition

➤ **Post-exertional malaise**

- 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**

- Regularly feeling unrefreshed after sleeping many hours

➤ **Cognitive impairments**

- Problems with thinking exacerbated by exertion, effort, 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

Proposed New Case Definition of ME/CFS

- **Patient has each of the following three symptoms *at least half of the time, to at least a moderately severe degree*:**
 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
- **PLUS at least one of the two following manifestations (chronic, severe):**
 1. Cognitive impairment OR
 2. Orthostatic intolerance

Institute of Medicine Report: New Case Definition

- **Until there is a “gold standard” pathological finding, it will not be possible to test the false negative and false positive rates of the proposed new case definition**
- **It will be possible to compare the performance of this case definition against prior ones in patients with ME/CFS as defined by experienced clinicians**
- **As pointed out in the Agency for Healthcare Research and Quality (AHRQ) report, such a new case definition needs to be tested empirically to verify that it is superior**

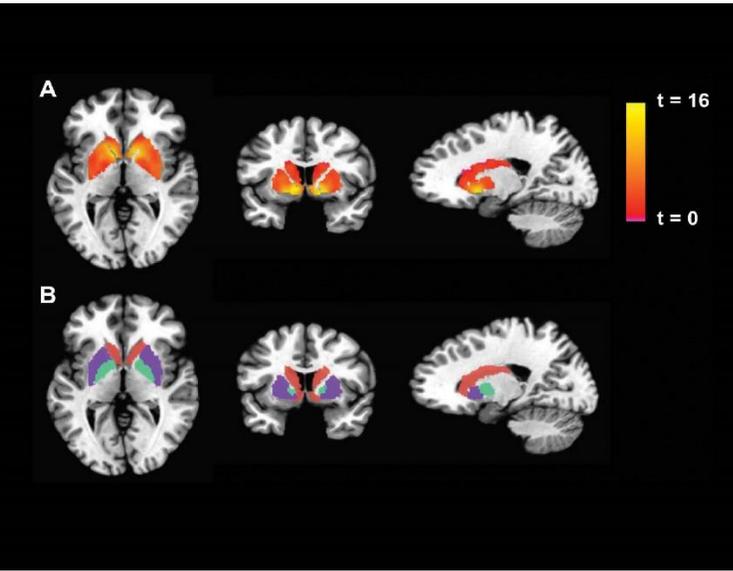
Institute of Medicine Report: New Name

- **The name “chronic fatigue syndrome” was coined in 1988, at the time the first case definition was proposed under CDC leadership**
 - The participants were focused on the case definition: little discussion of the name
- **Many patients and clinicians feel the name “chronic fatigue syndrome” trivializes and stigmatizes this often devastating illness**
- **Many different names have been proposed**
- **New name proposed by Institute of Medicine: systemic exertional intolerance disease (SEID)**

Institute of Medicine and NIH Reports: Summary

- **Patients with ME/CFS have underlying objective, biological abnormalities: their symptoms are not imaginary**
- **However, none of the abnormalities identified so far is sensitive and specific enough to constitute a good diagnostic test**
- **ME/CFS is an important disease, causing great suffering to many individuals and their families, and billions of dollars in lost productivity to society**
- **More research is urgently needed**

Post-Infectious Myalgic Encephalomyopathy/Chronic Fatigue Syndrome: Intramural Research at the National Institutes of Health



Avindra Nath, MD

Chief, Section of Infections of the Nervous System
National Institute of Neurological Diseases and Stroke

Pathways to Prevention Workshop: Advancing Research on ME/CFS

POSITION PAPER

Annals of Internal Medicine

National Institutes of Health Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Carmen R. Green, MD; Penney Cowan; Ronit Elk, PhD; Kathleen M. O'Neil, MD; and Angela L. Rasmussen, PhD

The National Institutes of Health (NIH) Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome was cosponsored by the NIH Office of Disease Prevention and the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group. A multidisciplinary working group developed the agenda, and an Evidence-based Practice Center prepared an evidence report through a contract with the Agency for Healthcare Research and Quality to facilitate the discussion. During the 1.5-day workshop, invited experts discussed the body of evidence and attendees

had the opportunity to comment during open discussions. After weighing evidence from the evidence report, expert presentations, and public comments, an unbiased, independent panel prepared a draft report that identified research gaps and future research priorities. The report was posted on the NIH Office of Disease Prevention Web site for 4 weeks for public comment.

Ann Intern Med. 2015;162:860-865. doi:10.7326/M15-0338 www.annals.org
For author affiliations, see end of text.

NIH Clinical Research Center



Rationale for Study of Immune Regulation in ME/CFS

RESEARCH ARTICLE



B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment

Øystein Fluge^{1*}, Kristin Risa¹, Sigrid Lunde¹, Kine Alme¹, Ingrid Gurvin Rekeland¹, Dipak Sapkota^{1,2}, Einar Kleboe Kristoffersen^{3,4}, Kari Sørland¹, Ove Bruland^{1,5}, Olav Dahl^{1,4}, Olav Mella^{1,4*}

OPEN ACCESS Freely available online



Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study

Øystein Fluge^{1*}, Ove Bruland^{1,2}, Kristin Risa¹, Anette Storstein³, Einar K. Kristoffersen⁴, Dipak Sapkota¹, Halvor Næss³, Olav Dahl^{1,5}, Harald Nyland³, Olav Mella^{1,5}

October 2011 | Volume 6 | Issue 10 | e26358

Post-Infectious –Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome (PI-ME/CFS)

Overall Hypothesis: PI-ME/CFS is triggered by a viral illness that results in immune mediated brain dysfunction

Phase I

To conduct a cross sectional study for deep phenotyping of PI-ME/CFS to define its pathophysiology

Phase II

To validate select biomarkers from Phase I in a longitudinal study and establish objective end points for an intervention study

Phase III

To conduct an early phase intervention study with an immunomodulatory agent that targets biomarkers validated in Phase II

Phase I of PI-ME/CFS Study

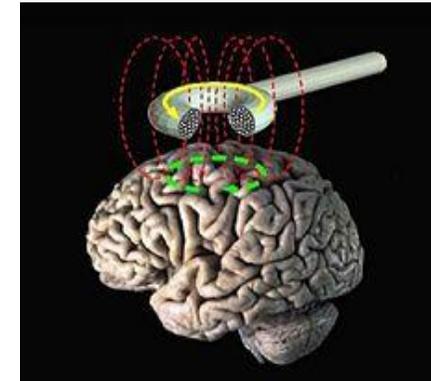
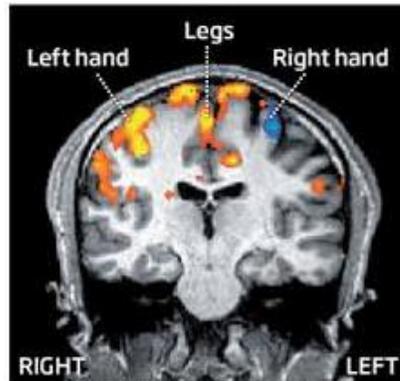
➤ **Aim 1: To define the clinical phenotype**

- History and physical exam and systemic assessment
- Neurological assessment
- Neurocognitive testing
- Psychiatric evaluation
- Pain/ headache evaluation
- Infectious disease and rheumatologic evaluation by specialists
- Neuro-endocrine evaluation
- Fatigue testing, exercise capacity

Phase I of PI-ME/CFS Study

➤ Aim 2: To determine the underlying physiology of fatigue (pre and post-exercise)

- Functional MRI
- Metabolic studies
- Transcranial magnetic stimulation
- Autonomic function



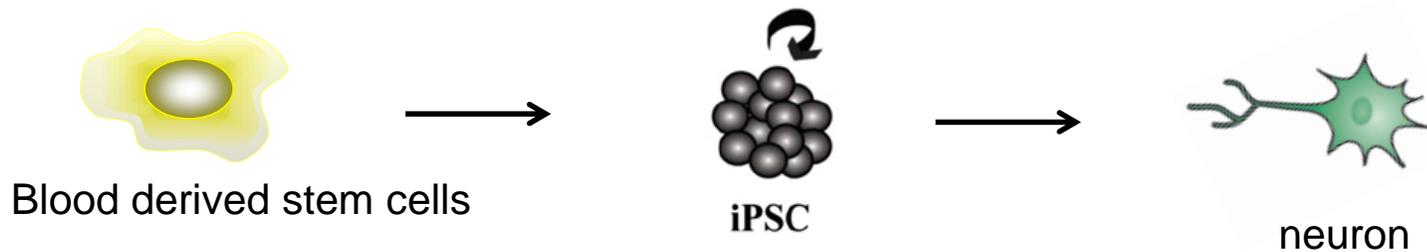
Phase I of PI-ME/CFS Study

- **Aim 3: To determine if there are abnormal immune and microbiome profiles**
 - Cytokine and chemokine profile in cerebrospinal fluid and blood; after T cell stimulation in culture
 - Flow cytometry
 - B and T cell cloning and T-cell antigen receptor sequencing
 - Immunoglobulin profile
 - Autoantibodies directed against brain antigens
 - Cerebrospinal fluid proteomics and metabolomics
 - Gut and oral microbiome
 - Serum tryptase
 - Viral discovery, antibodies to herpes viruses

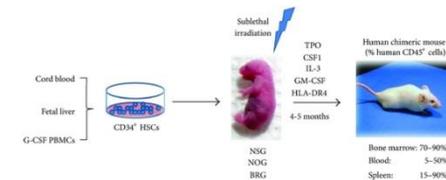
Phase I of PI-ME/CFS Study

➤ Aim 4: To determine if features can be reproduced in ex-vivo studies

- To determine if there are functional or mitochondrial abnormalities and electrophysiological properties in induced pluripotent stem cell (iPSC) derived neurons from patients with PI-ME/CFS



- Effect of serum and Cerebrospinal fluid on iPSC cells and derived neurons
- To determine if cerebrospinal fluid or antibodies injected in brain of rodents or humanized mice generated with cells from PI-ME/CFS patients can lead to fatigue or behavioral abnormalities



Protocol T-N-3495

➤ Selection criteria for PI-ME/CFS

- Documentation of acute onset infectious process
- Fatigue more than 6 months but less than 5 years
- Meet 1994 Case Definition and Canadian Consensus Criteria

➤ Study populations

- PI-ME/CFS (n=40)
- Healthy controls (n=20)
- Post-Lyme disease without fatigue (n=20)
- Functional movement disorders (n=20)

Fukuda K, Straus SE, Hickie I, et al. *Ann Intern Med.* 1994 Dec 15; 121(12) 953-9.

Carruthers BM, van de Sande MI, De Meirleir KL, et al. *J Intern Med.* 2011; 270(4) 327-338.

PI-ME/CFS: Post-infectious Myalgic encephalomyelopathy/chronic fatigue syndrome

Investigators

- **Principal Investigator: Avi Nath**
- **Lead Clinical Investigator: Brian Walitt**
- **Executive Committee: Elizabeth Unger, CDC; Ian Lipkin, Columbia University**
- **Patient advisory committee: To be determined**
- **Associate Investigators:**

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