ME/CFS Research Roadmap

Vicky Whittemore, PhD; NIH/NINDS

Lucinda Bateman, MD; Bateman Horne Center

Maureen Hanson, PhD; Cornell University

Development of an ME/CFS Research Roadmap

2019 Report to National Institute of Neurological Disorders and Stroke (NINDS) Advisory Council (NANDS) recommended the National Institutes of Health (NIH) initiate a strategic planning process for research on ME/CFS

Report of the NANDS Council Working Group for ME/CFS Research

NIH staff had plans in place to initiate the process when the Covid-19 pandemic occurred

Process restarted in fall 2022 and launched in February 2023

Charge to the Working Group of Council

The NANDS Council Working Group will develop a research roadmap to provide scientific guidance to the NANDS Council on how best to advance research on ME/CFS. Consistent with the charge, the working group will:

- Assess current ME/CFS research activities and identify opportunities and gaps in ME/CFS research to identify targets for the development of treatments.

NINDS ME/CFS Research Roadmap Working Group of Council

- Co-Chair: Lucinda Bateman, MD; Bateman Horne Center
- Co-Chair: Maureen Hanson, PhD; Cornell University
- Oved Amitay, Solve ME/CFS Initiative
- Simon Carding, Ph.D.; Norwich Medical School, University of East Anglia
- H Craig Heller, PhD; Stanford
- David Holcomb
- Leonard Jason, PhD; DePaul University
- Cort Johnson; Health Rising
- Chloe Jones; University of Alabama, Birmingham
- Laurie Jones; #MEAction
- Nancy Klimas, MD; Nova Southeastern University
- Anthony Komaroff, MD; Harvard Medical School
- Gudrun Lange, PhD; Mt. Sinai
- Susan Levine, MD; Private Practice, New York, NY
- W Ian Lipkin, MD; Columbia University
- Alain Moreau, PhD; University of Montreal
- Benjamin Natelson, MD; Mt. Sinai
- Beth Pollak; Massachusetts Institute of Technology
- Chris Ponting, PhD; The University of Edinburgh
- Richard Simpson; Invest in ME Research
- David Systrom, MD; Brigham and Women's Hospital, Harvard
- Linda Tannenbaum; Open Medicine Foundation
- Elizabeth Unger, MD, PhD; Center for Disease Control and Prevention
- Derya Unutmaz, MD; The Jackson Laboratories
- Sumeeta Varma, MD, MSCI
- Chris Wikman
- Jarred Younger, PhD; University of Alabama, Birmingham
- Executive Secretary: Vicky Whittemore, PhD; National Institute of Health/National Institute of Neurological Disorders and Stroke

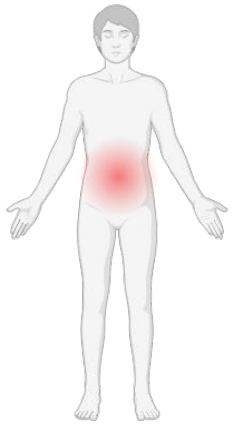
https://www.ninds.nih.gov/about-ninds/who-we-are/advisory-council/nandsc-mecfs-research-roadmap-working-group

Individuals with Lived Experience

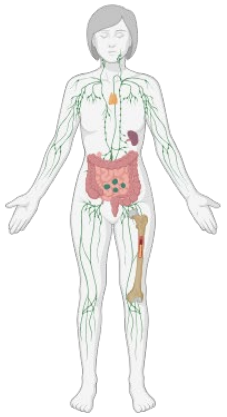
- Miriam Boyer
- Peter Cariani
- Tracy Duvall
- Gwynn Dujardin
- Lisa Engel
- Tess Falor
- Kenneth Friedman
- Thomas Gierach
- Nancy Harkness
- Michael Hermus
- David Holcomb
- James Holcomb
- Chloe Jones
- Ikuko Kato
- David Kim
- Roshan Kumar
- Derek Simmonds
- Hayla Sluss
- Lorraine Steefel
- Angela Termini
- Elizabeth Weaver

Domains for Webinar Planning Groups and Webinars

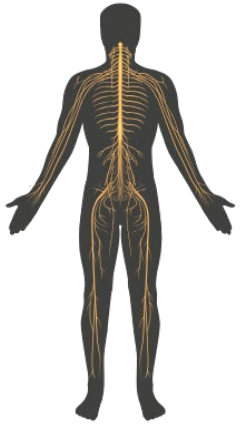
Chronic Infection



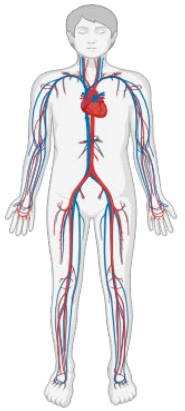
Immune System

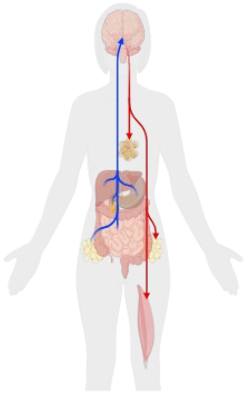


Nervous System

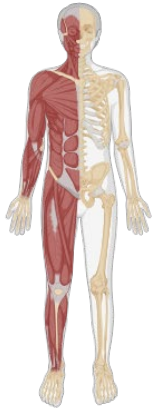


Circulation

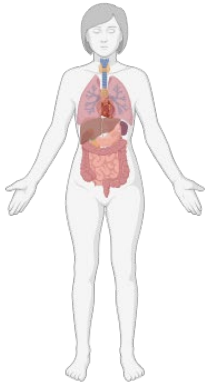




Metabolism



Physiology



Less Studied Pathologies

Genetics

Timeline of Development of ME/CFS Research Roadmap

August 2023 – January 2024

Held 8 Webinars

February – March 2024

Research Priorities posted on IdeaScale for community feedback

February 2024

Reports from all Webinars drafted by Chairs and reviewed by Webinar Planning Groups

March 2024

Overall Report completed and sent to Working Group of Council and PWLE for review and feedback

April/May 2024

Final report to be sent to NINDS leadership and NINDS Advisory Council

May 15, 2024

Report presented to NINDS Advisory Council for review and approval

Comments from an ME/CFS Clinician

Lucinda Bateman, M.D.
Bateman Horne Center, Salt Lake City

Prior to 2020, ME/CFS was estimated to affect up to 3.1 million people in the U.S costing $36-51 billion annually (direct and indirect)

Why is this project important?

"To assess current ME/CFS research activities and identify opportunities and gaps in ME/CFS research to identify targets for development of treatments via the NANDS Council to NIH…"

BUT ALSO TO:

- Create an updated summary of **an explosion of scientific progress** since the IOM evidence review/report that was published in 2015
- **Focus specifically on ME/CFS** while still recognizing the new knowledge we may gain from studying Long COVID
- Provide a forum to **consider the many dimensions of this complex multisystem disease** (emerge from our silos), foster creativity and create collaborations.
- Immortalize the combined expertise and make it publicly and widely available *(ex: The Research Roadmap Website, and Youtube "ME/CFS Research Roadmap Webinars")*

Webinar Subtopics Were Explored in Depth

- **Nervous System**
  - Cognition
  - Dysautonomia
  - Cerebral Spinal Fluid Studies
  - Neuroimaging
  - Sleep
  - Peripheral Nervous System
- **Immune System**
  - Clinical Immunology
  - Autoimmunity
  - Immune Cell type approaches
  - Immune Perturbations
  - Gut-Immune-Metabolic interplay
- **Metabolism**
  - Interplay of metabolism and immunology
  - Altered Metabolism in immune cells
  - Computational metabolomics
  - Microbial metabolism
  - Metabolism in biofluids
- **Genomics/Genetic Susceptibilities**
  - Large data-sets and Genome Wide Association Studies (GWAS) (4 speakers)
  - Enriched cohorts and Epigenetics (2 speakers)
- **Chronic Infections**
  - SARS COV2
  - Non-herpes viruses
  - Herpesvirus infection and reactivation
  - Endogenous retroviruses
- **Physiology**
  - Imaging whole body immune responses using PET
  - The Cell Danger Response
  - Non-refreshing sleep
  - Metabolism
  - BH4
  - Extracellular vesicles
- **Circulation**
  - Endotheliitis
  - Microclots
  - Hypovolemia
  - Cerebral Blood Flow
  - RBC abnormalities
  - Neurovascular dysregulation
- **Lesser Studied Pathologies**
  - Inclusion of comorbidities
  - Connective Tissue Disorders and spinal conditions
  - Mast Cell Activation Disorders
  - Gastrointestinal neuroimmune axis
  - Neuroendocrinology
  - Female Reproductive health and endometriosis

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RED and *= many topics new since the 2015 IOM r eport

WHAT IS ME/CFS?
MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

- **A chronic, complex, debilitating, multi-system illness involving:**
  - **Brain** (neuroinflammation, abnormal stress response, HPA-axis dysregulation)
  - **Peripheral nervous system** (especially small fiber nerves involving pain, sensation, and ANS function)
  - **Immune system** (impaired NK Cell function, abnormal T-cells, cytokines, autoimmune conditions, immune activation, mast cell activation)
  - **Circulatory system** (orthostatic intolerance, perfusion abnormalities)
  - **Impaired cellular metabolism** (mitochondrial dysfunction)

- While most frequently considered a post-viral or post-infectious syndrome, immune triggers, environmental factors, and traumatic events may also be associated with onset of ME/CFS
- Diagnosis is typically made late (years) so that evidence of cause(s) and early natural history have been lost. Theories parallel those emerging regarding post-COVID conditions (Long COVID)
- Deeper insights are emerging regarding the role of risk factors and overlapping/related conditions

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management. Bateman L, Bested AC, Bonilla HF, et al [the US ME/CFS Clinician Coalition] Mayo Clin Proc. 2021 Nov;96(11):2861-2878. doi: 10.1016/j.mayocp.2021.07.004. Epub 2021 Aug 25. PMID: 34454716

Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome. Komaroff AL. JAMA. 2019 Aug 13;322(6):499-500. doi: 10.1001/jama.2019.8312. PMID:31276153

The IOM/NAM* 2015 ME/CFS Clinical Diagnostic Criteria

The CORE criteria (required for diagnosis) ***Must be moderate-severe and present >50% of time**

1) **Impairment of normal function, accompanied by fatigue, persisting >6 months**
2) **PEM: post exertional malaise***
3) **Unrefreshing sleep***
4) Plus at least one of the following:
   - **Cognitive impairment***
   - **Orthostatic intolerance**

Additional common but not CORE features of illness in the ME/CFS population:

- **Chronic pain** (headache, muscle and joint aches, hyperalgesia, central sensitivity)
- **Immune/inflammatory manifestations** (allergy, inflammation, chemical sensitivities)
- **Infection manifestations** (viral or atypical infections, sore throat, tender lymph nodes, low grade fevers)

NIH National Institute of Neurological Disorders and Stroke

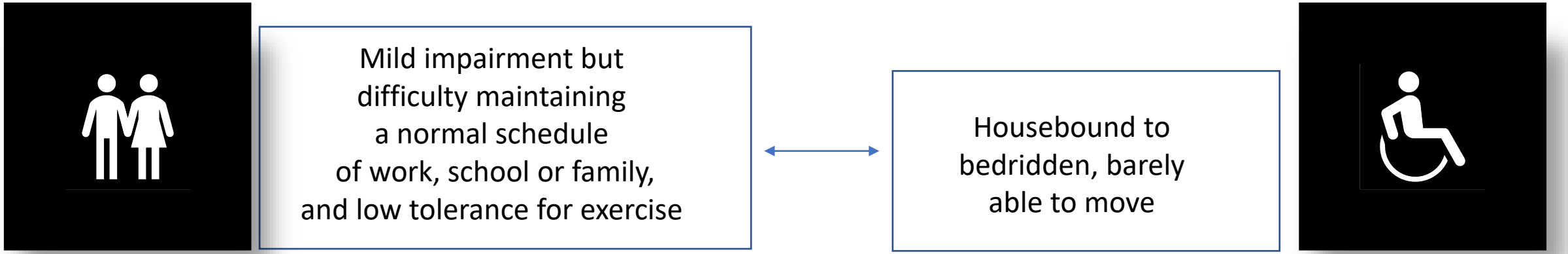
Beyond Myalgic Encephalomyelitis: Redefining an Illness. Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb 10. ISBN-13: 978-0-309-31689-7ISBN-10: 0-309-31689-8

***National Academy of Medicine (NAM)**

ME/CFS is distinguished from other types of chronic fatigue by the amount of impairment/debilitation and the development of post-exertional malaise (PEM).

PEM is illness relapse or symptom worsening triggered by activity or stressors. These can be physical, cognitive, sensory, emotional or even being in upright posture.

ME/CFS illness severity and functional capacity ranges from:

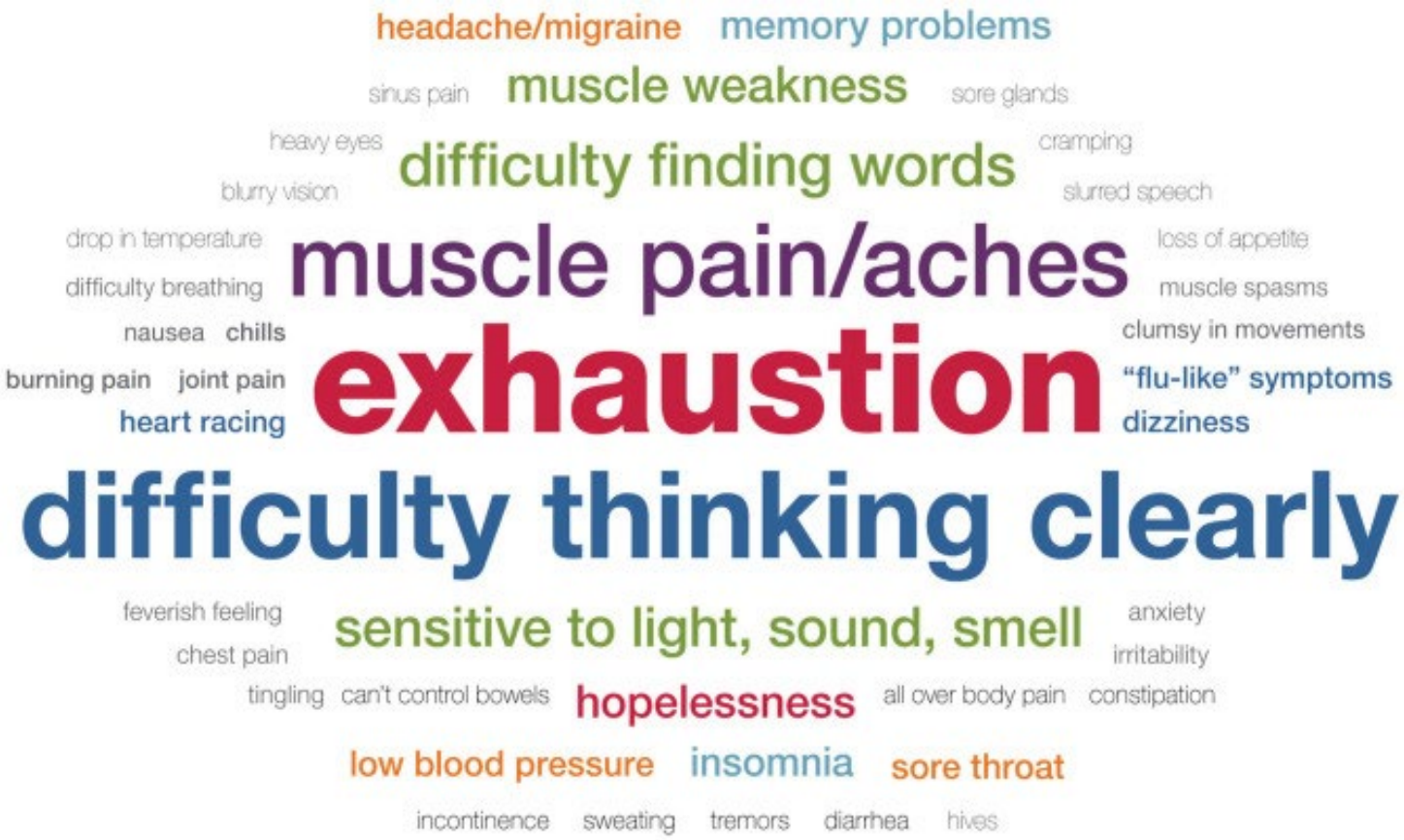


Up to 25% of ME/CFS cases may be severely ill at some point in their illness

The Experience of PEM

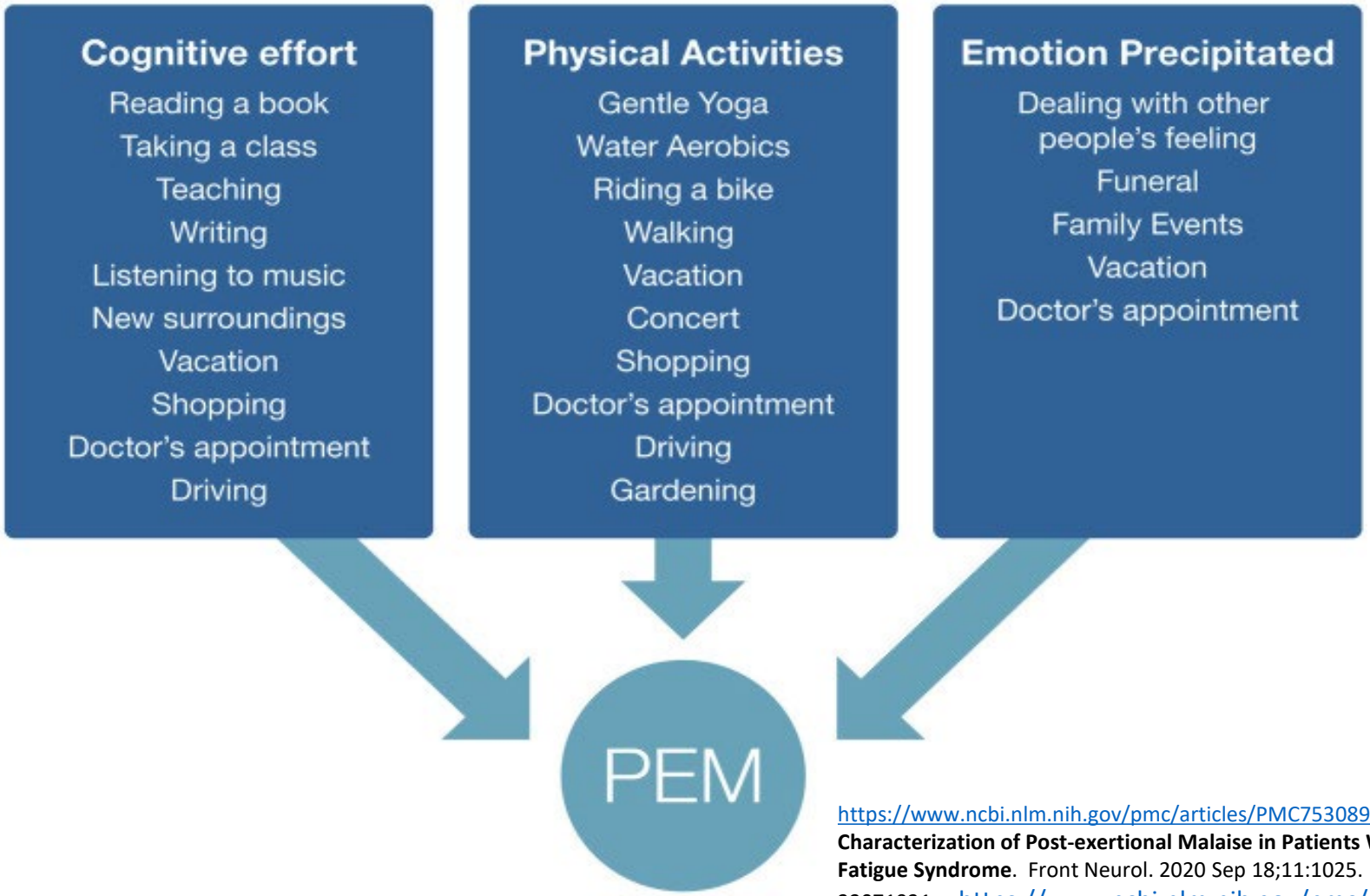
NIH intramural inpatient study of ME/CFS (2020):

- PEM was characterized in 43 individuals participating in focus groups
- Three core symptoms emerged (exhaustion, cognitive difficulties, and neuromuscular complaints), but participants' descriptions were notable for their unique individual variations.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7530890/ Stussman B, Williams A, Snow J, … et al.
Characterization of Post-exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.
Front Neurol. 2020 Sep 18;11:1025. doi: 10.3389/fneur.2020.01025. PMID: 33071931; PMCID: PMC7530890.

Examples of Activities that Cause PEM



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Heterogeneity

Heterogeneity in cross sectional research studies can be related to:

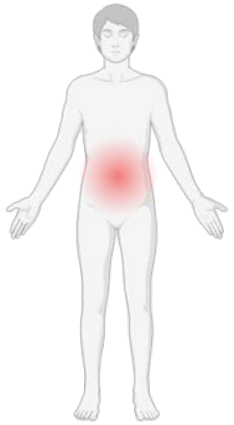
- Illness triggers and secondary consequences
- Stage and duration of illness
- Presence, severity, nature of PEM
- Co-morbid conditions (or overlapping conditions)
- Age, sex, and environmental factors
- Genetics

Comments from an ME/CFS Scientist

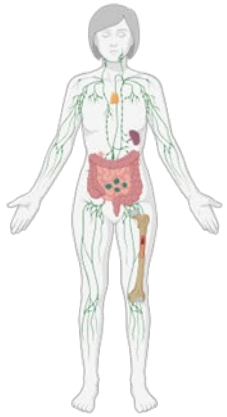
Maureen Hanson, Ph.D.
Cornell University, Ithaca, NY

What are some key points regarding research priorities in the 8 domains?

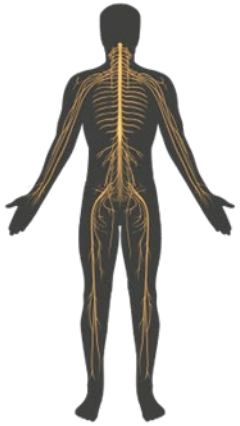
Chronic Infection



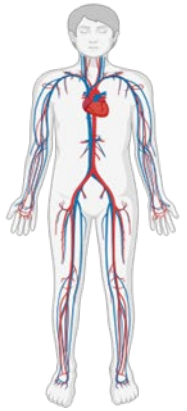
Immune System

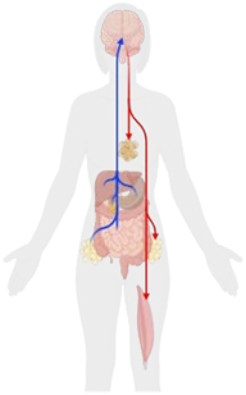


Nervous System

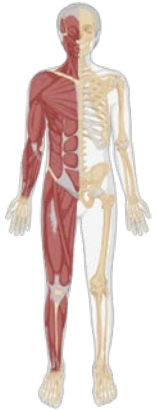


Circulation

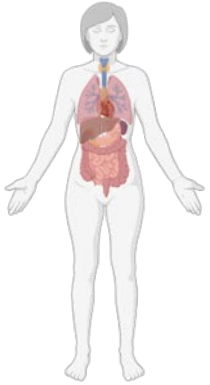




Metabolism

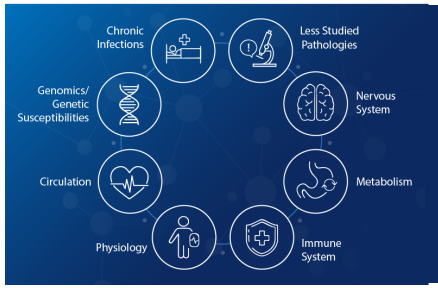


Physiology



Less Studied Pathologies

Genetics



Chronic Infection

About ¾ of individuals with ME/CFS mention onset following a flu-like illness or mononucleosis

Outbreaks have occurred multiple times in the last 100 years—most recently during the mid-1980s

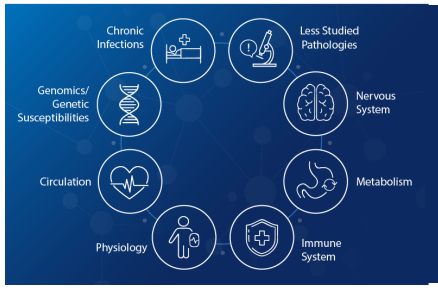
Evidence for enteroviruses as the pathogen in some outbreaks

Which viruses can incite ME/CFS outbreaks and sporadic cases?

Can EBV incite ME/CFS, reactivate and maintain the illness, or is it only a susceptibility factor?

Does altered activity of endogenous retroviruses play a role in ME/CFS?

Are the inciting viruses or derivatives of them still present in some ME/CFS cases?



Immune System

Abundant evidence of alterations in the immune system in ME/CFS

Is autoimmunity a key factor in some or all ME/CFS cases?

Is a “persistent antigen” causing immune cell exhaustion?

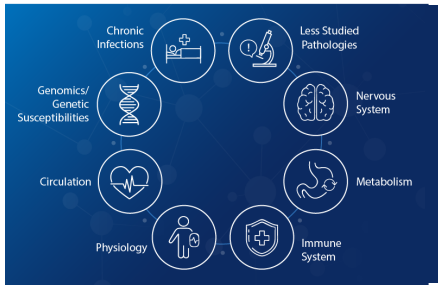
Which signaling pathways are disrupted?

What is the role of less studied immune cell types such as granulocytes or platelets?

Are immune cells are functioning abnormally in tissues and organs?

Where is inflammation occurring?

What is the nature of gut microbiome/immune system interplay?



Nervous System

Among the IOM diagnostic criteria for ME/CFS are unrefreshing sleep, cognitive impairment, and orthostatic intolerance

Evidence for neuroinflammation and reduced cerebral blood flow

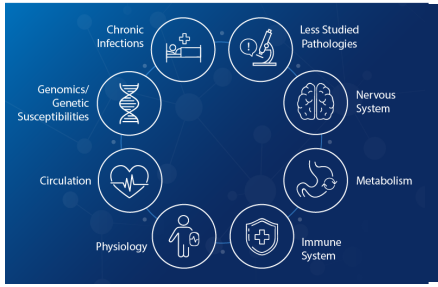
Small fiber neuropathy has been documented in a subset of ME/CFS cases

Improve tools for assessing cognition in ME/CFS

Investigate the role of circulatory dysfunction in neural symptoms

Examine cerebrospinal fluid for inflammatory and other abnormalities

Determine what drives orthostatic intolerance



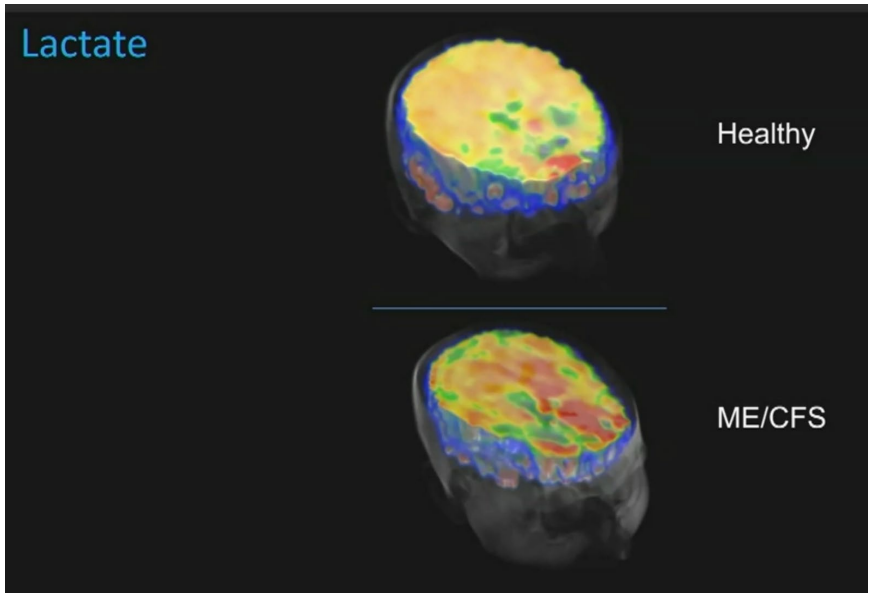
Nervous System

Use the latest neuroimaging technology to uncover abnormalities in ME/CFS and the effect of treatment trials

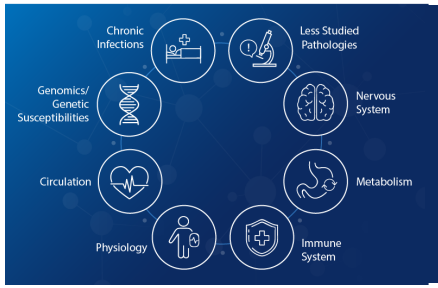
NIH Videocast of Advancing ME/CFS Research Conference in December 2023
https://videocast.nih.gov/watch=52738

Develop biomarkers for non-restorative sleep

Understand the causes of sleep phase reversal in ME/CFS



Jarred Younger Magnetic Resonance Spectroscopy



Five Additional Webinar Topics

Many topics overlap; for example, the nervous system is involved in many other systems

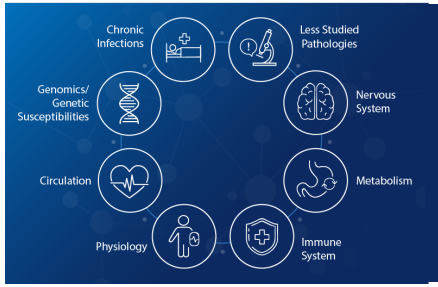
Circulation

Metabolism

Physiology

Less studied pathologies

Genetics



Circulation

Endotheliitis

Inappropriate vasoconstriction and dilation

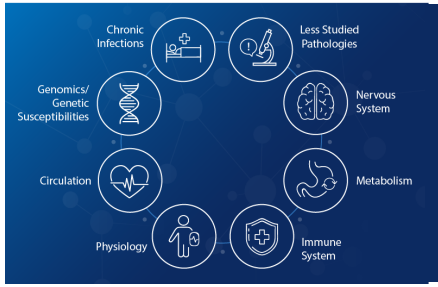
platelet hyperactivation, microclots

Low blood volume

Orthostatic intolerance and low cerebral blood flow

Impaired oxygen sensitivity of red blood cells

Neurovascular dysregulation during exercise



Metabolism

Metabolism-immunology interplay

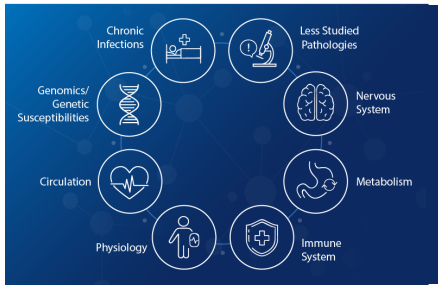
Consequence of altered metabolism, including disruption of immunometabolism

Promise of single-cell Raman technology for identifying abnormalities in ME/CFS

Metabolomics complexity: decode with AI and machine learning

The possible effects of altered gut microbiota on human metabolism

Metabolic characterization of biofluids; importance of proper controls groups—healthy sedentary individuals, control of dietary influences, and longitudinal studies



Physiology

PET Imaging for whole body immune responses

The Cell Danger Response– a hypothesis that signaling of injury or infection results in suppression of metabolism and thus causes fatigue

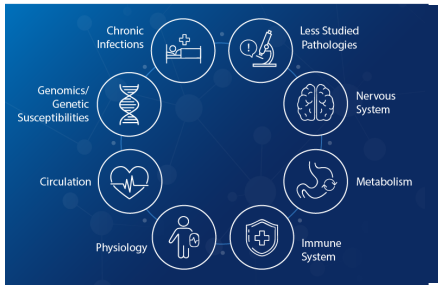
The Itaconate shunt—a hypothetical mechanism--impaired energy production occurs in cells through disturbance of the TCA cycle in mitochondria

Similarities between critically ill people in the ICU and ME/CFS

Non-refreshing sleep; importance of movement of cerebrospinal fluid during sleep and glymphatic flow

The enzyme BH4 and nitric oxide signaling

Signaling by circulating extracellular vesicles



Less Studied Pathologies

Connective tissue disorders

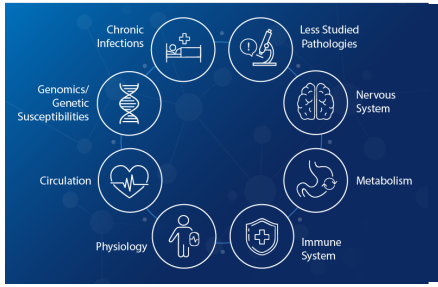
Spinal and mechanical conditions: e.g. Cranial Cervical Instability and Tethered Cord

Mast Cell Activation Disorders

Gastrointestinal conditions

Neuroendocrine dysfunction: sex differences

Reproductive health conditions



Genomics/Genetic Susceptibility

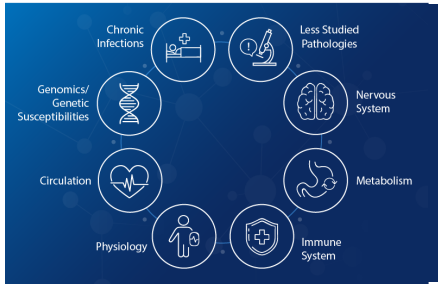
Small individual effects of genetic factors in ME/CFS

Genome-Wide-Association Studies

- mining of UK biobank data
- 25,000 participants in UK DECODE ME study
- recommendation for large US study

Family studies and case reports

Epigenetics



Overarching Priorities

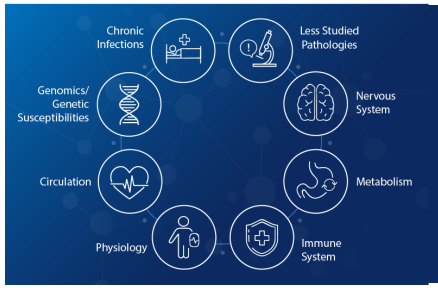
Collaboration between researchers, clinicians, people with ME/CFS, and advocacy groups:
multidisciplinary research, cooperation, data sharing
take advantage of n-of-1 anecdotal reports of efficacy of treatments

Innovative approaches needed to develop diagnostic markers, therapeutic targets and personalized treatments

Urgency: individuals with ME/CFS who became ill in the 1980s outbreaks have been ill most of their lives; without treatment, more recent cases will suffer the same fate

Expansion of biobanks essential to facilitate studies by investigators new to ME/CFS
Cerebrospinal fluid, tissue and organ samples needed, not only blood derivatives

Individual-centered care: important to involve people affected by ME/CFS in research and in decisions
many indicated acceptance of more risk due to lack of treatment options
heterogeneity means that treatments must be tailored to sub-groups



Overarching Priorities

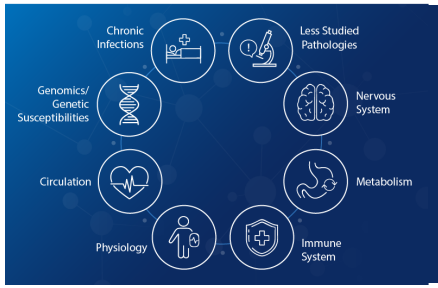
Rigorous research should include adequate cohort sizes and representative demographics, with a focus on differences in sex, age, stage of illness, and comorbid conditions

Sex-specific data analysis is essential given female predominance and existing knowledge of differences at the molecular level

Sub-types of ME/CFS must be considered when analyzing data or efficacy of treatments

Take advantage of advanced machine learning and artificial intelligence methods for data analysis

Education of health care providers; value of a simple objective diagnostic test



Overarching Priorities

Clinical trials should begin immediately

- Expert clinicians who became involved during the 1980s ME/CFS outbreaks are now aging out of the profession
- Guidance needed for those who will be responsible for the millions with ME/CFS

Adequate information is available to begin clinical trials, even though more fundamental research is also needed

- Clinical trials must incorporate correctly diagnosed individuals
- Clinical trials networks should be established or existing networks such as NeuroNEXT should be expanded
- Known drugs can be repurposed for ME/CFS treatment according to existing knowledge

By comparing biomaterials from individuals before and after treatment, insights into the pathophysiology of the disease may be obtained

Longitudinal studies of individuals over time will provide more information than single time-point comparisons of case and control cohorts

Standardized and validated tools are available to assess outcomes of treatment trials now

Promising objective markers (e.g neuroimaging) can also be used but clinical trials need not wait while additional measures are developed

Next Steps

- Trans-NIH ME/CFS Working Group will develop a plan to address the research priorities identified in the ME/CFS Research Roadmap together with federal partners, non-profit organizations and people with lived experience
- Potential next steps:
  - New funding opportunity - Concept approved at February 2024 Council
  - ME/CFS Genetics Consortium
  - ME/CFS Clinical Trial Working Group/Roundtable
  - Additional plans to be announced

Information on the ME/CFS Research Roadmap Initiative

For more information about the ME/CFS Research Roadmap Initiative and access to the webinars:

https://www.ninds.nih.gov/about-ninds/who-we-are/advisory-council/nandsc-mecfs-research-roadmap-working-group

Questions and Discussion