

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

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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.

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, multifaceted condition characterized by extreme fatigue and other symptoms, including pain, impaired memory, sleep disturbance, and insomnia that are not improved by rest. Persons with ME/CFS may have substantial disability, and some may even become homebound and bedbound. The cause and pathogenesis remain unknown, and there are no laboratory diagnostic tests or known cures for ME/CFS. One million persons (mostly women) are affected. Myalgic encephalomyelitis/chronic fatigue syndrome is an unmet public health issue with an estimated economic burden between \$2 billion and \$7 billion in the United States. It results in major disability for many persons. Limited knowledge and research funding create an additional burden for patients and health care providers. The research and health care community has frustrated its constituents by not appropriately assessing and treating the disease and by allowing patients to be stigmatized.

On 9 and 10 December 2014, the National Institutes of Health (NIH) convened the Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Its purposes were to identify research gaps, determine methodological and scientific weaknesses, and provide future research recommendations. An independent panel considered a systematic review of the scientific evidence report done by the Pacific Northwest Evidence-based Practice Center and opinions presented by a group of experts and the ME/CFS community during the public meeting. They weighed the evidence and developed conclusions. The **Appendix** (available at www.annals.org) lists the panel members,

speakers, and working group members. This article presents their findings and recommendations. The report is also available at <https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs/workshop-resources>.

INCIDENCE, PREVALENCE, AND MANIFESTATIONS

Myalgic encephalomyelitis/chronic fatigue syndrome clearly exists, but a universally accepted definition is absent. A workshop speaker stated that the Centers for Disease Control and Prevention estimates that 1 million adults in the United States have ME/CFS. The lack of a universally accepted case definition makes determining incidence and prevalence difficult and leads to variability in such estimates. The lack of a specific and sensitive diagnostic test and clearly defined diagnostic criteria has hampered research on pathogenesis, treatment, and conceptualization of ME/CFS as a distinct entity.

The syndrome has a tremendous effect at the individual, family, and societal level. Clinicians have a poor understanding of the condition, and patients are typically underserved. Studies are fraught with methodological problems, preventing a clear understanding of who is affected. There are no agreed-on variables for defining ME/CFS and no accurate ways to identify and diagnose it; as 1 speaker pointed out, the syndrome has 163 possible combinations of symptoms. Small sample sizes; inclusion of participants with differing symptoms across studies; and the dearth of men, minorities, homebound persons, and rural residents in current studies limit their applicability. Some instruments used to evaluate ME/CFS are not validated, are inappropriate, and may be misleading. All of these issues contribute to inconclusive research results and a lack of definitive knowledge about incidence, prevalence, and potential causes and treatments.

See also:

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Fatigue has been the defining symptom and focus of recent research. According to a workshop speaker, patients with ME/CFS have neurocognitive dysfunction with abnormalities on functional magnetic resonance imaging and positron emission tomography. Strong evidence indicates that immunologic and inflammatory pathologic conditions, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities are potentially important for the definition and treatment of ME/CFS. Whether the available evidence in adults applies to children with similar symptoms remains unclear. Thus, other symptoms, primarily neurocognitive deficit ("brain fog"), postexertion malaise, and pain, must be explored across the life span. Other problems surrounding ME/CFS research include few disease-specific clinical trials; a disconnect on how patients, clinicians, and researchers define meaningful outcomes; a lack of well-controlled, multifaceted studies using large, diverse samples; and limited public and private research dollars.

Both society and the medical profession have contributed to the disrespect and rejection experienced by patients with ME/CFS. They are often treated with skepticism, uncertainty, and apprehension and labeled as deconditioned or having a primary psychological disorder. Patients often make extraordinary efforts at extreme personal and physical costs to find a physician who will correctly diagnose and treat their symptoms; some are treated inappropriately, causing additional harm. Overall, the debilitating effects can cause financial instability due to the consequences of the illness (such as the loss of employment or a home).

WAYS TO FOSTER RESEARCH AND ENHANCE DEVELOPMENT OF TREATMENTS

The public, provider, and research communities are frustrated with the minimal progress to improve the state of science for ME/CFS over the past 20 years. Patients want their concerns to be heard, a meaningful recovery (not just incremental improvement), and a cure. Educational efforts are needed to assist patients and clinicians in better understanding ME/CFS. The scientific community also has a responsibility to address issues that are meaningful to patients.

Limited patient and professional education has impaired progress in managing ME/CFS, and treatments remain unproven. Clinical studies have focused on predominately white, middle-aged women. Representative, ethnically diverse samples across the life span are lacking. Investigations of natural history and familial linkages may identify genetic predispositions and lead to early identification and preventive strategies.

Although psychological repercussions (such as depression) may accompany ME/CFS, it is not a primary psychological disease. Several symptoms associated with ME/CFS substantially overlap with other pathologic diseases (such as fibromyalgia, major depressive disorder, and several chronic pain or inflammatory conditions). Although focusing on fatigue alone may iden-

tify many cases, it does not capture the essence of this complex condition. Previous studies may have inadequately excluded persons with these distinct diseases, leading to delayed or conflicting diagnoses, contradictory treatments, suboptimal care, and inappropriate health care use. Future studies that aim to better define cellular and molecular mechanisms for targeted treatments should distinguish among ME/CFS alone, ME/CFS with comorbid conditions, and other diseases.

Carefully designed and adequately powered studies defining the spectrum of ME/CFS in urban and rural communities are lacking, and the available evidence base has limited applicability to an increasingly diverse society. It is critical that research studies include patients with limited access to clinical services (such as nonambulatory patients). Although research has shown that patients often have a consistent constellation of symptoms, including fatigue, postexertion malaise, neurocognitive deficit, and pain, a clear case definition, as well as validated diagnostic tools for it, is urgently needed. Agreeing on a definition and clarifying comorbid conditions could launch bench-to-bedside science.

Patients with ME/CFS remain hopeful that research will lead to a cure. However, cross-sectional studies and small clinical trials with limited applicability have provided few insights into treatment. Adequately powered clinical trials require large investments of time and energy, and interventions tested in trials may be associated with harms, such as precipitating increased symptoms or medication toxicity. Existing treatment studies examining counseling and behavior therapies or graded exercise therapy demonstrate measureable improvements but may not yield improvements in quality of life (QoL). Therefore, these interventions are not a primary treatment strategy and should be used only as a component of multimodal therapy.

Small clinical trials of ME/CFS, most with methodological limitations and all constrained by the lack of a gold standard for diagnosis, have led to confusion. Most studies have significant methodological limitations and take place primarily in specialty clinics in relatively homogeneous populations. These trials often use subjective, unclear, and poorly defined end points (which may not be meaningful to patients) and do not provide information explaining the high withdrawal rates. Therefore, variability in inclusion and exclusion criteria, such as the case definition, comorbid conditions, patient population, and disease severity, has significantly hampered progress in the clinical and research domains focused on assessing and treating ME/CFS.

Little attention is given to how self-management may empower and improve health and QoL for patients with ME/CFS. Physicians are inadequately trained to instruct patients in self-management skills (such as pacing, realistic goals, physical self-awareness, basic rights, understanding emotions, exercise, and relaxation), and limited data demonstrate the efficacy of self-management on health outcomes. The focus on exercise programs has discouraged patient participation in

any type of physical activity (such as mild stretching) due to concerns of precipitating increased symptoms.

There is little understanding of the inciting event or the cellular and molecular mechanisms that underlie ME/CFS, preventing quantitative assessments of disease severity or prognosis. Failure to give adequate attention to the severity of the physical, social, and emotional effects of ME/CFS has caused harm and diminished hope. Various symptoms are often "lumped" into ME/CFS. Carefully defining comorbid conditions is necessary to determine ME/CFS subgroups and move the field forward. Interdisciplinary collaborations to develop tools or disease measures that encompass the full spectrum of possible signs and symptoms are needed.

Defining ME/CFS requires standard, validated tools and measures. Individual studies are too small to have power for subgroup analyses, rarely meet the criteria for good-quality evidence, seldom address early disease or ME/CFS in children, do not adequately evaluate harms or patients who withdrew and why, and have inadequate length of follow-up. In addition, participant variability at different study centers may be partially responsible for conflicting results.

The following end points need to be clarified: what is statistically significant, what is clinically significant, and what is significant to the patient. To move ME/CFS research forward, there is an urgent need to obtain all of the information from the control population and patients who responded and did not respond to treatment. Simple patient-centered tools need to be developed to ensure patient comprehension. Overall, there is a need to simplify measures while prioritizing face-to-face interactions.

Practical retrospective, prospective, and longitudinal studies that are reproducible are needed to advance the field. Longer follow-up and a life span perspective are needed to understand ME/CFS effects on the whole person (such as patient expectations, decision making, sexual health, and childbearing). The symptoms that patients consider clinically meaningful are not in the scientific literature; this discordance must be rectified.

Current research has neglected many of the biological factors underlying disease onset and progression. Research priorities should shift to include basic science and mechanistic work that will contribute to development of tools and measures, such as biomarker or therapeutics discovery. The following questions need to be answered: What is the pathogenesis of ME/CFS? What are the roles of virologic mechanisms, especially herpesviruses? Does mononucleosis lead to ME/CFS in adolescents? What are the roles of other pathogenic agents? Is this a genetic disease? Is there a gene-environment interaction? Is it a spectrum disease? Are different pathways responsible for different symptoms?

FUTURE DIRECTIONS AND RECOMMENDATIONS

Overall, we have not implemented what we already know for patients with ME/CFS while the disease steals

their health and well-being. Scientifically rigorous research is needed to improve this situation. The subjective nature of ME/CFS, associated stigma, and lack of a standard case definition have stifled progress. Patients must be at the center of the research efforts, and their engagement is critical, as is outreach to underserved and vulnerable populations.

Innovative biomedical research is urgently needed to identify risk and therapeutic targets. The scientific community and funding agencies are responsible for conducting trials in an ethical way that is meaningful for patients. The influence of health literacy and cognitive impairment on informed consent must be considered. Investigators have a responsibility to hear the patient's perspective, engage the community, and be accountable for translating and reporting research results to the ME/CFS community while responding to their feedback. The dissemination of diagnostic and therapeutic recommendations should begin by focusing on primary care providers and expand to other areas, such as neurology, rheumatology, and infectious disease. Potential conflicts of interest among investigators need to be properly vetted, discussed, and addressed by all stakeholders.

To accelerate the progress of ME/CFS treatment, we recommend several overarching research strategies.

1. Define Disease Variables

A team of stakeholders (such as patients, clinicians, researchers, and federal agencies) should be assembled to reach a consensus on the definition and variables of ME/CFS. A national and international research network should be developed to clarify the case definition and advance the field. Agencies of the NIH that are not represented in the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group should be incorporated to capitalize on the tremendous opportunities to learn from other disciplines and diseases (such as the Gulf War syndrome, Lyme disease, fibromyalgia, multiple sclerosis, and Parkinson disease).

2. Create New Knowledge

Investing in bench-to-bedside research for ME/CFS is recommended. Developing biomarkers and diagnostic tests should be a priority. The field could be energized and diversified by creating opportunities for involvement of junior and new investigators. The NIH institutes and centers (such as the National Center for Advancing Translational Sciences and the National Center for Complementary and Integrative Health) and other U.S. Department of Health and Human Services agencies should coordinate research efforts to promote efficiency and effectiveness while using public-private partnerships to leverage existing NIH infrastructure and dollars. Specific activities should focus on the following:

Valid prognostic tests that can guide treatment strategies using genomic, epigenomic, proteomic, and metabolomic strategies to identify critical biomarkers that will be clinically applicable should be developed. Gene expression, protein, or metabolite signatures that

can correctly diagnose ME/CFS and distinguish it from other chronic conditions while predicting disease severity and clinical outcomes are needed. Determining the most important physiologic measures and pathophysiology, as well as genome-wide association studies and phenotyping, are essential for stratifying patients. Functional magnetic resonance imaging and imaging technologies should be further studied as diagnostic tools and methods to better understand the neurologic dysfunction of ME/CFS.

Biological samples (such as serum and saliva, RNA, DNA, whole blood or peripheral blood mononuclear cells, and tissues) and deidentified survey data should be linked in a registry or repository to understand pathogenesis and prognosis and facilitate biomarker discovery. Further exploration is needed of the intestinal microbiome and the effect, if any, of the environment and microbiome on ME/CFS development using cutting-edge technologies (such as high-throughput sequencing), neurocognitive tests, and neuroimaging.

Epidemiologic studies of ME/CFS, including incidence and prevalence, persons who are at high risk, risk factors, geographic distribution, and the identification of potential health care disparities, are critical. A repository for qualitative and quantitative research is needed.

Previously collected research data should be analyzed to advance knowledge and inform trial development and design and facilitate necessary clinical studies. In particular, drug therapies used for fibromyalgia or other pain-related syndromes and disorders should be examined for effectiveness in ME/CFS. Existing registries should be leveraged.

Studies that stratify by clinical characteristics should be used to develop diagnostic and prognostic algorithms to identify who will develop ME/CFS after infection or other triggers.

There is a need for “omics”-based drug repurposing and neurobiology studies. With the use of bioinformatics techniques, large data sets should be developed and stored in a central, publicly accessible database for future investigations. New knowledge might include an understanding of molecular mechanisms underlying ME/CFS, new ways to perform pathway analyses, or new pharmacogenomic drug discovery or repurposing.

An integrated, systems-level approach should be followed to understand how immunologic, neurologic, and metagenomic factors may contribute to ME/CFS. Immunologic mechanisms of ME/CFS and pathways associated with disease progression must be defined and characterized (such as defining cytokine profiles involved in pathogenesis, studying inflammation, and comprehending the basis for the natural killer cell dysfunction seen in many patients). Longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction in ME/CFS remain important.

Studies of identical twins to identify gene expression biomarkers are needed. Both male and female models must be used to explore the role of sex,

X-chromosome genes, and hormones in developing ME/CFS.

How patients' background medications (including psychiatric drugs) affect function and outcome should be explored. Patients often choose clinical trials or complementary and alternative medicine because effective treatment is not available and traditional health care does not meet their needs. Studies investigating homeopathy, nonpharmacologic, complementary and alternative medicine treatments, and biopsychosocial variables (including the mind-body connection), function, and QoL should be encouraged.

3. Improve Methods and Measures

The need for improved measures to identify ME/CFS while including the patient's voice through patient-reported outcomes is critical. Without a diagnostic test, stratification must occur to reduce and comprehend variability (such as onset, time course, and comorbid conditions) and to identify clearly defined end points for treatment trials and interventions. The NIH should develop an ME/CFS methodological workgroup.

A community-based participatory research approach is needed to increase patient involvement in determining priorities for research and care.

Use of already well-validated measures developed by the NIH, such as the Patient Reported Outcomes Measurement Information System and the Center for Epidemiologic Studies Depression Scale, should be encouraged. Although ME/CFS is not a psychiatric disease, exploring psychiatric comorbid conditions, such as depression, anxiety, and fear, is critical to improve QoL. Response burden must be considered; a battery of simplified measures is strongly encouraged, as well as the triangulation of qualitative and quantitative data. The NIH should leverage the power of other longitudinal studies (such as the Health and Retirement Study and Nurses' Health Study) to better understand ME/CFS.

Telemedicine or home visits for patients who cannot participate in clinical trials or treatment in person as well as outreach to underserved communities are needed. New technologies to address underserved populations and unmet needs (such as mobile technology and online tracking tools) should be developed and used to measure progress and enable communication, especially for patients who are not helped in the clinic setting.

4. Provide Training and Education

Many clinicians do not fully understand ME/CFS. We believe that it is a distinct disease that requires a multidisciplinary care team (such as physicians, nurses, case managers, social workers, and psychologists). Primary care clinicians will be instrumental in ensuring that patients are treated appropriately and care is optimized. Therefore, a properly trained workforce is critical, and we strongly encourage engaging with the following groups: health professional licensing and accreditation agencies to ensure a curriculum that facilitates ME/CFS knowledge acquisition; Health Resources and Services Administration to facilitate training; pro-

professional societies and patient organizations to facilitate a public-private partnership, as well as training and funding of health care professionals; and clinicians and researchers, who have a responsibility to encourage and track progress. Patients must also actively participate in their overall treatment.

5. Finding New Funding Resources

With a relatively small number of researchers in the field and finite resources, partnerships across institutions are needed to advance the research and develop new scientists. New collaborative models, investigator-initiated studies, career development, and small grant mechanisms with specific attention to developing a cadre of junior investigators, including women and minorities, who may offer innovative new approaches, are needed. Opportunities exist within the U.S. Department of Health and Human Services to engage new ME/CFS working group members (such as the National Institute on Minority Health and Health Disparities, National Cancer Institute, U.S. Department of Education's National Center for Medical Rehabilitation Research, and U.S. Department of Defense); create efficiency; and co-fund research to promote diversity in the pipeline, eliminate disparities, and enhance the quality of the science.

A network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences, should be created. These centers would be charged with determining the biomarkers associated with diagnosis and prognosis, epidemiology (such as health care use), functional status and disability, patient-centered QoL outcomes, cost-effectiveness of treatment studies, and the role of comorbid conditions in clinical and real-life settings. They would also be responsible for completely characterizing control populations and persons who recover from ME/CFS. These collaborative studies should recruit from the broad spectrum of patients and use reproducible measures.

A central archive of deidentified data and tissue samples from previous and ongoing studies to enable sharing of data and samples should be established.

6. Conduct Clinical Trials

An ongoing need for participants in clinical trials was noted. The NIH should work with ME/CFS partners and stakeholders to create a Web site for patient and clinician educational materials as well as information about clinical trials. Opportunities to use the NIH Clinical Center for clinical trials and fast-track testing of new therapies should also be explored.

7. Improve Treatment

Patients should be active participants in care and decision making. Such lessons as communication and symptom management to improve the quality of care can be learned from palliative care. Studies examining the role of self-management techniques as part of a comprehensive treatment plan for patients with ME/CFS during and after clinical interventions should be explored. The modest benefit from cognitive behav-

ioral therapy should be studied as an adjunct to other methods. Future treatment studies should evaluate multifaceted therapies focusing on biomedical and supportive care. Comparative effectiveness research is also needed. We recommend that the NIH and U.S. Food and Drug Administration convene a meeting on the state of ME/CFS treatment.

CONCLUSIONS

Quality care begins with assessment and depends on optimizing patient and clinician decision making. Interpersonal factors (such as age, race, ethnicity, sex, class, and personality) and patient- and clinician-related factors (such as perceptions, knowledge, communication styles, and stigma) influence the quality of care. Patients with ME/CFS want their stories to be heard, and the ME/CFS community may benefit from education on how to effectively communicate their concerns to clinicians. Clinicians could benefit from enhanced active listening skills and increased education. Education alone cannot fix this problem, but it will facilitate a partnership in medical decision making, thereby optimizing care. Furthermore, the multiple case definitions for ME/CFS have hindered progress. In particular, continuing to use the Oxford definition may impair progress and cause harm. Therefore, for progress to occur, we recommend that this definition be retired; the ME/CFS community concur on a single case definition (even if it is not perfect); and patients, clinicians, and researchers agree on a definition for meaningful recovery.

Attention should be focused on providing access to high-quality, multidisciplinary care; refining assessment; and clarifying end points that suggest improvement and quality care. We believe that multimodal therapies have a specific role. Although no data on primary prevention were presented, this does not prohibit secondary and tertiary prevention efforts. Once a cause is determined, primary prevention efforts should begin. The NIH should incorporate concepts from public health prevention and U.S. Department of Health and Human Services efforts to decrease disability and promote health and well-being for the ME/CFS population across the life span.

New and ongoing policies can spark innovation and fund new research. For example, new avenues are needed to fund research, such as the Prescription Drug User Fee Act. The NIH should work with the Centers for Medicare & Medicaid Services and the Patient-Centered Outcomes Research Institute to develop demonstration projects of patient-centered medical homes for patients with ME/CFS. This should be done using a framework of comparative effectiveness research that has clear end points and continuous evaluations to improve health care and to determine the best evidence-based practices. These practices should then be translated to primary care clinicians. Federal agencies (such as the Agency for Healthcare Research and Quality and the U.S. Department of Veterans Affairs) and professional societies should work together to create quality metrics and a standard of care. We

also recommend that federal departments, advocacy groups, and industry work together in public-private partnerships to help advance research. We recommend that the NIH Office of Disease Prevention convene another expert panel in 5 years to monitor progress. We hope our work has dignified ME/CFS and affected persons while providing expert guidance to the NIH and the broader research community.

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Note: The independent panel was charged with providing guidance to the NIH on research gaps and research priorities for ME/CFS. While this manuscript was being developed, the Institute of Medicine developed a report titled “Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness” and released their findings in February 2015. Although many would like the panel to consider and incorporate the Institute of Medicine’s recommendations within this report, it is beyond the scope and charge. Nonetheless, the panel believes that it is important for federal agencies, clinicians, patients with ME/CFS, and ME/CFS advocates to consider both reports to move the science forward. Furthermore, the panel believes that its recommendations provide many opportunities to incorporate both reports and new knowl-

edge during the deliberations of the other proposed meetings and, more specifically, if and when the panel is reconvened in 5 years.

In general, a 2-week public comment period is provided. The panel’s initial report was completed in December 2014. The public comment period was extended to 4 weeks to allow for maximum participation of persons with ME/CFS who may have significant physical, social, and emotional disabilities and to accommodate the 2014 holidays. Unfortunately and inadvertently, some of the comments from the final day were not included and considered by the panel during the review period. Once this oversight was identified, publication was paused to consider these comments as individual panel members and then as a panel via conference call. An opportunity was provided to consider all public comments. The panel believes that this process allowed for a rigorous and inclusive review and a final product that moves the science forward.

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APPENDIX: PANEL MEMBERS, SPEAKERS, AND WORKING GROUP MEMBERS FOR THE WORKSHOP

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