National Institutes of Health

Draft Statement

NATIONAL INSTITUTES OF HEALTH

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

December 9–10, 2014

DRAFT EXECUTIVE SUMMARY

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This National Institutes of Health (NIH) workshop is co-sponsored by the NIH Office of Disease Prevention (ODP) and the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group. A multidisciplinary working group developed the workshop agenda, and an Evidence-based Practice Center prepared an evidence report through a contract with the Agency for Healthcare Research and Quality (AHRQ) to facilitate the workshop discussion. During the 1½-day workshop, invited experts discussed the body of evidence, and attendees had opportunities to provide comments during open discussion periods. After weighing evidence from the evidence report, expert presentations, and public comments, an unbiased, independent panel prepared this draft report, which identifies research gaps and future research priorities. This draft report will be posted on the ODP website, and public comments will be accepted for 4 weeks. The final report will be released several weeks later.

Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by extreme fatigue and other symptoms that are not improved by rest. The etiology and pathogenesis remain unknown; there are no laboratory diagnostic tests; and there are no known cures. An estimated one million people, mostly women, are affected. ME/CFS is an unmet public health need with an economic burden estimated to be greater than $1 billion. ME/CFS results in major disability for a large proportion of the people affected. Limited

knowledge and research funding creates an additional burden for patients and health care providers.

Unfortunately, ME/CFS is an area where the research and medical community has frustrated its constituents, by failing to assess and treat the disease and by allowing patients to be stigmatized.

On December 9–10, 2014, the National Institutes of Health (NIH) convened a Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Specifically, the workshop sought to clarify the following key issues:

- How the research on ME/CFS, using multiple case definitions, has contributed to the state of the current scientific literature on diagnosis, pathophysiology, treatment, cure, and prevention of ME/CFS
- How the measurement outcomes (tools and measures) currently used by ME/CFS researchers are able to distinguish among those patients diagnosed with ME/CFS, including the sensitivity of tools and measures to identify subsets of patients according to the duration, severity, nature, onset characteristics, and other categorizations of the illness
- How the research on treatments or therapies shown to be effective in addressing symptoms of ME/CFS will lead to an understanding of the underlying pathology
- How innovative research approaches have provided an understanding of the pathophysiology of ME/CFS, and how this knowledge can be applied to the development of effective and safe treatments.

We critically reviewed the scientific literature and opinions presented by a group of experts and the ME/CFS community during the public meeting, weighed the evidence, and developed a set of conclusions. This report presents our findings and recommendations.

What is the incidence and prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and whom does it affect?

ME/CFS exists. Despite the absence of a clear definition, an estimated million people have ME/CFS, and it overlaps with many other diseases (e.g., fibromyalgia, major depressive disorder, chronic pain). There is no agreement from the research community on what needs to be studied, no U.S. Food and Drug Administration (FDA)-approved drug treatments, and there are no primary prevention strategies. The lack of a universally accepted case definition for ME/CFS has led to difficulty in determining its prevalence and incidence, and has contributed to variability in the estimates reported. The Oxford criteria (published in the Journal of the Royal Society of Medicine in February 1991) are flawed and include people with other conditions, confounding the ability to interpret the science. The lack of a consistent, specific, sensitive diagnostic test and set of criteria has hampered all downstream research on pathogenesis and treatment, causing harm and preventing ME/CFS from being considered as a distinct pathologic entity.

ME/CFS has a physical, psychological, social, and economic impact at the individual, family, and societal level. Patients are typically underserved, and clinicians have a poor understanding of ME/CFS. We heard throughout the workshop that ME/CFS can affect anyone. Education, financial security, and social standing will not prevent the disease.

Studies of ME/CFS are fraught with methodological problems, preventing a clear understanding of who is affected by ME/CFS: there are no agreed-upon parameters for defining ME/CFS, no accurate ways of identifying and diagnosing ME/CFS, and 163 symptoms have been associated with ME/CFS. Small sample sizes, the inclusion of participants with differing symptoms across studies, and the lack of inclusion of the homebound, rural residents, and a research focus on men limits the applicability of current studies. Minorities also are rarely represented in studies, so there are no data to confirm whether minorities have a higher or lower risk. Many instruments used to evaluate ME/CFS are not validated, are inappropriate, and may be misleading. All this leads to inconclusive results and a lack of knowledge of ME/CFS prevalence (i.e., how many people have ME/CFS), incidence (new cases per year), and potential causes and treatments.

Fatigue has been the defining focus of recent research, but many other symptoms need to be explored, primarily neurocognitive deficit ("brain fog"), post-exertion malaise, and pain. Most ME/CFS studies focus on adults, excluding children with similar symptoms. We noted few disease-specific clinical trials; a disconnect on ways in which patients, clinicians, and researchers define meaningful outcomes; the lack of well-controlled, multifaceted studies using large, diverse samples; and the limited research dollars directed at ME/CFS from both the public and private sectors.

Often, patients with ME/CFS are labeled as lazy, deconditioned, and disability-seeking; this hampers scientific progress. Both society and the medical profession often treat patients with ME/CFS with disdain, suspicion, and disrespect. Patients are frequently treated with psychiatric and other inappropriate drugs that may cause harm. Patients usually have to make extraordinary efforts, at extreme personal costs, to find a physician who will correctly diagnose and treat ME/CFS symptoms. In addition to high medication costs, the debilitating effects of ME/CFS can

result in financial instability due to the physical consequences of the illness (e.g., the loss of employment, home, and other basic necessities). All of these factors contribute to the poor quality of epidemiologic studies.

Given the unique challenges to ME/CFS, how can we foster innovative research to enhance the development of treatments for patients?

Over the last 20 years, minimal progress has been made to improve the state of the science for patients with ME/CFS, and the public and provider community is frustrated. Patients want their concerns to be heard, a meaningful recovery (not just incremental improvement), and a cure. Educational efforts are needed to help patients and their health care providers better understand this disease and scientific processes. The scientific community also has a responsibility to address issues that are meaningful to patients.

There is reproducible evidence of neurocognitive dysfunction with abnormalities in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies. Strong evidence indicates immunologic and inflammatory pathologies, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities in ME/CFS, potentially important for defining and treating ME/CFS.

Overall, limited patient and professional education has impaired progress in managing ME/CFS. Furthermore, treatments remain unproven. Clinical studies have focused on predominantly Caucasian, middle-aged women. Representative, ethnically diverse samples across the lifespan are lacking. Investigations of natural history and familial linkages may identify genetic predispositions and lead to early identification and primary prevention.

Although psychological repercussions (e.g., depression) often follow ME/CFS, this is not a psychological disease in etiology. A multitude of symptoms are associated with ME/CFS, with substantial overlap with other pathologic diseases (e.g., fibromyalgia, major depressive disorder, and a variety of chronic pain or inflammatory conditions). Focusing on fatigue alone may identify many ME/CFS cases. However, this symptom taken in isolation fails to capture the essence of this complex condition. Prior studies may have inadequately excluded individuals with the distinct diseases listed above, leading to delayed diagnosis, conflicting diagnoses, contradictory treatments, suboptimal care, and inappropriate health care utilization. Future studies should distinguish between ME/CFS alone, ME/CFS with comorbidities, and other diseases to better define cellular and molecular mechanisms for targeted treatments.

Carefully designed and adequately powered studies defining the spectrum of ME/CFS in urban and rural communities are lacking, limiting their applicability to an increasingly diverse society. Specifically, it is critical to include patients with limited access to clinical services (e.g., non-ambulatory patients). A clear case definition with validated diagnostic tools is required before studies can be conducted. We noted a consistent constellation of symptoms: fatigue, post-exertional malaise, neurocognitive deficit, and pain.

Patients with ME/CFS are hopeful that research will lead to a cure. However, the few cross-sectional studies with limited applicability have provided few insights to the disease or its treatment. Clinical trials require large investments of time and energy, and may be associated with other harms (e.g., increased symptoms, medication toxicity). Future studies must be collaborative, multicenter efforts and must include large, diverse samples across the lifespan. Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy [GET]) demonstrate measurable improvement, but this has not translated to improvements in

quality of life (QOL). Thus, they are not a primary treatment strategy and should be used as a component of multimodal therapy. Overall, agreeing on a case definition and clarifying comorbidities could launch bench-to-bedside science.

What does research on ME/CFS tell us about the presentation and diagnosis of ME/CFS in the clinic?

Limited time during the clinical encounter has impaired patient/clinician communication and quality of care for patients with ME/CFS. Patients experience stigma from the diagnosis of ME/CFS, including social isolation and judgment. They often experience financial instability due to the physical consequences of the illness and the inability to continue employment. Negative interactions with the health care system are frequent, and the emotional burden is heavy.

Small, poor-quality studies and a lack of a gold standard for diagnosis and treatment of ME/CFS has led to confusion. Most studies lack specificity and sensitivity, while primarily using specialty clinics and homogeneous populations. Furthermore, they are observational in nature, with unclear and poorly defined endpoints (which may not be meaningful to patients) and do not provide information on why there were high dropout rates.

In general, little attention was 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 (e.g., pacing, realistic goals, physical self-awareness, basic rights, understanding emotions, exercise, relaxation), and there is a lack of data demonstrating the efficacy of self-management on health outcomes. The focus on exercise programs has further stigmatized and discouraged research participation. In many cases, lack of instructions or guidance for including graded exercise therapy often causes additional suffering, creating fear of

harm from a comprehensive self-management program that may include some physical activity (e.g., mild stretching).

What tools, measures, and approaches help define individuals with ME/CFS?

and

How are tools and measures used to distinguish subsets of patients with ME/CFS?

Many patients with ME/CFS are misdiagnosed and treated erroneously with potentially toxic therapies that may cause harm and diminish hope. 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. There is a failure to give adequate attention to the severity of the physical, social, and emotional implications of ME/CFS. Furthermore, a variety of symptoms are often "lumped" into ME/CFS. Carefully defining comorbid conditions is necessary to define ME/CFS subgroups and to move the field forward. There is also a lack of interdisciplinary collaboration to develop tools or disease measures that encompass the full spectrum of possible ME/CFS signs and symptoms.

Defining ME/CFS requires standard, validated tools and measures. Individual ME/CFS studies are too small to have power for subgroup analyses; rarely meet the criteria for good quality evidence; frequently do not address early disease or ME/CFS in children; fail to adequately address harms or who dropped out and why; and include only a short follow-up. In addition, participant variability at different study centers may, in part, be responsible for conflicting results.

Endpoints need to be clarified: what is statistically significant, what is clinically significant, and what is significant to the patient. To move the research forward, there is an urgent need to get all

of the information possible from the control population, responders, and non-responders. Patient-centered tools that use simple statements need to be developed to ensure that the patients understand the questions. Overall, there is a need to simplify measures while prioritizing face-to-face interactions.

To advance the field, retrospective, prospective, and longitudinal studies that are practical and reproducible are needed. Longer follow-up and a lifespan perspective are needed to understand ME/CFS effects on the whole individual (e.g., patient decision-making, patient expectations, sexual health and childbearing). The symptoms 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 ME/CFS onset and progression. Research priorities should be shifted to include basic science and mechanistic work that will contribute to the 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 is the role of virologic mechanisms, especially herpes viruses? Does mononucleosis lead to ME/CFS in adolescents?
- What is the role of other pathogenic agents?
- Is this a genetic disease? Is there a gene-environment interaction?
- Is ME/CFS a spectrum disease?
- Are different pathways responsible for different symptoms?

Future Directions and Recommendations

ME/CFS is a chronic, complex condition of unknown cause and with no cure. We have learned some about the mechanisms of the disease, but nothing has improved the lives of the patients. Overall, there has been a failure to implement what we already know for patients with ME/CFS while it steals their health and well-being. However, scientifically rigorous research is needed. The subjective nature of ME/CFS, associated stigma, and the lack of a standard case definition has 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, and for translation efforts. The scientific community is responsible for conducting trials in a way that is meaningful and ethical 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 focus on primary care providers. Potential conflicts of interest among investigators need to be properly vetted, discussed, and addressed by all stakeholders.

The panel was charged with: (1) identifying research gaps, (2) determining methodological limitations, and (3) providing future research recommendations. During the workshop, we learned that the potential cause of ME/CFS and possible treatments are poorly understood, and that there are many unresolved issues, including overlapping comorbid conditions. Findings in the literature are inconsistent, and there are many gaps (e.g., Is ME/CFS one disease?).

To accelerate the progress of ME/CFS treatment, we recommend the following overarching research strategies:

1. *Define disease parameters.* Assemble a team of stakeholders (e.g., patients, clinicians, researchers, federal agencies) to reach consensus on the definition and parameters of ME/CFS. A national and international research network should be developed to clarify the case definition and to advance the field. There are tremendous opportunities on which we have not yet capitalized to learn across disciplines and from other diseases such as Gulf War Syndrome, Lyme disease, fibromyalgia, multiple sclerosis, and Parkinson's disease, to determine commonalities and differences. Additional NIH Institutes and Centers not presently represented in the Trans-NIH ME/CFS Working Group should be included in the effort. Thus, we encourage the convening of a conference of scientific leaders that is open, inclusive, and transparent.

2. *Create new knowledge.* Investing in bench-to-bedside to policy research for ME/CFS is recommended and will create opportunities for junior and new investigators in the field, thereby energizing and diversifying the field. The NIH Institutes and Centers (e.g., the National Center for Advancing Translational Sciences [NCATS], the National Center for Complementary and Alternative Medicine [NCCAM]) and other U.S. Department of Health and Human Services (HHS) agencies should coordinate research efforts to promote efficiency and effectiveness, while also using public/private partnerships to leverage and catalyze the use of existing NIH infrastructure and dollars. Specific activities should focus on:

    - Developing valid prognostic tests that can guide treatment strategies using genomic, epigenomic, proteomic, and metabolomic strategies to identify critical biomarkers

that will be clinically applicable. Gene expression, protein, or metabolite signatures that can correctly diagnose patients with ME/CFS and distinguish them from patients with 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 (GWAS) and phenotyping, is essential for stratifying patients. fMRI and imaging technologies should be further studied as diagnostic tools and as methods to better understand the neurologic dysfunction of ME/CFS.

- Biologic samples—which may include serum and saliva, RNA, DNA, whole blood or *peripheral blood mononuclear cell*, and tissues—as well as de-identified survey data—should be linked in a registry/repository for studies of pathogenesis, prognosis, and biomarker discovery. Research is needed investigating the effect of the intestinal microbiome on ME/CFS using cutting-edge technologies such as high-throughput sequencing. In addition, further exploration of the effect, if any, of the environment and microbiome on ME/CFS development using neurocognitive tests and neuroimaging should be conducted.

- Epidemiological studies of ME/CFS, including incidence and prevalence, who is at high risk, risk factors, geographical distribution, and the identification of potential health care disparities are critical. Researchers should be encouraged to develop a repository for qualitative and quantitative work. Similar to cancer registries, there is much to learn by developing a registry/repository of all patients with ME/CFS.

- While there is a clear need for more trials, previously collected research data should be analyzed to advance knowledge and inform clinical trial development and design.

For instance, drugs therapies used for fibromyalgia or other pain-related syndromes and disorders should be examined for their effectiveness in those with ME/CFS, and existing registries should be leveraged.

- Studies that stratify by clinical characteristics should be used to develop diagnostic and prognostic algorithms to identify those patients who will develop ME/CFS following infection or other triggers.
- There is a need for "omics"-based drug repurposing and neurobiology studies. Using bioinformatics techniques, large datasets such as those generated by "omics" methods should be developed and stored in a central, publicly accessible database for future investigations as new knowledge is developed. This new knowledge might include a new understanding of molecular mechanisms underlying ME/CFS, new ways to perform pathway analyses, and/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 (e.g., defining cytokine profiles involved in pathogenesis; studying inflammation; and comprehending the basis for natural killer cell dysfunction observed in many patients with ME/CFS). These also should be longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction in ME/CFS.

- We need studies of gene expression among identical twins to identify gene expression biomarkers. Any animal model used should include males and females to explore the role of gender, X-chromosome genes, and hormones in the development of 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 because traditional health care is not meeting their needs. Studies investigating homeopathy, non-pharmacologic, complementary, and alternative medicine treatments are needed. Studies addressing biopsychosocial parameters (including the mind-body connection), function, and QOL should be encouraged.

3. *Improve methods and measures.* There is a critical need for improved measures to identify ME/CFS while including the patient's voice through patient-reported outcomes. Without a diagnostic test, stratification must occur to reduce and comprehend variability (e.g., onset, time course, comorbid conditions), and to identify clearly defined endpoints 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 (PROMIS) and the Center for Epidemiological Studies Depression scale (CESD) should be encouraged. Although ME/CFS is not a psychiatric disease, exploring psychiatric comorbidities such as depression, anxiety, and fear is critical to improve quality of life. 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 (e.g., the Health and Retirement Study, the Nurses' Health Study) to better understand ME/CFS.

- Telemedicine or home visits for those unable to participate in clinical trials/treatment in person and outreach to underserved communities are needed. New technologies to address underserved populations and unmet needs (e.g., mobile technology, online tracking tools) should be employed. Mobile monitoring instruments should be developed to measure progress and to enable communication. Research methodology should include strategies for reaching patients who are not served in the clinic setting to ensure that their voice is heard.

4. *Provide training and education.* Although many health care providers do not fully understand ME/CFS, primary care clinicians will be instrumental in ensuring that patients are treated or referred to appropriate specialists. We believe ME/CFS is a distinct disease that requires a multidisciplinary care team (e.g., physicians, nurses, case managers, social workers, psychologists) to optimize care. Thus, properly training that workforce is critical, and we strongly encourage engaging with:

- Health professional licensing and accreditation agencies to ensure a curriculum that facilitates ME/CFS knowledge acquisition
- Health Resources and Services Administration (HRSA) to facilitate training
- Professional societies (e.g., International Association for the Study of Pain) and patient organizations (e.g., International Alliance of Patients' Organizations) to

facilitate a public-private partnership, as well as training and funding of health care professionals

- Clinicians and researchers, who have a responsibility to encourage and track progress
- Patients—in addition to the medical therapies they are receiving, patients must become active participants in their overall treatment.

5. *Finding new funding resources.* With a relatively small number of researchers in the field and finite resources, there is a need for partnerships across institutions 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 HHS to engage new ME/CFS working group members, to create efficiency, and to co-fund research that will promote diversity in the pipeline, eliminate disparities, and enhance the quality of the science (e.g., the National Institute on Minority Health and Health Disparities [NIMHD], the National Cancer Institute [NCI], the Department of Education's National Center for Medical Rehabilitation Research, [NCMRR], the Department of Defense [DoD]).

- Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences. These centers will be charged with determining the biomarkers associated with diagnosis and prognosis, epidemiology (e.g., health care utilization), functional status and disability, patient-centered QOL outcomes, cost-effectiveness of treatment studies, and the role of comorbidities in clinical and real-life settings. The centers should provide a complete characterization of control populations, as well as those who recover from ME/CFS. Ideally, these

collaborative studies will recruit from the broad spectrum of Americans and will use measures that are reproducible.

- Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable data and sample sharing.

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 website for patient and clinician educational materials as well as information regarding clinical trials. Opportunities to utilize the NIH Clinical Center for clinical trials and to fast-track new therapies should also be explored.

7. *Improve treatment.* Patients should be active participants in care and decision-making. Lessons can be learned from palliative care, such as compassion, communication, and symptom management to improve the quality of 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 CBT should be studied as adjunct to other modalities of treatment such as self-management. Future treatment studies should evaluate multimodal therapies. Comparative effectiveness research is also needed. We recommend that the NIH and the FDA convene a meeting on the state of ME/CFS treatment.

Conclusions

Quality care begins with assessment and depends upon optimizing patient and clinician decision-making. Unfortunately, patient- and clinician-related barriers were identified (e.g., attitudes, perceptions, knowledge, communication styles, time constraints, stigma) that inhibit quality care.

For example, patients do not want to be labeled as complainers and want their stories to be heard. Interpersonal factors (e.g., age, race, ethnicity, gender, class, personality) influence communication. Patients and their advocates may benefit from education on how to effectively communicate their symptoms and concerns to clinicians, while health care providers could benefit from enhanced active listening skills and increased education. We note that education alone cannot fix this problem, but will facilitate a partnership in medical decision-making, thereby optimizing care. Furthermore, the multiple case definitions for ME/CFS have hindered progress. Specifically, continuing to use the Oxford definition may impair progress and cause harm. Thus, for needed progress to occur we recommend (1) that the Oxford definition be retired, (2) that the ME/CFS community agree on a single case definition (even if it is not perfect), and (3) that 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 endpoints that suggest improvement and quality care. We believe there is a specific role for multimodal therapy. 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 HHS efforts to decrease disability and promote health and well-being for the ME/CFS population.

There is a role for new and ongoing policies to spark innovation and fund new research. For instance, 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 (CMS) and the Patient-Centered Outcomes Research Institute (PCORI) to develop demonstration projects of

patient-centered medical homes for people with ME/CFS. This should be done using a comparative effectiveness research framework with clear endpoints and continuous evaluations to improve health care and to determine best practices that are evidence-based. Best practices should then be translated to primary care clinicians. Federal agencies (e.g., AHRQ, the U.S. Department of Veterans Affairs [VA]) 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 for ME/CFS. Lastly, we recommend that the ODP convene another ME/CFS Expert Panel in the future to monitor progress. We hope our work has dignified ME/CFS and those affected, while providing expert guidance to the NIH and the broader research community.

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Working group members provided their input at a meeting held January 6–7, 2014. The information provided here was accurate at the time of that meeting.

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