

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.

1 Introduction

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

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

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

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

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

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

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

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

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

48 Studies of ME/CFS are fraught with methodological problems, preventing a clear understanding
49 of who is affected by ME/CFS: there are no agreed-upon parameters for defining ME/CFS, no
50 accurate ways of identifying and diagnosing ME/CFS, and 163 symptoms have been associated
51 with ME/CFS. Small sample sizes, the inclusion of participants with differing symptoms across

52 studies, and the lack of inclusion of the homebound, rural residents, and a research focus on men
53 limits the applicability of current studies. Minorities also are rarely represented in studies, so
54 there are no data to confirm whether minorities have a higher or lower risk. Many instruments
55 used to evaluate ME/CFS are not validated, are inappropriate, and may be misleading. All this
56 leads to inconclusive results and a lack of knowledge of ME/CFS prevalence (i.e., how many
57 people have ME/CFS), incidence (new cases per year), and potential causes and treatments.

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

65 Often, patients with ME/CFS are labeled as lazy, deconditioned, and disability-seeking; this
66 hampers scientific progress. Both society and the medical profession often treat patients with
67 ME/CFS with disdain, suspicion, and disrespect. Patients are frequently treated with psychiatric
68 and other inappropriate drugs that may cause harm. Patients usually have to make extraordinary
69 efforts, at extreme personal costs, to find a physician who will correctly diagnose and treat
70 ME/CFS symptoms. In addition to high medication costs, the debilitating effects of ME/CFS can
71 result in financial instability due to the physical consequences of the illness (e.g., the loss of
72 employment, home, and other basic necessities). All of these factors contribute to the poor
73 quality of epidemiologic studies.

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

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

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

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

92 Although psychological repercussions (e.g., depression) often follow ME/CFS, this is not a
93 psychological disease in etiology. A multitude of symptoms are associated with ME/CFS, with
94 substantial overlap with other pathologic diseases (e.g., fibromyalgia, major depressive disorder,
95 and a variety of chronic pain or inflammatory conditions). Focusing on fatigue alone may

96 identify many ME/CFS cases. However, this symptom taken in isolation fails to capture the
97 essence of this complex condition. Prior studies may have inadequately excluded individuals
98 with the distinct diseases listed above, leading to delayed diagnosis, conflicting diagnoses,
99 contradictory treatments, suboptimal care, and inappropriate health care utilization. Future
100 studies should distinguish between ME/CFS alone, ME/CFS with comorbidities, and other
101 diseases to better define cellular and molecular mechanisms for targeted treatments.

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

108 Patients with ME/CFS are hopeful that research will lead to a cure. However, the few cross-
109 sectional studies with limited applicability have provided few insights to the disease or its
110 treatment. Clinical trials require large investments of time and energy, and may be associated
111 with other harms (e.g., increased symptoms, medication toxicity). Future studies must be
112 collaborative, multicenter efforts and must include large, diverse samples across the lifespan.
113 Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy
114 [GET]) demonstrate measurable improvement, but this has not translated to improvements in
115 quality of life (QOL). Thus, they are not a primary treatment strategy and should be used as a
116 component of multimodal therapy. Overall, agreeing on a case definition and clarifying
117 comorbidities could launch bench-to-bedside science.

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

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

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

130 In general, little attention was given to how self-management may empower and improve health
131 and QOL for patients with ME/CFS. Physicians are inadequately trained to instruct patients in
132 self-management skills (e.g., pacing, realistic goals, physical self-awareness, basic rights,
133 understanding emotions, exercise, relaxation), and there is a lack of data demonstrating the
134 efficacy of self-management on health outcomes. The focus on exercise programs has further
135 stigmatized and discouraged research participation. In many cases, lack of instructions or
136 guidance for including graded exercise therapy often causes additional suffering, creating fear of
137 harm from a comprehensive self-management program that may include some physical activity
138 (e.g., mild stretching).

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

140 *and*

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

142 Many patients with ME/CFS are misdiagnosed and treated erroneously with potentially toxic
143 therapies that may cause harm and diminish hope. There is little understanding of the inciting
144 event or the cellular and molecular mechanisms that underlie ME/CFS, preventing quantitative
145 assessments of disease severity or prognosis. There is a failure to give adequate attention to the
146 severity of the physical, social, and emotional implications of ME/CFS. Furthermore, a variety of
147 symptoms are often “lumped” into ME/CFS. Carefully defining comorbid conditions is
148 necessary to define ME/CFS subgroups and to move the field forward. There is also a lack of
149 interdisciplinary collaboration to develop tools or disease measures that encompass the full
150 spectrum of possible ME/CFS signs and symptoms.

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

157 Endpoints need to be clarified: what is statistically significant, what is clinically significant, and
158 what is significant to the patient. To move the research forward, there is an urgent need to get all
159 of the information possible from the control population, responders, and non-responders. Patient-
160 centered tools that use simple statements need to be developed to ensure that the patients

161 understand the questions. Overall, there is a need to simplify measures while prioritizing face-to-
162 face interactions.

163 To advance the field, retrospective, prospective, and longitudinal studies that are practical and
164 reproducible are needed. Longer follow-up and a lifespan perspective are needed to understand
165 ME/CFS effects on the whole individual (e.g., patient decision-making, patient expectations,
166 sexual health and childbearing). The symptoms patients consider clinically meaningful are not in
167 the scientific literature; this discordance must be rectified.

168 Current research has neglected many of the biological factors underlying ME/CFS onset and
169 progression. Research priorities should be shifted to include basic science and mechanistic work
170 that will contribute to the development of tools and measures such as biomarker or therapeutics
171 discovery. The following questions need to be answered:

- 172 • What is the pathogenesis of ME/CFS? What is the role of virologic mechanisms,
173 especially herpes viruses? Does mononucleosis lead to ME/CFS in adolescents?
- 174 • What is the role of other pathogenic agents?
- 175 • Is this a genetic disease? Is there a gene-environment interaction?
- 176 • Is ME/CFS a spectrum disease?
- 177 • Are different pathways responsible for different symptoms?

178 **Future Directions and Recommendations**

179 ME/CFS is a chronic, complex condition of unknown cause and with no cure. We have learned
180 some about the mechanisms of the disease, but nothing has improved the lives of the patients.

181 Overall, there has been a failure to implement what we already know for patients with ME/CFS

182 while it steals their health and well-being. However, scientifically rigorous research is needed.
183 The subjective nature of ME/CFS, associated stigma, and the lack of a standard case definition
184 has stifled progress. Patients must be at the center of the research efforts, and their engagement is
185 critical, as is outreach to underserved and vulnerable populations.

186 Innovative biomedical research is urgently needed to identify risk and therapeutic targets, and for
187 translation efforts. The scientific community is responsible for conducting trials in a way that is
188 meaningful and ethical for patients. The influence of health literacy and cognitive impairment on
189 informed consent must be considered. Investigators have a responsibility to hear the patient's
190 perspective, engage the community, and be accountable for translating and reporting research
191 results to the ME/CFS community while responding to their feedback. The dissemination of
192 diagnostic and therapeutic recommendations should focus on primary care providers. Potential
193 conflicts of interest among investigators need to be properly vetted, discussed, and addressed by
194 all stakeholders.

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

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

- 202 1. *Define disease parameters.* Assemble a team of stakeholders (e.g., patients,
203 clinicians, researchers, federal agencies) to reach consensus on the definition and

204 parameters of ME/CFS. A national and international research network should be
205 developed to clarify the case definition and to advance the field. There are
206 tremendous opportunities on which we have not yet capitalized to learn across
207 disciplines and from other diseases such as Gulf War Syndrome, Lyme disease,
208 fibromyalgia, multiple sclerosis, and Parkinson's disease, to determine commonalities
209 and differences. Additional NIH Institutes and Centers not presently represented in
210 the Trans-NIH ME/CFS Working Group should be included in the effort. Thus, we
211 encourage the convening of a conference of scientific leaders that is open, inclusive,
212 and transparent.

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

- 222 • Developing valid prognostic tests that can guide treatment strategies using
223 genomic, epigenomic, proteomic, and metabolomic strategies to identify
224 critical biomarkers that will be clinically applicable. Gene expression, protein,
225 or metabolite signatures that can correctly diagnose patients with ME/CFS and
226 distinguish them from patients with other chronic conditions, while predicting

227 disease severity and clinical outcomes, are needed. Determining the most
228 important physiologic measures and pathophysiology, as well as genome-wide
229 association studies (GWAS) and phenotyping, is essential for stratifying
230 patients. fMRI and imaging technologies should be further studied as
231 diagnostic tools and as methods to better understand the neurologic
232 dysfunction of ME/CFS.

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

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

248 • While there is a clear need for more trials, previously collected research data
249 should be analyzed to advance knowledge and inform clinical trial

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

- 254 • Studies that stratify by clinical characteristics should be used to develop
255 diagnostic and prognostic algorithms to identify those patients who will
256 develop ME/CFS following infection or other triggers.
- 257 • There is a need for “omics”-based drug repurposing and neurobiology studies.
258 Using bioinformatics techniques, large datasets such as those generated by
259 “omics” methods should be developed and stored in a central, publicly
260 accessible database for future investigations as new knowledge is developed.
261 This new knowledge might include a new understanding of molecular
262 mechanisms underlying ME/CFS, new ways to perform pathway analyses,
263 and/or new pharmacogenomic drug discovery or repurposing.
- 264 • An integrated, systems-level approach should be followed to understand how
265 immunologic, neurologic, and metagenomic factors may contribute to
266 ME/CFS. Immunologic mechanisms of ME/CFS and pathways associated
267 with disease progression must be defined and characterized (e.g., defining
268 cytokine profiles involved in pathogenesis; studying inflammation; and
269 comprehending the basis for natural killer cell dysfunction observed in many
270 patients with ME/CFS). These also should be longitudinal studies to explore
271 the possibility of a progressive immune exhaustion or dysfunction in
272 ME/CFS.

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- We need studies of gene expression among identical twins to identify gene
274 expression biomarkers. Any animal model used should include males and
275 females to explore the role of gender, X-chromosome genes, and hormones in
276 the development of ME/CFS.
 - How patients' background medications (including psychiatric drugs) affect
277 function and outcome should be explored. Patients often choose clinical trials
278 or complementary and alternative medicine because effective treatment is not
279 available and because traditional health care is not meeting their needs.
280 Studies investigating homeopathy, non-pharmacologic, complementary, and
281 alternative medicine treatments are needed. Studies addressing
282 biopsychosocial parameters (including the mind-body connection), function,
283 and QOL should be encouraged.
284
- 285 3. *Improve methods and measures.* There is a critical need for improved measures to
286 identify ME/CFS while including the patient's voice through patient-reported
287 outcomes. Without a diagnostic test, stratification must occur to reduce and
288 comprehend variability (e.g., onset, time course, comorbid conditions), and to identify
289 clearly defined endpoints for treatment trials and interventions. The NIH should
290 develop an ME/CFS methodological workgroup.
- A community-based participatory research approach is needed to increase
291 patient involvement in determining priorities for research and care.
 - Use of already well-validated measures developed by the NIH such as the
292 Patient-Reported Outcomes Measurement Information System (PROMIS) and
293 the Center for Epidemiological Studies Depression scale (CESD) should be
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295

296 encouraged. Although ME/CFS is not a psychiatric disease, exploring
297 psychiatric comorbidities such as depression, anxiety, and fear is critical to
298 improve quality of life. Response burden must be considered; a battery of
299 simplified measures is strongly encouraged, as well as the triangulation of
300 qualitative and quantitative data. The NIH should leverage the power of other
301 longitudinal studies (e.g., the Health and Retirement Study, the Nurses' Health
302 Study) to better understand ME/CFS.

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

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

317 • Health professional licensing and accreditation agencies to ensure a
318 curriculum that facilitates ME/CFS knowledge acquisition

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- Health Resources and Services Administration (HRSA) to facilitate training
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- Professional societies (e.g., International Association for the Study of Pain)
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- and patient organizations (e.g., International Alliance of Patients’
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- Organizations) to facilitate a public-private partnership, as well as training and
- 323
- funding of health care professionals
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- Clinicians and researchers, who have a responsibility to encourage and track
- 325
- progress
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- Patients—in addition to the medical therapies they are receiving, patients must
- 327
- become active participants in their overall treatment.
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5. *Finding new funding resources.* With a relatively small number of researchers in the
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- field and finite resources, there is a need for partnerships across institutions to
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- advance the research and develop new scientists. New collaborative models,
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- investigator-initiated studies, career development, and small grant mechanisms with
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- specific attention to developing a cadre of junior investigators, including women and
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- minorities who may offer innovative new approaches, are needed. Opportunities exist
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- within HHS to engage new ME/CFS working group members, to create efficiency,
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- and to co-fund research that will promote diversity in the pipeline, eliminate
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- disparities, and enhance the quality of the science (e.g., the National Institute on
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- Minority Health and Health Disparities [NIMHD], the National Cancer Institute
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- [NCI], the Department of Education’s National Center for Medical Rehabilitation
- 339
- Research, [NCMRR], the Department of Defense [DoD]).
- Create a network of collaborative centers working across institutions and
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- disciplines, including clinical, biological, and social sciences. These centers
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342 will be charged with determining the biomarkers associated with diagnosis
343 and prognosis, epidemiology (e.g., health care utilization), functional status
344 and disability, patient-centered QOL outcomes, cost-effectiveness of
345 treatment studies, and the role of comorbidities in clinical and real-life
346 settings. The centers should provide a complete characterization of control
347 populations, as well as those who recover from ME/CFS. Ideally, these
348 collaborative studies will recruit from the broad spectrum of Americans and
349 will use measures that are reproducible.

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

352 6. *Conduct clinical trials.* An ongoing need for participants in clinical trials was noted.
353 The NIH should work with ME/CFS partners and stakeholders to create a website for
354 patient and clinician educational materials as well as information regarding clinical
355 trials. Opportunities to utilize the NIH Clinical Center for clinical trials and to fast-
356 track new therapies should also be explored.

357 7. *Improve treatment.* Patients should be active participants in care and decision-
358 making. Lessons can be learned from palliative care, such as compassion,
359 communication, and symptom management to improve the quality of care. Studies
360 examining the role of self-management techniques as part of a comprehensive
361 treatment plan for patients with ME/CFS during and after clinical interventions
362 should be explored. The modest benefit from CBT should be studied as adjunct to
363 other modalities of treatment such as self-management. Future treatment studies
364 should evaluate multimodal therapies. Comparative effectiveness research is also

365 needed. We recommend that the NIH and the FDA convene a meeting on the state of
366 ME/CFS treatment.

367 **Conclusions**

368 Quality care begins with assessment and depends upon optimizing patient and clinician decision-
369 making. Unfortunately, patient- and clinician-related barriers were identified (e.g., attitudes,
370 perceptions, knowledge, communication styles, time constraints, stigma) that inhibit quality care.
371 For example, patients do not want to be labeled as complainers and want their stories to be heard.
372 Interpersonal factors (e.g., age, race, ethnicity, gender, class, personality) influence
373 communication. Patients and their advocates may benefit from education on how to effectively
374 communicate their symptoms and concerns to clinicians, while health care providers could
375 benefit from enhanced active listening skills and increased education. We note that education
376 alone cannot fix this problem, but will facilitate a partnership in medical decision-making,
377 thereby optimizing care. Furthermore, the multiple case definitions for ME/CFS have hindered
378 progress. Specifically, continuing to use the Oxford definition may impair progress and cause
379 harm. Thus, for needed progress to occur we recommend (1) that the Oxford definition be
380 retired, (2) that the ME/CFS community agree on a single case definition (even if it is not
381 perfect), and (3) that patients, clinicians, and researchers agree on a definition for meaningful
382 recovery.

383 Attention should be focused on providing access to high-quality, multidisciplinary care; refining
384 assessment; and clarifying endpoints that suggest improvement and quality care. We believe
385 there is a specific role for multimodal therapy. Although no data on primary prevention were
386 presented, this does not prohibit secondary and tertiary prevention efforts. Once a cause is

387 determined, primary prevention efforts should begin. The NIH should incorporate concepts from
388 public health prevention and HHS efforts to decrease disability and promote health and well-
389 being for the ME/CFS population.

390 There is a role for new and ongoing policies to spark innovation and fund new research. For
391 instance, new avenues are needed to fund research, such as the Prescription Drug User Fee Act.
392 The NIH should work with the Centers for Medicare & Medicaid Services (CMS) and the
393 Patient-Centered Outcomes Research Institute (PCORI) to develop demonstration projects of
394 patient-centered medical homes for people with ME/CFS. This should be done using a
395 comparative effectiveness research framework with clear endpoints and continuous evaluations
396 to improve health care and to determine best practices that are evidence-based. Best practices
397 should then be translated to primary care clinicians. Federal agencies (e.g., AHRQ, the U.S.
398 Department of Veterans Affairs [VA]) and professional societies should work together to create
399 quality metrics and a standard of care. We also recommend that federal departments, advocacy
400 groups, and industry work together in public-private partnerships to help advance research for
401 ME/CFS. Lastly, we recommend that the ODP convene another ME/CFS Expert Panel in the
402 future to monitor progress. We hope our work has dignified ME/CFS and those affected, while
403 providing expert guidance to the NIH and the broader research community.