

CFSAC Review of the Draft P2P Report on ME/CFS. January 13, 2014

On January 13, 2014, CFSAC held a special session to review and approve proposed comments to be submitted to the P2P Panel regarding the Executive Summary of NIH P2P Workshop on ME/CFS. These comments were based on the efforts of a CFSAC Workgroup since the P2P Executive Summary was released on December 18, 2014.

Included below is an *unofficial* version of the outcome of that discussion. The sections include:

1. The preface that CFSAC is providing in its submission to P2P.
2. The original draft of the Executive Summary (389 line version) produced by the P2P panel along with the specific and approved recommendations for changes. When discussed, the rationale for those changes is also included.
 - a. **CFSAC's recommended changes to the Executive Summary are listed in italicized red and the rationale for the changes and any other comments are listed in blue.**
 - b. Where CFSAC made recommendations to delete text, the deleted text was struck through.
 - c. Note that this document does not include a full transcript of the discussion on each recommendation, just the resultant recommendation for change and any discussed rationale.

The official copy of CFSAC's submission will be posted on the CFSAC website although that may not happen before the January 16, 2015 deadline for submission of P2P comments. **This unofficial version of CFSAC's recommended changes and rationale was captured from an audio recording. As a result, this document may not exactly reflect the official version of the CFSAC comments that will be submitted to P2P but it should be close.**

1. Preface to CFSAC's Comments to P2P on the Executive Summary of the P2P ME/CFS Workshop

This document contains the comments of the CFSAC on the 389 line version of the Draft Executive Summary for the December 2014 Pathways to Prevention (P2P) Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Many of the observations highlighted in the draft executive summary support recommendations made to the Secretary by this Committee. (See Appendix A). These observations have also been made by stakeholders and ME/CFS experts who recommend use of the 2003 Canadian Consensus Criteria to define the disease until further research warrants modification.

During our review, the Committee identified several important areas that should be addressed. Those areas are reflected in the "Comments" section of this document.

Additionally, if the Panel did not review *The Voice of the Patient* series of reports published in September 2013 following the U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis, we encourage you to do so.

We also ask that you review the Report from the National Institutes of Health (NIH) State of Knowledge Workshop during which researchers and stakeholders reached consensus on a number of key issues. Some of these issues may be of importance to the P2P Panel during the revision process. We also ask that you take note of the fact that among the 234 disease categories supported by NIH in 2014, chronic fatigue syndrome ranked 228th with an estimated \$5 million in funding.

In order to move forward, it is vital that this issue be addressed.

We ask that the Panel explicitly address the urgent need for government funding in order to advance the research for ME/CFS.

Without a substantial change in funding at the national level, CFSAC believes it will be virtually impossible to address the comprehensive list of recommendations outlined in the Panel's Draft Executive Summary.

2. CFSAC's recommended changes to the P2P Executive Summary

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.

Replace existing text line 2-7 with the following:

“Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by hallmark symptoms of neurological dysfunction, sleep disturbances, and post exertional malaise with predominant symptoms of immunological and endocrinological dysfunction. Post exertional malaise is defined as “an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period—usually 24 hours or longer.

“The etiology and pathogenesis of ME/CFS remains unknown and there are no known cures. There is no single diagnostic test or standard set of tests being used to diagnose ME/CFS in the clinic at this time. However, a number of common biomarkers are being used by experts in the field to aid diagnosis, to strategize treatment, to define comorbid states and for research. Strong evidence indicates immunologic and inflammatory pathologies, neuroendocrine findings, and abnormalities in gene expression of energy and other related proteins post-exertionally in ME/CFS patients which differ from findings among age and sex matched normal control populations. Additionally, there is reproducible evidence of abnormalities in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies.

“Research has clearly shown that ME/CFS is not a psychiatric or a psychological disease. ME/CFS is a distinct pathological entity that can affect both sexes and all racial, age, and socioeconomic groups regardless of education, financial security, or social standing. The U.S. Centers for Disease Control and Prevention (CDC) reports over 1 million adults with ME/CFS in the United States, and recent evidence has shown a higher prevalence in females compared to males. Certain racial/ethnic groups have also been found to be at an increased risk for ME/CFS; most notably Native American and African American populations.

“The economic burden of ME/CFS in the U.S., including annual health care costs, is estimated to be between \$1.9 billion and \$7.2 billion. When considering indirect costs to society as a whole, the annual estimate jumps to between \$18.7 and \$23 billion in the U.S. alone. ME/CFS results in major disability for a large proportion of patients and in its most severe form, can lead to individuals becoming housebound, dependent on wheelchairs, or bedbound and forced to turn to caregivers for all basic activities of daily living. Limited knowledge and research funding creates an additional burden for patients and health care providers.

[Note: The last sentence in red was read at the meeting but is unchanged from the original text]

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:

15-17: 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

18-21: 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

22-23: 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

24-26: 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.

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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

Replace existing text in line 32-35 with the following:

“ME/CFS Exists. Despite the absence of a clear definition, an estimated million people have the disease and it often presents with co-morbidities, (e.g. allergies, fibromyalgia and other pain conditions, depression, interstitial cystitis, multiple chemical sensitivity.)”

Rationale (paraphrased) was that the committee disagreed with the statement on overlap with other diseases. They also asked to delete the statement that the research community does not agree on what to study (lines 34-35) because researchers do agree that pathophysiology, epidemiology and evolving definitions of the disease needs to be studied.

Note: It wasn't explicitly stated but it appears that the rest of the deleted sentence becomes a new sentence: “There are 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.~~

Replace existing text in line 40-43 with the following:

“The lack of a universally accepted set of criteria has hampered some, but not all, downstream research on pathogenesis and treatment, causing harm.”

Rationale (quoted): “Recent research studies show that laboratory testing can reveal important aspects of subsets and direct treatment. The vast majority of the scientific community agrees that this is a real pathological entity and the committee is justifiably concerned that the original statement along with the implication that ME/CFS is not considered as a distinct pathological entity is counterproductive to the panel’s intent to forward the research for this disease. Additionally, we do not agree that the lack of a diagnostic test has hampered all downstream research and request that the statement be removed. There are many recognized pathological entities, several of them multi-system/symptom disorders which do not have definitive evidence regarding etiology and/or do not have a specific sensitive diagnostic test.”

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.

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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~~

Replace existing text in line 48-50 with:

“Although dedicated researchers have identified parameters for defining ME/CFS, those parameters have not been universally adopted. As a result, studies of ME/CFS are fraught with methodological problems, preventing a clear understanding of who is affected by the disease.”

Replace text in line 50 on 163 symptoms with the following:

“and a multitude of symptoms have been associated with ME/CFS.”

Rationale (paraphrased): This is based on Dr. Nacul’s presentation at P2P. CFSAC included a transcript of that

portion of the P2P meeting.

Note: At P2P, Nacul said that Fukuda was non-specific and based on the absence of symptoms. He also stated that Fukuda has 163 distinct combinations of symptoms, of which only 35 combinations had PEM and stated that there was an advantage to more restrictive criteria.

~~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

The CFSAC is asking for the addition of “children and adolescents” to line 51 and 52 regarding the limiting of the applicability. The CFSAC is also asking for a clarification on the statement about a “research focus on men” and whether that was intended to say that most studies of this disease focus on men or not.

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

The CFSAC is asking for clarification on comment about “Many instruments used to evaluate ME/CFS are not validated...”As written, its unclear what instruments this is referring to.

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~~

Replace existing text in line 58 and 59 with the following:

“Fatigue has been a focus of some recent research but many other symptoms need to be explored further, including neurocognitive deficit, brain-fog, post-exertional malaise, pain, non-restorative sleep, orthostatic intolerance, metabolic [unclear] energy production and endocrine and immunological changes.”

~~60 ME/CFS studies focus on adults, excluding children with similar symptoms. We noted few~~

Replace existing text in line 60 with the following:

“Most ME/CFS studies focus on adults. The Panel’s charge did not include a review of evidence related to children and adolescents with ME/CFS. However, such a review should be done. ME/CFS in children and youth often presents somewhat differently from that in adults. Symptoms more prominent in children include gastrointestinal upset, orthostatic intolerance and headaches among others. [Reference provided] “

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

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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.~~

Replace existing text in line 80-81 with the following:

“The Department of Health and Human Services and other government agencies as well as the scientific community have a responsibility to 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.

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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

Replace existing text in line 93-95 with the following:

“A multitude of symptoms are associated with ME/CFS, as are a number of comorbidities [and we provided the list of comorbidities from above].”

Note: The comorbidities listed above include allergies, fibromyalgia and other pain conditions, depression, interstitial cystitis, and multiple chemical sensitivity.

~~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

Replace existing text in line 95-97 with the following text:

“Focusing on fatigue alone may identify many ME/CFS cases but might also capture many individuals who do not have ME/CFS. This symptom taken in isolation fails to capture the essence of this disease including the hallmark of post-exertional malaise and neurocognitive deficits.”

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.

The CFSAC requests that the panel add sleep disorders to the list of symptoms in line 106-107 because sleep disorders were consistently mentioned during the workshop.

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. (new sentence
here]

Request the addition of a new sentence after 112:

“In addition to supporting clinical trials on diverse but well defined subgroups of patients with ME/CFS over a lengthy period of time, this disease should be compared not only to age and sex matched normal controls but to other groups of chronically ill patients in addition to healthy controls. Biological models which can measure changes in the hypothalamic pituitary axis (HPA) concomitant with changes in immune function, pre and post exercise and their homeostatic regulatory mechanisms should be developed.”

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

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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

Replace existing text in line 113-116 with the following:

“Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy [GET]) demonstrate modest improvement, but this has not translated to improvements in quality of life (QOL). Thus, they are not primary treatment strategies. Where appropriate, pharmaceuticals and other clinical treatments should first be employed to address underlying pathologies and manage symptoms to the extent possible. CBT might then be suggested to help patients adjust and learn to cope with the realities of a chronic disease. Exercise therapy should only be considered if and when appropriately trained professionals are involved and fully understand how to ensure that the exercise does not induce post-exertional malaise or cause other physical harm.”

Rationale (quoted): “Although the panel has indicated that CBT and GET should not be used as primary strategies, a recommendation to include them as a component of multimodal therapy should be carefully clarified. Far too many patients have been subjected to these treatments by uneducated or misinformed clinicians only to result in further debility. Additionally, while small studies have shown modest improvements, the PACE (Pacing, graded activity, and cognitive behavioral therapy, a randomized evaluation study), which purports to demonstrate measurable improvements, used the Oxford criteria for subject selection. We agree with the panel’s assessment that continuing to use the Oxford definition may impair progress and cause harm and also that the Oxford criteria should be retired. We therefore encourage the panel to rethink referencing the PACE trial since the Oxford criteria were used to identify patients for this study.”

D. Pearson also noted that the term “graded exercise” was not used because it implies that you build up past your limits.

117 comorbidities could launch bench-to-bedside science.

Modify existing sentence in line 117 to include subgroups in addition to comorbidities

“Overall, agreeing on a case definition and clarifying comorbidities and subgroups 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. [\[new sentence as below\]](#) Patients experience stigma from the
diagnosis of

Discussion to add the following sentence after the sentence in 120-121 but this was tabled and they didn't have time to go back to it.

[“There are other factors which impair the patient-clinician communication and quality of care, including time constraints that prevent the clinician from obtaining an accurate medical history, the number of symptoms which need to be reported and discussed and patients struggling with cognitive dysfunction.”](#)

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

Replace existing text in line 121 -122 with the following:

“Patients experience stigma from the negative attitudes, psychological connotations and misinformation associated with the diagnosis of ME/CFS including social isolation and judgment.”

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

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137 harm from a comprehensive self-management program that may include some physical activity

138 (e.g., mild stretching).

Add a sentence at the end of line 138.

“While self-management may empower some patients with ME/CFS, more [unclear] affected individuals may be harmed by this process. It is essential that clinicians who follow patients with ME/CFS keep abreast of the literature, participate in clinical trials, communicate with the patient’s primary caregiver and primary care doctor and assess any changes in clinical presentation at each patient encounter.”

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

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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.

The CFSAC is asking for a clarification on this statement on line 166-167, which says that the symptoms meaningful to patients are not in the literature.

The CFSAC states, “there is research and evidence for post-exertional malaise in ME/CFS and cognitive symptoms have been demonstrated for decades in this patient population. Therefore further clarification on this statement would be helpful since the epidemiological literature does [unclear] the most common symptoms reported by patients.”

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:

172-173: 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?

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?

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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.

Replace existing text in line 183-185 with the following:

“The methods of quantitatively and qualitatively characterizing the disease remain subjective at this time. The failure to adopt the Canadian Consensus Criteria universally has stifled progress. Patients must be at the center of the research efforts, their engagement is critical as is the outreach to underserved and vulnerable populations.”

Rationale (quoted) “There is published objective data about ME/CFS and the disease itself is not subjective in nature. The CFSAC fully expects that the pathophysiology of this disease will eventually be unveiled.”

Note: the last sentence (i.e. patients at the center of efforts) was read as part of the change but is unchanged from the original text.

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

Replace existing text in line 191-192 with the following:

“The dissemination of diagnostic and therapeutic recommendations should focus on primary care providers and all other health care providers dealing with symptoms specific to this disease including but not limited to cardiologists, endocrinologists, neurologists, rheumatologists, psychiatrists, clinical immunologists and infectious disease specialists.”

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?).

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

202-211: 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.

Replace existing text in line 202-205 with:

“Assemble a team of stakeholders (e.g patients, clinicians, researchers, federal agencies) to review the results of the study by the Institute of Medicine and to reach consensus on a path forward. HHS should adopt a universal case definition to help advance the field.”

Rationale (quoted): “this recommendation is needed to identify and incorporate the need for stakeholders to review, analyze and/or reject the IOM recommendation on this matter.”

212-220: 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:

Add new bullet to the list of activities that starts after line 220:

- *“Developing a list or set of diagnostic tests or indications that could be used by health care providers.”*
- **Line 221-230:** Developing valid prognostic tests that can guide treatment strategies using genomic, epigenomic, proteomic, and metabolomic strategies to identify critical biomarkers

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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. (CPET to be added to this sentence)

Modify line 228 to 230 to include 2 day cardiovascular testing with gas exchange that should be studied further as an additional diagnostic tool.

- **Line 231-238:** 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. [new sentence here] 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.

Add new sentence after line 231-234

“The NIH should adapt the architecture of the National Autism Research Database, [unclear] provide ongoing support for data and biobank sharing platform for ME/CFS research and this platform should allow for both phenotype and biologic data.”

- **Line 239-243:** 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. [\[new sentence here\]](#) Similar to cancer registries, there is much to learn by developing a registry/repository of all patients with ME/CFS.

Add new sentence after line 241-242

“Inventorying and describing existing registries and repositories to identify gaps and opportunities for sharing would be a first step.”

- **Line 244-248:** 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.

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~~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.~~

Replace existing text in line 246-248

“For instance, using well-characterized ME/CFS patients from existing practices as well as patient samples from existing registries for this disease, [drugs?] previously targeted only for autoimmune, neurodegenerative and viral diseases should be examined for their effectiveness in patients with ME/CFS. Pharmacological treatments that address the symptoms of autonomic, immunologic and endocrine dysfunction should be explored as well.”

Rationale (quoted): [“Citing drugs for fibromyalgia and pain related symptoms may give an incorrect imprecision on the nature of this disease. Based on promising research, the requested revision is more appropriate.”](#)

- **Line 249-251:** 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.
- **Line 252-258:** 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.
- **Line 259-266:** 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.

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- **Line 267-269:** 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.
- **Line 270-276:** ~~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.~~

Replace existing text in line 270-271 on background medication

“How patients background medication, including statins, anti-inflammatories, psychiatric drugs, sleep and pain medication affect function and outcome should be explored.”

Rationale (quoted): “the inclusion of additional medications is needed so as not to imply that ME/CFS is a psychiatric illness.”

Replace existing text in line 275-276 that called for study of biopsychosocial parameters

“Use of outcome measures such as QOL and function should be encouraged in the studies of immunologic, neurologic and genomic factors as well as the other valuable studies outlined in the “Create New Knowledge” section of this workshop report.”

Rationale (quoted): “CFSAC has heard repeated public testimony from advocates objecting to a perceived emphasis on research that is focused on psychosocial factors as possible contributors to ME/CFS or the use of psychological, social and behavioral interventions. Based on the history of research funding for ME/CFS, the CFSAC is concerned that the study of biopsychosocial parameters will divert research funding from higher priority studies of pathogenesis, prognosis, biomarkers, drug repurposing and other discoveries. The proposed edit would encourage biologically focused studies that incorporate outcome measures such as QOL and function.”

Line 277-282: 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.

- **Line 283-284:** A community-based participatory research approach is needed to increase patient involvement in determining priorities for research and care.
- **Line 285-293:** 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

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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.

- **Line 294-300:** 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.

Line 301-306: 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:

- **Line 307-308:** Health professional licensing and accreditation agencies to ensure a curriculum that facilitates ME/CFS knowledge acquisition
- **Line 309:** Health Resources and Services Administration (HRSA) to facilitate training
- **Line 310-313:** 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

- **Line 314:** Clinicians and researchers, who have a responsibility to encourage and track progress
- **Line 315-316:** Patients—in addition to the medical therapies they are receiving, patients must become active participants in their overall treatment.

Line 317-327: 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]). [\[new sentence here\]](#)

Add new sentence after line 321-327

“Since ME/CFS is a multi-systemic disease, there are also opportunities for other institutes to add ME/CFS to their portfolio. These opportunities will help advance ME/CFS on multiple fronts.”

Rationale (quoted): “We urge encourage the panel to address the needs for funding to achieve the goals outlined in this draft and [unclear] research for ME/CFS.”

- Line 328-336: 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

CFSAC provided a comment about the report statement in line 328-226

“CFSAC wholeheartedly endorses the recommendation. A CFSAC working group is currently meeting to define the component. We caution the NIH to refrain from tagging ME/CFS into the existing interstitial cystitis program. That program could serve as a model to link and coordinate a research portfolio that will truly deliver the key needs - biomarkers, translational trials and phase 2 and phase 3 clinical trials for ME/CFS.”

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

- **Line 337-338:** Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable data and sample sharing.

Line 339-343: 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.

Add new sentence after line 339-343

“[Unclear] High quality clinical trials to facilitate the development of effective drugs for ME/CFS are recommended.”

Rationale (quoted): “there are no approved drugs for ME/CFS and this gap should be specifically addressed.”

Line 344-352: 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.

353 **Conclusions**

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

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357 For example, patients do not want to be labeled as complainers and want their stories to be heard.
358 Interpersonal factors (e.g., age, race, ethnicity, gender, class, personality) influence
359 communication. ~~Patients and their advocates may benefit from education on how to effectively~~
360 ~~communicate their symptoms and concerns to clinicians, while health care providers could~~
361 ~~benefit from enhanced active listening skills and increased education.~~ We note that education

Replace existing sentence in line 359-361 with:

“However, patients and their advocates should continue to communicate their symptoms to clinicians to the best of their ability. Health care providers will benefit from increased education about the realities of this disease.”

362 alone cannot fix this problem, but will facilitate a partnership in medical decision-making,
363 thereby optimizing care. Furthermore, the multiple case definitions for ME/CFS have hindered
364 progress. Specifically, continuing to use the Oxford definition may impair progress and cause
365 harm. ~~Thus, for needed progress to occur we recommend (1) that the Oxford definition be~~
366 ~~retired, (2) that the ME/CFS community agree on a single case definition (even if it is not~~
367 ~~perfect), and (3) that patients, clinicians, and researchers agree on a definition for meaningful~~
368 ~~recovery.~~

Replace existing sentence in line 365-368 with:

“Thus, for needed progress to occur, we recommend (1) that the Oxford definition be retired and that studies using the Oxford definition not be used to inform treatment recommendations for ME/CFS, (2) that the CCC be universally adopted until such time that updated criteria are accepted (3) that the ME/CFS community review the clinical diagnostic criteria recommendation produced by the Institute of Medicine and then agree on a single clinical diagnostic case definition, even if its not perfect, to be used by all health care providers caring for patients with ME/CFS (4) that the single clinical diagnostic case definition be followed by development of a research case definition for use by all conducting research on ME/CFS and (5) that patients, clinicians, and researchers agree on a definition for meaningful recovery.”

369 Attention should be focused on providing access to high-quality, multidisciplinary care; refining
370 assessment; and clarifying endpoints that suggest improvement and quality care. We believe
371 there is a specific role for multimodal therapy. Although no data on primary prevention were
372 presented, this does not prohibit secondary and tertiary prevention efforts. Once a cause is
373 determined, primary prevention efforts should begin. The NIH should incorporate concepts from
374 public health prevention and HHS efforts to decrease disability and promote health and well-
375 being for the ME/CFS population.

376 There is a role for new and ongoing policies to spark innovation and fund new research. For
377 instance, new avenues are needed to fund research, such as the Prescription Drug User Fee Act.
378 The NIH should work with the Centers for Medicare & Medicaid Services (CMS) and the
379 Patient-Centered Outcomes Research Institute (PCORI) to develop demonstration projects of

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380 patient-centered medical homes for people with ME/CFS. This should be done using a
381 comparative effectiveness research framework with clear endpoints and continuous evaluations
382 to improve health care and to determine best practices that are evidence-based. Best practices
383 should then be translated to primary care clinicians. Federal agencies (e.g., AHRQ, the U.S.
384 Department of Veterans Affairs [VA]) and professional societies should work together to create
385 quality metrics and a standard of care. We also recommend that federal departments, advocacy
386 groups, and industry work together in public-private partnerships to help advance research for
387 ME/CFS. Lastly, we recommend that the ODP convene another ME/CFS Expert Panel in the
388 future to monitor progress. We hope our work has dignified ME/CFS and those affected, while
389 providing expert guidance to the NIH and the broader research community.

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