Dear Colleagues,

Thank you for the opportunity to contribute to this Request for Information. As directed, we, the Board of the International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (IACFS), have highlighted emerging opportunities, research needs, and continuing challenges in the field of chronic fatigue syndrome/ myalgic encephalomyelitis. This document is by no means exhaustive and, as such, is a snapshot in time as the research continues to evolve. Please do not hesitate to contact us at membership@iacfsme.org for further information or details.

Sincerely,

Lily Chu, MD, MSHS – Co-Vice-President

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Emerging Opportunities:

Currently, there is no easily available, well-established, objective diagnostic test for ME/CFS. Here are a few areas that may yield a diagnostic test or biomarker for ME/CFS. Some tests might not be suitable for clinical use but might provide a gold standard test for research purposes. may also provide clues to the pathophysiology of this disease and even to future treatments.

1) **Low natural killer cell activity (NKCA) as a diagnostic marker:**
   In a review of 17 studies, Strayer et al. (1) found that 88% of studies suggested ME/CFS patients tended to have lower natural killer cell activity than healthy controls. Furthermore, low natural killer cell activity has been shown to be correlated with functional status (2) and decreased in a dose-response manner in a family with multiple patients (3). Low NKCA was downgraded as a requirement for the Institute of Medicine's SEID criteria for two main reasons: a) low NKCA can occur for reasons other than ME/CFS and b) it was not clear what percentage of ME/CFS patients have low NKCA. However, no diagnostic test in medicine is 100% sensitive and specific: clinicians just need a test to be sensitive and specific enough. Test results coupled with history, physical exam, and clinical course together make the diagnosis.

   We encourage NIH to support research that a) can confirm or refute the finding of low NKCA in a larger population of ME/CFS patients and b) elucidate such a test's operating characteristics (i.e. sensitivity, specificity, positive predictive value, negative predictive value).

2) **2-day repeated cardiopulmonary exercise testing:**

Post-exertional malaise is considered to be a cardinal and disabling symptoms of ME/CFS by both clinicians and patients. A major feature of post-exertional malaise is the inability to repeat the same frequency, intensity, or type of activity from one day to the next or repeatedly, regularly. 2-day CPET may be able to detect and quantify this symptom.

Healthy and even sick individuals are able to reproduce certain cardiometabolic parameters within a 7% margin of error when physically exercised on two separate days, Three separate groups (4-7) have shown this is not the case for ME/CFS subjects. One or more of 4 cardiometabolic parameters can decrease from 8% to 55% from the first day's value to the second day's value.

Further studies of 2-day repeated cardiopulmonary testing in larger populations can confirm if this test can be used as an objective marker of PEM and/ or as a gold standard test for ME/CFS. Most studies have not specifically inquired subjects about presence, onset, and duration of PEM and linked cardiometablic changes to the time course of symptoms so future studies should try to correct this gap. Researchers should be aware not every ME/CFS subject will have the physical capacity to undergo CPET nor be willing to risk the adverse effects of CPET. Tests which can detect PEM in patients unable to or concerned about undergoing CPET should be devised. For comparison purposes, both sick and healthy controls should be recruited for studies.

3) **<u>Neuropsychological testing related to information processing:</u>**

Neurocognitive symptoms are common in ME/CFS and may be more disabling than physical fatigue or pain. This manifests in patients' lives in a variety of ways, for example, being unable to drive, understand/ participate in a conversation, or read and remember a book. When tested formally, diminished information processing speed, appears to be a common characteristic that distinguishes subjects from healthy or sick controls. (8) Some subjects may perform normally with no time limits but abnormalities are particularly unmasked under time pressure. Furthermore, some researchers believe that slowed information processing speed is at the root of other neurocognitive symptoms such as poor attention and memory.

Validated tests of information processing that have already shown abnormalities in some subjects, such as the simple/ complex reaction time tests in the CANTAB (9) or CalCap (10) batteries, the Paced Auditory Serial Addition Test (PASAT), or visual information processing tests, could be applied to larger populations of subjects to confirm this finding. Objective findings should also be linked to subjective symptoms. Confounding factors such as medication, sleep deprivation, and co-morbid depression will need to be accounted for in such studies (11). Finally, other than time restrictions, researchers should also consider testing subjects after they have experienced cognitive loading (e.g. a day of work or school) or chart the course of the cognitive performance over time. Patients report post-exertional malaise due to cognitive activity; in one study, subjects

took an average of 57 hours to recover from a 3-hour cognitive battery whereas healthy controls had recovered their energy in 7 hours (11).

4) **Tilt table testing:**

Orthostatic intolerance (OI) is very common in ME/CFS patients, affecting up to 80% of patients (8, 12). Consequently, OI symptoms were included as part of the IOM definition. OI can also exacerbate post-exertional malaise and impacts function significantly and independently (13); if identified, there are effective treatments available. Tilt table testing is the gold standard for diagnosing different types of OI yet the full benefits of using tilt table testing to diagnose and help guide treatment in ME/CFS has not been fully explored.

Studies exploring the prevalence of OI symptoms, the prevalence of positive tilt table tests, and the correlation of symptoms with objective tilt table testing would be informative not only for diagnostic purposes but for treatment purposes.

5) **Neuroinflammation:**

ME/CFS patients experienced many symptoms that may be related to the neurological system. Aside from problems with cognition and sleep, experienced clinicians have also observed ataxia, muscle weakness, sensory hypersensitivity, visual issues, neuropathic pain, and bowel and bladder issues (14, 15). These symptoms may be related to infection and/or inflammation of nervous tissue: in a series of autopsies, patients were found to have inflammation of the dorsal root columns of the spinal cord (16) while a neuroimaging study with a small sample size showed widespread inflammation in the brain which was correlated with neuropsychological symptoms (17). These studies warrant further follow-up.

6) **Unrefreshing sleep, heart rate variability, and sympathetic predominance:**

Unrefreshing sleep is experienced by over 90% of ME/CFS patients and remains an issue even in patients who are able to fall and stay asleep, uninterrupted, for prolonged periods (8). Patients frequently report that upon awakening, they feel as if they had not slept at all. Routine polysomnography of has not revealed any striking differences between patients and healthy controls (8). In contrast, several studies show that the autonomic system of ME/CFS subjects, as measured by heart rate variability, might be overactivated and that this might be leading to poor sleep (18-20).

This is an area that would benefit from further investigation. Subjects selected for such studies should report current unrefreshing sleep despite, often with the use of medications, no problems falling asleep or staying asleep. Natelson et al. found abnormalities primarily in those reporting being sleepier in the morning (21). Those who felt less sleepy in the morning were no or little different from healthy controls. Furthermore, physical activity the prior day improved sleep in the “less-sleepy-AM”

group while it had no benefit or even disrupted the sleep of those in the "more-sleepy-AM" group (22).

7) **Familial studies:**

A number of past studies have shown that family members of patients are at higher risk than the general population for developing ME/CFS (23, 24, 25). These studies need to be replicated and followed up. Studies of pedigrees, coupled with technologies such as genetic analysis or human leukocyte antigen (HLA) testing, could help identify markers for the disease and lead to an understanding of its pathophysiology. Such studies could also stimulate work examining prevention of ME/CFS in at-risk family members or members of the general public.

8) **Energy metabolism issues and lactate processing in muscle and brain:**

Several studies suggest that patients have problems with energy metabolism. Four different studies of 2-day repeated cardiopulmonary exercise testing show that the anaerobic threshold, the time when production of lactic acid exceeds its removal, decreases by 7% to 26% on the second day in patients (4-7). Accumulation of lactic acid results in muscle pain and fatigue. Consequently, it is not surprising that patients report being able to accomplish an activity one day but not being able to repeat it again later.

Supporting this fall in anaerobic threshold are other studies documenting issues with lactate processing. Shungu et al. in a series of studies found high levels of lactate in the cerebrospinal fluid of subjects (26-28). Newton et al. found that, after an exercise challenge, the muscles of some ME/CFS subjects retained 20 times the acid amount of healthy controls (29). Her group also linked low cerebral blood flow, which might encourage anaerobic metabolism and higher levels of lactate, with muscle pH (30).

These studies suggest an underlying mechanism that could account for both physical and cognitive fatigue in patients. As with neuropsychological testing and sleep research, subjects who are recruited for such studies need to endorse these symptoms and not merely be enrolled based on fitting a specific criterion.

9) **Post-infectious triggers:**

Up to 80% of patients report a post-infectious trigger close to the beginning of the onset of their illness. Prospective studies have shown that, following infection with a wide variety of microbes (e.g. Epstein-Barr virus, Coxiella Burnetti, Girardia, influenza), approximately 10% of patients come down with ME/CFS (31-33).

Because current diagnostic criteria require that patients must be sick for at least 6 months prior to diagnosis, researchers may be missing the early stage of the illness. One study

already suggests that the immune system of patients who have been sick less than 3 years differs from those who have been sick longer (34).

Encouraging studies to follow patients who come down with known ME/CFS-associated infections prospectively might yield answers to the etiology, pathophysiology, prognosis, and even early interventions that might prevent or ameliorate the severity of this disease.

Treatment:

Currently, not one well-established, FDA-approved treatment exists for ME/CFS. Thus, it is urgent that this area be pursued.

1) **Rituximab**

In 3 decades of ME/CFS research, no treatment has shown as much promise as rituximab. Three studies have been published supporting the effectiveness of rituximab in treating ME/CFS with two of those being trials showing about two-thirds of subjects responding positively (35-37) with no major side effects. Some individuals sustained substantial improvement, enough to return to work or school.

These studies however have consisted of small sample sizes so replication is needed. The approximately 30% of ME/CFS subjects who fit Canadian Consensus Criteria, have higher levels of immunoglobulin G subsets 1-3, and possess antibodies to certain cholinergic or muscarinic receptor might be most likely to benefit (38). Questions to be answered include what dose, frequency, and duration of rituximab works best and what types and severity of short-term/ long-term side effects are expected and how to mitigate them. Future trials should also include more detailed subjective outcome measure and objective outcome measures (e.g. 2-day CPET, pedometers to measure steps walked, return to work/ school).

2) **Anti-virals for targeted groups:**

Up to 80% of ME/CFS patients identify an infectious precipitant associated with their condition yet most do not have objective tests documenting active or acute infection. However, a subset of subjects do. Subjects with persistence of Epstein-Barr virus IgM and or evidence of chromosomally integrated human herpes virus 6 respond positively to the appropriate anti-virals (39-41). Yet, trials of anti-virals in undifferentiated groups of subjects might obscure any positive results. Replication of these studies would confirm or refute prior results.

3) **Self-management – pacing:**

Graded exercise therapy (GET) has been touted as a treatment for ME/CFS subjects. Yet in the largest trial of GET to date, in spite of lenient recovery criteria (42, 43), only 22% of subjects were considered recovered compared to 15% of subjects receiving usual care (44). Additionally, outside of trials, both experienced clinicians and up to 50% of

patients report worsening with GET (45). In contrast, pacing, a method of self-management involving balancing activity with rest and monitoring/ modifying activities to match energy levels, is recommended by many experts (46) and endorsed as the most effective treatment currently by patients in managing their condition (47, 48) with no or minimal side effects.

Yet, hardly any trials of pacing have been carried out. The UK PACE trial (49) claimed that pacing (termed "APT") conferred no benefits above that of usual care but some would contend their version of pacing is different from the type employed by patients or some clinicians. Two other studies (50, 51) suggest pacing may help decrease symptoms and increase ability to carry out activities of daily living but replication in much larger samples are needed. Identifying which components of a pacing program are most effective, who would implement such an intervention, and how pacing could complement other treatments are also other areas that warrant exploration.

4) **Isoprinosine**

Isoprinosine, an older antiviral and immunomodulator with minimal side effects, has been used for years by ME/CFS specialists for patients who present with abnormally low natural killer cell activity. It has been shown to elevate NK cell activity (52) and to improve function in some patients (53). These results need to be explored and further replicated.

One obstacle to studying isoprinosine is that is it not currently FDA-approved for any medical condition in the US. It was originally FDA-approved for subacute sclerosing panencephalitis (SSPE) but because this is a rare condition, the manufacturers did not seek to renew their approval after several years. It is obtainable in countries like Canada, Ireland, and New Zealand with a prescription.

5) **Low dose naltrexone**

Naltrexone, a medication traditionally used for the treatment of opioid and alcohol dependence, has been used off-label in low doses to treat pain, sleep, and inflammation in ME/CFS subjects for years with minimal side effects. There is some evidence naltrexone may work by decreasing the production of pro-inflammatory cytokines and neurotoxic superoxides by microglial cells (54). Low-dose naltrexone also reduces pain substantially in some patients with fibromyalgia, a common co-morbid condition in ME/CFS (55, 56).

Studies of naltrexone in ME/CFS subjects with and without fibromyalgia would be helpful to confirm the effectiveness and safety of this drug in ME/CFS.

6) **Intravenous immunogloblulin for targeted groups:**

In patients who come down with ME/CFS following a documented parvovirus infection, early treatment with IVIG in some cases has been shown to cure ME/CFS (57. 58). Similarly, a 1997 trial in Australia showed that IVIG increased function 25% above that

of placebo in adolescents (59). The few IVIG trials in adults have shown mixed results; however, a recent German study (60) demonstrated that about a quarter of ME/CFS subjects had lower IgGs whereas another 25% had elevated immunoglobulins. It is possible that the former group may benefit from IVIG whereas IVIG may have no benefit for the latter.

Research Needs:

1) **Basic Epidemiology** –

Basic facts about ME/CFS are missing due to a lack of community-based and longitudinal studies. There have only been a few large community-based studies in the US. Most study subjects have been drawn from tertiary care centers or from already diagnosed or self-identified ME/CFS subjects. Thus, we do not have as good a grasp on prevalence and incidence. Secondly, there are very few long-term studies of ME/CFS despite recognition that it is a chronic condition. The studies that do exist generally track people for less than 5 years and are not detailed in their collection of subjective or objective data. Thus, we have a mediocre grasp of co-morbidities, natural history, and prognosis.

Misconceptions about ME/CFS have also influenced the paucity of data. ME/CFS is not viewed as a fatal condition even though there have been cases of people dying with this illness (61) and three studies link it with development of cancer (62-64). Mortality data needs to be tracked and explored. ME/CFS is also not viewed as a condition associated with outbreaks even though up to 80% of cases are reported to be associated with an infectious onset and there have been reports of outbreaks in the past (65) and more recently (33). Thus, any potential outbreak-associated ME/CFS cases would not be noticed and reported.

Community-based studies are especially important for this condition, not only because studies in tertiary care might distort the true picture of this condition, but also because up 91% of people affected are estimated to be undiagnosed (66). A community-based study with a surveillance component would pick up these subjects even if they were not diagnosed by their treating clinicians.

2) **Neglected/ special subgroups:**

The overwhelming majority of subjects studied have been self-identified, middle-aged, Caucasian women of higher socio-economic backgrounds being seen in tertiary care clinics. Subject-associated factors, such as access to healthcare or a positive view of research, might account for some of this bias but clinician/ researcher-associated factors,

such as preconceptions about who might be affected or convenience sampling, might also have contributed.

Researchers should be encouraged and incentivized to recruit for subjects beyond this group. We know from other medical conditions that characteristics like age, sex, or ethnicity can affect diagnostic test characteristics, prognosis, and treatment recommendations.

a) Children/ younger people/ elderly: There appears to be two age peaks of ME/CFS onset, in the 10-20 age range and in the 30-40 age range (67). Yet the average age of most ME/CFS studies is around 50. Since the full recovery rate of ME/CFS is estimated at 5% (68), many people remain sick for years to decades. Despite this, there is only one study of patients focusing on patients over age 65 (63).
b) Men: In most studies, men account for about 25%-30% or less of subjects. Some of this might come down to biology and ME/CFS affecting the sexes disproportionately but rural studies and pediatric studies suggest the ratio is closer to 1:1 (67, 68). Studies can confirm or refute these ratios.
c) Homebound/ Bedridden patients: 25% of patients are estimated to be homebound or bedridden at any one point and up to 93% of patients experience these statuses at some point during their illness (47). Yet, except for two studies (69-71), almost all have required subjects to be able to go to a clinic, often multiple times, and few have formally included accommodations to recruit the severely ill. NIH could include supplements for technology, travel expenses, or additional staff that allow this group to be reached.
d) Ethnic minorities: The few studies specifically including ethnic minorities show that ME/CFS might affect some groups more commonly and more severely than even Caucasian groups (66). Yet most studies do not actively recruit or focus on these groups exclusively. Future studies are needed to confirm past studies' results and also to provide equity of care.
e) Lower socio-economic classes: Similar to ethnic minorities, some studies suggest the poor are disproportionately affected by ME/CFS than wealthier groups (66).
f) Pregnancy – Many women affected by ME/CFS are of child-bearing age yet there has only been one study of pregnancy in ME/CFS (72). A review article relied partly on clinician experience to give recommendations (73). Consequently, women, their families, and their providers are left with no or little answers during this critical stage of their lives. Some women also report near remission of ME/CFS during some stages of pregnancy and this could be an interesting phenomenon to study.

3) **Palliative treatment and treatment for co-morbid conditions**:

Research targeting treatments that effectively palliate common symptoms and co-morbid conditions would be valuable. For example, currently, practitioners are instructed to treat the sleep problems inherent to ME/CFS the same way as they treat sleep problems in the general population, with behavioral measures mostly. Yet, this may not be optimal as many patients do not have bad sleep habits to begin with. Experienced ME/CFS

clinicians also utilize certain sleep medications, like trazodone and zolpidem (74), yet there is no research on what may work best for patients. Similarly, ME/CFS patients with orthostatic intolerance are treated the same way as those with OI only yet some treatments for that condition, such as physical exercise, might have to be titrated more cautiously in those affected by both conditions.

4) **Pain**:

Pain is a very common symptom of ME/CFS and up to 70% of patients may have co-morbid fibromyalgia. Yet, with the exception of a few papers (75,76), there is hardly any research on the types of pain (muscle, gut, headaches, neuropathic, sore throat, etc.) patients experience, the severity of pain, its impact on function, and what treatments work best (e.g. for neuropathic pain, anecdotally, some patients have experienced relief with anti-virals). Rather studies on pain tend to conflate the different types of pain into one category, which does not provide much illumination into the symptom. Much more work needs to be done in this area.

5) Post-exertional malaise:

Post-exertional malaise (PEM) is a common, disabling, and hallmark symptom of ME/CFS yet relative to its importance, not enough research has examined this symptom in detail. Most research has focused on only one PEM symptom, fatigue, yet patients and clinicians report exacerbation of multiple symptoms as part of PEM. The few studies that have examined other symptoms suggest that patients have a paradoxically abnormal response to physical activity. Rather than improving their mood, sleep, pain thresholds, or energy, as it does for healthy people or even people with other chronic illnesses, physical activity worsens these domains (8). Secondly, most studies have focused on or introduced a physical activity stressor yet patients report that cognitive activity, emotional distress, poor sleep, orthostatic distress, infections, and even weather can affect PEM (8, 77). Thirdly, PEM studies usually last only a few days when patients report PEM can start at and last for days after a trigger is introduced. Finally, most studies have utilized only subjective outcomes yet studies with objective outcomes have found a range of abnormalities, from immunologic to autonomic (8). Future studies of PEM should consider these under-researched aspects and incorporate them into the research design.

6) **Outcome measures relevant to ME/CFS patients**:

In 2012, Haywood et al. (78) performed a systematic review of patient-reported outcome measures (PROMs) used in ME/CFS studies and concluded that a) psychometric traits like validity, reliability, responsiveness etc. had not been established in ME/CFS patients for the outcomes used and b) researchers had not integrated the input of patients in selecting or designing outcome measures. While generic measures such as the Short Form-36 (SF-36) are valuable for their usefulness in comparing ME/CFS patients to patients with other conditions, the lack of any ME/CFS-specific PROMs means that many aspects of ME/CFS are overlooked. For example, current sleep PROMs do not

focus on unrefreshing sleep and there are no PROMs covering the phenomenon of PEM comprehensively. Furthermore, objective measures that correspond with subjective improvement need to be established for ME/CFS. It is not certain how well common measures such as the 6-minute walk test work for ME/CFS. Finally, concrete, measurable functional outcomes such as number of hours worked need to be considered. Downstream, the lack of good established outcome measures hinders the Food and Drug Administration's ability to draw the attention of and to guide pharmaceutical companies (79).

7) **Validated questions, questionnaires, and physical examination findings for bedside diagnosis**:
Although the Institute of Medicine published a Clinician Guide with interview questions, questionnaires, and physical examination findings that healthcare providers can use to diagnose ME/CFS now (80), many of those items were based on expert opinion and consensus. Consequently, the IOM recommended, as an urgent need, that "a toolkit [comprising such elements and] appropriate for screening and diagnosing patients with myalgic encephalomyelitis/chronic fatigue syndrome" (8) be developed and tested. NIH should especially prioritize diagnostic questions, questionnaires, and procedures that can be performed easily and inexpensively at the bedside in a busy clinic environment.

8) **Other symptoms experienced by ME/CFS subjects:**
ME/CFS patients and clinicians report a host of other symptoms that have not been or are only rarely studied by researchers. For example, in a survey of 561 subjects (47), over 40% reported flu-like symptoms, gastrointestinal problems, temperature intolerance (feeling hotter or colder than others), or hypersensitivity to various stimuli as "major problems" independently yet little formal research has been published on these symptoms. The Canadian Consensus Criteria and Myalgic Encephalomyelitis – International Consensus Criteria are two other resources that list under-studied symptoms.

Continuing Challenges:

1) **Some case definitions may be too broad and all case definitions need validation:**
Although the Fukuda 1994 criteria has been the most widely used criteria in the last 3 decades, many in the ME/CFS community are concerned that it may be overly broad and select for subjects who are quite different from another and/or are actually affected by another medical condition. Therefore, a number of case definitions have been with the most recent one being the Institute of Medicine's Systemic Exertion Intolerance Disease (SEID). To clarify this situation, studies validating existing definitions, comparing how they perform head-to-head, relating them to one another (e.g. are definitions recruiting subjects with entirely different conditions or variations of the same condition?), and linking them with objective findings would be invaluable.

In the absence of solid evidence, we advise NIH to defer from requiring investigators to use any one specific definition. Rather, they should be encouraged to assist the ME/CFS community in finding the most valid definition(s) possible.

2) **Heterogeneity generated by case definitions and lack of subgrouping lead to conflicting/ contradictory study results and decrease comparability across studies:**
Currently all the case definitions for ME/CFS involve polythetic criteria, that is, subjects may qualify for any case definition via different symptom combinations. To decrease the heterogeneity this creates both within and across studies, NIH should request that researchers elaborate on the specific symptoms used to recruit subjects or that their subjects experienced. For example, regardless of the definition used, all subjects were affected by PEM, unrefreshing sleep, fatigue and slow information processing speed OR that X % of subjects in this study experienced sleep, and Y% experienced problems thinking, etc. This would allow grant reviewers and readers a better sense of who exactly constituted a study's subjects and permit easier comparisons between studies.

Another way to reduce heterogeneity is for researchers to focus on specific subgroups, as defined, for example, by demographic traits, illness onset type, duration of illness, lack of or presence of certain co-morbidities, and/ or specific test abnormalities like low natural killer cell activity or inability to reproduce cardiometabolic parameters.

3) **Current study subject recruitment strategies are biased towards the 10% of patients who already have a diagnosis.:**
Our understanding of ME/CFS is limited and may even be distorted by the clinic- or convenience-based (e.g. support-group based) subject recruitment strategies used in almost all studies. Up to 91% of people affected by ME/CFS may not have received any diagnosis or a correct diagnosis from their regular physician and of the ones who do, multiple physician visits and months-years often pass before they obtain an answer (8). Although expensive, resource-demanding, and time-consuming, community-based studies that actively and randomly find cases are necessary to give a clear picture of ME/CFS. Certain groups, such as men, ethnic minorities, and the poor, should be oversampled intentionally to assure adequate representation.

4) **Collection and publication of different types of data at varying levels of detail by researchers impedes creation of a clear, accurate picture of ME/CFS and decreases comparability among studies:**
In March of 2012, several members of the US CFS Advisory Committee collaborated with the Centers for Disease Control and Prevention to publish a paper describing minimal and additional data elements that should be included in every ME/CFS study (81). That paper should be used as a starting point to standardize data collection and publication in this field.

5) **Collaboration and sharing of data, resources, and expertise among different institutions will accelerate progress:**

We applaud the National Institute of Neurological Disorders and Stroke's recent decision to create a research consortium of universities and institutions to study ME/CFS. The lack of funding, resources, and career support, both externally and from their own institutions, has often meant researchers cannot study this medical conditions as broadly or as deeply as they would prefer. A consortium spanning multiple institutions and groups across the US would help accelerate progress in this field by, for example, recruiting adequate numbers of subjects so that solid conclusions can be made and exploiting resources and expertise unique to each site to answer questions across sites.

6) **To decrease confounding, studies need to take into account the impact co-morbidities may have on results:**

Many ME/CFS patients are affected by other medical conditions. Common co-morbidities include fibromyalgia, hypothyroidism, obstructive sleep apnea, orthostatic intolerance, depression, anxiety, and irritable bowel syndrome. Yet, most studies have not considered if and how these co-morbidities may affect results. For example, Natelson et al. found, counterintuitively, that ME/CFS subjects without depression experienced more cognitive problems than those with depression (83). This finding supported the conclusion that ME/CFS is not the same disease as depression. NIH should encourage researchers to think about the effect of co-morbidities in study design, analysis, and interpretation. Conversely, researchers studying co-morbidities frequently found in ME/CFS could also be encouraged to screen their subjects for ME/CFS. This latter strategy could increase the number of investigators interested in this condition and generate new research avenues to explore.

7) **Studies using only healthy controls will not help clinicians to distinguish ME/CFS patients from other patients with similar clinical presentations nor help researchers separate out epiphenomena from the true effects of ME/CFS:**

Many ME/CFS studies have recruited age- and sex-matched healthy controls. These studies show how ME/CFS patients differ from healthy people yet, in the clinic, the question healthcare providers usually face is not whether the patient is healthy or not but rather what medical condition(s) or situation(s) is causing distress for the patient. Thus, NIH should support studies that also compare ME/CFS subjects to subjects who might present similarly at the doctor's office. Examples might include subjects who have delayed recovery from a variety of infections, who have chronic fatigue after undergoing cancer chemotherapy successfully, who are healthy but physically sedentary, or who are healthy but suffer from primary insomnia. In the latter two cases, such controls can help account for findings that are epiphenomena, i.e. existing because of physical inactivity or insomnia itself, rather than uniquely due to ME/CFS.

8) **<u>Lack of awareness and appropriate education about ME/CFS results in challenges recruiting and retaining researchers and attracting funding to this field.</u>**

Only about a third of medical schools (84) even mention ME/CFS superficially and only about 40% of medical textbooks (85) include any information. Furthermore, misconceptions and biases about the condition continue to exist. Researchers will not be drawn to a field if they have never heard of it, learn inaccurate disparaging information about it, are discouraged (86,87) from pursuing it by their peers and superiors, and cannot find a strong support system providing them with potential mentors/ collaborators, resources, and support. While a dedicated cadre of researchers exists currently, there are not enough of them and many are aging or retiring without an adequate number of replacements. Likewise, funders, whether governmental, nonprofit, for-profit, or pharmaceutical often are not familiar with ME/CFS. For example, even in recent years, other than the Office for Research in Women's Health, few NIH institutes have stepped up to the plate to claim ME/CFS for their research portfolios and some institutes, like the National Institute on Aging, have even withdrawn support even though there is a pressing need for research on aging and ME/CFS.

We applaud the positive steps NIH has taken, especially over the last year, but hope these are not only continued but expanded. Extramurally, for example, NIH could educate researchers about and mention ME/CFS as an under-researched, emerging area in conferences, online webcasts, newsletters, listservs, or other media they control or are involved in. Even if NIH cannot cover all the complexity or details of ME/CFS, just mentioning ME/CFS might pique the interest of readers, watchers, and listeners. Training and career development grants targeting both early stage as well as mid-career investigators are needed. The former would assist junior scientists to jumpstart their careers and the latter would allow more experienced scientists to contribute their expertise to this field. Loan forgiveness programs are yet another avenue to attract professionals.

Intramurally, the awareness and education of NIH-associated staff, including program officers, institute senior officials, and grant reviewers, probably reflects that of the mainstream scientific community. Consequently, it is vital NIH staff are appropriately and regularly educated about ME/CFS, especially with staff turnover or changes. Otherwise, grant submissions may not be given adequate guidance, directed to the appropriate review section, or receive a fair and thorough review. The State-of-the-Knowledge Conference held by NIH in 2011 to promote discussion and learning between NIH staff and extramural researchers/ clinicians was very useful and some version of it could be repeated in the future.

National Institute of Health – RFI: Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Bibliography

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