MEadvocacy Comments

Rejecting ICD-10-CM Proposal Changes for
Chronic Fatigue Syndrome and Myalgic Encephalomyelitis
and the Addition of Systemic Exertion Intolerance Disease

Revised Version - November 2, 2018

Prepared by advocate Jerrold Spinhirne

Addressing the issue of whether the existing ICD-10-CM reflects current scientific knowledge regarding chronic fatigue syndrome

From the 2017 International Association for CFS/ME (IACFS/ME) "Proposal for modifications to ICD-10-CM for Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, and Postviral fatigue syndrome." (IACFS/ME, 2017):

> *The existing ICD-10-CM classification for these terms [CFS, ME, PVFS] especially the classification of chronic fatigue syndrome with unspecified chronic fatigue, does not reflect current scientific knowledge, best clinical practices, or the 2015 report of the National Academy of Medicine concerning this condition.*

Comment: Current scientific knowledge of Chronic Fatigue Syndrome (CFS) is based primarily on research using the 1988 Holmes definition of CFS (Holmes, 1988) and the 1994 Fukuda definition of CFS. (Fukuda, 1994) The 2005 Reeves definition of CFS (Reeves, 2005), referenced in the IACFS/ME proposal, was subsequently determined by the Centers for Disease Control and Prevention (CDC) (Reeves, 2007) to increase the 2003 estimated prevalence for Fukuda CFS (Reyes, 2003) by 10 times, from 0.235 to 2.54%, and became disused in research as overly inclusive.

The 1988 Holmes paper defined CFS as, "*an operational concept designed for research purposes that physicians must recognize not necessarily as a single disease but as a syndrome – a complex of potentially related symptoms that tend to occur together – that may have several causes*." (Holmes, 1988)

As such, CFS was defined as a diagnosis of exclusion. As Holmes et al. stated, *"Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination, and appropriate laboratory findings."* (Holmes, 1988)

The 1994 Fukuda paper was presented as *"a conceptual framework to guide the development of studies relevant to the chronic fatigue syndrome."* As such, CFS was again defined as a diagnosis of exclusion. As Fukuda et al. stated, *"Diagnosis of the chronic fatigue syndrome can be made only after alternative medical and psychiatric causes of chronic fatiguing illness have been excluded."* (Fukuda, 1994)

In a 2010 paper (Switzer, 2010), the CDC stated that symptoms and signs such as those allowed by the 2003 Canadian Consensus Criteria (CCC) definition of ME/CFS (Carruthers, 2003) *"may signal the presence of a neurologic condition considered exclusionary for CFS."*

As a diagnosis of exclusion based on self-reported symptoms, and never redefined more specifically, the US ICD-CM has always classified CFS as an ill-defined condition – first under 780.71 under Symptoms, Signs, and Ill-Defined Conditions in ICD-9-CM; then as R53.82 in Chapter 18 of ICD-10- CM, Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, under R53 Malaise and fatigue.

In ICD-10-CM, Chronic fatigue syndrome NOS is listed under R53.82 Chronic fatigue, unspecified as a more specific diagnosis than chronic fatigue, unspecified and with an Excludes1 note for postviral fatigue syndrome G93.3.

This classification is consistent with research showing CFS to be heterogeneous requiring more specifically defined subtypes:

> *Chronic fatigue syndrome (CFS) is a heterogeneous illness characterized by a high prevalence of psychiatric problems.* (Natelson, 1995)

> *The notion that patients currently diagnosed as having CFS constitute a single homogeneous class was rejected.* (Hickie, 1995)

> *Criteria-based approaches to the diagnosis of CF and related syndromes do not select a homogeneous patient group.* (Wilson, 2001)

> *CFS is a heterogeneous multifactorial disease characterised by severe fatigue and an inability to function at optimal levels [1].* (Brenu, 2010; See the paper for reference cited.)

> *Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating illness characterized by post-exertional malaise (PEM), sleep dysfunction, and cognitive impairment [1, 2] [Fukuda,1994; IOM, 2015]; however, individuals with this illness present with significant symptom heterogeneity.* (Huber, 2018)

However, more homogeneous subtypes of CFS have never been formally defined. Research using the Fukuda definition of CFS with neurological findings, therefore, can only apply to undefined subtypes of CFS, rather than the heterogeneous CFS diagnosis as a whole.

It is important to note that Fukuda CFS research subjects, except in rare cases, are not evaluated for ME. What may appear to be a subset of CFS in studies with neurological findings may actually be ME subjects mislabelled as CFS subjects. There is no way to know unless subjects are evaluated to see if they meet the ME International Consensus Criteria (ICC). (Carruthers, 2011; Carruthers, 2012)

Significantly, the 2014 Japanese study Nakatomi et al. finding evidence of neuroinflammation used ME subjects meeting the ICC. (Nakatomi, 2014) The Nakatomi et al. neuroinflammation study specifically is an ME study, not a CFS study. The subjects also met the less specific

Fukuda criteria, but the results can only be properly applied to people with ME meeting the ICC, not the broader Fukuda CFS group.

Typically CFS subjects aren't screened for ME. This means the results of many Fukuda CFS studies may be influenced by the inclusion of mislabelled ME subjects. According to ICC guidelines, people who meet the IC criteria have ME and should not also be given the less specific CFS diagnosis. From the 2012 IC Primer:

> *Patients diagnosed using broader or other criteria for CFS or its hybrids (Oxford, Reeves, London, Fukuda, CCC, etc.) should be reassessed with the ICC. Those who fulfill the criteria have ME; those who do not would remain in the more encompassing CFS classification.* (Carruthers, 2012)

For thirty years, research on CFS repeatedly has shown the need for defining more homogeneous subsets of CFS. In study after study, the authors suggest their findings as a possible physical basis for subtyping CFS. Yet subsequent CFS research continues to use the nonspecific Fukuda criteria making results difficult to interpret or apply to an identifiable patient group.

Inexplicably, the most obvious identifiable group within CFS is ignored – people actually with ME but misdiagnosed with CFS. This identifiable group has already been well-defined by the 2011 ICC and 2012 IC Primer. Doctors and researchers simply need to recognize that it is irrational and counterproductive not to separate people with ME from the broader diverse CFS group.

Separating ME from CFS is not only common sense, but would allow more specific medical treatment for people with ME and would also remove a highly confounding factor from research studies. As the 2012 IC Primer states concerning research:

> *The logical way to advance science is to select a relatively homogeneous patient set that can be studied to identify biopathological mechanisms, biomarkers and disease process specific to that patient set, as well as comparing it to other patient sets. It is counterproductive to use inconsistent and overly inclusive criteria to glean insight into the pathophysiology of ME if up to 90% of the research patient sets may not meet its criteria (Jason 2009). Research on other fatiguing illnesses, such as cancer and multiple sclerosis (MS), is done on patients who have those diseases. There is a current, urgent need for ME research using patients who actually have ME.* (Jason, 2009; Caruthers, 2012)

The 2015 National Academy of Medicine (NAM) report (IOM, 2015), written when the NAM was known as the Institute of Medicine (IOM) cannot be said to apply to CFS because the report redefines an ambiguous mixed condition, ME/CFS – combining myalgic encephalomyelitis (ME), a separate neurological disease defined by the 2011 ME-ICC (Carruthers, 2011), with CFS defined by the 1994 Fukuda criteria. (Fukuda, 1994)

The IOM report acknowledges that ME and CFS are separate conditions in the opening paragraph on page 1, but then combines the two incompatible diagnoses as one because they have "similar symptoms."

Myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are serious, debilitating conditions that impose a burden of illness on millions of people in the United States and around the world.

Over a period of decades, clinicians and researchers developed separate case definitions and diagnostic criteria for ME and CFS, although the terms denote conditions with similar symptoms.

For the purposes of this report, the umbrella term "ME/CFS" is used to refer to both conditions. (IOM, 2015)

It is flawed scientific reasoning to combine two incompatible, mutually exclusive diagnostic groups into a single group creating a muddle.

Because neither new research using undefined subsets of CFS nor the 2015 IOM report apply to the heterogeneous group of CFS patients as a whole diagnosed by the 1994 Fukuda CFS criteria, the existing ICD-10-CM does reflect current scientific knowledge of CFS.

Addressing the issue that changes should be made to the current classification of CFS as R53.82

From the IACFS/ME proposal:

Rationale for each of these recommendations:

a) Separating chronic fatigue syndrome from chronic fatigue, unspecified: For the last 3 decades in the United States, chronic fatigue syndrome (CFS) has been recognized as an individual diagnostic entity in its own right and not merely an individual symptom. Every CFS case definition that has been used in the United States includes symptoms beyond only chronic fatigue. [1] For example, the most used diagnostic case definition, Fukuda 1994, requires severe, disabling fatigue of at least 6 months accompanied by at least 4 out of 8 other symptoms (e.g. muscle pain, unrefreshing sleep, problems with concentration, sore throat, etc.). Consequently, it is medically inaccurate to classify CFS under "chronic fatigue, unspecified." Doing this is the equivalent, for example, of classifying asthma under "cough, unspecified" merely because coughing may be one symptom of asthma.

Comment: Although the term CFS has, indeed, been used as if it were a distinct diagnostic entity, CFS has never been formally case-defined as such. The Fukuda definition of CFS, a diagnosis of exclusion that selects a heterogeneous group of patients and excludes recognizable neurological disorders, was still in use for the diagnosis of CFS until July 2017 when replaced on the CDC website with a link to the 2015 Institute of Medicine report on ME/CFS (SEID). (CDC, 2017) "Information for Healthcare Providers" based on the IOM report was added in July 2018. (CDC, 2018a)

That CFS requires more symptoms for diagnosis than chronic fatigue is already recognized in ICD-10-CM by placing CFS under chronic fatigue, unspecified as a more specific term. CFS

logically was placed under chronic fatigue, unspecified in ICD-10-CM because the only symptom all patients diagnosed with CFS have in common is self-reported chronic fatigue.

That chronic fatigue syndrome NOS cannot be assumed to be postviral is recognized by the note added to R53.82, "Excludes1: postviral fatigue syndrome (G93.3)." Patients only meeting CFS criteria cannot also be coded under the Diseases of the nervous system code G93.3 which includes Benign myalgic encephalomyelitis (ME) as a more specific diagnosis under Postviral fatigue syndrome (PVFS).

The existing separate, mutually exclusive codes for ME and CFS are consistent with the Fukuda definition of CFS as a diagnosis of exclusion. Additionally, separate, mutually exclusive codes for ME and CFS are consistent with ME-ICC which call for the removal of patients who satisfy the ICC from the broader category of CFS:

> *The purpose of diagnosis is to provide clarity. The criterial symptoms, such as the distinctive abnormal responses to exertion can differentiate ME patients from those who are depressed or have other fatiguing conditions. Not only is it common sense to extricate ME patients from the assortment of conditions assembled under the CFS umbrella, it is compliant with the WHO classification rule that a disease cannot be classified under more than one rubric.* (Carruthers, 2012)

Without the existing mutual Excludes1 notes for ME and CFS, doctors would be allowed to give both the ME and CFS codes for a single patient without first ruling out ME before making the broader CFS diagnosis. As stated above, such a double diagnosis would be inconsistent with both the International Consensus diagnostic criteria for ME and Fukuda diagnostic criteria for CFS.

From the IACFS/ME proposal:

> *Reinforcing this point, a 2015 report by the National Academy of Medicine (NAM) on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) noted that ME/CFS is different than medically unexplained chronic fatigue, that the level of fatigue is "more profound, more devastating, and longer lasting that [sic] that observed in patients with other fatiguing disorders," and that "this complex illness presentation entails much more than the chronic presence of fatigue."*

Comment: The quality of fatigue reported by some patients given the broad CFS diagnosis may indeed be "more profound, more devastating." However, self-reported fatigue of any type is not a required symptom of ME, according to descriptions of the disease in the medical literature and the ICC.

A single new diagnostic group simply cannot replace two distinct diagnoses, such as ME and CFS, even though they have some similar symptoms in common. (Twisk, 2016) Therefore, the term "ME/CFS" as used in the IOM report – combining ME, an established neurological diagnosis not requiring fatigue as a symptom, and CFS, a heterogeneous diagnosis of exclusion, under a single term – is a misnomer.

The meaning of the term "ME/CFS" as used in the IOM report in different contexts is unclear. Sometimes "ME/CFS" appears to be used as an umbrella term referring to both of the separate, mutually exclusive diagnoses ME and CFS. At other times, "ME/CFS" appears to be used to

refer to a vague single illness. As the IOM report states that what it considers to be "ME/CFS" requires the symptom of self-reported fatigue and does not have the characteristic features of ME, inflammation of the central nervous system and myalgia, it appears that what the IOM report calls "ME/CFS" is not ME but, in fact, a fatigue-based condition more similar to CFS.

> *The committee deemed the term "myalgic encephalomyelitis," although commonly endorsed by patients and advocates, to be inappropriate because of the general lack of evidence of brain inflammation in ME/CFS patients, as well as the less prominent role of myalgia in these patients relative to more core symptoms.* (IOM, 2015, page 11, comments on Recommendation 3)

An incongruent term such as "ME/CFS" combining diagnoses from different sections of the ICD is not classifiable by WHO rules. Also, the term "ME/CFS" as defined by the CCC, does not require "profound fatigue" for diagnosis but "a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level." (Carruthers, 2003) It is, therefore, unclear what the term ME/CFS refers to as used by the IOM report in different contexts. Sometimes ME/CFS is used as an umbrella term for the separate diagnoses ME and CFS. However, other times the same term is used as if it identifies a single diagnosis indeterminately combining elements of both ME and CFS.

From the IACFS/ME proposal:

> *Given that CFS is the diagnostic code used in the United States for the disease ME/ CFS, it is important that CFS not be reduced to one of its symptoms or use the same code as the symptom of chronic fatigue. We recommend that CFS no longer share a code with chronic fatigue, unspecified.*

Comment: The assumption that the CFS diagnostic code is used for "ME/CFS" in the US is unfounded and misleading. CFS, before the 2017 revision of the CDC CFS website, was diagnosed using criteria based on the Fukuda CFS definition and coded as CFS 780.71 in ICD-9-CM with no reference to ME, and as CFS R53.82, after October 1, 2015, in ICD-10-CM with the code for PVFS and ME, G93.3, specifically excluded.

The code recommended for ME/CFS as defined by the CCC is the ME code G93.3, not the CFS code. (Carruthers, 2005). Again, that CFS is already a more specific term than chronic fatigue, unspecified is shown by its placement in R53.82 under chronic fatigue, unspecified as a more specific term. **Allowing CFS now to be classified otherwise would require a new case definition for CFS**.

The reclassification of CFS is a somewhat moot issue now because since July 2017, the CDC has replaced the Fukuda diagnostic criteria for CFS with the IOM SEID criteria for a new fatigue-based disorder the CDC is calling "ME/CFS" (CDC, 2017). New CDC "ME/CFS" (SEID) despite the name, is a much broader diagnosis than ME diagnosed using the ICC, CFS diagnosed using the Fukuda criteria, and ME/CFS diagnosed using the CCC. New CDC "ME/CFS" (SEID), as an incongruent hybrid term, cannot be classified following ICD rules.

Addressing the issue whether CFS should be moved to the neurological chapter

From the IACFS/ME proposal:

> *b) Moving CFS to the neurological chapter: There is substantial scientific evidence of neurological impairment in ME/CFS. [3] Consequently, the World Health Organization and all countries except for the United States classify CFS under G93.3 in the neurological chapter of ICD-10, along with "Postviral fatigue syndrome" and "Myalgic encephalomyelitis." Furthermore, in developing ICD-11, the World Health Organization explicitly recommended that, "...in the absence of compelling evidence mandating a change, legacy should trump with regard to the question of moving certain conditions to new chapters."[4] WHO staff have stated that chronic fatigue syndrome will not be placed in the Symptoms and Signs chapter in the forthcoming ICD-11. [5]*

Comment: As stated above, any "substantial scientific evidence of neurological impairment in ME/CFS" must be based on research using undefined subsets of heterogeneous CFS, or CCC-defined ME/CFS that cannot be considered to be CFS.

It is incorrect and highly misleading to claim "*Consequently, the World Health Organization and all countries except for the United States classify CFS under G93.3 in the neurological chapter of ICD-10, along with "Postviral fatigue syndrome" and "Myalgic encephalomyelitis.*" "

A check of the WHO ICD-10 classification G93.3 will show that CFS is not listed there with PVFS and ME.
http://apps.who.int/classifications/icd10/browse/2016/en#/G93.3

CFS was added to the index volume only of the WHO ICD in 1992 referenced to G93.3 when CFS was defined by the now little-used Holmes definition, which required more symptoms and signs to diagnose a case of CFS than required by the subsequent Fukuda definition of CFS.

The coded terms remain PVFS and ME. Therefore, in any case, using the G93.3 code requires PVFS diagnosed using PVFS criteria or ME diagnosed using ME criteria. **CFS diagnosed using less specific, non-neurological CFS criteria does not qualify for the G93.3 code.** CFS has never been listed in the tabular volume, the one with the codes, of the WHO ICD under any classification.

Claiming that the proposed ICD-11 will not place CFS in the Symptoms and Signs chapter is hardly evidence that CFS is a neurological disorder of the brain (G93) when CFS has never been defined or diagnosed as such.

How then can the heterogeneous diagnosis of exclusion, CFS, be considered as neurological and placed in the neurological chapter of US ICD-10-CM under G93, Other disorders of the brain? Where is the new compelling evidence to reclassify CFS? What in the Fukuda definition of CFS, which according to the CDC excludes conditions with neurological signs and symptoms from the CFS diagnosis, justifies reclassifying CFS in the ICD-10- CM Chapter 6, Diseases of the nervous system under G93, Other disorders of brain?

Addressing the issue whether NOS should be removed from the current term "chronic fatigue syndrome NOS"

From the IACFS/ME proposal, continuing rationale b):

> *Further, in ICD-10, the term is "chronic fatigue syndrome," not "chronic fatigue syndrome, NOS." The rationale given by NCHS in 2011 for adding the term "NOS" (not otherwise specified) to chronic fatigue syndrome in ICD-10-CM was that it indicates that CFS is "not specified as being due to a past viral infection." [6] However, as discussed below, CFS definitions do not preclude a viral onset.*
>
> *Thus, in accordance with scientific findings and international standards, we recommend placing CFS under G93.3 in the Neurological chapter. We also recommend removing the term "NOS" from "chronic fatigue syndrome" since the rationale for its addition is not correct and more specific versions of CFS have not been defined.*

Comment: Given the heterogeneous nature of CFS and the lack of a requirement for a viral infection to precede the onset of CFS symptoms in the Holmes and Fukuda CFS definitions (Holmes, 1988; Fukuda, 1994), the 2011 NCHS rationale for adding NOS to the CFS entry that CFS is "not specified as being due to a past viral infection" is correct.

In fact, the 1994 Fukuda CFS definitional paper does not recommend testing for viral infections when diagnosing CFS:

> *In clinical practice, no additional tests, including laboratory tests and neuroimaging studies, can be recommended for the specific purpose of diagnosing the chronic fatigue syndrome. Tests should be directed toward confirming or excluding other etiologic possibilities. Examples of specific tests that do not confirm or exclude the diagnosis of the chronic fatigue syndrome include serologic tests for Epstein-Barr virus, retroviruses, human herpesvirus 6, enteroviruses, and Candida albicans; …* (Fukuda, 1994)

Indeed, "CFS definitions do not preclude a viral onset," however, they also do not preclude any type of sudden or insidious onset. The possibility of a viral infection preceding the development of CFS symptoms does not mean such a viral infection has occurred. Therefore, the NCHS rationale is appropriate, and NOS, indicating that a preceding viral infection has not been confirmed, should remain after the R53.82 CFS entry.

The NOS differentiates the CFS diagnosis, based on self-reported symptoms, from the more specific neurological diagnosis of postviral fatigue syndrome (PVFS) for cases in which a viral infection is confirmed preceding, and linked to, a prolonged fatigue syndrome, but the patient does not meet the more specific criteria for ME. As noted in Ramsay and Dowsett's 1990 study "Myalgic encephalomyelitis – a persistent enteroviral infection?" regarding ME:

> *First, there has been a failure to distinguish the syndrome from post-viral debility following Epstein-Barr mononucleosis, influenza and other common fevers. Compared with ME, these lack the dramatic effect of exercise upon muscle function, the multisystem involvement, diurnal variability of symptoms and prolonged relapsing course.* (Dowsett, 1990)

Addressing the issue if the G93.3 title term should be modified

From the IACFS/ME proposal:

> c) Modifying the G93.3 title term: Part of the stated rationale for not following the ICD-10 and classifying CFS at G93.3 in the neurological chapter of ICD-10-CM was the view that ME is postviral while the term "Chronic fatigue syndrome" was intended for cases where "the physician has not established a post viral link."[7] However, ME definitions explicitly include non-viral precipitants such as bacteria and parasites and CFS definitions allow viral precipitants. Further, while ME and CFS often occur after an infection or infection-like episode, a variety of other triggers such as immunization, pregnancy, surgery, and physical trauma have also been observed.

Comment: There was sufficient evidence of viral involvement in 1969 for the WHO to include Benign myalgic encephalomyelitis (ME) under Postviral fatigue syndrome as a more specific diagnosis.

The rigorous 1990 study by Drs. A. Melvin Ramsay and Elizabeth Dowsett, "Myalgic encephalomyelitis – a persistent enteroviral infection?," using 420 well-characterized ME subjects, supported the association of ME with persistent non-polio enteroviruses (NPEV).

> Coxsackie B neutralization tests, in 205 of these, demonstrated significant titres in 103/205 (50%), while of 124 additionally investigated for enteroviral IgM, 38/124 (31%) were positive. (Dowsett, 1990)

The 2011 ICC, designed to be used as both diagnostic and research criteria for the neurological disease ME, states:

> Most patients have an acute infectious onset with flu-like and/or respiratory symptoms. A wide range of infectious agents have been reported in the subsets of patients,including xenotropic murine leukaemia virus-related virus (XMRV) [79] and other murine leukaemia virus (MLV)-related viruses [80], enterovirus [81-83], Epstein–Barr virus [84], human herpes virus 6 and 7 [85-87], Chlamydia [88], cytomegalovirus [89], parvovirus B19 [90] and Coxiella burnetti [84]. Chronic enterovirus infection of the stomach and altered levels of D Lactic acid-producing bacteria in the gastrointestinal tract have been investigated [82, 91]. (Carruthers, 2011; See the paper for references cited.)

The unreferenced claim by the IACFS/ME proposal, "*ME definitions explicitly include non-viral precipitants such as bacteria and parasites and CFS definitions allow viral precipitants,*" is not supported by the 2011 definitional paper "Myalgic encephalomyelitis: International Consensus Criteria" published in the Journal of Internal Medicine. Bacteria are only mentioned in the statements, "*Some viruses and bacteria can infect immune and neural cells and cause chronic inflammation.*" and, as quoted above, "*Chronic enterovirus infection of the stomach and D Lactic acid-producing bacteria in the gastrointestinal tract have been investigated.*" "Parasites" are not mentioned anywhere in the ICC. (Carruthers, 2011)

The 2012 "Myalgic Encephalomyelitis – Adult & Paediatric: International Consensus Primer for Medical Practitioners," supplemental information for clinicians, rather than an ME definitional paper, states on page 2 under "Infectious agents associated with ME":

> *Bacteria: Chlamydophila pneumonia [32], Mycoplasma [33], Coxiella burnettii [27]. It is unclear whether these infectious agents initiated ME or are opportunistic and developed due to an impaired immune system.* (Carruthers, 2012)

Finding these bacteria present in some ME patients does not imply that ME is not predominantly associated with a preceding and persistent viral infections. As noted in the IC Primer, these infectious agents in ME patients may be opportunistic and develop due to the impaired immune system found in many ME patients.

The only mention of "parasites" in the IC Primer is in the listing of laboratory tests on page 11 to consider when diagnosing ME, "stool for WCB - D-lactic acid bacteria balance, ova & parasites." Testing for possibly opportunistic infections is not evidence that ME is not predominantly associated with preceding and persistent viral infections.

Neither does the 1986 Ramsay definition of ME (Ramsay, 1986) nor the ME research definition used in Ramsay and Dowsett's 1990 paper (Dowsett, 1990) "explicitly include non-viral precipitants such as bacteria and parasites." Therefore, the above claim regarding causal "non-viral precipitants" in ME definitions appears to be misleading and unsupported by the primary ME definitions.

Again, that CFS definitions allow the possibility of "viral precipitants" does not imply that the heterogeneous CFS diagnostic group can be regarded as postviral. As stated above, the 1994 Fukuda CFS definitional paper does not recommend testing for viral infections when diagnosing CFS.

> *Examples of specific tests that do not confirm or exclude the diagnosis of the chronic fatigue syndrome include serologic tests for Epstein-Barr virus, retroviruses, human herpesvirus 6, enteroviruses, and Candida albicans; ...* (Fukuda, 1994)

The availability of the less specific CFS diagnosis R53.82 does provide "where the physician has not established a post viral link" a diagnostic code for patients for whom a linked preceding viral infection has not been confirmed, and who do not meet the more specific requirements of the ICC ME diagnosis. That both ME and the symptoms of CFS sometimes occur after a triggering event does not mean that ME does not have precipitating and persistent viral involvement, or that CFS should be considered neurological and postviral.

As the arguments for considering CFS as a neurological postviral disorder of the brain are either invalid or not supported by any new compelling evidence that apply to the CFS diagnosis as a whole, rather than to only an undefined subset, there is no justification for modifying the G93.3 title term and creating an unwarranted disparity between the US ICD-10-CM and the WHO ICD-10.

Ironically, the proposed new umbrella title term for G93.3, "Postviral and related fatigue syndromes" will be inappropriate for ME, listed under G93.3 since 1969. "Myalgic encephalomyelitis" is proposed to be re-coded as G93.32 under the new G93.3 group title.

The other three diagnoses under the new umbrella term – SEID, PVFS, and CFS – are all based on the symptom of self-reported chronic fatigue. PVFS includes "postviral" in the name, but SEID and CFS need not have a confirmed preceding viral infection for diagnosis. This makes SEID and CFS "related fatigue syndromes" only. However, as discussed above, there is substantial research evidence that ME, which occurs in documented epidemic clusters, cannot be considered "postviral" but is associated with persistent, ongoing viral infections. As ME specialist Dr. Elizabeth Dowsett said in 1992:

> **'Post-viral fatigue syndrome'**, *another British name, describes one essential feature (the association of the illness with viral infection) but **gives the impression that the infection was antecedent rather than, as we now know, persistent.** [Emphasis added] I prefer to use the more specific term 'myalgic encephalomyelitis' as it emphasizes the essential encephalitic component of the illness, the muscle pain, and the close clinical and epidemiological similarity to poliomyelitis.* (Dowsett, 1992)

The ICC authors also recognize the probability that persistent viruses play role in the etiology of ME:

> *A growing body of evidence suggests that a primary cause of ME is neuropathic viruses that may infect neurological and immune cells and damage the capillaries and micro-arteries in the CNS bed causing diffuse brain injury. The initial infection may cause profound dysregulation of immune system pathways that may become chronic or cause autoimmunity even when the level of the infectious agent is reduced. [35]* (Carruthers, 2012; See the IC Primer for the reference cited.)

Also, it is incorrect to consider ME a "related fatigue syndrome." As discussed above, self-reported fatigue has never been a required symptom for the diagnosis of ME. Nor do the ICC require self-reported fatigue of any type for the diagnosis of ME stating:

> *Fatigue in other conditions is usually proportional to effort or duration with a quick recovery and will recur to the same extent with the same effort or duration that same or next day. The pathological low threshold of fatigability of ME described in the following criteria often occurs with minimal physical or mental exertion and with reduced ability to undertake the same activity within the same or several days.* (Carruthers, 2011)

As ME can be considered neither as postviral nor as a fatigue syndrome, ME should be reclassified elsewhere in ICD-10-CM, if the title term of G93.3 is changed as proposed to "Postviral and related fatigue syndromes."

We propose the following modifications and new coding for myalgic encephalomyelitis if the proposed new title, "Postviral and related fatigue disorders" for G93.3 is implemented:

Proposal for modification of the classification of Myalgic encephalomyelitis within Chapter 6: Diseases of the nervous system (G00-G99):

If the following proposed revisions to G93.3 are implemented:
G93.3 Postviral and related fatigue syndromes

G93.30   Systemic exertion intolerance disease, unspecified

G93.31   Postviral fatigue syndrome

G93.32   Myalgic encephalomyelitis

G93.33   Chronic fatigue syndrome

G93.39   Other postviral and fatigue syndromes

Then, the following modifications are recommended:

Requested modifications to tabular listings under G93.3:

Add   **Excludes1:** Myalgic encephalomyelitis (G04.82)

Delete   **G93.32   Myalgic encephalomyelitis**

Revise   **G93.32   Chronic fatigue syndrome**

Delete   **G93.33   Chronic fatigue syndrome**

Requested modifications to tabular listings under G04:

G04   Encephalitis, myelitis and encephalomyelitis

       Includes:

       acute ascending myelitis

       meningoencephalitis

       meningomyelitis

       Excludes1:

       encephalopathy NOS (G93.40)

       Excludes2:

       acute transverse myelitis (G37.3-)

       alcoholic encephalopathy (G31.2)

Delete   benign myalgic encephalomyelitis (G93.3)

       multiple sclerosis (G35)

       subacute necrotizing myelitis (G37.4)

       toxic encephalitis (G92)

       toxic encephalopathy (G92)

Requested modification to G04.8:

Inflammatory diseases of the central nervous system (G00-G09)

> **G04.8 Other encephalitis, myelitis and encephalomyelitis**
>
> **Code also** any associated seizure (G40.-,R56.9)
>
> **G04.81 Other encephalitis and encephalomyelitis**
>
> > Noninfectious acute disseminated encephalomyelitis
> >
> > (noninfectious ADEM)

New code   **G04.82 Myalgic encephalomyelitis**

Add   **Excludes1:**

Add   Systemic exertion intolerance disease, unspecified (G93.30**)**

Add   Postviral fatigue syndrome (G93.31)

Add   Chronic fatigue syndrome (G93.32**)**

> **G04.89 Other myelitis**

Rationale: The term "encephalomyelitis" was used in a 1956 paper by Dr. A. Melvin Ramsay describing an outbreak of infectious disease at the London Royal Free Hospital in 1955, "Encephalomyelitis simulating poliomyelitis," published in the Lancet. In the same May 26, 1956 issue of the Lancet, an editorial attributed to Dr. E.D. Acheson suggested use of the name "benign myalgic encephalomyelitis."

> *The objections to any but a purely descriptive name for a disorder without a known cause or established pathology are obvious. For this reason, the term "benign myalgic encephalomyelitis" may be acceptable. It in no way prejudices the argument for or against a single or related group of causal agents; and it does describe some of the striking features of a syndrome...* (Lancet, 1956)

The appropriateness of the name ME, indicating muscle pain and inflammation of the central nervous system, was confirmed by the 2011 ICC:

> *In view of more recent research and clinical experience that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology.* (Carruthers, 2011)

Neuroinflammation in ME was also supported by the 2014 Nakatomi et al. study using subjects with ME selected using the ICC, "*Neuroinflammation is present in widespread brain areas in CFS/ME patients and was associated with the severity of neuropsychologic symptoms.*" (Nakatomi, 2014)

The IC Primer notes regarding abnormalities of the central nervous system found in ME on page 4:

> *Structural and functional abnormalities within the brain and spinal cord are consistent with pathological dysfunction of the regulatory centers and communication networks of the brain, CNS and ANS, and are essential for effective ongoing self-organization. [1, 75] Reduced brainstem gray matter volume is consistent with insult to the midbrain at fatigue onset. Feedback control loops may suppress cerebral motor and cognitive activity, disrupt CNS homeostasis, and reset elements of the ANS. [76] These abnormalities play crucial roles in neurological and neurocognitive symptoms. [1, 5, 11, 57, 65] Greater source activity and more parts of the brain are utilized in cognitive processing, which supports patients' perception of greater effort. [73, 77, 78] Reduced duration of uninterrupted sleep may explain reported unrefreshed sleep, pain and overwhelming fatigue. [79] These observed pathological changes are consistent with neurological disorders but not psychiatric conditions.* (Carruthers, 2012; See the IC Primer for references cited.)

The members of the ICC panel, based on their extensive clinical experience with patients identified as having ME, regard these CNS abnormalities consistent with widespread inflammation and an inflammatory disease of the central nervous system justifying the continued inclusion of "encephalomyelitis" in the name for the disease "myalgic encephalomyelitis."

It is, therefore, fitting that ME should be classified under Inflammatory diseases of the central nervous system (G00-G09); G04.8 Other encephalitis, myelitis and encephalomyelitis with the new code G04.82 and removed from connection with fatigue syndromes, reflecting that self-reported fatigue is not symptom required for the diagnosis of ME.

Regarding the issue of removing "Benign" from the 1969 WHO ICD diagnostic entry "Benign myalgic encephalomyelitis": Indeed, ME cannot be considered "benign" in the sense "not harmful in effect." The IC Primer states under "Prognosis" on page 1:

> *Currently there is no known cure. Early intervention and appropriate treatment strategies may lessen severity of symptoms. Restoration to full pre-morbid health and function is rare. [4] Prognosis for an individual cannot be predicted with certainty.* (Carruthers, 2012; See the IC primer for the reference cited.)

"Benign" was added to the term "myalgic encephalomyelitis" when ME was entered in the ICD to indicate mortality was not proximate with the onset of the disease. Now, however, "benign," in the sense "not harmful in effect" is almost universally recognized as inappropriate and the "benign" has been dropped when the term "ME" is used in practice.

Because having "benign" in the ICD listing has little current effect on the perception of ME, dropping "benign" from the ICD listing for ME in the US will have a negligible effect on how ME is perceived. However, implementing the other proposed modifications to the existing G93.3 entry will have a detrimental effect on how ME is perceived.

Grouping the recognized neurological disease ME with ill-defined CFS and unvalidated SEID under a new inappropriate umbrella title for G93.3, "Postviral and related fatigue syndromes" will mischaracterize ME and damage its credibility by association.

Addressing the issue if the mutual Excludes1 notes should be removed from R53.82 and G93.3

Because CFS is defined as diagnosis of exclusion, and ME is a neurological disease with a similar clinical presentation, ME must be regarded as an exclusionary condition for a CFS diagnosis. Therefore, no single patient can be given both diagnoses at the same time, according to the Holmes and Fukuda definitions of CFS and the ICC definition of ME. This makes the mutual Excludes1 notes for R53.82 and G93.3 vitally important for accurate and appropriate patient diagnosis. The mutual Excludes1 notes are consistent with the ICC which call for ME to be removed from overly inclusive diagnoses such as CFS.

Both NCHS Proposals 1 and 2 remove the essential mutual Excludes1 notes for ME and CFS, and place both ME and CFS under G93.3, blurring vital distinctions between the two separate, mutually exclusive diagnoses. This change will legitimize the expanded use of the often unintelligible term "ME/CFS." It is now impossible to determine what the ambiguous term "ME/CFS" refers to without further information. This is for three reasons.

First, CFS has always been defined as a diagnosis of exclusion, CFS cannot be meaningfully combined with another diagnosis, such as ME, with a similar clinical presentation, in accordance with both the Holmes and Fukuda definitions of CFS. This makes the hybrid term "ME/CFS" logically incoherent, like the term "square/circle," by combining two terms with contradictory definitions and, therefore, meaningless. Both the "ME" and the "CFS" in the hybrid term ME/CFS are being used in a way inconsistent with their standard case definitions – the ICC for ME and the Fukuda criteria for CFS.

Second, the term "ME/CFS" has come to be used now in two very different ways. ME/CFS is used as an umbrella term referring to both ME and CFS separately defined – Fukuda CFS as a diagnosis of exclusion with 163 possible combinations of symptoms with only unexplained chronic fatigue common to all, and ME as an established neurological disease with an over 60-year history under that name and not requiring self-reported fatigue as a symptom. Yet ME/CFS is also used now, irrationally, as a single diagnostic term to refer to "this disease," which now can mean almost anything anyone wants it to mean.

Third, as discussed above, the CDC, since 2017, has redefined ME/CFS using the nonspecific IOM SEID criteria. Research at DePaul (Jason, 2015) found new CDC ME/CFS, or SEID, to have a prevalence estimate of 1.2%. Previously, the term ME/CFS had been defined by the CCC, combining the two terms because the authors inaccurately claimed ME and CFS "probably are the same illness." Research in England (Nacul, 2011) found CCC ME/CFS to have a prevalence estimate of 0.11% – less than one-tenth that for CDC ME/CFS.

Even if these prevalence estimates have a large margin of error, new CDC ME/CFS (SEID) is clearly not the same condition as CCC ME/CFS. The overly inclusive CDC ME/CFS (SEID) patient group most closely resembles the 2005 Reeves CFS patient group. (Reeves, 2005) The CCC ME/CFS patient group, on the other hand, consists almost entirely of people with ME also meeting the ICC.

Reclassifying ill-defined CFS together with the established neurological disease ME under G93.3 and removing their mutual Excludes1 notes will legitimize the continued use of the now unintelligible term ME/CFS which is already creating a muddle.

Addressing the issue if SEID should be considered a valid diagnostic entity justifying its inclusion in ICD-10-CM

The 15 authors of the 2015 IOM report, all from the US, claim there is a new diagnostic entity they named "systemic exertion intolerance disease" (SEID), that should replace both the ME and CFS diagnoses. (IOM, 2015) Accordingly, since July 2017, the CDC refers to the IOM report for diagnosis of the new hybrid condition "ME/CFS."

Based on community input largely opposing the name "systemic exertion intolerance disease," the CDC chose the name "ME/CFS" to refer to the new hybrid, fatigue-based condition diagnosed using the IOM criteria. Apparently, the CDC now regards "ME/CFS" not as an umbrella term, referring to ME and CFS as separate diagnoses, but as a single diagnostic entity defined by the IOM criteria.

The rationale for the IOM report to include ME is unclear. ME was already well- defined by the 2011 ICC, which are both diagnostic and research criteria. The 26 ICC authors from 13 countries were highly qualified having collectively diagnosed and treated over 50,000 cases of ME. Also, the ICC have now been used successfully to select research subjects for a number of significant studies in Japan and Australia. (A partial list: Nakatomi, 2014; Huth, 2015; Wong, 2015; Brenu, 2016; Balinas, 2017; Nguyen, 2017; Marshall-Gradisnik, 2018; Staines, 2018) The 2012 IC Primer gives detailed information for doctors on how to diagnose ME, including numerous laboratory and imaging tests helpful in confirming the diagnosis.

There was no objective need for the IOM report to include ME as part of its new fatigue condition SEID. ME has its own criteria, the 2011 ME-ICC, not requiring fatigue as a symptom and separating ME from CFS and its variants. It was the Fukuda CFS criteria that required revision because of their lack of specificity selecting a heterogeneous group of patients and not explicitly excluding ME.

Thirty years of research on CFS has failed to identify a common underlying pathology. The relevance of much of CFS research will be lost going forward because it will be unclear how Fukuda CFS research applies to the more diverse SEID patient group. Also, the inclusion of subjects with ME mislabelled as CFS subjects has always been a confounding factor in CFS research.

The logic for replacing both the existing Fukuda criteria for CFS and the ICC for ME with a single new set of diagnostic criteria was fundamentally flawed. As observed by Frank Twisk in his 2016 review paper, "Replacing Myalgic Encephalomyelitis and Chronic Fatigue Syndrome with Systemic Exertion Intolerance Disease Is Not the Way Forward":

> *Firstly, a new diagnostic entity cannot replace two distinct, partially overlapping, clinical entities such as ME and CFS. Secondly, due to the nature of the diagnostic*

criteria, the employment of self-report, and the lack of criteria to exclude patients with other conditions, the SEID criteria seem to select an even more heterogeneous patient population, causing additional diagnostic confusion. (Twisk, 2016)

ME specialist Dr. Derek Enlander commented in 2015 when the IOM report was published:

The notion to rename the disease Myalgic Encephalomyelitis (which, if we mention, we should also mention 'Chronic Fatigue Syndrome,' just to be clear) to "SEID" is highly unnecessary. This will confuse not only patients but physicians who are expert in the disease as well as those who are not familiar with the condition.

The criteria that are quoted are a truncated version of the Canadian Consensus Criteria (CCC), truncated in a manner that allows the over-diagnosis of the disease. These criteria would also allow the diagnosis to include psychiatric conditions that are specifically excluded by both the Fukuda and CCC. (Enlander, 2015)

Clearly, because the IOM criteria require "often profound" fatigue and post-exertional malaise as core symptoms, which are not included in the eight required ICC ME symptoms, it would be inappropriate and contrary to medical good practice standards to use the IOM criteria to diagnose suspected cases of ME.

It was also misleading for the CDC to include "ME" in its name for SEID, "ME/CFS." Including "ME" as part of the name suggests the IOM criteria diagnose ME when, in fact, they do not.

CDC ME/CFS, or SEID, is:

a disorder of more than six months duration comprising unexplained fatigue, post-exertional malaise, unrefreshing sleep and either cognitive dysfunction or orthostatic intolerance. (Nagy-Szakal, 2018)

The SEID criteria also omit significant exclusions for conditions with similar symptoms found in the Fukuda criteria for CFS, the CCC for ME/CFS, and the ICC for ME. The ICC require a minimum of eight symptoms for making the diagnosis of ME:

A patient will meet the criteria for postexertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories (C), and at least one symptom from energy metabolism/transport impairments (D). (Carruthers, 2011)

Based on their extensive clinical experience diagnosing ME, the ICC authors stated, "*Symptom patterns interact dynamically because they are causally connected.*" To the contrary, the IOM report authors required four Fukuda CFS symptoms for the diagnosis of SEID, with the option that orthostatic intolerance may be substituted for cognitive impairment. Subsequent research has shown the required SEID symptoms are not causally related and are commonly reported by patients with a variety of medical and psychiatric disorders.

Because the CDC's new IOM criteria do not diagnose ME, there is no rational basis for the CDC to include the ICC among the three sets of criteria on its webpage for former criteria, all replaced by the IOM criteria, "Understanding Historical Case Definitions and Criteria." (CDC, 2018b)

The IOM report recommends a new ICD-10-CM diagnostic code on page 222:

> *A new code should be assigned to this disorder in the International Classification of Diseases, Tenth Revision (ICD-10), that is not linked to "chronic fatigue" or "neurasthenia."* (IOM, 2015)

Apparently, "this disorder" refers to SEID because the mixed term ME/CFS, combining diagnoses from different sections of the ICD, cannot be classified according in WHO ICD rules requiring that individual categories and subcategories must remain mutually exclusive.

As the cardinal symptom of SEID is 6 months of impairment "accompanied by fatigue," **it is unclear why the IOM report authors would request a new ICD-10-CM code not linked to "chronic fatigue**."

It should be noted that CFS has not been linked to "neurasthenia" in the government-issued ICD-10-CM. The IOM report authors apparently found "neurasthenia" mentioned in unofficial "Clinical Information" added to the R53.82 CFS entry by a commercial website. (ICD10Data.com, 2018) Therefore, requesting a new code not linked to "neurasthenia" in ICD-10-CM is a non-issue.

In regards to any entry at all for SEID in ICD-10-CM, the new SEID criteria have not yet been validated by independent research as a diagnostic entity. Nor can past research based on the more specific Fukuda and Canadian criteria be applied to SEID because the IOM criteria select an expanded and significantly different patient group. Such research validation would require determining the IOM criteria define 1) a diagnostic entity separate from similar conditions, and 2) a diagnostic entity associated with a common underlying disease pathophysiology. (Asprusten, 2018)

Rather than confirming SEID as a valid diagnostic entity, recent research has shown the contrary. Not only are the four required SEID symptoms nonspecific and reported in a variety of medical and psychiatric disorders, but the lack of adequate specified exclusions allows symptoms explained by more appropriate diagnoses to be diagnosed as SEID. Most notably, this would include primary psychiatric disorders. As stated in Jason et al. "Unintended Consequences of not Specifying Exclusionary Illnesses for Systemic Exertion Intolerance Disease":

> *In addition, Ze-dog [8] pointed out that this new SEID definition lacks exclusion criteria, and as a consequence, it is easier for a person with a primary psychiatric diagnosis to be labeled as having SEID.* (Jason, 2015; Ze-dog, 2015)

Accordingly, epidemiological research at DePaul University has concluded:

> *The findings indicate that many individuals from major depressive disorder illness groups as well as other medical illnesses were categorized as having SEID… The current study suggests that the core SEID symptoms are not unique to SEID, as some patients*

with other illnesses, such as those evaluated in this study, have comparable symptoms. (Jason, 2015)

Jason et al. in 2015 found 24% and 27% of subjects in two primary major depressive order (MDD) groups met the SEID criteria. The study also found 47% of a group diagnosed with melancholic depression, a severe form of clinical depression excluded by the Fukuda CFS criteria, met the SEID criteria. (Jason, 2015) These results are comparable to a 2009 finding that 38% of subjects with a diagnosis of MDD were misclassified as having CFS using the 2005 Reeves definition of CFS. (Jason, 2009)

Because the SEID symptoms lack of specificity and the IOM report fails to specify adequate exclusions, the estimated prevalence of SEID was found to be 1.2% – five times that of the CDC 2003 estimate for Fukuda CFS of 0.24% (Jason, 2015; Reyes, 2003) This increase in prevalence can only be explained by the SEID criteria selecting medical and psychiatric disorders with similar symptoms previously excluded by the Fukuda CFS criteria.

This means as much as 80% of SEID will consist of misdiagnosed patients for whom there are more appropriate diagnoses, or patients unnecessarily burdened with a diagnosis of comorbid SEID. The actual percentage may be higher because not all patients meeting the Fukuda CFS criteria will report the same four CFS symptoms required for a SEID diagnosis.

SEID will most closely resemble the diverse group of patients selected by the 2005 Reeves criteria which increased the CFS prevalence estimate ten times to 2.54% – as compared to 2015 IOM criteria increasing the CFS prevalence five times to 1.2%. Therefore, it seems premature that the IOM SEID criteria should have replaced the Fukuda CFS criteria on the CDC website before being adequately validated by independent research.

The precipitous action by the CDC in declaring in 2017 that "ME/CFS" is now diagnosed using the untested IOM criteria has rendered the mixed term "ME/CFS" meaningless without additional information. Does "ME/CFS" refer to the patient group diagnosed by the 2003 CCC for ME/CFS, which requires a minimum of eight symptoms to diagnose and corresponds most closely to ME? Or alternatively, does "ME/CFS" refer to the greatly expanded patient group diagnosed by the 2015 IOM criteria for SEID, which requires a minimum of four symptoms to diagnose and most closely corresponds to the diverse group selected by the 2005 Reeves criteria? (Reeves, 2005)

Nacul et al. found CCC ME/CFS to have an estimated prevalence of 0.11%. (Nacul, 2011) Jason et al. found IOM ME/CFS to have an estimated prevalence of 1.2%, over 10 times greater. (Jason, 2015) Without specifying every time the term "ME/CFS" is used whether it is CCC ME/CFS or CDC ME/CFS, the term for "this disease" is unintelligible.

The case for SEID replacing the ICC ME has even less evidentiary support. A 2015 Australian study (Johnson, 2015) found about half of subjects (171 of 333) meeting the Fukuda CFS criteria also met the ICC. Estimating the prevalence of ME as half of that for CFS gives 0.24% / 2 or 0.12%. This means people with ME will make up as little as 10% of the new SEID diagnosed using the IOM criteria. This is an unacceptable replacement for the ICC which diagnose ME exclusively.

As Johnson et al. suggests, because the ME diagnosis is rarely made in the US given that US doctors are unfamiliar with the ICC and IC Primer, about one half of the US patient group diagnosed with CFS actually have ME. All US CFS patients should be evaluated using the ICC and IC Primer, and patients who have ME removed from the overly inclusive CFS diagnosis. (Carruthers, 2012) The CDC's alternative has been to take people with ME out of the overly inclusive CFS diagnosis and move them to the even more overly inclusive SEID diagnosis, which the CDC has misleadingly relabelled as "ME/CFS."

The problem of misdiagnosis with CFS will be greatly compounded given now, by CDC directive, patients will be only evaluated using the less specific SEID criteria. It will be unknown which patients in the SEID group have ME, or which would have qualified for the more specific Fukuda CFS diagnosis.

Misdiagnosis with SEID (CDC ME/CFS) will produce significant problems for people with ME. For example, including subjects with a SEID diagnosis in clinical trials who have a a primary depressive disorder producing their symptoms but were misdiagnosed with SEID, will create unreliable, and possibly harmful, treatment results for people with ME. (Jason, 2015)

The ill-defined SEID diagnosis is already producing questionable results in research. A recent study at the Sleep Center at the Emory University School of Medicine (Maness, 2018), "Systemic exertion intolerance disease/chronic fatigue syndrome is common in sleep centre patients with hypersomnolence: A retrospective pilot study," found 21% of 187 patients with hypersomnolence (excessive daytime sleepiness) met the criteria for SEID.

The study authors interpreted the results of the study to mean that SEID is a common comorbidity in the hypersomnolent population. An alternate interpretation is that the SEID criteria do not distinguish between patients with a hypothesized exertion intolerance disease and those whose symptoms are associated with a more appropriate existing diagnosis. Research at DePaul found 48% of subjects with a clear medical reason for their fatigue met the SEID criteria. (Jason, 2015)

These research findings suggest SEID is not a valid diagnostic entity separate from other diagnoses with similar symptoms. A recent Norwegian study (Asprusten, 2018) "Systemic exertion intolerance disease diagnostic criteria applied on an adolescent chronic fatigue syndrome cohort: evaluation of subgroup differences and prognostic utility" stated that the new SEID criteria have not been validated and questioned their discriminant and prognostic validity. Also, the study found the SEID criteria select patients with more depressive symptoms.

Additionally, the Asprusten et al. study found, "*No cardiovascular, infectious, inflammatory, neuroendocrine or cognitive biomarker differed significantly between the SEID-positive and the SEID-negative groups.*" This, and the large increase in the prevalence estimate for SEID from CFS, suggest there is no likely common underlying pathophysiology for the diverse SEID patient group.

Because SEID has failed to be validated as a diagnostic entity and appears to be more heterogeneous than Fukuda CFS, there is no rational or evidentiary basis for including SEID in ICD-10-CM at this time as a neurological disorder, or even as a validated diagnostic entity.

Summary:

In summary, there is no new compelling evidence that CFS is now a neurological diagnosis after 30 years of being classified as an ill-defined condition. CFS is still diagnosed using the same Fukuda criteria that select a heterogeneous group of patients and exclude any recognized neurological disorders with similar symptoms, by definition.

Research on Fukuda CFS showing neurological involvement or abnormalities is done using undefined subsets of CFS which can't be considered representative of the heterogeneous CFS diagnostic group as a whole. Also, CFS research subjects are rarely screened for ME. ME research subjects mislabeled as CFS may influence the results in what appears to be a CFS study.

CFS also cannot be considered to be postviral because a preceding viral infection is not required for a CFS diagnosis using the Fukuda criteria. Evidence of a viral infection preceding and associated with the development of a prolonged fatigue syndrome would indicate possible PVFS, rather than CFS.

No new biomedical research was done as part of the IOM report. Neither can the IOM report be said to apply to CFS, but only to a newly hypothesized systemic exertion intolerance disease, SEID, diagnosed using four self-reported symptoms, which has not been validated by independent research. Therefore, there is no new compelling evidence, based on the IOM report, to confirm CFS as a neurological disorder of the brain classifiable under G93.3.

For purposes of classification, SEID also has not been shown to be a neurological disorder, or even a valid diagnostic entity appropriate for inclusion in ICD-10-CM under any classification. It is, therefore, premature to list SEID, named only in 2015, in ICD-10-CM. ME was named and described in 1956. It was another 13 years before "Benign myalgic encephalomyelitis" was entered in the WHO ICD in 1969.

WHO ICD policy is, as cited in the IACFS/ME proposal, *"[I]n the absence of compelling evidence mandating a change, legacy should trump with regard to the question of moving certain conditions to new chapters."* Because there is no new valid evidence that either CFS or SEID are neurological disorders requiring changes to ICD-10-CM, we reject the proposed modification of the existing ICD-10-CM.

References:

Asprusten TT et al. Systemic exertion intolerance disease diagnostic criteria applied on an adolescent chronic fatigue syndrome cohort: evaluation of subgroup differences and prognostic utility. BMJ Paediatrics Open 2018;2:e000233.

Balinas C et al. Investigation of mast cell toll-like receptor 3 in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Systemic Mastocytosis participants using the novel application of autoMACS magnetic separation and flow cytometry. Asian Pac J Allergy Immunol. 2017 Dec 10.

Brenu EW et al. Immune and hemorheological changes in Chronic Fatigue Syndrome. Journal of Translational Medicine 2010 8:1.

Brenu EW et al. A Preliminary Comparative Assessment of the Role of CD8+ T Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis. Journal of Immunology Research Volume 2016, Article ID 9064529.

Carruthers BM et al. Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatment protocols. J of Chronic Fatigue Syndr 2003; 11:7-154.

Carruthers BM et al. Myalgic encephalomyelitis/chronic fatigue syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners, An Overview of the Canadian Consensus Document. 2005. Available online: http://mefmaction.com/images/stories/Overviews/ME-Overview.pdf (Accessed October 10, 2018)

Carruthers BM, van de Sande MI et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 2011; 270:327–38.

Carruthers BM et al. Myalgic Encephalomyelitis – Adult & Paediatric: International Consensus Primer for Medical Practitioners. 2012. http://www.investinme.org/Documents/Guidelines/Myalgic%20Encephalomyelitis%20International%20Consensus%20Primer%20-2012-11-26.pdf (Accessed October 10, 2018)

Centers for Disease Control and Prevention (CDC) website. ME/CFS > Symptoms and Diagnosis. Page last updated: July 3, 2017. Available online: https://www.cdc.gov/me-cfs/symptoms-diagnosis/diagnosis.html (Accessed October 10, 2018)

Centers for Disease Control and Prevention (CDC) website. ME/CFS > Information for Healthcare Providers. Page last updated: July 12, 2018a Available online: https://www.cdc.gov/me-cfs/healthcare-providers/index.html (Accessed October 19, 2018)

Centers for Disease Control and Prevention (CDC) website ME/CFS > Understanding Historical Case Definitions and Criteria. Page last updated July 12, 2018b. Available online: https://www.cdc.gov/me-cfs/healthcare-providers/case-definitions-criteria.html (Accessed October 10, 2018)

Dowsett E et al. Myalgic encephalomyelitis – a persistent enteroviral infection?. Postgrad Med J (1990) 66, 526 530.

Dowsett E et al.. Conversation Piece. Postgrad Med J. 1992 Jan; 68(795): 63–65.

Enlander, D. Comment on the IOM's "Beyond Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Redefining an Illness" report. February 10, 2015 Available online: https://www.facebook.com/DrEnlander/ (Accessed October 10, 2018)

Fukuda K et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994; 121:953–959.

Hickie I et al. Can the chronic fatigue syndrome be defined by distinct clinical features?. Psychol Med. 1995; 25:925–935.

Holmes G et al. Chronic Fatigue Syndrome: A Working Case Definition. Ann Intern Med.1988; 108:387-9.

Huber KA et al. Latent class analysis of a heterogeneous international sample of patients with myalgic encephalomyelitis/chronic fatigue syndrome.
Fatigue. 6:3,163-178,DOI:10.1080/21641846.2018.1494530.

Huth TK et al. Pilot Study of Natural Killer Cells in Chronic Fatigue Syndrome / Myalgic Encephalomyelitis and Multiple Sclerosis. Scand J Immunol, 83: 44-51.

IACFS/ME. Proposal for modifications to ICD-10-CM for Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, and Postviral fatigue syndrome. IACFS/ME Newsletter Volume 10, Issue 3, August 2017. Available online: http://iacfsme.org/PDFS/2017AugustNewsletter/Proposal-for-modifications-to-ICD-10-IACFSME-July.aspx (Accessed October 2, 2018)

ICD10Data.com. Available online: https://www.icd10data.com/ICD10CM/Codes/R00-R99/R50-R69/R53-/R53.82 (Accessed October 10, 2018)

Institute of Medicine. Myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington (DC): National Academies Press; 2015.

Jason LA et al. Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition. Journal of Disability Policy Studies 2009,20(2),93-100.

Jason LA et al. Unintended Consequences of not Specifying Exclusionary Illnesses for Systemic Exertion Intolerance Disease. Diagnostics 2015, 5(2), 272-286.

Johnston S et al. Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. Clinical Epidemiology 2016, 8, 97-107.

Lancet. Editorial: A New Clinical entity?. 1956 May 26;270(6926):789-90.

Maness C et al. Systemic exertion intolerance disease/chronic fatigue syndrome is common in sleep centre patients with hypersomnolence: A retrospective pilot study. J Sleep Res. 2018 Apr 6:e12689.

Marshall-Gradisnik S et al. Decreased Expression of TRPM3 and mAChRM3 in the Small Intestine in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. IJCM Vol.09 No.05(2018), Article ID:85005.

Nacul LC et al. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. BMC Med. 2011 Jul 28;9:9.

Nagy-Szakal N et al. Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics. Scientific Reports volume 8, Article number: 10056 (2018).

Nakatomi Y et al. Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study. J Nucl Med 2014; 55:945–950.

Natelson B et al. Reducing heterogeneity in chronic fatigue syndrome: a comparison with depression and multiple sclerosis. Clin Infect Dis. 1995 Nov; 21(5):1204-10.

Nguyen T et al. Novel characterisation of mast cell phenotypes from peripheral blood mononuclear cells in chronic fatigue syndrome/myalgic encephalomyelitis patients. Asian Pac J Allergy Immunol. 2017 Jun;35(2):75-81.

Ramsay AM. Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free Disease; Gower Publishing Corporation: London, 1986.

Reeves WC et al. Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study. BMC Medicine December 2005; 3:19. PMID: 16356178.

Reeves WC et al. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia Population Health Metrics 2007; 5:5.

Reyes M et al. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Int Med 2003, 163: 1530-1536.

Staines D et al. Transient Receptor Potential Ion Channels in the Etiology and Pathomechanism of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. IJCM Vol.9 No.5, May 2018.

Switzer WM et al. Absence of evidence of Xenotropic Murine Leukemia Virus-related virus infection in persons with chronic fatigue syndrome and healthy controls in the United States. Retrovirology 2010 Jul 1; 7(1):57.

Wilson A et al. What is chronic fatigue syndrome? Heterogeneity within an international multicentre study. Aust N Z J Psychiatry. 2001 Aug; 35(4): 520-7.

Wong N et al. A Comparison of Cytokine Profiles of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis Patients. IJCM 2015;6(10)

Ze-dog, D. A Major Flaw in the IOM's Definition of ME/CFS. Available online: http://on.fb.me/1vWYv9g (Accessed on October 6, 2018).