EUROPEAN ME NETWORK (EUROMENE) Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe

1. Luis Nacul*: London School of Hygiene and Tropical Medicine, London, UK. And BC Women's Hospital, Vancouver, Canada. Luis.nacul@lshtm.ac.uk; https://orcid.org/0000-0003-1411-8088 (**corresponding author**)
2. François Jérôme Authier*. Faculty of Medicine Créteil - Paris Est, CRETEIL, France. https://orcid.org/0000-0002-0182-2052
3. Carmen Scheibenbogen. Institute for Med. Immunology Charité, Berlin https://orcid.org/0000-0002-8554-9638
4. Lorenzo Lorusso. Neurology and Stroke Unit – Neuroscience Dept. – A.S.S.T.-Lecco, Italy, https://orcid.org/0000-0002-5894-8545
5. Ingrid Bergliot Heland. Barneavdeling for nevrofag, Rikshospitalet, OUS, https://orcid.org/0000-0002-2575-3573
6. Jose Alegre Martin. Vall d'Hebron University Hospital (VHIR), Barcelona, Spain. https://orcid.org/0000-0002-7582-7585
7. Carmen Adella Sirbu. Titu Maiorescu University, Central Military Emergency University Hospital, Bucharest, Romania. https://orcid.org/0000-0003-4471-7612
8. Anne Marit Mengshoel. University of Oslo, Norway https://orcid.org/0000-0003-1800-4440
9. Olli Polo. Bragée ME/CFS Center, Stockholm, Sweden https://orcid.org/0000-0002-1067-4151
10. Uta Behrends. Technical University of Munich, School of Medicine, Department of Pediatrics, Munich, Germany, uta.behrends@mri.tum.de
11. Henrik Nielsen. Privat Hospitalet Danmark, Charlottenlund, Denmark. hnreum@dadlnet.dk.
12. Patricia Grabowsky. Charite Medical School, Berlin, Germany, https://orcid.org/0000-0003-1376-2728
13. Slobodan Sekulic. Medical Faculty Novi Sad, Novi Sad, Serbia. https://orcid.org/0000-0001-7889-310X
14. Nuno Sepulveda. Centre of Statistics and Application of University of Lisbon, Lisbon, Portugal. https://orcid.org/0000-0002-8542-1706
15. Fernando Esteves Lopez. Erasmus MC University Medical Center, Rotterdam, Netherlands. https://orcid.org/0000-0003-2960-4142
16. Pawel Zalewski. Nicolaus Copernicus University, Torun; Collegium Medicum, Bydgoszcz, Poland. https://orcid.org/0000-0001-8453-7785
17. Derek Pheby: independent researcher, https://orcid.org/0000-0003-1726-0717
18. Jesus Castro-Marrero. Vall d'Hebron University Hospital Research Institute, Barcelona https://orcid.org/0000-0002-2481-3052
19. Giorgos K Sakkas. University of Thessaly, Greece. https://orcid.org/0000-0002-2462-995X
20. Enrica Capelli. Univesity of Pavia, Italy, https://orcid.org/0000-0003-0085-6688
21. Ivan Brundsdlund. Univ Hospital of Southern Denmark, https://orcid.org/0000-0002-4203-5442
22. John Cullinan. National University of Ireland Galway, https://orcid.org/0000-0003-3509-0635
23. Angelika Krumina. Riga Stradins University, Riga, Latvia https://orcid.org/0000-0003-0726-3375
24. Jonas Bergquist. Uppsala University, Uppsala, Sweden, https://orcid.org/0000-0002-4597-041X
25. Modra Murovska. Riga Stradins University, Riga, Latvia. https://orcid.org/0000-0003-0971-1784

26. Ruud Vermuelen**. CFS/ME Medical Centre, Amsterdam, Netherlands https://orcid.org/0000-0002-5039-2167
27. Eliana M Lacerda**. London School of Hygiene and Tropical Medicine, Keppel Street, London, UK. https://orcid.org/0000-0002-5077-7868

on behalf of European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE)

*Shared first authorship, ** shared last authorship

Abstract

Designed by a group of ME/CFS researchers and health professionals, the European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE) has received funding from the European Cooperation in Science and Technology (COST) (https://www.cost.eu/cost-actions/what-are-cost-actions/) - COST action 15111 - from 2016 to 2020. The main goal of the Cost Action was to assess the existing fragmented knowledge and experience on health care delivery for people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in European countries, and to enhance coordinated research and health care provision in this field.

We report on the recommendations for clinical diagnosis, heath services and care for people with ME/CFS in Europe, as prepared by the group of clinicians and researchers from 22 countries and 55 European health professionals and researchers, who have been informed by people with ME/CFS (https://www.cost.eu/actions/CA15111/#tabs|Name:overview).

Keywords

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; diagnosis, Health services, care

Introduction

Standardization of clinical procedures and Services for Myalgic Encephalomyelitis or chronic fatigue syndrome (ME/CFS) in Europe: The origins

Initially designed by a group of ME/CFS researchers and health professionals, the European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE) has received funding from the European Cooperation in Science and Technology (COST) (https://www.cost.eu/cost-actions/what-are-cost-actions/) - COST action 15111 - from 2016 to 2020. The main goal of the Cost Action was to assess the existing fragmented knowledge and experience on health care delivery for people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in European countries, and to enhance coordinated research and health care provision in this field.

One of the aims of the network was to *define a standardised clinical diagnosis for ME/CFS for clinical and research use.* With the paucity and lack of integration of clinical guidelines in European countries (Strand et al., 2019), a high need has been identified for addressing the uncertainties around diagnosis and treatment, and to support the development of health services and standard clinical practices for people with ME/CFS across the continent. We here report on the recommendations for clinical diagnosis and management of ME/CFS in Europe, as prepared by the group of clinicians and researchers from 22[1] countries participating in the network activities (including the Near Neighbouring Countries-NNC), and 55 European researchers[2] and health professionals, who have been informed by people with ME/CFS (https://www.cost.eu/actions/CA15111/#tabs|Name:overview).

The population burden of the disease and the need for better recognition

ME or CFS (ME/CFS) is characterised by intolerance to efforts expressed by profound or pathological fatigue, malaise, and other symptoms aggravated by physical or cognitive efforts at intensities previously well tolerated by the individual. Intolerance to efforts may be experienced immediately or typically be delayed for hours or a day or more after exertion and is associated with slow recovery, which may extend to one or more days (post-exertional malaise (PEM) or aggravation of symptoms following exertion). Other key symptoms include unrefreshing sleep, cognitive impairment, orthostatic intolerance, and pain, including muscle and joint pain and headaches. The symptoms are persistent or recurrent over long periods of time, and lead to a significant reduction in previous levels of functioning. Diagnosis is clinical, owing to the absence of biomarkers, and based on detailed clinical history and physical examination by a competent clinician (Carruthers et al., 2003, Carruthers et al., 2011, Rowe e, al, 2017, Jason & Sunquist, 2018). There is no causal treatment for the disease. With symptom-oriented support many improve with time or learn to manage their illness. There is little evidence on long term prognosis. However, full recovery is not the norm, particularly in adults (Carruthers et al., 2003, Carruthers et al., 2011, Institute of Medicine, 2015, Nacul et al, 2020).

Prevalence rates have been estimated as between 0.1 and 0.7%, and incidence rate as 0.015 new cases/1000-year (Nacul et al., 2011b). This could represent between 1 million and over 5 million people, probably around 3 million in the European continent living with ME/CFS. However, there are no

[1] Austria, Belarus (NNC), Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovenia, Spain, Sweden, United Kingdom.
[2] The researchers' names and affiliations are listed in the COST Action website.

European-wide estimates of disease burden (Estevez-Lopez et al., 2018). A much larger number of people will have chronic fatigue for other reasons, and many of them will also be significantly incapacitated. At least 2/3 of the cases are in women (Nacul et al., 2011b, Valdez et al., 2019), with young people in their most productive phases of life being preferentially affected. However, ME/CFS has been reported in all age groups (Valdez et al., 2019). (Bakken et al, 2014). Quality of life of those with ME/CFS is on average lower than with other chronic or disabling diseases, such as multiple sclerosis (Kingdon et al., 2018), cancer, rheumatoid arthritis, depression (Nacul et al., 2011a), diabetes, epilepsy, or cystic fibrosis (Kennedy et al., 2010). Economic costs are considerable (Jason et al., 2008b, Valdez et al., 2019, Lloyd and Pender, 1992, Hunter et al., 2017, Pheby et al, 202), with repercussions for the individual affected, their families and society, as well as to educational and occupational services. Many will be unable to work or do so on a part-time basis; with some in the milder spectrum of the disease able to work full-hours, however, often at the cost of enduring significant symptoms and sacrificing their social life and other interests due to the need to rest when not working (Castro-Marrero et al., 2019, Lacerda et al., 2019). In the absence of economic analysis on the costs of the disease in Europe, we estimate, based on data from the UK (Hunter et al., 2017), ME/CFS may cost some 40 Billion Euros per year to health services and society. There is, however, a large degree of imprecision in these estimates, due to variation in coverage and costs of health services provision and living costs across the Continent.

Despite the substantial disease burden, the health needs of people with ME/CFS remain largely unmet in Europe, as in many other parts of the world. Clinical services for people with the disease are in small numbers and sparse. A large proportion of the population with the disease has very limited access to health services, including in the public, mixed, and private sectors. The still limited knowledge of health professionals about the disease, including those in primary care, who are often the first port of call for those with ME/CFS, means diagnosis is often missed or delayed, and not infrequently patients remain undiagnosed and do not receive appropriate care for long periods of time. While waiting for diagnosis, patients often encounter difficulties in getting help from the health and other services, and their suffering and needs are not fully recognised, not only by health professionals, but also by employers and educators. On the other hand, on some occasions, patients are over-investigated, with inherent risks and unnecessary costs to individuals and society. People with ME/CFS may easily get trapped into a situation where while unable to carry on or start meaningful work- or school-related activities, they receive very little guidance from the health sector or support from social services – where they feel disbelieved and neglected, and are often failed by the welfare system (Bhatia et al., 2019). Their disability contributes to social isolation, which adds to their burden, and limits their chances of recovery or re-integration in society.

Methods

Development of recommendations

The EUROMENE network activities were organised in Working Groups (WG), including the Clinical Group, tasked to explore existing methods used for the diagnosis of cases in Europe, and to develop recommendations for the diagnosis and treatment of people with ME/CFS in the continent. The recommendations for standardising the diagnostic criteria for ME/CFS to be used by European researchers, are covered in related EUROMENE document (Mudie at al., 2020), which will allow comparability and better estimates.

We have not systematically reviewed the evidence in relation to diagnostic criteria and interventions, as this has been done by others. Thus, the following recommendations are pragmatic and were based on

the working group member's collective and consensual assessment of key documents on clinical definitions of ME/CFS (Carruthers et al., 2003, Fukuda et al., 1994, Rowe et al., 2017, Institute of Medicine (IOM), 2015, Friedberg et al., 2012, Rowe et al, 2017, Jason & Sunnquist, 2018), and existing studies and guidelines for clinical assessments and care used in Europe and internationally (reviewed by (Strand et al., 2019)). The WG members met on various occasions (WG meetings) to agree on key documents and to consider them based on the members' experiences and expertise and relevance for clinical practice in Europe. We recognise that there is still limited evidence-based research on ME/CFS; as we witness progresses in this field, we recognise the need for frequent reviews of these recommendations, in line with emerging evidence.

Considerations on ME/CFS diagnosis for clinical purposes

Many diagnostic criteria have been proposed for use in clinical practice, of which the one by the Institute of Medicine (currently, National Academy of Medicine), know as IOM criteria has received international recognition. Its relative simplicity makes it ideal for use in primary care.

A case of ME/CFS requires the presence of symptoms for at least 6 months and which are typically present for at least half of the time (Box 2).

Box 1. IOM criteria for the diagnosis of ME/CFS

Required symptoms

1. substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social or personal life) with profound fatigue of new onset, which is present for at least 6 months, is not explained by ongoing or unusual excessive exertion and is not substantially relieved by rest
2. Post-exertional malaise (PEM)
3. Unrefreshing sleep

At least one of the following:

1. Cognitive impairment
2. Orthostatic intolerance

For full details, see Institute of Medicine (IOM), 2015

The Canadian Consensus Criteria (CCC) is particularly suitable for diagnosis confirmation and case sub-grouping in secondary care, as well as in research (Box 2). The CDC-1994/Fukuda et al. criteria (Fukuda et al., 1994) may also be used as a screening tool for diagnosis in clinical practice, but we recommend that only cases with post-exertional malaise (PEM) (which is optional in that definition), are included for diagnosis (Box 3). Note that although the CDC-1994 criteria have been developed for research purposes, it has often been used for diagnosis purposes in clinical practice and is still a preferred case definition by some in Europe.

For children, the IOM (Institute of Medicine, 2015) and Rowe et al., 2017 criteria (Box 4) may be used. The latter is based on 6 cardinal paediatric symptoms and a disease duration of 6 months; a diagnosis of "postinfectious fatigue syndrome" (PFS) is made when the symptoms are present for 3 months following an acute infection. The Canadian Consensus criteria (Carruthers et al, 2013) may also be used in

children, as proposed by Jason et al (Jason et al., 2006, Jason & Sunnquist, 2018. However, using 3 months of symptoms are sufficient for diagnosis in children and adolescents.

Diagnosis in both adults and children can be suspected earlier, and the primary care physician should be proactive in starting diagnostic investigations. Initial management and referral may be considered when diagnosis is suspected or with 3 months of symptoms, as appropriate.

Box 2. Canadian Consensus Criteria for the diagnosis of ME/CFS

The required symptoms, listed below, must be persistently or recurrently present for at least 6 months in adults (3 months in children and adolescents), and must not be explained by other conditions. Exclusionary conditions should be ruled out by a combination of clinical history, physical examination, and complementary tests.

- Pathological fatigue
- Post-exertional malaise and worsening of symptoms
- Sleep dysfunction
- Pain
- Cognitive symptoms (at least two symptoms from a list provided)

In addition, at least one symptom from two from the following categories of symptoms are required:

- Autonomic
- Neuroendocrine
- Immune

For full details, see (Carruthers et al., 2003). The structure of the CCC definition in adults and some aspects of the CDC-1994 (Fukuda et al, 1994) criteria were used to create a paediatric cases definition of ME/CFS (Jason et al., 2006, Jason & Sunnquist, 2018).

Box 3. Modified* CDC-1994 Criteria for the diagnosis of ME/CFS

Primary symptoms

Clinically evaluated, unexplained, persistent, or relapsing chronic fatigue that is:

- of new or definite onset (has not been lifelong),
- is not the result of ongoing exertion,
- is not substantially alleviated by rest,
- results in substantial reduction in previous levels of occupational, educational, social, or personal activities,
- is associated with post-exertional malaise (PEM)*

Additional symptoms

The concurrent occurrence of three or more of the following symptoms:

- substantial impairment in short-term memory or concentration,
- sore throat,

- tender lymph nodes,
- muscle pain,
- multi-joint pain without swelling or redness,
- headaches of a new type, pattern, or severity,
- unrefreshing sleep

These symptoms must have persisted or reoccurred during 6 or more consecutive months of illness and must not have stated before the fatigue.

*modified for use in clinical diagnosis of ME/CFS, to include PEM as compulsory symptom (EUROMENE recommendation). Source: Fukuda et al. 1994.

Box 4. Paediatric diagnosis of ME/CFS

A diagnosis is based on persistent symptoms as below:

Compulsory symptoms:
- Impaired function
- Post-exertional symptoms
- Fatigue

In addition, 2 of 3 groups of symptoms are required:
- Sleep problems
- Cognitive problems
- Pain

A diagnosis is made if all the criteria below apply:
- Symptoms are persistent for 6 months (or for 3 months if post-infection) and at least some occur daily and are at least of moderate severity
- Other diagnoses are excluded by history, physical examination, and medical testing, including learning disabilities.
- Severity of symptoms over a pre-determined cut-off score

For full details, see reference (Rowe et al., 2017). For research we recommend using the DePaul Symptom Questionnaire Pediatric (DSQ-Ped) (Jason and Sunnquist, 2018)

Approach to the diagnosis and characterisation of patients

Steps to recognising ME/CFS cases in clinical practice

Clinical history

History reveals the main symptoms, including extreme fatigue, fatigability and cognitive difficulties that are worsened by physical or mental effort. Physical fatigue is often expressed as “lack of energy or stamina”, profound tiredness or general weakness (Box 5).

Mental fatigue is expressed as cognitive problems, such as slowness of response, attention, and concentration problems; they are often referred by patients as “brain-fog” and result in reduced ability to perform “mental tasks”.

There is significant intolerance to efforts, both physical and mental, with post-exertional aggravation of symptoms, or PEM. PEM typically has delayed onset, often noticed hours later or the following day, and lasts for variable and often extended periods of time – e.g. from a day in milder cases to many days or weeks in moderately and severely affected individuals.

Sleep is characteristically "non-restorative" or "unrefreshing", and difficulty in initiating or maintaining sleep are common.

Orthostatic intolerance may be manifested with light-headedness and worsening of symptoms (such as fatigue, malaise, dizziness, nausea, palpitations) when assuming or persisting in the upright position for some time, usually a few minutes, but it may happen very soon after raising from the recumbent position or within up to 10 minutes or more, depending on severity of the dysautonomia. The most severely affected may be unable to stand for more than a few seconds.

Pain can be generalised and referred to joints, muscles, and adjacent soft tissues, with frequent headaches commonly reported. Pain may be migratory and variable in nature and is not associated with signs of inflammatory arthritis or myositis, with typical absence of join swelling or redness.

There is considerable symptoms overlap between ME/CFS and fibromyalgia (Faro et al., 2014), and a concomitant diagnosis of fibromyalgia (Ferrari and Russell, 2013, Wolfe et al., 2016) is often made. The latter requires pain to be generalised (present in at least 4 of 5 body regions) and widespread and accompanied by other symptoms, such as fatigue, poor sleep and cognitive difficulties (Wolfe et al., 2016).

Importantly, the symptoms of ME/CFS lead to substantial reduction in previous levels of activity and function. Some individuals will still manage full-time work or education, at least for some time, However, very often patients are unable to take up or continue full-time work or education, or any at all, with a significant minority (often quoted as corresponding to 25% of all patients) virtually home- or bedbound. Educational, social, and economic consequences take their toll, with resulting compromise in emotional wellbeing.

Box 5. Symptoms and complaints to consider when taking a clinical history

Key symptoms

- Persistent debilitating symptoms that include extreme fatigue or lack of energy, assessed by the impairment in the ability to work, study, or undertake domestic tasks, leisure activities and social interactions
- Persistent exhaustion or unusually high levels of fatigue, aggravated by low levels of exertion, still upright position and stress (physical or emotional, such as infections or raised anxiety levels).
- Post-exertional malaise, or post-exertional exacerbation of symptoms: any or all symptoms can get worse following physical or mental efforts and stress - this can happen immediately or more typically delayed after a period following the exertion, e.g. which may be longer than 24 hours; recovery to previous levels of functioning and symptom severity may last long (typically from a day to weeks).
- Sleep dysfunction with unrefreshing sleep, i.e. waking up not feeling rested as one would expect following a good night's sleep.

- Complaints of cognitive impairment, such as poor memory, attention, and concentration, slow thinking, reasoning difficulties, sense of disorientation, or "brain fog".
- Pain: muscle and joint pains, which may affect multiple sites and be migratory, but without local signs of inflammation; headaches (tension or migraine type); existing musculoskeletal symptoms may worsen.

Additional symptoms

- Orthostatic intolerance, defined by symptoms occurring only or worsened in the upright position (particularly when not associated with movement – i.e. in the still position), and improved by lying down, e.g. palpitations, tremors, light-headedness, dizziness, weakness, nausea
- Over-sensitivity to stresses and sensory stimuli such as light, noise, temperature changes or touch
- Intolerance to dietary and environmental factors, such as to alcohol, selected or multiple food intolerances and medications, new allergies
- Infection- like immune symptoms, e.g. frequent and prolonged symptoms of upper respiratory tract infections, such as flu-like symptoms, tender cervical lymph nodes, sore throat, congested nose, shortness of breath
- Symptoms of irritable bowel syndrome
- Weight loss or gain
- Sicca-symptoms (dry eyes, mouth, or the opposite: hypersalivation)
- Emotional instability, anxiety, and depression

Symptoms characteristics

Symptoms may start following infectious or other insults or insidiously. These are persistent, but they may fluctuate from day to day or during the day. Some people experience temporary partial remission of symptoms, which are followed by recurrence, and may occur after physical or mental exertion beyond their tolerance level.

Although *specific symptoms* vary in presentation and severity, the symptoms tend to follow a typical pattern of inter-relatedness. This means that patients may have difficulties in distinguishing whether their symptoms arise from lack of energy, pain, or sleep deprivation, for example.

Fatigue and intolerance to efforts are key symptoms which are not always easy to interpret

- *Fatigue* is a main symptom, but its description and interpretation are variable. It usually represents a feeling of intense lack of physical energy or stamina and mental tiredness (reduced mental clarity with slowness in thinking and difficulty in understanding and processing information, focusing attention and forgetfulness), which restricts the ability to undertake physical and mental activities.
- *Intolerance to efforts is a key symptom, which relates to disease severity and previous levels of functioning.* The most severely affected may be limited in simple movements in bed, speaking, or engaging in conversation, eating, and activities of daily living such as going to bathroom, bathing, showering or dressing), milder cases who were previously very active (e.g. athletes) may remain active, though much less than previously.

Clinical examination

- General physical examination may be entirely normal. However, some patients present with general aspect of tiredness or of being unwell. Nutritional status is usually satisfactory, though overweight or obesity may result from long-term inactivity or as a neuro-endocrine manifestation of the disease. On the other hand, signs of weight loss or low body mass index (BMI) may be present, more commonly in severely affected patients, though they may also raise suspicion of other severe morbidity; signs of neglect or poor care with basic needs, if noticed, should raise concerns about the wellbeing of the patient. Paleness and cold extremities may be noted.

- Orientation and cognition; patients are oriented but they may show signs of slow thinking, poor attention and short memory and be lost for words; long consultations may elicit increasing cognitive and physical difficulties as the patient tire; on the other hand, some patients may show signs of anxiety and "wire-tiredness", where they are restless in spite of being very tired physically and mentally. Emotional responses may be triggered as patients go through their histories and common difficulties experienced with their symptoms and lack of validation of their diagnosis and degree of disability, which are often not obvious to the untrained observer. In general patients are highly motivated and willing to do whatever may be needed to improve their symptoms. However, secondary anxiety and depressed mood may be observed, and lack of motivation or despondency should raise the possibility of associated low mood.

- Skin: paleness and cold extremities may be noted, often aggravated by upright position, which may be associated with low peripheral perfusion or autonomic dysfunction. Redness of lower extremities when sitting or standing may also be noted as a consequence of venous congestion.

- Head and neck: enlarged lymph nodes may be noted especially on the neck and might be tender, non-exudative pharyngitis might be observed and crimson crescents in the oral pharyngeal region have often been described (Lapp, 2019).

- Chest and cardio-vascular: Examination of the lungs and heart are usually unremarkable, except for possible changes in heart rate and blood pressure. Mild regular tachycardia may be present at rest. Postural tachycardia (standing heart rate of >30/min in patients older than 20 years and > 40/min in younger patients compared to laying down or >120 standing heart rate at any age) may happen immediately or within 10 minutes or more after standing up from the recumbent or sitting position; it may result from dysautonomia or relative hypovolemia and result in the diagnosis of postural tachycardia syndrome (POTS). Some patients develop hypotension upon standing, sometimes after a brief period of raised blood pressure. These signs are more common in the young and in some over-medicated patients and may be associated with postural hyperemia or cold extremities.

- Abdomen: general standard examination is conducted to rule out other explaining diseases; mild diffuse abdominal tenderness is not uncommon.

- Musculoskeletal: joints appearance is usually normal (no oedema or redness); tenderness of joints and soft tissues may also be present. Some patients have hypermobile joints or fulfill the clinical criteria of hypermobile Ehlers-Danlos syndrome (hEDS) (Beighton et al., 1973; Bragée et al., 2020), which should be recognized as a comorbidity.

- Brief neurological examination: This is usually normal, muscle fatigability is shown by lower handgrip strength compared to healthy individuals, or by a rapid fall in grip strength measures during

repetitive muscle contractions, particularly in severely affected cases (Nacul et al., 2018). Sensory examination may be normal though hyperalgesia or allodynia may be present. Cognitive difficulties, and the occasional fasciculation may be noticeable (Hickie et al., 2009) . Brisk symmetrical reflexes in arms and legs may be observed. Cranial nerve examination is usually normal; however, pupil reaction might be slow. Subtle gait abnormalities may be associated with a feeling of instability; although full-blown Romberg sign at examination is atypical (Boda et al, 2015). A brief psychiatric assessment may show signs of associated anxiety or mood disorders or the presence of an alternative diagnosis. Signs suggestive of specific neurological or psychiatric abnormalities should be investigated further.

- In the more severely affected, signs of frailty may be evident; patients may be virtually bed-bound, sit in a wheel-chair, they may have a pale and puffy face, cold extremities and may not be able to remain or may feel very uncomfortable in the upright position for longer than a few seconds or minutes. There is a general sense of weakness and lack of stamina, and short periods of break during clinical assessment may be required as the patient becomes visibly tired and shows signs of increasing cognitive difficulty. Symmetrical reduction in limb muscle strength may be observed on formal neurological examination, and hand grip manometer will usually show reduced power, with decreasing values on repeated measurements.

Differential Diagnosis

Since fatigue is a common complaint in daily life and in association with a range of medical problems, it is important to note that most people with ongoing fatigue do not have ME/CFS, but rather have symptoms that are caused by other conditions, emotional well-being or life-style-factors. The presence of PEM, however, raises the level of suspicion, as this is quite typical, though not specific of ME/CFS.

The list of co-morbid conditions and differential diagnoses is exhaustive. Examples are listed in Boxes 6 and 7. Some conditions are often present concomitantly to ME/CFS (co-morbidities). Other conditions may potentially exclude a diagnosis, if they fully or mainly explain the symptoms. However, such conditions may also be co-morbid, when their presence does not explain most of the symptoms and signs observed. In general, when one of these conditions are present and are not well-controlled, the patient should be offered optimum treatment and stabilization, before a diagnosis of ME/CFS is considered. Severe conditions should be explored early and excluded or treated promptly. Action is prompted by clinical suspicion and red flags, such as: unintentional weight loss, prolonged fever ≥ 38 °C, persistently elevated inflammatory markers, significant abnormalities in physical examination, or suicidal ideation. Box 8 includes suggested diagnostic sub-categories, which may change as the clinical picture and further clinical and related information arise.

Box 6. Co-morbid conditions which do not exclude ME/CFS diagnosis

• Fibromyalgia • Restless legs syndrome, periodic limb disorder • Postural orthostatic tachycardia syndrome (POTS) • Neuro-mediated hypotension • Irritable bowel syndrome • Food intolerances and atopic conditions • Mild anxiety • Mild depression	• Hypermobility Ehlers-Danlos syndrome • Myofacial pain syndrome • Small fibre neuropathy • Sicca symptoms • Chronic pelvic pain, endometriosis • Interstitial cystitis • Hashimoto thyroiditis; hypothyroidism (controlled clinically) • Migraine • Mast cell activation disorder, eosinophilic esophagitis

Box 7. List of diseases where fatigue may be a prominent feature. **These usually exclude diagnosis of ME/CFS**, if symptoms are mostly or largely explained by the condition (other than ME/CFS). They may be co-morbid with ME/CFS if condition is well controlled and not expected to lead to most of the manifestations within the ME/CFS spectrum (fatigue, cognitive complains, sleep dysfunction, PEM).

- Hypothyroidism
- Hyperthyroidism
- Malignancy
- Rheumatoid arthritis, systemic lupus erythematosus, polymyositis, Sjogren syndrome, psoriasis arthritis
- Crohn's disease, ulcerative colitis, coeliac disease
- Post-concussion syndrome, post-ICU syndrome, post-traumatic stress disorder
- Heart disease, such as heart failure
- Severe chronic obstructive pulmonary disease, other severe respiratory diseases
- Severe anaemia, vitamin B12 deficiency, hemochromatosis
- Renal failure
- Diabetes mellitus
- Addison's or Cushing's disease, hyperparathyroidism and other endocrine disorders
- Bipolar disorder, schizophrenia, major depression, anorexia, bulimia, autism
- Multiple sclerosis, myasthenia gravis, other neuroimmunological diseases, paraneoplastic syndromes
- Parkinson's disease, Alzheimer's disease, stroke, other serious neurodegenerative diseases
- Sleep apnoea
- Narcolepsy
- Hepatitis, tuberculosis, HIV/AIDS, neuroborreliosis, other chronic infections
- Excessive consumption/abuse of alcohol or other substances

Detailed clinical characterization, laboratory, and other tests

Further patient characterization may involve the use of standard questionnaires – which may be self-completed or applied by an interviewer, and physical measures, which are used to assess function and disease severity. They are useful for patient's baseline evaluation and when repeated subsequently, they provide indicators of disease course and evaluation of response to treatment. Core assessments shown in Box 8 include examples of tests that may be used routinely for that aim. When research studies are linked to clinical practice, these and other questionnaires and instruments may also be used (see Mudie et al, submitted to preprints).
Further laboratory tests and imaging studies may be needed to identify potential co-morbidities, and/or to exclude other diagnoses. These should be guided by clinical assessment and the need to exclude severe conditions that may explain the symptoms.

Examples of useful screening tests for initial investigations in primary care include: Full blood count, ferritin, liver enzymes, renal function, thyroid function, high-sensitivity C reactive protein (CRP) or erythrocyte sedimentation rate, electrolytes including sodium, potassium, calcium, inorganic phosphate, creatine phosphokinase (CK), and fasting glucose or glycated haemoglobin.

Serology screening for EBV, hepatitis B and C, HIV, Lyme and other tick-borne diseases may be useful according to clinical and epidemiological features (Twisk, 2014).

Other tests may be required according to availability of resources, or as clinically guided. These are usually reserved for specialist centres or are done through referral to other specialities. These are usually aimed at differential diagnosis, but could also be used for better characterization of pathology or for the assessment of function and disability (Box 6). Examples include anti-CCP, transglutaminase antibodies, morning cortisol, vitamin B12, NT-pro BNP, and vitamin D3 or 25(OH)D. In some cases an extended auto-immune screening, allergy testing, serum tryptase levels, and/or lymphocyte differentiation may be required. Imaging and other specialised tests may be appropriate in some cases, but are usually reserved for specialist centres e.g. brain or spine MRI, cardiopulmonary exercise testing (CPET), cognitive testing panel, echocardiography, and tilt table or standing test.

Tests results will often be unremarkable, though subtle abnormalities may be observed (Nacul et al., 2019). Routine inflammatory markers are usually not elevated in ME/CFS. Low CK suggests severe disease or very low physical activity levels. Elevated LDH and GPT/GOT are found in a subset of patients. Elevated NT-pro BNP might be found and is associated with lower cardiac volume (Tomas et al., 2017); this should be investigated further. A subset of patients has diminished IgG/A/M levels and/or IgG subclass deficiency (Guenther et al., 2015). Marked abnormalities should raise the suspicion of an alternative diagnosis.

Box 8. Core and additional assessments that may be recommended for ME/CFS secondary care services

Domain or specific clinical situations	**Clinical, laboratory, and imaging assessments or measurement instruments**
CORE ASSESSMENTS	
Severity assessment	UKMEB-PQsymp; DPQ, RAND-36, Pain and fatigue analogue scales
Disability screening	RAND-36 summary scales (physical and mental component summaries)
Muscle power and general health	Hand grip measurements, dynamometer
ADDITIONAL ASSESSMENTS	
Routine tests not done recently and justified clinically	Tests as appropriate
If clinical history suggests autoimmune or immunodeficiency	ANA, ENA, TPO, AMA, APA, immunoglobulins and others according to clinical findings
Serious neurocognitive symptoms, that increase risks for patients	Neurocognitive tests - e.g. Creteil battery of tests (Auon Sebaiti et al; submitted to Cortex*); NIH CDE Toolbox (National Institute of Neurological Disorders and Stroke (NINDS), 2018)
Neuro-imaging as needed for further neurological investigations	MRI scan, CT
Obstructive sleep apnoea suspected	Sleep studies, polysomnography
Signs of small fibre neuropathy, peripheral neuropathy, marked muscle symptoms, objective peripheral findings	Nerve conduction studies, electromyography (EMG), skin (for intradermal nerve fibre density) or muscle (rarely necessary) biopsy
POTS, orthostatic intolerance	Tilt table test or repeated recumbent and standing heart rate and blood pressure (standing test)
Objective assessment of PEM or disability	2-day CPT (use with caution as can cause or aggravate PEM)

*a selection or the full range of tests may be conducted routinely or in support of disability assessment. AMA: anti-mitochondrial antibody. ANA: anti-nuclear antibodies. APA: anti-phospholipid antibodies. CPT: cardio-pulmonary testing. DPQ: DePaul Symptom Questionnaire. ENA: extractable nuclear antigens. PEM: post-exertional malaise. POTS: postural orthostatic tachycardia syndrome. TPO: thyroid peroxidase. UKMEB PQsym.: UK ME/CF Participant Questionnaire

Steps to recognising the ME/CFS in children

None of the criteria used in adults have been validated for the diagnosis of paediatric ME/CFS. Diagnosis of ME/CFS in children is especially challenging for two main reasons: First, younger children may not report symptoms accurately and might assume fatigue as normal, when not remembering the experience of full health. Second, there are differences in how children perceive and report symptoms of ill health, and proxy reporting by parents may not always accurately reflect children's experience. To account for the latter, paediatric ME/CFS should be diagnosed if CCC are fulfilled for as little as 3 months

and no other underlying disease has been identified (Box 2). Owing to differences in manifestations and their ascertainment in children, compared to adults, a paediatric case definition that uses the structure of the CCC 2003 adults definition and some aspects of the CDC-1994 criteria was published in 2006 (Jason et al., 2006) and modified in 2018 (Jason and Sunnquist, 2018), and most recently, a group of experienced paediatricians suggested a "Clinical Diagnostic Worksheet" (Rowe et al., 2017) (Box 4). This guidance refers to "impaired function" or a "substantial reduction in the child's ability to take part in personal, educational, and/or social activities" associated with fatigue and PEM as cardinal symptoms. Other symptoms including headaches, myalgia, joint pain, sore throat, painful lymph nodes, and abdominal pain are scored as "pain"(Rowe et al., 2017).

Symptoms usually start acutely, often following symptoms of infection, e.g. flu-like symptoms, or gastroenteritis, but may have insidious or episodic onset. In children, about half of the cases of ME/postinfectious fatigue syndrome manifest after typical Epstein-Barr-virus (EBV)-associated infectious mononucleosis (Rowe, 2019, Williams et al., 2019). Symptoms are usually fluctuating in type and severity (especially in the early stages of the disease), with patients typically reporting "good" and "bad" days. A more careful analysis of the pattern of symptoms may reveal correlation with physical or mental efforts.

Primary care professionals may suspect a diagnosis in children and adolescents presenting with persistent or recurrent moderate to severely impaired function, fatigue and post-exertional symptoms, especially if associated with autonomic symptoms, sleep disturbance, neurocognitive problems, and pain (e.g. headaches and abdominal pain), following history, clinical examination, and routine tests that exclude other diagnoses that may explain the symptoms. We recommend paediatricians use the full criteria from Rowe et al. (2017) as part of diagnostic approach, and the CCC 2003 criteria (Carruthers et al., 2003) or if symptoms are present for 3 months.

Diagnostic categories

A proposed diagnostic characterization of patients, which builds on previous disease criteria definitions, is shown in Box 9, which also suggests stratification variables that may be used for sub-grouping of cases.

Box 9. Diagnostic categories and sub-grouping

Symptom description

Prolonged fatigue: persistent profound fatigue or lack of energy, usually (but not necessarily) accompanied by other symptoms; should be present for at least one month

Chronic fatigue (CF): persistent fatigue or lack of energy, that leads to reduced activity levels lasting over 3-6 months*. This may be explained by a condition other than ME/CFS (e.g. cancer-related fatigue), or unexplained ("idiopathic chronic fatigue"). It does not require other symptoms that are typically found in ME/CFS

Post-infectious fatigue or post-viral illness (PIF or PVI): new onset symptom complex including persistent profound fatigue with exercise intolerance following an infectious trigger, and which are not otherwise explained by a diagnosed condition or lifestyle. It is usually accompanied by at least 2 further symptoms** from: post-exertional malaise, unrefreshing or poor sleep quality, cognitive or autonomic symptoms for at least 3 months

Diagnostic categories

- ***ME or ME/CFS:*** persistent fatigue or lack of energy, that leads to reduced activity levels lasting over 3-6 months, when diagnostic criteria according to IOM or Canadian Consensus criteria (CCC) are fully met for adults; and CCC or Rowe's criteria are fully met in children.

- ***ME/PVFS (ME/Post-viral fatigue syndrome or post-infectious fatigue syndrome, post-infectious ME/CFS):*** As for ME/CFS, when symptoms follow a presumed or confirmed infection (e.g. post-COVID-19 fatigue syndrome, post-mononucleosis fatigue syndrome, post-Lyme ME/CFS)

- ***Non-ME chronic fatigue:*** chronic fatigue cases that do not fulfill the diagnostic criteria for ME/CFS, lasting for at least 3-6 months

- ***ME/CFS of combined aetiology:*** when symptoms are attributed to a combination of ME/CFS and other known disease(s), e.g. ME-CFS/diabetes type 2

Examples of stratification categories:

- Age-group (e.g. children, adolescents, adults, elderly), gender
- Illness onset: acute or gradual; post-infection, following other triggers, e.g. environment exposure
- Presence of co-morbidities, e.g. fibromyalgia, hypermobility, mild mood disorders
- Phase of disease (or disease duration), e.g. early, established and complicated disease (Nacul et al, 2020)
- Severity (based on symptoms score or measures of function); a broad category of severe/ non-severe is based on being virtually house-bound or able to regularly be outside home. Very severe cases are virtually bed-bound.
- Clinical phenotype: Based on predominance of symptoms by type (e.g. based on CCC symptoms sub-groups); e.g. neuro-cognitive, immune, sleep phenotypes.
- Molecular phenotype: i.e. based on well-defined profiles based on results of specialised investigations, e.g. metabolic, immunological.

*CCC 2003, IOM 2015, and Rowe et al., 2017 criteria require 6 months of symptoms; experienced clinicians should be able to diagnose adults with 3 months of symptoms. For children, CCC criteria requires 3 months, and Rowe et al., 2017 require 3 months in post-infectious cases.

** the 2 additional symptoms criterium is not required when the fatigue symptoms can be clearly linked to the triggering infection and are not explained by other pathologies

Chronic fatigue-spectrum disorder (CFSd) is an encompassing term and may be used to refer to persistent profound fatigue for over 3-6 months associated with other symptoms, including the following sub-categories: a) cases meeting diagnostic criteria for ME/CFS; b) cases that do not fully meet diagnostic criteria (Non-ME chronic fatigue-Sd) but cannot be explained otherwise; c) cases totally or partially explained by other diseases known to cause chronic fatigue (disease-associated CFS; or ME/CFS of combined aetiology)

Recommendations for health care provision

Primary care professionals have an important role in the initial diagnosis, including consideration of alternative conditions leading to similar symptoms. It is important to note that many symptoms

commonly reported in ME/CFS have a low disease-specificity and may occur in a number of diseases. Acute infectious onset and PEM should always prompt to consider ME/CFS. Although diagnostic confirmation may require a 3- to 6-month period, it is important to contemplate the diagnosis at earlier stages, so that disease management may start and diagnosis and treatment of alternative diseases are not delayed (See Box 7).

Careful medical history, including social and occupational history and circumstances associated with the start of symptoms and subsequent progress will give significant clues on diagnosis. Information should be obtained on current and previous treatments, including prescribed and over the counter medicines and supplements as well as self-management strategies and alternative therapies. It is important to check for medications potentially leading to fatigue as well as autonomic-related and other symptoms. Physical examination and routine bloods tests are required to increase diagnostic accuracy and detect alternative conditions explaining the symptoms.

Patients with ME/CFS tend to be multi-symptomatic and often have long clinical histories, which may include various failed attempts to obtain a diagnosis and treatment. Multiple previous investigations are not uncommon, however, often symptoms presented are discarded by clinicians as “exaggerated” or “imagined”, related to excessive work or studies or as mood-related. Such scenario is to be avoided through early recognition and diagnosis, which are reliant on better knowledge of the disease and education of doctors and other health professionals.

When a diagnosis is suspected in primary care, regular reviews are warranted, when the possibility of alternative diagnoses are explored at the same time as initial management strategies are put in place. In such cases, it may be helpful to ask the patient to record their symptoms and other health parameters using standard instruments in advance of follow-up consultations (see Core Assessments, Box 8,).

Education of patients in advance to, during, and following consultation may be useful, and reliable educational materials should be recommended, e.g. booklets, videos, or other online information materials. These should cover concepts and practical recommendations for “pacing” with adequate rest periods or breaks in activity, sleep hygiene and pain management strategies. Both mental and physical activities should be taken in such a way to avoid over-exertion, which may trigger post-exertional aggravation of symptoms or “crashes”, and as key strategy to optimise chances of recovery. A main goal of educational activities is to empower the patient for self-management and to be in control of their disease and healing process.

Criteria for referral for specialist services

Although with good education of primary care physicians, diagnosis and monitoring of people with ME/CFS in primary care are possible and desirable, referral for specialist services may be indicated in some circumstances (Box 10): Confirmation of diagnosis, when there is doubt; for cases who may benefit from a multi-disciplinary team with specific expertise, including drug treatments or care of those with severe or complicated disease, and a range of service offerings, such as occupational therapy, supportive counselling, education on self-management and energy/activity management with “pacing”, social services, and advise on access to community support, e.g. for educational, occupational, and social matters, such as benefits (see below on secondary services). Patients with more recent disease onset, such as those with less than 1-2 years of symptoms and the young (children, adolescents, and young adults) may also benefit from referral for initiation of multicomponent therapy, as early referral

at this age might especially affect long-term prognosis. The more severely affected including those who are house- or bedbound and severely disabled should also be priority for referral, esp. where appropriate home-visits or telemedicine are available and, when necessary, for occupational, educational, and disability support. Note that some cases may be best served by referral to alternative services, esp. where ME/CFS or Complex Chronic Diseases (CCD) Services are not well developed, such as to pain management, rehabilitation, neurology, psychiatry, and rheumatology services.

Box 10. Examples of criteria for referral to secondary services caring from people with ME/CFS

Diagnosis confirmation
Young people
Severe cases or significant disability, especially if local support is limited
Short duration of symptoms (less than 1 or 2 years)
Rapid deterioration of symptoms
Complex diseases, where diagnosis and treatment are challenging
Inability to provide adequate care in the community or when management and treatment are only availalbe at specialist services

The continuing role of primary care and the general practitioner

In general, irrespective of referral to secondary care, whenever possible, the primary care team should continue to take responsibility for the long-term care and monitoring of patients with ME/CFS and their treatment, whenever possible in partnership with the specialist team. This includes facilitating the provision of emotional, social care, and occupational health support, and medical advice to teachers, employers, and caretakers, in response to specific needs of patients. This could involve access to resources in the community, such as to physiotherapy, occupational therapy, dietician, or home visits by the primary care team (esp. the more severely affected), e.g. by district nurses. Support for self-management, education, and work activities may require further contacts with the patients and their carers/ family as well as with educators and employers. Here, online educational materials may be of value, as well as group educational activities for patients. Organization of care for people with ME/CFS and in particular the severely affected may be complex and requires communication of the primary care professional with others from various disciplines.

The primary care provider will still have major responsibilities for searching for alternative diagnoses, where relevant and dictated by clinical judgement, for dealing with co-morbidities and other diseases that may be not directly related to the diagnosis of ME/CFS, and for referring to different specialists as appropriate. Pharmacological and non-pharmacological approaches to treatment and clinical progress should be reviewed. It is important to consider that patients with ME/CFS may be more sensitive to a range of medications; this also needs to be considered when treating other conditions; having in mind also the possibility of drug interactions.

Needless to say, the strength of primary and secondary care services in particular settings will be relevant to determine roles at each care level, and best ways of cooperation between services at different levels. We appreciate limitations of access and service provision in primary care in many places, and local solutions will need to be found in line with local needs and resources. Virtual healthcare or virtual support from the specialist to the primary care team may have an important role.

The ME/CFS specialist consultation

Preparing for the consultation and the waiting room

Before specialist consultation, it may be helpful to obtain relevant information, using standardised questionnaires or data/ information otherwise obtained that may help with diagnostic confirmation, characterization of symptoms and their severity, and life impact. Forms may also be used as baseline clinical information for monitoring disease progress and response to management or treatment. These can be completed before consultation.

Standard questionnaires include the UKMEB Symptoms Assessment Questionnaire (SAQ), to aid diagnosis and the Participant Phenotyping Questionnaire (PPQ), for severity profiling (Lacerda et al., 2017) or the DePaul Symptom Questionnaire, allowing diagnosis and symptom severity profiling (Bhatia et al., 2019). The Impact on function and quality of life may be measured by standard instruments, such as Rand-36 (Hays et al., 1993, Varni et al., 2001), some of which have been validated in many languages. The Epworth Sleepiness Scale (Johns, 1991) can be used to assess excess daytime sleepiness and as a screening for obstructive sleep apnoea. Other instruments may be used to screen for mood disorders, e.g. neuroQOL (Northwestern University, 2020) or HADS (Zigmond and Snaith, 1983) for depression and anxiety, or GAD-7 (Spitzer et al., 2006) for anxiety. Fatigue severity may be measured by instruments validated for ME/CFS (e.g. fatigue severity scale (Krupp et al., 1989); visual scales such as pain and fatigue analog scales are simple to use (Huskisson, 1974, Tseng et al., 2010). The same applies to sleep disorders (e.g. Pittsburgh Sleep Quality Index (Buysse et al., 1989)), and autonomic symptoms (e.g. Compass 31(Sletten et al., 2012)). A diagnosis of fibromyalgia may be established with good degree of confidence by the annotation of pain symptomatology in pictorial representation of the human body (https://acrabstracts.org/abstract/2016-revisions-to-the-20102011-fibromyalgia-diagnostic-criteria/). The same is true for the evaluation of hypermobility syndromes, using the Beighton criteria (Beighton et al., 1973).

Diagnosis confirmation and continued search for alternative diagnoses and co-morbidities

The list of differential diagnosis of fatigue is exhaustive. Examples are listed in Box 7. Some conditions are often present concomitantly to ME/CFS (co-morbidities). Other conditions may potentially exclude a diagnosis, if they may fully or mainly explain the symptoms. However, such conditions may also be co-morbid, when their presence does not explain most of the symptoms and signs observed.

For diagnosis confirmation, we recommend the use the CCC in both adults and children (Carruthers et al., 2003). Additional tools for adults include The IOM criteria (Institute of Medicine (IOM), 2015), and for children the paediatric “Diagnostic Work Sheet” (Rowe et al., 2017) and/or the DSQ-PED (Jason and Sunnquist , 2018). Full consideration needs to be given to differential diagnosis and co-morbidities, and the need for detailed history, physical examination, and complementary tests, as appropriate, cannot be under-estimated. Further tests may be recommended in secondary care settings, according to the need for supporting ME/CFS diagnosis and/or severity, and for differential diagnosis. Box 8 lists some assessments that may be suggested. Those marked are suggested to be run routinely at the first assessment, and the others should be evaluated on a case-by-case basis, based on the clinical presentation. RAST tests for specific allergies, echocardiography and serology for specific infectious diseases as guided by clinical and epidemiological information are other modalities that may be considered as appropriate.

Treatment for children and young people should usually be started by a paediatrician or a ME/CFS secondary care specialist centre that includes a paediatrician.

Further referral may be required, when alternative diagnoses are suspected. This may include referral to a neurology or multiple sclerosis (MS) clinic and/or to specialists in ophthalmology, ENT, immunology (autoimmunity, immune dysfunction), allergology, orthopaedics, physical therapy, infectious diseases (travel-related disease), psychiatry, or gastroenterology.

Management and treatment

In the absence of disease-specific treatment, key roles of the health professional include confirming the diagnosis, explaining to the patient the importance of avoiding overexertion and mental stress, “pacing”, and symptomatic medication as needed and appropriate for the patient. Regular monitoring is important, when progress should be assessed, and the possible development of new diagnoses and co-morbidities considered, as the management plan is reviewed. “Pacing” refers to breaking physical or mental activities with periods of rest, before a significant level of tiredness or exacerbation of symptoms is achieved or is expected following exertion, e.g. PEM, which may manifest many hours after the effort. A general rule of thumb is the recommendation to keep the activity at 2/3 of the duration and of the intensity that is expected (based on previous experience) to cause post-exertional symptoms.

The goal of management/treatment program is to treat the most distressing symptoms (sleep disturbance, pain, orthostatic intolerance, or others) and empower the patients to be in control of symptoms and the disease by encouraging them to trust their own experiences, and enhance their awareness of the activities and environments in which they can cope without exacerbating symptoms, and “pace” themselves accordingly. The program should aim at optimizing the patient’s ability to maintain function in everyday activities, being as active as possible within their boundaries, and then gently extending those boundaries(Carruthers et al., 2003). This may be challenging, especially in the more severely affected who may be able to tolerate only very low levels of activity; those with less severe forms of disease are likely to “over-do” and may have frequent exacerbations of symptoms (“crashes”) as a consequence.

Wearables can assist objective measurement of activity and sleep patterns, and in some cases heart rate variability. They may be combined with a symptom diary, which will help the interpretation of symptoms and management.

Professional-patient partnership, self management, and support

It is important to establish a supportive and collaborative relationship with the patient suffering from ME/CFS and, as appropriate, with their caregivers. Engagement with the family may be essential, especially for children and young people, and for people with severe ME/CFS. A named healthcare specialist should be involved for coordinating care for the person with ME/CFS. Information to people at all disease stages should be according the person’s circumstances, including clinical, personal, and social factors. Information should be available in a variety of formats as appropriate (printed materials, electronic videos and audios).

The doctor-patient partnership, informed choices and risk minimisation are essential components of care. Partnership between patient and health care providers should be based on trust, and consider their interactions as encounters between two experts with different, but complementary backgrounds (the patient and the healthcare provider), who recognise the incomplete knowledge about the disease and its management. Basic management principles should apply, but often, different treatments may be attempted (preferably one at a time, on a trial and error basis), and reassessed according to response or potential adverse effects. This is when the strength of the partnership becomes even more important, as partners engage in a journey where uncertainty is gradually replaced by increasing understanding of the disease/health process, as treatment and management strategies are regularly reviewed and adapted to suit patient characteristics and preferences. Over-investigation and over-treatment are discouraged, but a very passive approach to illness may also be counterproductive.

Managing patients' expectations

It is essential that the professional is upfront in explaining the current limits of treatment and understanding of potential pathophysiology, and the approach to symptom management. This will greatly address discrepancies between patients' and doctors' expectations and set up the conditions for an open and positive patient-doctor relationship, where patients are empowered to make informed choices.

There is no known pharmacological treatment or cure for ME/CFS. However, symptoms should be managed as in usual clinical practice. Physicians may consider starting symptomatic treatment at a lower than usual doses, due to frequent medication sensitivities in this population. The dose may be carefully increased. Treatment and repeat prescription may be continued in primary care, depending on the patient's preference and local circumstances.

Non-pharmacological treatment for symptoms relief and available support therapies

Recommendations considered appropriate are shown in Box 11. It is important that these are provided by practitioners with experience in ME/CFS.

Box 11. Recommendations for a non-pharmacological approach to the relief of ME/CFS symptoms

Pain

- Relaxation/ meditation
- Manual methods (e.g. physiotherapy, acupuncture and acupressure)

Sleep

- Sleep hygiene
- Relaxation strategies

Autonomic dysfunction/POTS

- Stockings
- Increase in water intake (>2 litres/day) or rehydration solutions, drinking frequently
- Increase in salt intake
- Sleep with feet in higher position (a few centimetres higher, increasing very slowly each night, up to what is tolerated)

Diet

- Healthy and balanced diet
- Anti-inflammatory diet
- Reduce ingestion of simple carbohydrates
- Adequate fluid intake
- Adequate ingestion of protein
- Increase unsaturated fatty acids and omega-3 fatty acids
- May try exclusion diets with support from dietician, especially for food with reported intolerances by the patient. It may be worth trying to avoid gluten, lactose, or fructose during a few weeks to test if there is any improvement in symptoms (Haß et al., 2019).

Support measures

- "Pacing" and activity management to work with the "energy envelope" (Jason et al., 2008a)
- Supporting therapies, that could help with coping and adapting to changes in life due to symptoms, within the "energy envelope", and counseling or psychotherapy
- Occupational therapy provided by professionals with experience in ME/CFS patients
- Social workers who could help with social welfare
- Educational needs: Welfare and educational sectors should be involved in the planning and care for affected patients, particularly children, adolescents, and young adults

A professional view on symptom management and relief

"Periods of rest and "pacing" are important components of all management strategies for ME/CFS patients. Physicians should advice people with ME/CFS on the role of adequate rest, how to introduce breaks into their daily routine, and their frequency and length which may be appropriate for each patient. Excessive rest may be counterproductive, except in the initial stages of disease, in the very severe cases, or in cases of acute exacerbation; so it is important to introduce 'low level' physical and cognitive activities, according to the severity of symptoms.
Sleep management is tailored to the individual, the role and effect of disordered sleep is explained, common changes in sleep dysfunction that may exacerbate fatigue symptoms are identified; common manifestations include insomnia, hypersomnia, sleep reversal, altered sleep-awake cycle and non-refreshing sleep. The professional provides general advice on good sleep hygiene and encourages gradual changes in sleep pattern. Relaxion techniques appropriate for ME/CFS should be offered for the management of pain, sleep problems and comorbid stress or anxiety. Examples include guided visualisation, breathing techniques or mindfulness, which can be incorporated into daily routines and rest periods. Although exclusion diets are not generally recommended for managing ME/CFS, many people find them helpful for some symptoms, including bowel symptoms. The patient may attempt an exclusion diet or dietary manipulation under professional guidance and supervision, e.g. from a dietitian. For those with nausea, advice includes eating small portions and snacking on dry starchy food and sipping fluids. The use of anti-emetic drugs should be considered if the nausea is severe." Dr. L. Lorusso

Symptoms relief and management using available pharmacological drugs

Treatment of pain and sleep dysfunction are key, as they may have an indirect impact on other symptoms. Options for the pharmacological treatment of fatigue, including mental fatigue are more restricted. A balance between benefits and side effects, and significant individual variability in treatment response call for individualised treatment. Costs are also a consideration, especially in settings where patients pay for medications out of pocket or where there are restrictions in prescribing medications.

Evidence of effect of various drugs or supplements are scarce and often based on their use for related conditions or on reported use in ME/CFS and clinicians experience. It is important to observe legislations in different countries and to ensure prescription of any drugs not specifically approved or licensed for ME/CFS are discussed with the patient and an informed choice is made. In some settings it may be appropriate to obtain formal signed consent from the patient before introduction of a drug that has not been approved for use in ME/CFS. Regulations on supplements and over the counter medications are usually much less strict, but again, use by patients should be based on informed decision. Finally, it is important to note that many patients have already been taking a range of medications and supplements before reaching the ME/CFS specialist; again, in these cases it is important to discuss continuation or otherwise with the patient, and evidence of benefit on the individual patient, costs, potential side effects, or interactions with other medicines are important considerations. Some examples of pharmacological drugs that could be considered, where appropriate, are listed in Box 12. The use of medications that may address multiple symptoms may be considered.

Box 12. Examples of pharmacological approaches for relieving/managing ME/CFS symptoms*

Pain

- Paracetamol
- NSAID (for short periods, e.g. up to 7 days)
- Gabapentin or pregabalin
- Tricyclics, such as amitriptyline
- Low dose naltrexone
- Duloxetine
- Venlafaxine

Sleep

- Tricyclics, e.g. amitriptyline
- Trazodone
- Melatonin
- Doxepin low dose
- Diphenhydramine
- Promethazine
- Benzodiazepines and Z-drugs (for short periods only)
- Gabapentin/pregabalin

Autonomic dysfunction/POTS

- Fludrocortisone
- SSRI
- Midodrine
- Ivabradine
- Pyridostigmine

Anti-allergic/ anti-inflammatory

- Antihistamines e.g fexofenadine or famotidine
- Sodium cromoglicate

Supplements which may be tried for symptoms such as fatigue or cognitive dysfunction

- Iron (if ferritin < 50 ug/l, transferrin saturation < 20 %)
- Vitamin D
- L-carnitine or acetyl-carnitine
- CoQ-10 or MitoQ
- NADH
- Vitamin B12.
- α-lipoic acid
- Magnesium
- Omega-3 or omega-3/omega-6 combination
- D-Ribose
- Vitamin B1, B2, and/or B6
- Vitamin C

**refer to local guidelines on the use of medications that are not specifically licensed for use in ME/CFS*

Following the consultation and clinical monitoring

Regular follow-ups are opportunities for education, including on self-management, assessment of usefulness of medications and other treatments and side-effects. Follow-up should include monitoring of symptoms, using similar instruments to those used at or before the initial consultation. Examples of instruments that may be used in monitoring patients include: hand grip strength measurement, standing test, serum CK, severity assessment using specific instruments or scales, such as analogue scales for pain, fatigue, sleep, and other symptoms, and specific questionnaires for assessing symptom severity.

Needs of patients with different severities

People who have severe ME/CFS may be unable to carry out activities of daily living and may spend a significant proportion, or all, of the day in bed. The symptoms experienced by patients with severe ME/CFS are diverse and debilitating, and these may fluctuate and change, both in type and in severity. It is therefore important that the management and care plan are flexible and reviewed regularly. People may have severe ME/CFS for years, and recovery is uncertain. Health services need to be prepared to attend to the specific needs of the severely affected, including for home visits or virtual health consultations.

Concluding remarks and recommendations for developing and organising ME/CFS services

The following are general recommendations for fully implemented services, but we appreciate that they are not achievable in the short term in many places, especially where knowledge and training in the field are limited or other resources are scarce. We encourage countries and regions to plan for their services, training, and educational needs according to the specific needs and characteristics of their population and patients, and their organizational structures and resources. A national champion for each country or regions within countries would be highly desirable, especially in places with no or very scarce provision of services for ME/CFS.

For fully functioning services, we recommend 2-4 ME/CFS specialist doctors /1 million population, with a supporting multi-disciplinary team, to include professionals such as nurses, nurse practitioners, occupational therapists, psychologists, dieticians, social workers etc; these would staff outpatient services for diagnosis and follow up. The specialist may be a doctor with expertise in ME/CFS. Internists, neurologists, immunologists, rheumatologists, infectious diseases specialists and general practitioners are particularly suited for this role, but it may be done by doctors of any specialty, as long as they have the right expertise or training. For children, this role is to be filled by paediatricians. At the time of writing we are not aware of any specific programme for the training of doctors to become specialists in ME/CFS, something that has often occurred informally so far. The training and provision of services in secondary care should be aligned with training of primary care physicians to manage cases in the community. We recognize the above target is ambitious, considering the current capacity and status of service provision in the continent. They should be seen as tentative and should not replace the assessment of patients' needs and structure and capacity of services at local and national levels.

The current reality of health services, suggest that, where specialist services are not well developed, we follow a minimum standard of care for those with ME/CFS, that may rely on virtual health and app-technology as well as strong partnership with primary care.

The minimum desirable is one ME/CFS centre providing specialist services for a 10 Million population. These services should also consider the characteristics of the population, including ethnic and cultural diversity. Furthermore, we recommend the specialist services to have the primary aim of confirming diagnosis and setting up treatment/management plans, which should be agreed and carried out by a multidisciplinary team. The follow up could use multi-media approaches, such as remote consultations or telemedicine, as appropriate according to local circumstances and medical regulations. Local care for people with significant disability may need to be provided by primary care teams or local doctors with knowledge about ME/CFS, with support from the specialist services as appropriate. The option of smaller satellite clinics linked to the specialist service would provide full assistance for most and the "eyes" of a competent health professional, in support of remote consultations from the specialist for complex cases.

Finally, it is important to consider that addressing the high needs of people with ME/CFS requires a multi-sectoral approach (Box 13), as well as ensuring health services are organised and delivered effectively. Much of the needs of people affected by ME/CFS arise from their reduced ability to function in society and in more extreme cases to be totally dependent on care for basic needs. Work life and education may be disrupted, with substantial economic and personal impact to individuals and their families; lack of understanding and support, and often stigma, add to the burden of physical suffering from symptoms. It is extremely important to prioritize research and education of health professionals and others in society, so as to address the scientific and societal poor understanding of the dimension of the problem faced.

Box 13. Multi-sectoral approach to ME/CFS

Specific societal sectors

Higher education:

- Development of training for under-graduates and post-graduates, including training for primary care staff and occupational physicians

Educational sector:

- Development of materials for teachers and education staff, as well as for pupils with ME/CFS and their parents

Work & pensions:

- Development of adequate instruments for assessing disability and flexibility in workplaces, particularly after returning to work, to minimise the risk of relapse

Health sector and public health:

- Adoption of guidelines, flexibility on the use of medications for management of symptoms
- Public health strategy for raising awareness about stigma, importance of care and education to avoid aggravation of symptoms and/or relapse
- ME/CFS services development and evaluation

Funding agencies and pharmaceutical industry:

- Research funding and support for well-designed clinical trials

Author's contributions

LN, JA, RV, and EL conceived and designed the outline of these recommendations. All authors contributed with review of evidence, discussions. All authors contributed to the final editing and have read and approved the final manuscript. The work was part of the activities of the EUROMENE.

Ethics statement

CS has a clinical study grant and speaker honoraria from Takeda and Fresenius and is consultant for Celltrend. RV is consultant for Alfasigma SpA Bologna Italy. JAM has collaborated with Vitae, Pharmanord, Vinas Laboratories in research on coenzyme Q10, NADH, selenium and melatonin, and has a patent with Grifols Laboratories for the use of alpha-1-antiprypsin in CFS. All other authors declare no conflict of interests. The manuscript does include patient-related data or samples.

References

BAKKEN, I.J., TVEITO, K., GUNNES N. 2014. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008-2012. *BMC Med, 12:167*.

BEIGHTON, P., SOLOMON, L. & SOSKOLNE, C. L. 1973. Articular mobility in an African population. *Ann Rheum Dis,* 32**,** 413-8.

BHATIA, S., OLCZYK, N., JASON, L. A., ALEGRE, J., FUENTES-LLANOS, J. & CASTRO-MARRERO, J. 2019. A Cross-National Comparison of Myalgic Encephalomyelitis and Chronic Fatigue Syndrome at Tertiary Care Settings from the US and Spain. *American Journal of Social Sciences and Humanities,* 5**,** 104-115.

BODA, W.L., NATELSON, B.H., SISTO, S.A., TAPP, W.N. 1995. Gait abnormalities in chronic fatigue syndrome. *J Neurol Sci.; 131(2):156-61*.

BRAGÉE, B., MICHOS, A., DRUM, B., FAHLGREN, M., SZULKIN, R. & BERTILSON, B. C. 2020. Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Frontiers in Neurology,* 11.

BUYSSE, D. J., REYNOLDS, C. F., 3RD, MONK, T. H., BERMAN, S. R. & KUPFER, D. J. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res,* 28**,** 193-213.

CARRUTHERS, B., JAIN, A. K., DE MEIRLEIR, K. L., PETERSON, D. L., KLIMAS, N. G., LERNER, A. M., BESTED, A. C., FLOR-HENRY, P., JOSHI, P., POWLES, A. P., SHERKEY, J. A. & VAN DE SANDE, M. I. 2003. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *Journal of chronic fatigue syndrome* 11**,** 7-115.

CARRUTHERS, B. M., VAN DE SANDE, M. I., DE MEIRLEIR, K. L., KLIMAS, N. G., BRODERICK, G., MITCHELL, T., STAINES, D., POWLES, A. C., SPEIGHT, N., VALLINGS, R., BATEMAN, L., BAUMGARTEN-AUSTRHEIM, B., BELL, D. S., CARLO-STELLA, N., CHIA, J., DARRAGH, A., JO, D., LEWIS, D., LIGHT, A. R., MARSHALL-GRADISBIK, S., MENA, I., MIKOVITS, J. A., MIWA, K., MUROVSKA, M., PALL, M. L. & STEVENS, S. 2011. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med,* 270**,** 327-38.

CASTRO-MARRERO, J., FARO, M., ZARAGOZA, M. C., ALISTE, L., DE SEVILLA, T. F. & ALEGRE, J. 2019. Unemployment and work disability in individuals with chronic fatigue syndrome/myalgic

encephalomyelitis: a community-based cross-sectional study from Spain. *BMC Public Health,* 19**,** 840.

ESTEVEZ-LOPEZ, F., CASTRO-MARRERO, J., WANG, X., BAKKEN, I. J., IVANOVS, A., NACUL, L., SEPULVEDA, N., STRAND, E. B., PHEBY, D., ALEGRE, J., SCHEIBENBOGEN, C., SHIKOVA, E., LORUSSO, L., CAPELLI, E., SEKULIC, S., LACERDA, E., MUROVSKA, M. & EUROPEAN NETWORK ON, M. C. 2018. Prevalence and incidence of myalgic encephalomyelitis/chronic fatigue syndrome in Europe-the Euro-epiME study from the European network EUROMENE: a protocol for a systematic review. *BMJ Open,* 8**,** e020817.

FARO, M., SÁEZ-FRANCÀS, N., CASTRO-MARRERO, J., ALISTE, L., COLLADO, A. & ALEGRE, J. 2014. Impacto de la fibromialgia en el síndrome de fatiga crónica. *Medicina Clínica,* 142**,** 519-525.

FERRARI, R. & RUSSELL, A. S. 2013. A Questionnaire Using the Modified 2010 American College of Rheumatology Criteria for Fibromyalgia: Specificity and Sensitivity in Clinical Practice. *The Journal of Rheumatology,* 40**,** 1590.

FRIEDBERG, F., BATEMEN, L., BESTED, A. C., DAVENPORT, T., FRIEDMAN, K. J., GURWITT, A., JASON, L. A., LAPP, C. W., STEVENS, S. R., UNDERHILL, R. A. & VALLINGS, R. 2012. ME/CFS: A Primer for Clinical Practitioners. *In:* IACFS/ME (ed.). International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

FUKUDA, K., STRAUS, S. E., HICKIE, I., SHARPE, M. C., DOBBINS, J. G. & KOMAROFF, A. 1994. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med,* 121**,** 953-9.

GUENTHER, S., LOEBEL, M., MOOSLECHNER, A. A., KNOPS, M., HANITSCH, L. G., GRABOWSKI, P., WITTKE, K., MEISEL, C., UNTERWALDER, N., VOLK, H. D. & SCHEIBENBOGEN, C. 2015. Frequent IgG subclass and mannose binding lectin deficiency in patients with chronic fatigue syndrome. *Hum Immunol,* 76**,** 729-35.

HAß, U., HERPICH, C. & NORMAN, K. 2019. Anti-Inflammatory Diets and Fatigue. *Nutrients* 11.

HAYS, R. D., SHERBOURNE, C. D. & MAZEL, R. M. 1993. The RAND 36-Item Health Survey 1.0. *Health Econ,* 2**,** 217-27.

HICKIE, I., DAVENPORT, T., VERNON, S. D., NISENBAUM, R., REEVES, W. C., HADZI-PAVLOVIC, D. & LLOYD, A. 2009. Are chronic fatigue and chronic fatigue syndrome valid clinical entities across countries and health-care settings? *Aust N Z J Psychiatry,* 43**,** 25-35.

HIVES, L., BRADLEY, A., RICHARDS, J., SUTTON, C., SELFE, J., BASU, B., MAGUIRE, K., SUMNER, G., GABER, T., MUKHERJEE, A. & PERRIN, R. N. 2017. Can physical assessment techniques aid diagnosis in people with chronic fatigue syndrome/myalgic encephalomyelitis? A diagnostic accuracy study. *BMJ Open,* 7**,** e017521.

HUNTER, R. M., JAMES, M. & PAXMAN, J. 2017. Counting the cost - Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *2020health.* London UK: The Optimum Health Clinic Foundation

HUSKISSON, E. C. 1974. Measurement of pain. *Lancet,* 2**,** 1127-31.

INSTITUTE OF MEDICINE (IOM) 2015. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies Press.

JASON, L., MULDOWNEY, K. & TORRES-HARDING, S. 2008a. The Energy Envelope Theory and myalgic encephalomyelitis/chronic fatigue syndrome. *Aaohn J,* 56**,** 189-95.

JASON, L. A., BENTON, M. C., VALENTINE, L., JOHNSON, A. & TORRES-HARDING, S. 2008b. The economic impact of ME/CFS: individual and societal costs. *Dyn Med,* 7**,** 6.

JASON, L. A., JORDAN, K., MIIKE, T., BELL, D. S., LAPP, C., TORRES-HARDING, S., ROWE, K., GURWITT, A., DE MEIRLEIR, K. & VAN HOOF, E. L. S. 2006. A Pediatric Case Definition for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. *Journal of Chronic Fatigue Syndrome,* 13**,** 1-44.

JASON, L.A, SUNNQUIST, M. 2018. The Development of the DePaul Symptom Questionnaire: Original, Expanded, Brief, and Pediatric Versions. *Front Pediatr*, 6;6:330.

JOHNS, M. W. 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep,* 14**,** 540-5.

KENNEDY, G., UNDERWOOD, C. & BELCH, J. J. 2010. Physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. *Pediatrics,* 125**,** e1324-30.

KINGDON, C. C., BOWMAN, E. W., CURRAN, H., NACUL, L. & LACERDA, E. M. 2018. Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls. *PharmacoEconomics - Open,* 2**,** 381-392.

KRUPP, L. B., LAROCCA, N. G., MUIR-NASH, J. & STEINBERG, A. D. 1989. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol,* 46**,** 1121-3.

LACERDA, E. M., BOWMAN, E. W., CLIFF, J. M., KINGDON, C. C., KING, E. C., LEE, J. S., CLARK, T. G., DOCKRELL, H. M., RILEY, E. M., CURRAN, H. & NACUL, L. 2017. The UK ME/CFS Biobank for biomedical research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Multiple Sclerosis. *Open J Bioresour,* 4.

LACERDA, E. M., MCDERMOTT, C., KINGDON, C. C., BUTTERWORTH, J., CLIFF, J. M. & NACUL, L. 2019. Hope, disappointment and perseverance: Reflections of people with Myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Multiple Sclerosis participating in biomedical research. A qualitative focus group study. *Health Expect,* 22**,** 373-384.

LAPP, C. W. 2019. Initiating Care of a Patient With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Frontiers in pediatrics,* 6**,** 415-415.

LLOYD, A. R. & PENDER, H. 1992. The economic impact of chronic fatigue syndrome. *Med J Aust,* 157**,** 599-601.

MUDIE, K., ESTEVES-LOPEZ, F., SEKULIK, S., IVANOVS, A., SEPULVEDA, N., ZALEWSKY, P., MENGSHOEL, A.M., DE KORWIN, J., HINIC CAPO, N., ALEGRE-MARTIN, J., CASTRO-MARRERO, J., MUROVSKA, M., NACUL, L., LACERDA, E. 2020. Recommendations for Epidemiological Research in ME/CFS from the EUROMENE Epidemiology Working Group. *Preprints* **2020**, 2020090744 (doi: 10.20944/preprints202009.0744.v1).

NACUL, L., O'Boyle, S, PALLA, L, NACUL, F.E., MUDIE, K. KINGDON, C.C., CLIFF, J. M., CLARK, T.G., DOCKRELL, H.M., LACERDA, E.M. 2020. How Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Progresses: The Natural History of ME/CFS . Frontiers in Neurology 11.

NACUL, L., DE BARROS, B., KINGDON, C. C., CLIFF, J. M., CLARK, T. G., MUDIE, K., DOCKRELL, H. M. & LACERDA, E. M. 2019. Evidence of Clinical Pathology Abnormalities in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) from an Analytic Cross-Sectional Study. *Diagnostics (Basel),* 9.

NACUL, L. C., LACERDA, E. M., CAMPION, P., PHEBY, D., DRACHLER MDE, L., LEITE, J. C., POLAND, F., HOWE, A., FAYYAZ, S. & MOLOKHIA, M. 2011a. The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers. *BMC Public Health,* 11**,** 402.

NACUL, L. C., LACERDA, E. M., PHEBY, D., CAMPION, P., MOLOKHIA, M., FAYYAZ, S., LEITE, J. C., POLAND, F., HOWE, A. & DRACHLER, M. L. 2011b. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. *BMC Med,* 9**,** 91.

NACUL, L. C., MUDIE, K., KINGDON, C. C., CLARK, T. G. & LACERDA, E. M. 2018. Hand Grip Strength as a Clinical Biomarker for ME/CFS and Disease Severity. *Front Neurol,* 9**,** 992.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS). 2018. *Myalgic Encephalomyelitis/Chronic Fatigue Syndrome* [Online]. Available:

https://www.commondataelements.ninds.nih.gov/Myalgic%20Encephalomyelitis/Chronic%20Fatigue%20Syndrome#pane-166 2019].

NORTHWESTERN UNIVERSITY. 2020. *HealthMeasures* [Online]. Available: https://www.healthmeasures.net/explore-measurement-systems/neuro-qol.

PHEBY, D.F., ARAJA, D.; Berkis, U., BRENNA, E., CLLINAN, J., DE KORWIN, J.D., GITTO, L.; HUGHES, D.A., HUNTER, R.M., TREPEL, D., WANG-STEVERDING, X. The Development of a Consistent Europe-Wide Approach to Investigating the Economic Impact of Myalgic Encephalomyelitis (ME/CFS): A Report from the European Network on ME/CFS (EUROMENE). *Healthcare* **2020**, *8*, 88.

ROWE, K. S. 2019. Long Term Follow up of Young People With Chronic Fatigue Syndrome Attending a Pediatric Outpatient Service. *Front Pediatr,* 7**,** 21.

ROWE, P. C., UNDERHILL, R. A., FRIEDMAN, K. J., GURWITT, A., MEDOW, M. S., SCHWARTZ, M. S., SPEIGHT, N., STEWART, J. M., VALLINGS, R. & ROWE, K. S. 2017. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer. *Front Pediatr,* 5**,** 121.

SLETTEN, D. M., SUAREZ, G. A., LOW, P. A., MANDREKAR, J. & SINGER, W. 2012. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clinic proceedings,* 87**,** 1196-1201.

SPITZER, R. L., KROENKE, K., WILLIAMS, J. B. & LÖWE, B. 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med,* 166**,** 1092-7.

STRAND, E. B., NACUL, L., MENGSHOEL, A. M., HELLAND, I. B., GRABOWSKI, P., KRUMINA, A., ALEGRE-MARTIN, J., EFRIM-BUDISTEANU, M., SEKULIC, S., PHEBY, D., SAKKAS, G. K., SIRBU, C. A., AUTHIER, F. J. & ON BEHALF OF THE EUROPEAN NETWORK ON, M. C. 2019. Myalgic encephalomyelitis/chronic fatigue Syndrome (ME/CFS): Investigating care practices pointed out to disparities in diagnosis and treatment across European Union. *PLOS ONE,* 14**,** e0225995.

TOMAS, C., FINKELMEYER, A., HODGSON, T., MACLACHLAN, L., MACGOWAN, G. A., BLAMIRE, A. M. & NEWTON, J. L. 2017. Elevated brain natriuretic peptide levels in chronic fatigue syndrome associate with cardiac dysfunction: a case control study. *Open Heart,* 4**,** e000697.

TSENG, B. Y., GAJEWSKI, B. J. & KLUDING, P. M. 2010. Reliability, responsiveness, and validity of the visual analog fatigue scale to measure exertion fatigue in people with chronic stroke: a preliminary study. *Stroke research and treatment,* 2010**,** 412964.

TWISK, F. 2014. The status of and future research into Myalgic Encephalomyelitis and Chronic Fatigue Syndrome: the need of accurate diagnosis, objective assessment, and acknowledging biological and clinical subgroups. *Frontiers in Physiology,* 5.

VALDEZ, A. R., HANCOCK, E. E., ADEBAYO, S., KIERNICKI, D. J., PROSKAUER, D., ATTEWELL, J. R., BATEMAN, L., DEMARIA, A., JR., LAPP, C. W., ROWE, P. C. & PROSKAUER, C. 2019. Estimating Prevalence, Demographics, and Costs of ME/CFS Using Large Scale Medical Claims Data and Machine Learning. *Frontiers in pediatrics,* 6**,** 412-412.

VARNI, J. W., SEID, M. & KURTIN, P. S. 2001. PedsQL™ 4.0: Reliability and Validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in Healthy and Patient Populations. *Medical Care,* 39**,** 800-812.

WILLIAMS, M. V., COX, B., LAFUSE, W. P. & ARIZA, M. E. 2019. Epstein-Barr Virus dUTPase Induces Neuroinflammatory Mediators: Implications for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Clinical Therapeutics,* 41**,** 848-863.

WOLFE, F., CLAUW, D. J., FITZCHARLES, M.-A., GOLDENBERG, D. L., HÄUSER, W., KATZ, R. L., MEASE, P. J., RUSSELL, A. S., RUSSELL, I. J. & WALITT, B. 2016. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Seminars in Arthritis and Rheumatism,* 46**,** 319-329.

ZIGMOND, A. S. & SNAITH, R. P. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica,* 67**,** 361-370.