The European Network on

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

EUROMENE

Recommendations for a public health European-wide approach

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Disclaimer

The EUROMENE recommendations were based on shared expertise from the collaborating participants. Although the main recommendations were based on consensus within the working groups, they do not necessarily reflect the opinions of individual participants.

ABBREVIATIONS AND ACRONYMS

ACE-III	Addenbrooke's Cognitive Examination (31 questions)
BDI-II	Beck Depression Inventory II
CCC	Canadian Consensus Criteria
CDC	Centers for Disease Control (USA)
CDE	Common Data Elements
COMPASS-31	Composite Autonomic Symptom Score
COST	European Cooperation is Science and Technology
DSQ	DePaul Symptom Questionnaire
EBV	Epstein-Barr virus
ECIs	Early career investigators
EUROMENE	European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
EuroQol-5D	Euro Quality of life - 5 Dimensions (EQ-5D)
IOM/NAM	Institute of Medicine/National Academy of Medicine
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MMSE	Mini-Mental State Examination
NINDS	National Institute of Neurological Disorders and Stroke
NNC	Near Neighbour Country
PEM	post-exertional malaise
PPP	Purchasing power parities
SF-36	Short Form 36-item Health Survey
STAI	State-Trait Anxiety Inventory
STSM	Short Term Scientific Mission
UKMEB-SA	UK ME/CFS Biobank Symptom Assessment
VAS	Visual Analog Scales
WG	Working Group

INTRODUCTION

Background

The European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE) was proposed by researchers from eight countries in Europe[1], and was established after a successful grant application to a continuous open call from the European Cooperation is Science and Technology (COST) – through the instrument named COST Action. According to this funding agency, this instrument intends to complement national research funds, by enabling researchers to assemble their interdisciplinary research networks (in any field) through grant provision for "*organising meetings, training schools, short term scientific missions or other networking activities*". (https://www.cost.eu/cost-actions/what-are-cost-actions/).

Initially designed by a group of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) researchers and health professionals, the proposed network was submitted to COST in 2015 aiming to assess the existing fragmented knowledge and/or experience on health care delivery for ME/CFS sufferers in the European countries and worldwide, and to enhance coordinated research and health care provision in this field.

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 two 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[1-3]. Other key symptoms include unrefreshing sleep, cognitive manifestations, orthostatic intolerance and pain, including muscle and join 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 [2, 4]. 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 [2-4].

Prevalence rates have been estimated as between 0.2 and 0.7% [5-8] with incidence rate of 0.015 new cases/1000-year [7]. 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 Europe-wide estimates of disease burden [9]. 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 [7, 10], with young people in their most productive phases of life being preferentially affected. However, ME/CFS was reported in all age groups [10]. Quality of life of those with ME/CFS is on average lower than with other chronic or disabling diseases, such as MS [11], cancer, depression [12], diabetes, epilepsy, or cystic fibrosis [13]. Economic costs are considerable [10, 14-

[1] Bulgaria, Germany, Italy, Latvia, Lithuania, Norway, Spain, and United Kingdom. Belarus also joined the collaborating countries, as a Near Neighbour Country.

16], with repercussions for the individual affected and their families and society, as well as to educational and occupational services. Many will be unable to work or do it 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 sacrificing their social life and other interests due to the need to rest when not working [17, 18]. Again, in the absence of economic analysis on the costs of the disease in Europe, we estimate, based on data from the UK [16], it may cost some 40 Billion Euros to health services and society [19]. There is, however, a large degree of imprecision in these estimates, due to different coverage and costs of health services provision as well as living costs.

Despite the substantial disease burden, the health needs of people with ME/CFS remain largely unmet in Europe, as in 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, private, and mixed 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 health and other services, and their suffering and needs are not 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

. Their disability contributes to social isolation, which add to their burden, and limits their chances of recovery or re-integration in society [18, 20, 21].

Objectives and target audience

To address the EUROMENE's aims, the proposal stated the overall strategic objective of creating "*an integrated network of researchers on ME/CFS in Europe and beyond*", which was detailed in the specific objectives, summarised as follows:

Specific objectives

- To define a standardised clinical diagnosis for ME/CFS for clinicians and researchers that allows the identification of relatively homogenous sets of patients, who can be studied to identify pathogenesis mechanisms, biomarkers and disease process in a stratified way, as well as to be compared with other researched populations.
- To develop strategies to collect population-based data on the prevalence of ME/CFS, including standardised procedures.
- To promote co-operation and involvement of research groups with an objective to assess potential biomarkers for ME/CFS.
- To coordinate efforts to determine the social impact of ME/CFS and to appraise the economic damage from the disease.

Additional specific objectives of the network were related to capacity-building, which included promoting involvement of early career investigators (ECIs), and establishing communication links with industrial organisations, especially small/medium-sized enterprise (SMEs), particularly in the pharmaceutical, biotechnology, and Information and Communication Technologies (ICT) industries. These are outside of the scope of these guidelines.

Starting with 16 researchers from 11 European countries[2]and 1 Near Neighbour Country (NNC)[3], the EUROMENE reached the end of the grant period with 22[4] countries participating in the network activities (including the NNC), and a number of 55 European researchers and/or health professionals, who have been informed by people with ME/CFS (https://www.cost.eu/actions/CA15111/#tabs|Name:overview).

Target audience

European National Health sectors including:

- Health policy makers
- Health-care providers

Public and private institutions with intersectoral activities with the local governments to improve community health, such as:

- The Work and Pensions sector
- The Education sector
- The Social Services sector

[2] Belgium, Bulgaria, France, Germany, Italy, Latvia, Norway, Serbia, Spain, Romania, United Kingdom
[3] Belarus
[4] Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovenia, Spain, Sweden, United Kingdom

METHODOLOGY AND PROCESS

The methodological approach presented in the EUROMENE proposal, was based on the establishment of interrelated working groups (WGs), where the participants joining the network would contribute with specific knowledge and viewpoints according to their specialties and/or areas of interest.

The official start of the EUROMENE occurred at a meeting on the 21st of April 2016, in Brussels (BE). The event was organised by COST per customary institution's protocol. The network's Management Group was appointed by vote, comprising the Action Chair, Vice-Chair, Grant Holder Scientific Representative, Short Term Scientific Mission (STSM) Coordinator, and WG leaders and Vice-Leaders. Afterwards, face-to-face meetings were regularly organised by the Grant Holder institution (Rīga Stradiņš University- LV) and the hosting institutions among the EU participating countries, during the entire grant period (Table 1).

Table 1. EUROMENE Management Group and Working Groups meetings occurred during the grant period, by place and time.

Year	Month	Hosting Institution (City/Country)	Participants
2016	April	COST (Brussels, BE)	Initial proponents and a newly joined country (Serbia)
	September	Rīga Stradiņš University (Riga, LV)	All Management Group and all WGs
2017	January	Charité (Berlin, DE)	Management Group, WGs on Epidemiology & on Clinical Research
	March	Vall D'Hebron Hospital (Barcelona, ES)	Management Group, WGs on Biomarkers & on Clinical Research
	September	Medical Faculty Novi Sad (Belgrade, RS)	Management Group, WG on Epidemiology
2018	February	National Center of Infectious and Parasitic Diseases (Sofia, BG)	Management Group, WG on Biomarkers
	April	Paris Est-Creteil University, Faculty of Medicine (Paris, FR)	Management Group, WGs on Socioeconomics & on Clinical Research
	September	London School of Hygiene & Tropical Medicine (London, UK)	Management Group, WGs on Socioeconomics & on Epidemiology
2019	February	Central Military Emergency Hospital Carol Davila (Bucharest, RO)	Management Group, WG on Clinical Research
	June	Nicolaus Copernicus University in Torun, and Collegium Medicum in Bydgoszcz (Warsaw, PL)	Management Group, WGs on Socioeconomics & on Epidemiology
	November	Charité (Berlin, DE)	Management Group, WGs on Biomarkers & on Clinical Research
2020	March	Rīga Stradiņš University (Riga, LV)	Conference & Management Group meeting *

* The Conference and Management Group meeting were compromised due to the restrictions of the pandemic WG – Working Group

There were four research related working groups, namely i) Working Group on Clinical Research Enablers and Diagnostic Criteria of ME/CFS, ii) Working Group on Epidemiology, iii) Working Group on Biomarkers, and iv) Working Group on Socioeconomics. In addition to the aforementioned face-to-face meetings, the research WGs members exchanged views on produced reports and drafted papers, and considered on the development and the feasibility of carrying-out the proposed tasks and achieving the planned deliverables at the end for the grant period.
The overall methodological approach adopted by the WGs was a free adaptation of the *Nominal group technique,* as the face-to-face meetings start with initial brainstorming or ideas among the WG members, followed by recording and discussion of ideas, before a final agreement on the next steps to address the aimed tasks. The activities on the months between face-to-face meeting involved examination of agree key documents, such as relevant scientific literature and existing recommendations and/or guidelines, for grounding the initial drafts. WG members' experiences and expertise were considered for the final drafts.

The description of specific processes adopted by the WGs for assessing evidence and developing the final recommendations, are placed at the beginning of each working group recommendations section, to provide a continuous flow of information, and facilitate the reading of each sub-section.

Declaration of interest by EUROMENE Working Groups members

The WG members in the table below completed a declaration of interests form. Three participanting members declared potential conflicts of interest, as their additional professional activities may be seen as conflicting with the participation in the process of contributing with these recommendations. The remaining members declare no conflict of interest, and do not consider the potential conflicts of interest declared have influenced the content of these recommendations.

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[5] COST – Near Neighbour Country – Management Committee Observer

[6] Prof CS declared having a clinical study grant and speaker honoraria from Takeda pharmaceutical company and Fresenius Medical care, and consultancy for CellTrend GmbH.

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[7]Dr RV declared consultancy for AlfaSigma pharmaceutical company.
[8] Dr LN declared being a Committee Member of UK NICE ME/CFS Guidelines, which are being reviewed.

RECOMENDATIONS

Working Group on Clinical Research and Diagnostic Criteria

Working process

This report was preceded by the report of survey on clinical criteria used in European countries to diagnose ME/CFS [22], which showed a paucity and lack of integration of guidelines in European countries.

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 [1-3, 23, 24], and existing studies/guidelines for clinical assessments and care used in Europe and internationally (as reviewed by Strand et al [22]). Firstly, the WG members met at distinct occasions (WG meeting) to agree on the key documents and to consider them based on the members' experiences and expertise. Then, the current best existing recommendations were extracted from the key documents considered; lastly, the extensive expertise within the network was applied to guide the additions/modifications to recommendations for ME/CFS clinical assessment and care. We recognise that there is still limited evidence-based research on ME/CFS, but as we witness the evolvement in this field, we strongly suggest frequent reviews of these guidelines, as they are likely to be improved by emerging evidence. The detailed recommendations are published and accessible for feedback on the following site: https://www.preprints.org/manuscript/202009.0688/v1/download (Nacul et al, 2020. PrePrints site)

ME/CFS diagnosis for clinical purposes

Several diagnostic criteria have been proposed for use in clinical practice, and after considering their usage by clinicians and researchers, the EUROMENE Working Group on Clinical Research and Diagnostic Criteria recommends the following:

For Primary Care

- The USA Institute of Medicine criteria – usually known as IOM criteria or IOM/NAM criteria [3], as the IOM was lately renamed as - National Academy of Medicine (NAM). The IOM criteria's relative simplicity makes it ideal for use in primary care.
- The CDC-1994/Fukuda et al criteria [23] 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.
- For children, the IOM [3] and Rowe et al [24] criteria, may be used.

For Secondary Care

- The Canadian Consensus Criteria [1], also known as CCC, is particularly suitable for diagnosis confirmation and case sub-grouping in secondary care, as well as in research.

- For children, the Canadian Consensus criteria [1] may also be used, as proposed by Jason et al [25]. However, using 3 months of symptoms are sufficient for ME/CFS diagnosis in this population.

We have recommended detailed steps to guide the recognition and characterisation of ME/CFS cases in adults and children, at clinical settings for primary and secondary care. These steps included the following topics:

1. Clinical history
2. Clinical examination
3. Differential Diagnosis
4. Patient detailed characterization, laboratory, and other tests

Recommendations for Health Care provision

We provide recommendations for health care provision considering organisation of primary and specialty services within the national health care systems, and the reference and counter-reference flow among the distinct levels of care.

Primary care professionals have an important role in the initial diagnosis, including consideration of alternative conditions leading to similar symptoms. Although with good education of primary care physicians, diagnosis, and monitoring of people with ME/CFS in primary care are possible and desirable, referrals for specialist services may be indicated in some circumstances. In Box 1, we provided some criteria for secondary care services.

Box 1. Examples of criteria for referral to secondary services caring for people with ME/CFS

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

The continuing role of primary care and the general practitioner, and the procedures of the specialist services have been outlined, including recommended standard questionnaires, a list of differential diagnosis and co-morbidities, considerations on management and treatment of symptoms. Furthermore, the group considered the importance of establishing a professional-patient shared expertise, which will also inform how to better manage patients' expectations, improve self-management and support [26].

The working group also considered the following recommendations (detailed at https://www.preprints.org/manuscript/202009.0688/v1/download Nacul et al, 2020. PrePrints site):

- Non-Pharmacological treatment for symptoms relief and available support therapies
- Symptoms relief and management using available pharmacological drugs.
- Needs of patients with different severities.

Additional considerations on the non-pharmacological approach, does not reflect the experiences from the majority of the working group participants [27, 28]

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.

The current reality of health services, suggest that, where specialist services are not well developed, we follow a minimum standard of case 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 plan, 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 2), 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, to address the scientific and societal poor understanding of the dimension of the problem faced.

Box 2. Multi-sectorial 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, for considering alternatives for schooling of children and adolescents with ME/CFS

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 weakening of symptoms and/or relapse
- ME/CFS Services development and evaluation

Funding Agencies and pharma industry:

- Research funding and support for well-designed clinical trials

Working group on Epidemiology

Working process

This section outlines the work of a multidisciplinary team of researchers, including epidemiologists, clinicians, statisticians, biomedical scientist and heath economists, who set out their recommendations to guide data acquisition for ME/CFS research, which will ultimately improve epidemiological research. An overarching principle of the present work was to suggest tools for collecting standardised data on the presence and severity of cardinal ME/CFS symptoms and dysfunctions that may impose a burden on patients' well-being and health-related quality of life. To ensure scalability of the suggested assessments, including applicability in population-based studies, most of them are based on self-reports. When circumstances (both resources and needs) allow it, additional objective measurements are suggested to obtain a more comprehensive picture of ME/CFS.

ME/CFS Standardised Research Guide

Selection of data variables was based on the following criteria: freely available and easy to use, validated and relevant for ME/CFS research, and consistent with current international practice in research. Having in mind relevance beyond European countries, topic-driven data elements such as the Common Data Elements (CDE) Project developed by the National Institute of Neurological Disorders and Stroke (NINDS) for ME/CFS clinical research were reviewed https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards .

The discussion began with a review of the literature of the current landscape of international ME/CFS research [9]. Data collection tools presently used within participating European countries were outlined by country representatives. Working group members focussed on four core domain areas for data collection: (i) general core information, (ii) provisional and confirmed diagnosis, (iii) clinical assessment, and (iv) symptom profiling. Within each of these topic areas, the group deliberated and agreed on the most appropriate tools to be used to collect data. Where consensus could not be made, members wrote a report comparing those tools identified. Afterwards, these reports were discussed by the entire group to reach a consensus.

We outline here the core domain areas for data collection, to improve the standardisation of epidemiological data in European countries and the comparison of research findings, allowing more reliable estimates on prevalence and incidence of ME/CFS in Europe [29]. A detailed version of the recommendations is available at the following site for comments and feedback: https://doi.org/10.20944/preprints202009.0744.v1 (Mudie & Estévez-López et al, 2020. PrePrints site)

General core information

We recommend the collection of data related to socio-demographics and the general health history of the participants. The epidemiology working group refers to the socio-economic working group for detailed recommendations on the essential socio-demographic data to be collected (Pheby et al., 2020). In brief, we recommend the collection of gender, date of birth, ethnicity, and level of education, as well as marital status, occupation, income, and living conditions. Given that data from different national health systems lack standardisation and are difficult to access, we agreed on the

need to elaborate a set of standardised questions for self-reporting health history that includes a comprehensive assessment of previous and current ill-health to uncover potential co-morbidities, conditions that may justify an alternative diagnosis, and information regarding the onset of the disease (infectious vs non-infectious).

Provisional diagnosis

A probable or provisional diagnosis can be ascertained based on questionnaire response, although diagnosis confirmation will usually require further assessment or confirmation by a health professional with experience in ME/CFS, which is preferably done through a face-to-face encounter. Two available questionnaires that have been used throughout the European participating countries to diagnose ME/CFS are the DePaul Symptom Questionnaire (DSQ) [30] and the UK ME/CFS Biobank Symptom Assessment (UKMEB-SA) [31].

Clinical assessment

Considering the lack of biomarkers, in addition to questionnaire, we suggest a brief clinical assessment to comply with the suggested diagnostic criteria. This may include:

- A general physical examination.
- Anthropometric measures, including height and weight at a minimum.
- Blood pressure and heart rate taken at one-minute intervals with the participant first lying down for five minutes and then standing still for up to ten minutes (or until no longer able). Patients with severe symptoms may be unable to be tested with these procedures.
- Pulse oximetry.
- A specific examination covering main body systems (skin, head and neck, heart and circulation, respiratory, abdomen, and limbs); mental status using a validated questionnaire (for example the Mini-Mental State Examination (MMSE) or the Addenbrooke's Cognitive Examination – ACE-III), coordination and gait, cranial nerves, cerebellar function, muscle strength and tone, sensory function, and reflexes.
- A directed examination targeted according to general health history, findings from the general clinical examination and specific symptoms reported.
- Hand grip strength.
- Routine blood tests are important to help identify other conditions and co-morbidities.

Diagnosis confirmation

The confirmation of the ME/CFS diagnosis is achieved by combining the use of a standard questionnaire (provisional diagnosis) and clinical assessment (identify co-morbidities and exclusionary conditions that could otherwise explain the symptoms). While further discussions are taking place across EUROMENE, with the leadership of the Clinical Working Group, we propose that any of the Canadian Consensus Criteria [1], CDC-1994 [23], or the IOM [3] criteria are acceptable for case diagnosis, although the combination of the Canadian Consensus and IOM criteria are preferable as these require post-exertional malaise symptoms. We also note that combined use of these 3 criteria provides a more specific diagnosis, which will often be desirable for research purposes [32].

Questionnaire-based symptom profiling

We recommend freely available for use and suggest questionnaires be validated in native languages, if necessary. These are detailed in the https://doi.org/10.20944/preprints202009.0744.v1 (Mudie & Estévez-López et al, 2020. PrePrints site)

- UKMEB Participant Questionnaire (UKMEBQ)

- Fatigue Severity Scale (FSS)
- Pittsburgh Sleep Quality Index
- COMPASS-31
- Beck Depression Inventory II (BDI-II)
- State-Trait Anxiety Inventory (STAI)
- Positive and Negative Affect Schedule
- Short Form 36-item Health Survey (SF-36) developed by RAND

Clinical measurements - instrument-based symptom profiling

The following analog scales are also freely available. The procedures for the scales and test are also detailed in the https://doi.org/10.20944/preprints202009.0744.v1 (Mudie & Estévez-López et al, 2020. PrePrints site)

- Visual Analog Scales (VAS) – for fatigue and pain
- Active standing test

Additional tools for symptom profiling

- Heart rate variability [33, 34]
- Accelerometers

Final Considerations

This research guide set out minimum standards of data collection and offer recommendations for additional tools that can be used to enhance ME/CFS epidemiological research, where resources and local needs allow.

The simplicity of the suggested tools and because they are currently used in Europe, enable us to take a pragmatic decision to encourage participating European countries to adopt this guide. This will enable users to synchronise the identification of cases, data collection, and input of data and samples relating to ME/CFS research. By doing so, it will be possible to create an international database for collecting consistent and comparable epidemiological data to further facilitate scientific and clinical research. The CDE Project developed by the NINDS for ME/CFS research also outlines uniform formats by which clinical data can be systematically collected, analysed, and shared across the research community. Many of the tools suggested by the NINDS are also recommended in this research guide; these include the clinical assessment (both physical examination and routine blood tests), the passive standing test to measure autonomic function, the RAND-36 to assess health-related quality of life, the PSQI to evaluate sleep quality, and the FAS and the FSS to quantify symptoms of fatigue. However, the adoption of the standardised data collection tools in the EUROMENE network also considers existing research practices among participating countries. This will make data systems and their use consistent with pre-existing approaches to data collection by participating countries, which have already been collecting data in standardised ways, while still allowing comparability with CDEs used in other parts of the world.

Working group on Biomarkers

Working process

The working group on biomarkers included a multidisciplinary team of researchers with clinical and/or biomedical background. Due to the complexity of biomarker studies in CFS initially the following approach was taken: 1. A survey on biomarkers in Europe was performed to establish an "European biomarker landscape" and identify all active research groups in Europe. 2. Special interest groups within the network were established to be able to focus on selected topics in a harmonised way.

European Biomarker landscape

In 2016 we performed a survey on biomarker studies for ME/CFS in the EU countries from 2012-16 [35]. Initially the members of the WG on Biomarkers searched for publications from 2012 – 2016 within their countries about potential biomarkers on ME/CFS. From this work, we identified 39 studies on potential biomarkers for ME/CFS, of which 15 (38.5%) were on immunology, 15 (38.5%) on metabolism, 5 (12.8%) on infection, and 4 (10.2%) on neurology.

None of the biomarkers described was useful as diagnostic test. Many biomarker studies identified were exploratory in design and lacked sex and age-matched control groups or validation cohorts thus having a low evidence level. Some studies reported inconsistent data, and some even contradict one another. Furthermore, the biomarkers from those studies failed to provide convincing performance for potential use of diagnostic tests, such as sensitivity and specificity (summarised in Box 1).

Reasons for these unreliable findings are numerous, and includes lack of appropriate funding, small sample sizes, heterogenous symptomology characterisation (which is intensified by the different diagnosis criteria), and lack of attention to possible subtypes (Jason 2005). Recommendations were given for future biomarker studies and development of diagnostic markers. The group concluded that prospective studies on biomarkers should use more stringent case definitions that allows subgroup analyses, considering age, sex, disease presentation (symptomology). Age- and sex-matched controls should be included into a well-powered sample size; and the proposed study protocols – including assays should be well described to allow reproducibility of results.

Box 1 Results of single biomarker studies

- Various studies on single immune, metabolic, infectious, or neurologic biomarkers
- alterations only in subsets of CFS/ME patients/ overlap with controls
- often not validated
- performed in single centres
- Insufficient control groups
- non-standardized assays and various case definitions

In the subsequent period 2017-20, the working group members continuously revised the published literature worldwide on potential biomarkers and considered their potential as ME/CFS diagnostic markers. The assessed studies in this period, were only considered if they have used the CDC-1994/Fukuda and/or the Canadian Consensus Criteria to recruit ME/CFS cases and if a healthy control group was included. Specific focuses were on marker for autoimmunity and chronic viral infections [36, 37]. Furthermore, one meeting focused on studies comparing subgroups of ME/CFS cases related to their specific biomarker(s). The examined papers were used to substantiate the present

recommendations from the Working Group on Biomarkers, the final draft was revised and agreed by the WG members.

Assessment of Potential Biomarkers for ME/CFS

Autoimmunity Markers

The pathomechanism(s) underlining ME/CFS is/are not completely understood yet, but currently there is convincing evidence that – at least in a subset of patients, ME/CFS has an autoimmune aetiology. Infection by various pathogens, including the Epstein-Barr virus (EBV), the human herpes virus-6 (HHV-6) and the human parvovirus (HPV)-B19, but also intracellular bacteria, are known as triggers of disease [38-40]. It is well known that infections can trigger autoimmunity. There is ample evidence that autoimmune mechanisms play a role in ME/CFS [37, 41]. However, clinical heterogeneity in disease onset (infection- versus non-infection triggered), presence of immune-associated symptoms, and divergent immunological alterations point to the existence of subgroups of ME/CFS patients with possibly different pathomechanisms. Therefore, it is important to have diagnostic markers to select patients with autoimmune mediated disease for clinical trials. The search for autoantibodies is of great importance enabling us to develop biomarkers for diagnosis and providing a rationale for therapeutic interventions. So far there is no autoantibody available for diagnostic use outside of clinical trials.

Markers for chronic viral infections

A review was performed to compile all studies on viral infections that could be associated with ME/CFS [36]. The suitability of serology was analysed as diagnostic test. Furthermore, potential mechanisms were discussed and strategies for future studies on the role of viral infections in ME/CFS were designed. Associations were described for various herpesviruses, enteroviruses, parvovirus B19, retroviruses and Ross River virus.

Currently available data on the role of chronic viral infection with ME/CFS is still controversial, showing potential viral involvement for at least a subgroup of ME/CFS patients. Therefore, it is necessary to assess the presence and markers of viral activity at the initial stage of the disease to evaluate possible etiological factors and conduct longitudinal studies in order to assess active viral infection and symptom severity variations over time. Moreover, results should be compared not only between ME/CFS patients and controls, but also with other disease groups. There is no serological test available for diagnostic use in ME/CFS.

Mitochondrial function and metabolic alterations

The profound and debilitating fatigue experienced by ME/CFS individuals led to the hypothesis that energy metabolism may be dysregulated. Defects in mitochondrial function in ME/CFS were shown in various studies (reviewed in Sotzny et al. and Tomas and Newton, respectively [37, 42]). Studies report about alterations in the mitochondrial function in different kind of cells, but again, the data are inconsistent. Another sign that points towards the mitochondria as a key factor is, that some of the most common symptoms of ME/CFS (chronic fatigue, post-exertional malaise, and muscle pain) are the same in patients with primary mitochondrial disorders. But enough differences to discriminate these diseases from one another have been reported [43]. However, the mitochondrial dysfunction could be the result of a problem in upstream signalling pathways or due to a serum factor. Bhupesh Prusty from the EUROMENE group could show in his studies that serum of ME/CFS patients induces mitochondrial fragmentation in a similar manner as HHV-6 [44]. In a similar manner a study from the Bergen group showed inhibition of pyruvate dehydrogenase by a serum factor [45].

During the last years there were several metabolic multiparameter studies on ME/CFS [46-49]. A substantial number of up to 832 metabolites were quantified. Metabolic profiling revealed different metabolic pathways to be affected (Naviaux et al and Germain et al [47, 49], reviewed by Tomas and

Newton [50]). The most common being related to: energy metabolism (including an increase of lactate production, and a reduction in oxidative metabolism and nucleotide, lipid and amino acids alterations). Although the compounds they measured are not all identical, overall, most of the altered metabolic pathways indicate an hypometabolic state and hypoxia in ME/CFS patients. Metabolic profiling requires, however, complex analysis and is not suitable as diagnostic test so far. A recent review comparing also concluded that no specific metabolite was consistently impaired across all of the studies [51].

A study by Eguchi et al. is of interest performing a proteomic analysis of the extracellular vesicles identifying altered proteins involved in various pathways including adhesion, actin skeletal regulation, phosphoinositide 3-kinase-Akt signalling and EBV infection [52]. This is the only study in which a disease control group of patients with depression was comparatively analysed. Other studies on extracellular vesicles have also been published with intriguing findings [53-55].

Considerations on Subgrouping

There is clinical evidence for existence of subgroups in ME/CFS. A literature review was performed and the considered studies could be classified into three main topics: “cytokines”, “genome/epigenome”, and “metabolism”, and their study population were sub-grouped by distinct aspects, such as: disease severity; duration and/or onset; post-exertion profiles; infectious x non-infectious onset; patterns of methylation from gene-sites; sex; metabolic pathways and comorbidity.

We reviewed these studies and discussed if assays might be suitable to be used as diagnostic assay for subgroups of patients. All subgroups discussed in this review show differences within the ME/CFS regarding either the disease duration and severity, symptoms, comorbidities, infectious or non-infectious onset, and sex. These factors are associated with alterations of cytokines, genetics/epigenetics and metabolism and lead to measurable differences in various biomarkers. To optimize diagnosis of and the therapeutic approaches for ME/CFS, we recommend to correlate changes in the putative(s) biomarker(s) with the following factors, by subgrouping the study population (Box 2).

Box 2 - Recommendation for considering the following sub-grouping categories for studies on biomarkers

- Disease severity, duration and/or onset
- Post-exertion profiles
- Infectious x non-infectious onset
- Patterns of methylation from gene-sites
- Sex and comorbidity

General limitations on ME/CFS studies

However, there are a few problems that are common for the studies about ME/CFS, even when it’s tried to get a homogenous patient sample (as far as possible) by choosing the same and specified diagnosis scheme for all patients included. Mostly the severe patients don’t participate in these studies, due to the lack of physical functioning which does not allow to visit a study centre and so on. Furthermore, there must be mentioned, that since it is among other things a criterium for the

diagnosis to have more than 6 months the unexplained fatigue, the really early stages of CFS cannot be investigated.

Another point is the normally small group of participants. The studies discussed in this review included between 20 and 298 patients with CFS, whereas a large sample like 298 does not occur often. It is striking, that there are often way more female than male patients, but on the other hand it appears to be 1,5 times more likely to come down with CFS for women than for men [56]. Besides, it is likely that not all subgroups are found by now, so there are still unknown subgroups which are combined in a heterogenous sample and might cloud the results.

Final Considerations

ME/CFS is a complex multifactorial syndrome in which dysregulations of the metabolic and immune system are evident. For studies exploring biomarkers on ME/CFS, we recommend research participants who comply with modified Fukuda (CDC-1994) case definition alongside the Canadian Consensus Criteria (CCC). Biomarkers with sufficient sensitivity and specificity for diagnosing ME/CFS are still not available yet. There are, however, several studies showing biomarkers characterizing subgroups of patients. The most obvious clinical subtype is an acute infection-triggered onset in about 2/3 of patients while in 1/3 disease onset is not related to infection or gradual. We enveloped a list of recommendations for future biomarker studies (Box 3, adapted from Scheibenbogen et al [35]).

Box 3. Recommendations for biomarker studies in ME/CFS

- Standardization of sample collection and assay procedures
- Use of a uniform clinical case definition
- Use of questionnaires to assess symptoms and severity to define subgroups
- Stratification of patients according to sex, disease onset, and disease duration
- Include sex- and age-matched healthy and disease control groups
- Sufficient sample size and predefined hypotheses (statistical power)
- Confirmation of results in validation and multi-centre cohort studies
- Study combinations of biomarkers, perform pathway analysis or functional studies

Working group on Socioeconomics

Working process

The EUROMENE Working Group (WG) on Socioeconomics includes clinical researchers, computational scientist, health economists, epidemiologists, and administrators, who have developed a Europe-wide approach to: i) investigating the economic impact of ME/CFS; ii) facilitating acquisition of information on the economic burden of ME/CFS; and, iii) allowing international comparisons of economic costs between countries. WG members have met face-to-face during the grant-period, where discussions and agreements took place on how to survey the existing data from European countries pertaining to economic losses attributable to ME/CFS. Furthermore, WG members considered approaches to calculating the direct and indirect economic burdens due to ME/CFS, to provide an integrated outcome assessment framework. During this process, significant challenges to the intended outcomes were identified, and are reflected on the recommendations agreed by the WG members.

The economic burden of ME/CFS in Europe

The economic burden of ME/CFS in Europe appears large, with productivity losses most significant, giving scope for substantial savings through effective prevention and treatment. The WG members considered how to coordinate efforts to determine the societal impact of ME/CFS, and how to appraise the economic implications from the disease. This would enable the estimation of the burden of ME/CFS to society and the provision of long-term trend estimates for societal impact. The following recommendations are resultant from this group work [19].

Recommendations

Case definition:

• That there should be Europewide adoption of the modified Fukuda (CDC-1994) case definition alongside the Canadian Consensus Criteria (CCC).

Case identification:

• That a common symptom checklist should be used, capable of being mapped by algorithms onto both the Fukuda case definition and the CCC.

Prevalence and incidence:

• Better descriptive epidemiological information is required, as a basis for economic investigation. This should include information concerning the proportion of severely affected people, as there are likely to be different cost implications for such people, in comparison with those with mild or moderate illnesses.

Economic investigation:

• Prevalence based cost of illness studies, based on these case definitions, should be carried out in different countries, to determine the overall cost burden attributable to ME/CFS.

Data items:

• A list of data items required for cost of illness studies has been identified (though not reported here). Individual participating countries should examine this, to ensure that, insofar as these are derivable from routine data collection, that systems are in place to ensure that they are collected.

Data audit:

• The availability in participating countries of the relevant data items referred to above which are required for cost-of illness studies should be examined, with a view to achieving convergence, and facilitating international comparisons.

Relationship between disease severity and economic impact:

• The EuroQol-5D instrument should be used as a generic measure of health status and as a multi-attribute utility instrument to determine the relationship between disease severity and economic impacts, and to inform future economic evaluations. The Italian study should be replicated in other countries, to enable international comparisons.

International comparisons and compilation of Europe-wide statistics:

• Given the diversity of patterns of health care organisations and funding health, as well as of outcomes and general levels of health, as well as of national wealth and levels of economic development, we recommend the use of purchasing power parities (PPP) in order both to make valid international comparisons and to collate meaningful statistics at a European level.

Summary of Recommendations

• Use of the modified Fukuda (CDC-1994) case definition and Canadian Consensus Criteria (CCC)

• A pan-European common symptom checklist.

• Implementation of prevalence-based cost-of-illness studies in different countries using an agreed data list.

• Use of purchasing power parities (PPP) to facilitate international comparisons.

• Use of EuroQol-5D as a generic measure of health status and multi-attribute utility instrument to inform future economic evaluations in ME/CFS.

References

1. Carruthers B, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, Bested AC, Flor-Henry P, Joshi P, Powles AP, Sherkey JA, van de Sande MI. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. Journal of chronic fatigue syndrome 2003;11(1):7-115.
2. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles AC, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270(4):327-38.
3. Institute of Medicine (IOM). Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies Press, 2015.
4. Carruthers, Jain A, De Meirleir K, Peterson D, Klimas N, Lerner A, Bested A, Flor-Henry P, Joshi P, Peter Powles A, Sherkey J, van de Sande M. Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndromeme. 2003;11(1).
5. Bakken I, Tveito K, Gunnes N, Ghaderi S, Stoltenberg C, Trogstad L, Haberg S, Magnus P. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008 inverted question mark2012. BMC Med. 2014;12(1):167.
6. Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, McCready W, Huang CF, Plioplys S. A community-based study of chronic fatigue syndrome. Arch Intern Med. 1999;159(18):2129-37.
7. Nacul LC, Lacerda EM, Pheby D, Campion P, Molokhia M, Fayyaz S, Leite JC, Poland F, Howe A, Drachler ML. 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;9(1):91.
8. Vincent A, Brimmer DJ, Whipple MO, Jones JF, Boneva R, Lahr BD, Maloney E, St Sauver JL, Reeves WC. Prevalence, incidence, and classification of chronic fatigue syndrome in Olmsted County, Minnesota, as estimated using the Rochester Epidemiology Project. Mayo Clinic proceedings. 2012;87(12):1145-52.
9. Estevez-Lopez F, Castro-Marrero J, Wang X, Bakken IJ, Ivanovs A, Nacul L, Sepulveda N, Strand EB, Pheby D, Alegre J, Scheibenbogen C, Shikova E, Lorusso L, Capelli E, Sekulic S, Lacerda E, Murovska M, European Network on MC. 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. 2018;8(9):e020817.
10. Valdez AR, Hancock EE, Adebayo S, Kiernicki DJ, Proskauer D, Attewell JR, Bateman L, DeMaria A, Jr., Lapp CW, Rowe PC, Proskauer C. Estimating Prevalence, Demographics, and Costs of ME/CFS Using Large Scale Medical Claims Data and Machine Learning. Frontiers in pediatrics. 2019;6:412-.
11. Kingdon CC, Bowman EW, Curran H, Nacul L, Lacerda EM. Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls. PharmacoEconomics - Open. 2018;2(4):381-92.
12. Nacul LC, Lacerda EM, Campion P, Pheby D, Drachler Mde L, Leite JC, Poland F, Howe A, Fayyaz S, Molokhia M. The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers. BMC Public Health. 2011;11:402.
13. Kennedy G, Underwood C, Belch JJ. Physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. Pediatrics. 2010;125(6):e1324-30.
14. Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The economic impact of ME/CFS: individual and societal costs. Dyn Med. 2008;7:6.
15. Lloyd AR, Pender H. The economic impact of chronic fatigue syndrome. Med J Aust. 1992;157(9):599-601.

16. Hunter RM, James M, Paxman J. Counting the cost - Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. London UK: The Optimum Health Clinic Foundation 2017.
17. Castro-Marrero J, Faro M, Zaragoza MC, Aliste L, de Sevilla TF, Alegre J. Unemployment and work disability in individuals with chronic fatigue syndrome/myalgic encephalomyelitis: a community-based cross-sectional study from Spain. BMC Public Health. 2019;19(1):840.
18. Lacerda EM, McDermott C, Kingdon CC, Butterworth J, Cliff JM, Nacul L. 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. 2019;22(3):373-84.
19. Pheby DFH, Araja D, Berkis U, Brenna E, Cullinan J, de Korwin JD, Gitto L, Hughes DA, Hunter RM, 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 (Basel). 2020;8(2).
20. Drachler Mde L, Leite JC, Hooper L, Hong CS, Pheby D, Nacul L, Lacerda E, Campion P, Killett A, McArthur M, Poland F. The expressed needs of people with chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. BMC Public Health. 2009;9:458.
21. Słomko J, Newton JL, Kujawski S, Tafil-Klawe M, Klawe J, Staines D, Marshall-Gradisnik S, Zalewski P. Prevalence and characteristics of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in Poland: a cross-sectional study. BMJ Open. 2019;9(3):e023955.
22. Strand EB, Nacul L, Mengshoel AM, Helland IB, Grabowski P, Krumina A, Alegre-Martin J, Efrim-Budisteanu M, Sekulic S, Pheby D, Sakkas GK, Sirbu CA, Authier FJ, on behalf of the European Network on MC. Myalgic encephalomyelitis/chronic fatigue Syndrome (ME/CFS): Investigating care practices pointed out to disparities in diagnosis and treatment across European Union. PLOS ONE. 2019;14(12):e0225995.
23. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12):953-9.
24. Rowe PC, Underhill RA, Friedman KJ, Gurwitt A, Medow MS, Schwartz MS, Speight N, Stewart JM, Vallings R, Rowe KS. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer. Front Pediatr. 2017;5:121.
25. Jason LA, Jordan K, Miike T, Bell DS, Lapp C, Torres-Harding S, Rowe K, Gurwitt A, De Meirleir K, Van Hoof ELS. A Pediatric Case Definition for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. Journal of Chronic Fatigue Syndrome. 2006;13(2-3):1-44.
26. Mengshoel AM, Helland IB, Meeus M, Castro-Marrero J, Pheby D, Bolle Strand E. Patients' experiences and effects of non-pharmacological treatment for myalgic encephalomyelitis/chronic fatigue syndrome – a scoping mixed methods review. International Journal of Qualitative Studies on Health and Well-being. 2020;15(1):1764830.
27. Zalewski P, Kujawski S, Tudorowska M, Morten K, Tafil-Klawe M, Klawe JJ, Strong J, Estévez-López F, Murovska M, Newton JL, The European Network On Me/Cfs E. The Impact of a Structured Exercise Programme upon Cognitive Function in Chronic Fatigue Syndrome Patients. Brain sciences. 2019;10(1):4.
28. Kujawski S, Cossington J, Słomko J, Dawes H, Strong JWL, Estevez-Lopez F, Murovska M, Newton JL, Hodges L, Zalewski P. Prediction of Discontinuation of Structured Exercise Programme in Chronic Fatigue Syndrome Patients. Journal of Clinical Medicine. 2020;9(11):3436.
29. Estévez-López F, Mudie K, Wang-Steverding X, Bakken IJ, Ivanovs A, Castro-Marrero J, Nacul L, Alegre J, Zalewski P, Słomko J, Strand EB, Pheby D, Shikova E, Lorusso L, Capelli E, Sekulic S, Scheibenbogen C, Sepúlveda N, Murovska M, Lacerda E. Systematic Review of the Epidemiological Burden of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Across Europe: Current Evidence and EUROMENE Research Recommendations for Epidemiology. Journal of clinical medicine. 2020;9(5):1557.
30. Jason LA, So S, Brown AA, Sunnquist M, Evans M. Test–retest reliability of the DePaul Symptom Questionnaire. Fatigue: Biomedicine, Health & Behavior. 2015;3(1):16-32.

31. Lacerda EM, Bowman EW, Cliff JM, Kingdon CC, King EC, Lee JS, Clark TG, Dockrell HM, Riley EM, Curran H, Nacul L. The UK ME/CFS Biobank for biomedical research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Multiple Sclerosis. Open J Bioresour. 2017;4.
32. Nacul L, Lacerda EM, Kingdon CC, Curran H, Bowman EW. How have selection bias and disease misclassification undermined the validity of myalgic encephalomyelitis/chronic fatigue syndrome studies? Journal of Health Psychology. 2017: doi:10.1177/1359105317695803.
33. Frith J, Zalewski P, Klawe JJ, Pairman J, Bitner A, Tafil-Klawe M, Newton JL. Impaired blood pressure variability in chronic fatigue syndrome--a potential biomarker. Qjm. 2012;105(9):831-8.
34. Słomko J, Estévez-López F, Kujawski S, Zawadka-Kunikowska M, Tafil-Klawe M, Klawe JJ, Morten KJ, Szrajda J, Murovska M, Newton JL, Zalewski P. Autonomic Phenotypes in Chronic Fatigue Syndrome (CFS) Are Associated with Illness Severity: A Cluster Analysis. Journal of Clinical Medicine. 2020;9(8).
35. Scheibenbogen C, Freitag H, Blanco J, Capelli E, Lacerda E, Authier J, Meeus M, Castro Marrero J, Nora-Krukle Z, Oltra E, Strand EB, Shikova E, Sekulic S, Murovska M. The European ME/CFS Biomarker Landscape project: an initiative of the European network EUROMENE. Journal of Translational Medicine. 2017;15(1):162.
36. Rasa S, Nora-Krukle Z, Henning N, Eliassen E, Shikova E, Harrer T, Scheibenbogen C, Murovska M, Prusty BK, the European Network on MC. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Journal of Translational Medicine. 2018;16(1):268.
37. Sotzny F, Blanco J, Capelli E, Castro-Marrero J, Steiner S, Murovska M, Scheibenbogen C, European Network on MC. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome - Evidence for an autoimmune disease. Autoimmun Rev. 2018;17(6):601-9.
38. Rasa S, Nora-Krukle Z, Henning N, Eliassen E, Shikova E, Harrer T, Scheibenbogen C, Murovska M, Prusty BK. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med. 2018;16(1):268.
39. Shikova E, Reshkova V, Kumanova A, Raleva S, Alexandrova D, Capo N, Murovska M, on behalf of the European Network on MC. Cytomegalovirus, Epstein-Barr virus, and human herpesvirus-6 infections in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Journal of Medical Virology. 2020;n/a(n/a).
40. Santa R-D, Svetlana Č, Angelika K, Yung-Cheng L, Modra M. Association of Human Parvovirus B19 Infection with Development and Clinical Course of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome. Proceedings of the Latvian Academy of Sciences Section B Natural, Exact, and Applied Sciences. 2019;73(5):411-8.
41. Blomberg J, Gottfries C-G, Elfaitouri A, Rizwan M, Rosén A. Infection Elicited Autoimmunity and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: An Explanatory Model. Frontiers in Immunology. 2018;9:229.
42. Tomas C, Newton J. Metabolic abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a mini-review. Biochem Soc Trans. 2018;46(3):547-53.
43. Hatziagelaki E, Adamaki M, Tsilioni I, Dimitriadis G, Theoharides TC. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-Metabolic Disease or Disturbed Homeostasis due to Focal Inflammation in the Hypothalamus? J Pharmacol Exp Ther. 2018;367(1):155-67.
44. Schreiner P, Harrer T, Scheibenbogen C, Lamer S, Schlosser A, Naviaux RK, Prusty BK. Human Herpesvirus-6 Reactivation, Mitochondrial Fragmentation, and the Coordination of Antiviral and Metabolic Phenotypes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. ImmunoHorizons. 2020;4(4):201.
45. Fluge O, Mella O, Bruland O, Risa K, Dyrstad SE, Alme K, Rekeland IG, Sapkota D, Rosland GV, Fossa A, Ktoridou-Valen I, Lunde S, Sorland K, Lien K, Herder I, Thurmer H, Gotaas ME, Baranowska KA, Bohnen LM, Schafer C, McCann A, Sommerfelt K, Helgeland L, Ueland PM, Dahl O, Tronstad KJ. Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome. JCI Insight. 2016;1(21):e89376.
46. Germain A, Barupal DK, Levine SM, Hanson MR. Comprehensive Circulatory Metabolomics in ME/CFS Reveals Disrupted Metabolism of Acyl Lipids and Steroids. Metabolites. 2020;10(1).

47. Germain A, Ruppert D, Levine SM, Hanson MR. Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism. Mol Biosyst. 2017;13(2):371-9.
48. Germain A, Ruppert D, Levine SM, Hanson MR. Prospective Biomarkers from Plasma Metabolomics of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Implicate Redox Imbalance in Disease Symptomatology. Metabolites. 2018;8(4):90.
49. Naviaux RK, Naviaux JC, Li K, Bright AT, Alaynick WA, Wang L, Baxter A, Nathan N, Anderson W, Gordon E. Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci U S A. 2016;113(37):E5472-80.
50. Tomas C, Finkelmeyer A, Hodgson T, MacLachlan L, MacGowan GA, Blamire AM, Newton JL. Elevated brain natriuretic peptide levels in chronic fatigue syndrome associate with cardiac dysfunction: a case control study. Open Heart. 2017;4(2):e000697.
51. Huth TK, Eaton-Fitch N, Staines D, Marshall-Gradisnik S. A systematic review of metabolomic dysregulation in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis/Systemic Exertion Intolerance Disease (CFS/ME/SEID). Journal of Translational Medicine. 2020;18(1):198.
52. Eguchi A, Fukuda S, Kuratsune H, Nojima J, Nakatomi Y, Watanabe Y, Feldstein AE. Identification of actin network proteins, talin-1 and filamin-A, in circulating extracellular vesicles as blood biomarkers for human myalgic encephalomyelitis/chronic fatigue syndrome. Brain, Behavior, and Immunity. 2020;84:106-14.
53. Almenar-Pérez E, Sarría L, Nathanson L, Oltra E. Assessing diagnostic value of microRNAs from peripheral blood mononuclear cells and extracellular vesicles in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Scientific Reports. 2020;10(1):2064.
54. Castro-Marrero J, Serrano-Pertierra E, Oliveira-Rodríguez M, Zaragozá MC, Martínez-Martínez A, Blanco-López MDC, Alegre J. Circulating extracellular vesicles as potential biomarkers in chronic fatigue syndrome/myalgic encephalomyelitis: an exploratory pilot study. J Extracell Vesicles. 2018;7(1):1453730.
55. Giloteaux L, O'Neal A, Castro-Marrero J, Levine SM, Hanson MR. Cytokine profiling of extracellular vesicles isolated from plasma in myalgic encephalomyelitis/chronic fatigue syndrome: a pilot study. Journal of translational medicine. 2020;18(1):387-.
56. de Vega WC, Erdman L, Vernon SD, Goldenberg A, McGowan PO. Integration of DNA methylation & health scores identifies subtypes in myalgic encephalomyelitis/chronic fatigue syndrome. Epigenomics. 2018;10(5):539-57.