



Evidence-based Commissioning Collaboration

Diagnostic Tests for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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The Trent Institute for Health Services Research is a collaboration between the Universities of Leicester, Nottingham and Sheffield, with support from the National Co-ordinating Centre for Research Capacity & Development. Members of staff in the Sheffield Unit, based in the School of Health and Related Research (SchARR), have been engaged in reviewing the effectiveness and cost-effectiveness of health care interventions in support of the National Institute for Clinical Excellence (NICE).

In order to share expertise on this work, we have set up a wider collaboration, InterTASC, with units in other regions. These are Southampton Health Technology Assessment Centre, University of Southampton; Aberdeen Health Technology Assessment Group, University of Aberdeen; Liverpool Reviews & Implementation Group, University of Liverpool; Peninsular Technology Assessment Group, University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration, University of Birmingham.

The Evidence-based Commissioning Collaboration (EBCC) is made up of 4 commissioning consortia - The North East Yorkshire & North Lincolnshire Primary Care Organisation (NEYNL), The North Derbyshire, South Yorkshire & Bassetlaw Commissioning Consortium (NORCOM), The Trent Commissioning Consortium (TrentCOM) and The West Yorkshire Primary Care Organisation (WYPCO) - which, on behalf of PCTs in their areas, are working with the School of Health and Related Research (SchARR). SchARR is based in the University of Sheffield and houses the northern arm of the Trent Institute for Health Services Research.

The objective of the Collaboration is to share research knowledge about the effectiveness and cost-effectiveness of service interventions to inform the commissioning process. These will usually be interventions which are not likely to be addressed by NICE in the near future. The main principle on which the arrangement is based acknowledges that PCTs have continually to review evidence on particular technologies in order to determine their commissioning priorities. Since different PCTs will be looking at the same issues, there are clear benefits and economies of scale through the avoidance of duplication of evidence reviews.

The choice of topics is determined collectively by the PCTs through their commissioning Consortia.

SchARR, in liaison with the Institute of Health Sciences and Public Health Research, University of Leeds will provide the capacity which the PCTs lack in evidence retrieval and assessment/review and in economic analysis.

As part of the process, a presentation of research evidence will usually be made to a workshop of the Collaboration on particular interventions. Clinicians

and DPHs from the PCTs represented will be invited to take part in the discussions.

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Executive summary

Objectives

To develop a brief report outlining the current recommendations for the use of diagnostic tests in Chronic Fatigue Syndrome (CFS).

Proposed Service

Currently there is no single diagnostic test for CFS since aetiology remains unknown and there are no specific disease markers. Instead it is diagnosed through a pattern of recognisable symptoms and the exclusion of other symptoms.

There are a number of tests which are under investigation in research studies and which have been offered commercially. These include tests for infectious agents, immunological tests, imaging techniques and experimental tests such as the Tilt Table Test.

Background

CFS is characterised by severe, disabling fatigue and a range of other symptoms including headaches, musculoskeletal pain, sleep disturbance and difficulties with concentration. Although the disorder is clinically recognisable, it assumes many different forms, is highly variable in severity and duration and lacks specific disease markers.

Community and primary care based studies have reported the prevalence to be 0.2-2.6% depending on the criteria used. It affects both genders, all racial, ethnic and socio-economic populations and both children and adults.

The cause of CFS remains unknown. It appears to be a heterogeneous disorder that affects multiple functional systems including hormonal, neurological and immunological.

Diagnosis

Diagnosis remains difficult because of uncertain aetiology and the lack of an available laboratory test. In addition, the symptoms of CFS may overlap with other common syndromes.

A formal diagnosis can have positive implications for both the patient and the doctor. There is some evidence that early diagnostic labelling can minimise the psychosocial impact of an illness, and a diagnosis can also initiate a suitable management plan.

Diagnosis is derived from a patient's clinical history, a physical and psychological examination and laboratory tests. The primary aim of these examinations and tests is to exclude other disorders.

Laboratory tests

A standard battery of laboratory tests would include a full blood count and film, erythrocyte sedimentation rate, urea, electrolyte and creatinine levels, serum calcium and phosphate levels, liver function tests, thyroid-stimulating hormone level, urinalysis for protein, blood and sugar.

For a laboratory test to be accepted as having diagnostic validity it would need to demonstrate high sensitivity (few false negatives) and high specificity (few false positives). Evidence indicates that these have neither high sensitivity nor high specificity.

Novel diagnostic tests

A number of tests are under investigation in CFS/ME research studies, some of which are offered commercially. These include tests for infectious agents, immunological tests, imaging tests and experimental tests, such as the Tilt Table Test.

Summary

Since the aetiology of the condition remains unknown, and the evidence is inconsistent, the utility of undertaking theoretical and novel diagnostic tests is limited. Current guidelines state that the only laboratory tests that are currently recommended for the routine evaluation of people with CFS/ME are those aimed at detecting alternative medical conditions.

Abbreviations

CFS	Chronic Fatigue Syndrome
CFIDS	Chronic Fatigue and Immune Dysfunction Syndrome
CMO	Chief Medical Officer
CNS	Central Nervous System
CT	Computerised Tomography
DoH	Department of Health
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr virus
fMRI	Functional Magnetic Resonance Imaging
GP	General Practitioner
IBS	Irritable Bowel Syndrome
ME	Myalgic Encephalomyelitis
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NK	Natural Killer Cell
NMH	Neurally Mediated Hypotension
NSF	National Service Framework
PCR	Polymerase Chain Reaction
PET	Photon Emission Tomography
PVFS	Post Viral Fatigue Syndrome
SPECT	Single Photon Emission Computerised Tomography
US CDC	United States Centre for Disease Control and Prevention

Definitions of terms

Chronic Fatigue Syndrome

Chronic Fatigue Syndrome (CFS) is characterised by severe disabling fatigue and a pattern of other symptoms including headaches, musculoskeletal pain, sleep disturbances and difficulties with concentration. It is diagnosed through recognisable symptoms and the exclusion of other symptoms since, currently, there are no specific diagnostic tests or physical findings for the syndrome.

Novel Diagnostic Tests

There are a number of tests which are under investigation in research studies and which have been offered commercially. These include tests for infectious agents, immunological tests, imaging techniques and experimental tests such as the Tilt Table Test.

1. Aims

To prepare a brief report outlining the current recommendations for the use of diagnostic tests in Chronic Fatigue Syndrome (CFS).

2. Introduction

2.1 Background

Chronic fatigue syndrome (CFS) is a descriptive term used to define a recognisable pattern of symptoms that cannot be attributed to any alternative condition. It is characterised by severe, disabling fatigue and a range of other symptoms including headaches, musculoskeletal pain, sleep disturbance and difficulties with concentration. Although the disorder is clinically recognisable, it assumes many different clinical forms, is highly variable in severity and duration, and lacks specific disease markers. These factors are likely to have contributed to the poor recognition of: the nature of the disease; its impact on the health and well-being of individuals; and its societal effects. The many names it has been given and the various case definitions have added to the difficulty of its characterisation, impeding both medical care and substantive research.

Despite intense medical research, there is no known cause for CFS, but it appears to be a heterogeneous disorder that affects multiple systems, including hormonal, neurological and immunological. Diagnosis requires knowledge of possible symptoms and utilises a method of exclusion, because there are, currently, no specific diagnostic tests or physical findings for CFS. CFS affects both genders; all racial, ethnic and socio-economic populations; and can begin as early as five years old.

2.2 Methods

In February 2004, the Department of Health and the Welsh Assembly Government formally requested the National Institute for Clinical Excellence (NICE) to prepare clinical guidelines for the investigation and management of CFS, the aim being to include guidelines around assessment, diagnosis, management of adjustment and coping, symptom management and the use of rehabilitative strategies. As a consequence, it was agreed that in the interim the Evidence-based Commissioning Collaboration would prepare a holding statement regarding the status of diagnostic testing for CFS. The aim was to use a series of substantial reports and current guidelines to ascertain current recommendations[1-6].

2.3 Nature of the evidence used

The main documents which were utilised within this report included the Independent Working Group report on CFS/ME, the Medical Research Council (MRC) CFS/ME Research Strategy, and the Royal Australasian College of Physicians clinical practice guidelines for chronic fatigue syndrome.

The Independent Working Group Report to the Chief Medical Officer (CMO), published in 2002, although not intended to be a comprehensive clinical guideline, aimed to help improve diagnosis, treatment and care for patients with CFS/ME.

Its objective was to “review management and practice in the field of CFS/ME with the aim of providing best practice guidance for professionals, patients and carers to improve the quality of care and treatment for people with CFS/ME”. In particular it sought to

- Develop good clinical practice guidance on the healthcare management of CFS/ME for NHS professionals using best available evidence;
- Make recommendations for further research into the care and treatment of people with CFS/ME;
- Identify areas which might require further work into the care and treatment of people with CFS/ME
- Identify areas which might require further work and make recommendations to the CMO [1].

The Government welcomed the publication of the report as the start of a process of improving awareness and understanding that would lead to improved diagnosis, management and treatment.

The MRC research strategy for CFS/ME was developed by a CFS/ME Research Advisory Group. This group was convened in response to the request from the Department of Health (DoH), that the MRC develop a broad strategy for advancing biomedical and health services research on CFS/ME. This request followed directly from the publication of the Independent Working Group on CFS/ME to the CMO which recommended research on all aspects of CFS/ME. The research strategy which has been developed aims to provide a framework for advancing the understanding of the illness and patient care. It has been informed by contributions from patients, carers, charities, patient groups, researchers and clinicians. It sets out key priorities for future investigation, offers guidance on research methods and emphasises the importance of the continuing involvement of people with CFS/ME, their carers and the groups representing them [6].

The Royal Australasian College of Physicians’ clinical practice guidelines for chronic fatigue syndrome are evidence-based guidelines primarily aimed at assisting GPs, but are also relevant to specialist physicians and other healthcare professionals involved in managing people with fatigue states. They were developed with the intention of providing a general guide to best practice in all areas of care and treatment [5].

Another source of information, utilised within this report, is the Centres for Disease Control and Prevention (CDC) Website[7]. The CDC provides information to enhance health decisions and “serves as the national focus for developing and applying disease prevention and control, environmental health and health promotion and education activities designed to improve the health of the people of the US”[8]. The CDC provides information and guidance about all aspects of the care and treatment of CFS/ME and developed one of the most utilised case definitions (see Appendix 1).

3. Background

3.1 Definitions

'A disease of a thousand names'[9]

There remains a great deal of dispute over an appropriate name and definition for the condition. The history of the condition is one associated with an array of different names and definitions around the world. Different sectors of the population and the research literature utilise different names, which have focused on the main cause (Myalgic Encephalomyelitis (ME)), the principal symptom (Chronic Fatigue Syndrome (CFS)) or an aggregation of the two (Chronic Fatigue and Immune Dysfunction Syndrome (C.F.I.D.S), and Post Viral Fatigue Syndrome (PVFS)).

3.1.1 Myalgic Encephalomyelitis

Myalgic Encephalomyelitis is sometimes diagnosed in the UK, but rarely in USA. The term myalgic refers to symptoms associated with muscles (i.e. pain, twitching) and encephalomyelitis refers to brain symptoms (i.e. difficulties with speech, memory and concentration). Some have argued, however, that the term does not accurately describe the condition. This is because myalgic is inappropriate for those with little muscle pain and encephalomyelitis meaning inflammation of the brain and spinal cord is incorrect because the term implies a pathophysiological process for which no evidence exists. Whilst many in the medical profession feel that the name ME should be dropped altogether, some sufferers feel the term more accurately reflects the nature of their condition.

3.1.2 Chronic Fatigue Syndrome

During the 1980s, the term Chronic Fatigue Syndrome became the popular and preferred name of the medical profession. The name does not suggest the cause, but stresses the long-term chronic nature of the illness and recognises the major symptom of the condition as fatigue. However, for some sufferers the term fatigue is problematic and considered demeaning because it does not accurately describe the patient's experience and fails to take into account the complex array of symptoms and the level of disability that many people suffer. Also fatigue, although invariably present, may not be the major symptom.

3.1.3 Post Viral Fatigue Syndrome

The name Post Viral Fatigue Syndrome was adopted at the beginning of the 1980s in the UK as an alternative to ME. Its principal benefit lies in that it offers a more accurate description for those whose illness was triggered by an acute viral infection, such as glandular fever. Its difficulty, however, is its inability to account for other possible causes.

3.1.4 Chronic Fatigue and Immune Dysfunction Syndrome

In the USA the name Chronic Fatigue and Immune Dysfunction Syndrome is commonly used. Like other names associated with the condition, however, there are some in the medical profession who feel that this is not an appropriate term. This is because although many doctors agree that abnormalities in the body's immune system take place in ME/CFS, they feel that these are not sufficiently uniform or profound enough to warrant becoming part of the official name.

3.1.5 Chronic Fatigue Syndrome / Myalgic Encephalomyelitis

Current evidence does not allow complete distinction between Chronic Fatigue Syndrome and Myalgic Encephalomyelitis or useful delineation of subgroups and the research literature refers to CFS being the same illness as ME, PVFS and all similar symptom complexes. Following the example of the UK working Group Report, this report will recognise that no current terminology is satisfactory to all and will use the composite term CFS/ME acknowledging that CFS is widely used among clinicians and ME among patients and the community[1].

3.2 Case definitions

There have been several attempts to develop a case definition to assist observation and research, and there are many case definitions that are available. No single case definition is, however, universally accepted. Case definitions have led to more reliable epidemiological data and to more consistent approaches for studies on clinical recognition and management. Current case definitions are, however, useful, primarily for research purposes only. The Royal Colleges of Physicians, Psychiatrists, and General Practitioners' Report in 1996 noted that meeting the case definitions does not constitute a diagnosis, since they are too broad as to exclude other similar conditions that require different management strategies [10]. Appendix 1 provides a list of the different case definitions.

The two most frequently used definitions for CFS/ME are the UK Oxford criteria and the US Centre for Disease Control (CDC) criteria. Both state that debilitating fatigue must be present for at least six months, that there is some functional impairment, and that these have not been caused by any other identifiable clinical condition. The definitions differ, however, in the number and severity of other symptoms that must be present. A different set of

criteria are sometimes used to diagnose ME, for example the Dowsett or London criteria.

The MRC CFS/ME Research Advisory Group considers that there should be an agreed standardised case definition and a classification of severity and any other relevant characteristics that define subgroups, and believes that accuracy and consistency of case definition and diagnosis is a crucial issue both for services and for research. Improved definitions of subgroups would then underpin further research on the causes, mechanisms and management of CFS/ME[6]. There is an ongoing effort by the CDC, through an international CFS study group to refine the current research definition of CFS[11].

3.3 Symptoms and effects

Patients with CFS/ME experience an individual array of symptoms from the overall range seen in the illness. Some such as physical and/or cognitive fatigue are seen in almost all patients, though their extent can vary. Others are very common, such as pain, disturbed sleep and gastrointestinal disturbance. Individual symptom complexes may vary according to the individuals' medical history and activity pattern. In some individuals the recurrence of symptoms from the triggering event is part of the symptom profile (e.g. recurrent sore throats and lymphadenopathy after glandular fever). In others old symptoms or susceptibilities relapse or recur with development of CFS (e.g. pain from old injuries, mood disturbance in patients with previous anxiety or depression). Symptoms such as postural hypotension and dizziness can in part reflect secondary effects of inactivity and/or isolation resulting from enforced inactivity. Box 1 outlines the symptoms commonly exhibited by sufferers of CFS/ME.

- Persistent/excessive tiredness or fatigue
- Cognitive impairment, including reduced attention span, impairment of short-term memory and the inability to plan or organise thoughts
- Postexertional malaise
- Pain, which may be muscular, rheumatic or headaches
- Sleep disturbance
- Recurrent sore throat
- Digestive disturbances
- Intolerances, including food
- Temperature disturbance
- Dizziness
- Postural hypotension

Box 1. Common symptoms exhibited by sufferers of CFS/ME.

A recent description has suggested 4 categories of severity in CFS/ME, mild, moderate, severe and very severe. Those suffering very severe CFS/ME are unable to mobilise or carry out any daily tasks for themselves and are likely to

remain in bed for the majority of the time. They will often be unable to tolerate any noise and are generally extremely sensitive to light [12].

There is widespread controversy surrounding the existence of CFS/ME. Patients, their carers and healthcare professionals encounter different levels of varying manifestations of disbelief and prejudice against people affected by the condition. The severity, complexity and longevity of the illness are poorly understood. Moreover, the disbelief and controversy that exists within the professions has done nothing to dispel public disbelief in the existence of such a seemingly and inconstant illness[1].

Yet CFS imposes a substantial burden on the health of the UK population. Estimates suggest that up to 25% of people with CFS/ME suffer a severe form, such that they are unable to perform most basic personal tasks and are confined to bed or spend the majority of the day in bed [1].

3.3.1 Impact on the patient and their carers

A sufferer's experience of CFS can be one of frustration about their inability to perform and function at previously normal levels, the lack of understanding or disbelief from people around them, and the continual setbacks they face. Anxiety or depression or anger and withdrawal from social interaction are relatively common consequences of suffering CFS. These understandable reactions add to distress, and in some cases become part of, or even dominate the clinical picture. In vulnerable patients or at difficult times, suicidal ideation can occur, and suicide becomes a serious risk. There can be a substantial impact on work, finance and education. People with CFS/ME frequently experience problems with accessing state benefits. This is partly because of the variable nature of CFS/ME and uncertain prognosis, but sufferers may also have difficulty obtaining a diagnosis, and thus in obtaining benefits.

Complex issues may also face patients as a result of their illness. Their role can change radically affecting their confidence and self-esteem. For example, they may cease to function as the breadwinner, the parent or the spouse and the loss of their working role and other social functioning can add to their difficulties.

Young people with CFS/ME especially of long duration are vulnerable to negative effects on growth, including physical, emotional and intellectual development, which may perpetuate impairment. The potential impact on education is of particular concern, as is the broader effects on family life.

The effect on carers is also substantial. Carers report despair and isolation resulting from society's misconceptions of the illness and the change in family circumstances owing to the impact of the illness. Many carers find that a restructuring of their lives as well as the sufferers' lives is necessary alongside an ongoing uncertainty as to whether the individual will ever return to previous levels of functioning. An additional potential burden is the loss of earnings when a carer has to assume a full-time caring role [1, 5, 6].

3.4 Incidence and Prevalence

Estimates of prevalence vary, and may be attributed to the diversity in diagnostic criteria and to variations in the extent to which alternative medical and psychiatric diagnoses are excluded. Community and primary care based studies have reported the prevalence to be 0.2-2.6% depending on the criteria used [13]. Most commonly, onset is reported to be early twenties to mid-forties. It is reported to be approximately twice as common in women as in men, affects all social classes to a similar extent and affects all ethnic groups. In children, the commonest age of onset is thirteen to fifteen years old, but cases can occur as young as five years old. The CFS/ME Working Group reported that a general practice with a population of 10,000 patients is likely to have 30-40 patients with CFS/ME, about half of whom may need input from specialist services[1].

The CFS/ME Working Group identified the following predisposing factors.

- Gender since incidence in females exceed that in males of any age
- Familial as the familial incidence of CFS/ME is slightly higher than expected. Twin studies suggest a hereditary component but family environmental factors may also have an influence
- Personality as certain personality traits may predispose some to develop CFS/ME.
- Other past or current medical disorders such as fibromyalgia and irritable bowel syndrome
- Previous mood disorders have been found among individuals with CFS/ME across a number of studies. This finding might simply reflect the fact that previous mood disorders predict future mood disorders, which often coexist with chronic illnesses, including CFS/ME. Alternatively, this finding could reflect a common predisposition to both mood disorders and CFS/ME [1].

3.5 Prognosis

It is generally recognised that prognosis is variable. Studies of prognosis have tended to focus on people attending specialist clinics who are likely to have had the condition for longer and to have a poorer outlook. Current evidence would indicate that CFS/ME patients exhibit wide variation in the time to recovery. Many patients suffering from CFS/ME improve quite quickly, although it is questionable as to whether they return completely to their previous healthy levels. However, in those who do not improve quickly the illness can persist for a long time. The prognosis tends to be worse for severely ill patients than for less severely ill patients. Individuals with acute onset illness appear to have a better prognosis than those with gradual onset. The findings from prospective natural history studies are varied. At 12-18 months, rates of self-reported global improvement in symptoms range from 11-64% and rates of self-reported worsening of symptoms ranged from 15-20% [5]. There would appear to be little evidence about which patients recover, or what factors pre-dispose to recovery, although it has been

suggested that poorer outcomes are associated with a longer duration of illness, subjective cognitive impairment and somatic symptoms[5].

Children with the syndrome seem to have a notably better outcome than adults. The report of the Royal Australasian College of Physicians reported that between 77% and 94% of children with CFS/ME, evaluated in studies, recovered or showed definite improvement in their condition[5].

3.6 Aetiology

The cause of CFS/ME remains unknown, although various hypotheses have been suggested that include one or more of the following factors: immunological, viral, psychological and neuroendocrine abnormalities. To what extent these abnormalities are part of the primary 'disease' process or secondary consequence remains open to debate. In addition, several predisposing factors, 'disease' triggers and maintaining factors have been identified. Several overarching possibilities which are not mutually exclusive have been proposed to explain the occurrence of CFS/ME [1].

- CFS/ME is an umbrella term for several different illnesses
- One (or more) 'core' disorder(s) exist
- Several different causative factors trigger a common 'disease' process
- The aetiology and/or pathophysiology are multifactorial
- Certain factors are necessary but not sufficient to cause CFS/ME
- Certain factors can influence individual manifestations or duration
- Some features are secondary consequences of the primary 'disease' process.

The research literature contains several hypotheses and proposals to explain how CFS/ME may be caused or maintained. The quality of the evidence is variable, however, and many suggested mechanisms are as yet based on associations rather than causes or linkages. Many reported findings are not published in the peer-reviewed literature or are not well described [5, 14]. The report of the Royal Australasian College of Physicians has assessed the strength of the evidence for a number of factors suggested as a cause of CFS/ME. In most cases, the evidence base was reported not to be large, with information coming from only a few studies and often conflicting[10].

It is important to outline the various hypotheses within this report, since it explains why certain diagnostic tests have been proposed.

3.6.1 Infectious

Many patients with CFS/ME attribute the onset of their illness to an acute influenza like infection and consequently the role of viruses as possible causative agents has been studied. Fatigue, cognitive disability and musculoskeletal pain are commonly found during the acute phase of many infectious diseases and generally disappear spontaneously with the emergence of a normal immune response. However, following certain infections a proportion of patients develop prolonged fatigue.

There is good quality evidence to indicate that certain infections are more common triggers for CFS/ME than others. Glandular fever, viral meningitis

and viral hepatitis are followed by CFS/ME in about 10% of cases, and up to 10% of patients with diagnosed infectious mononucleosis (infection with the Epstein-Barr virus (EBV)) can develop chronic post-infectious fatigue[1, 6].

A number of other viral pathogens, such as the Coxsackie virus, human herpes virus 6, measles, and the human T-cell lymphotropic virus, have also been implicated as possible causes of CFS/ME although there is no consistent or conclusive data. It is now, however, believed that CFS/ME is not specific to one pathogenic agent but could be a state of chronic immune activation [1, 5-7, 10].

3.6.2 Immunologic

Immunological abnormalities are common in patients with CFS/ME. Their relationship to the illness has not been established. The evidence suggests some immune dysregulation with activation or suppression of different components as indicated by changes in cytokine concentrations and cell surface markers. The data are, however, inconsistent and there does not seem to be a consensus on the nature and extent of immunologic disturbances [1, 5, 6].

3.6.3 Central nervous system

Many of the symptoms of CFS/ME suggest dysfunction of the central nervous system (CNS). These could include cognitive disturbance, central fatigue (for example when movement requires increased mental effort) and disrupted neural regulatory mechanisms (for example those involved in sleep and temperature regulation). One suggested primary change in the CNS of patients with CFS/ME is abnormal brain blood flow, particularly involving the brain stem. Diagnostic imaging studies have, however, provided inconsistent findings, and it is unclear whether changes that have been reported are involved in the cause of the disorder or are a consequence of the illness and persistent inactivity [1, 5, 6].

3.6.4 Autonomic nervous system

There is some evidence to suggest that the autonomic nervous system can play a part in causing CFS/ME although its role is not established. Diagnostic Imaging studies investigating this phenomenon as a cause of CFS/ME have not produced consistent results. There is inconsistent evidence as to whether autonomic abnormalities, in particular, neurally mediated hypotension are part of a primary 'disease' process or due mainly to inactivity associated with CFS/ME [1, 5].

3.6.5 Hypothalamic-pituitary-adrenal axis

Several studies have found subtle neuroendocrine abnormalities, particularly hypoactivity of the hypothalamic-pituitary adrenal axis. It is also possible that disturbances in hypothalamic function could contribute to some CFS/ME symptoms such as fatigue, sleep problems and disturbed thermoregulation [1, 5, 7].

3.6.6 Allergic

It has been suggested that patients with CFS/ME have a higher occurrence of allergies compared with normal populations. It has been argued that allergens, similar to infectious agents could serve as a triggering event for many of the symptoms specific to CFS/ME [1, 5].

3.6.7 Neurology

The report of the Working Group of the Royal Australasian College of Physicians indicated that there is conflicting evidence for neurological abnormalities in CFS/ME, but good evidence that muscle strength, endurance and recovery are normal. Early reports of inflammation of the brain, spinal cord or muscles have not been confirmed [5, 6].

4. Diagnosis

4.1 Difficulties associated with making a diagnosis of CFS

One of the key issues surrounding the management of people with CFS/ME, as identified by the Working Group Report to the CMO is the difficulty surrounding diagnosis [1]. Sufferers often experience a lack of belief in the illness as well as a 'slowness' to recognise that symptoms might be CFS/ME. There is also concern that the illness is not taken seriously by some in the medical profession, and that GPs do not always understand the complaint and its possible severity. A diagnosis of CFS/ME, as with several other chronic illnesses, remains difficult because of uncertain aetiology and the lack of an available laboratory test. Instead, it relies on the presence of a set of characteristic symptoms together with the exclusion of alternative diagnoses.

A further difficulty in diagnosis is that the symptoms of CFS/ME may overlap with other common syndromes such as fibromyalgia, irritable bowel syndrome (IBS), major depression and anxiety. Fibromyalgia, in particular, is a closely related syndrome, differing mainly in its relative emphasis on musculoskeletal pain rather than fatigue. Patients who complain of persisting fatigue or tiredness may be describing any one of a diverse range of clinical phenomena, ranging from muscle weakness to dyspnoea or depressed mood. In primary care, up to two-thirds of people presenting with persistent fatigue have some other identifiable medical or psychiatric disorder that accounts for the symptom and careful assessment to exclude these is essential before making a diagnosis of CFS [5].

4.2 The benefits of making a diagnosis of CFS

A formal diagnosis of CFS/ME can have positive implications for both the patient and the doctor. From the patient's perspective, an early authoritative positive diagnosis can minimise the impact of uncertainty surrounding the illness and relieve unwarranted fears and anxieties about the cause of the symptoms. It also validates the patient's experience of the illness and suffering, making it easier to inform others of the nature of the illness and legitimises the patient's entry into medical care. There is also some patient evidence that indicates that a lack of a name for the condition prevents people from coming to terms with their illness, and may also limit the ability to implement an effective management plan [1, 5].

The importance of an early diagnosis was a key issue highlighted by patients in the Working Group Report to the CMO [1], and there is some evidence that early diagnostic labelling can minimise the psychosocial impact of an illness, yet the research criteria (case definitions, see Appendix 1), stipulate that a diagnosis can be made only after the presence of a cluster of symptoms for six months. Delay of a diagnosis, however, may add to the impact of the illness and may have important consequences not only for healthcare but for aspects of the patient's life such as education and employment. The Working Group report to the CMO argues that a working or interim diagnosis is better than none since it allows active management to begin. Moreover, one of its

key conclusions was that the early recognition with an authoritative positive diagnosis is key to improving outcomes [1].

4.3 How physicians diagnose CFS

The majority of patients first present to their GP with no preconceived ideas of diagnosis. They are experiencing a complex, difficult and uncertain illness with no hard or fast rules to follow that would alleviate symptoms or expedite recovery. Without a validated test for the illness, diagnosis is based on the recognition of symptoms together with the exclusion of alternative conditions. Thus, a positive diagnosis can usually be made from clinical history, a physical and mental examination and a few appropriate laboratory tests, as in other chronic illnesses of uncertain nature.

The key symptoms of CFS/ME in adults broadly fit with existing research criteria, and form a recognisable pattern of characteristic symptoms. The first step in the investigation is obtaining a detailed medical history and performing a complete physical and mental examination of the patient. A standard series of laboratory tests of the patients' blood and urine would then be performed to help the GP identify other possible causes of the illness. If test results suggest an alternative explanation for the patient's symptoms, additional tests may be performed to confirm that possibility [1, 5].

In the clinical examination it is necessary to ascertain the character of the fatigue. One of the most common and characteristic complaints of adults, particularly in the early stages of the illness is of intolerance to both physical and mental exertion with delayed impact. The fatigue needs to be differentiated specifically from other symptoms such as weakness (indicative of neuromuscular disease), dyspnoea and effort intolerance (cardiac or respiratory disease), somnolence (primary sleep disorders) and loss of motivation and pleasure (major depression)[5].

Characteristically, there are no abnormal physical findings in people with CFS/ME. The psychological evaluation of the patient usually consists of two parts, the history and mental state examination. The characteristic mood state of people with CFS/ME is irritation, frustration and transient depression rather than persistent and profound sadness. This is unlike people with major depression who report marked weight loss, self-reproach and guilt, suicidal plans, persistent loss of motivation. The physical and mental examinations are therefore primarily directed towards excluding other disorders [1, 5].

Given the complex nature of the illness, several consultations may be necessary before the diagnosis is finally made.

4.4 Appropriate tests for routine diagnosis of CFS

While the number and type of tests performed vary from GP to GP, the following tests constitute a typical standard battery to exclude other causes of fatiguing illness: full blood count and film, erythrocyte sedimentation rate (ESR), urea, electrolyte and creatinine levels, serum calcium and phosphate levels, liver function tests, thyroid-stimulating hormone level, urinalysis for

protein, blood and sugar. Further testing may be required to confirm a diagnosis for illnesses other than CFS/ME [1, 5, 7].

4.5 Theoretical and Experimental tests

There are a number of tests, which are under investigation in CFS/ME research studies, some of which have been offered commercially. These include tests for infectious agents such as, the Epstein-Barr virus (EBV), enteroviruses, retroviruses, human herpesvirus 6, *Candida albicans* and *Mycoplasma incognita*. In addition immunological tests such as measurements of natural killer cell (NK) number or function, cytokine tests and cell marker tests are offered. Further experimental tests include the tilt table test for neurally mediated hypotension (NMH) and imaging techniques such as magnetic resonance imaging (MRI), photon-emission tomography (PET-scan) or single photon emission computerised tomography (SPECT) scan. Reports of a pathway marker for CFS/ME as well as a urine marker for CFS/ME are undergoing further study [1, 5-7].

4.5.1 The utility of undertaking theoretical and experimental tests

For a laboratory test to be accepted as having diagnostic validity it would need to demonstrate both high sensitivity, that is almost all people with CFS/ME have a positive result (few false negatives) and high specificity, that being that almost all healthy persons and people with fatigue not due to CFS/ME have a negative result (few false positives). Since the diagnosis of CFS/ME identifies a heterogeneous group of people, it is unlikely that a single reliable diagnostic test will emerge. The only laboratory tests that are currently recommended for the routine evaluation of people with fatigue states are aimed at detecting alternative medical conditions [1, 5, 6].

Below is a list of other tests, which have been suggested within the literature as a means of diagnosing CFS/ME. This information is derived primarily from the US CDC [7]. Other documents make reference to, but provide very little detail on, the nature of 'specialised tests'.

4.5.2 Tests for infectious agents

Epstein-Barr virus: This herpesvirus is associated with infectious mononucleosis, and was initially considered as the most likely candidate as the causative agent in CFS/ME. More recent studies make it clear that many CFS/ME cases have no association with EBV infection. Therefore, serological testing for EBV has no utility in diagnosing CFS/ME.

Enteroviruses: This group of viruses are mostly associated with clinical conditions affecting the nervous system. Epidemiological studies of enterovirus infection in CFS/ME patients have been inconclusive, and while some patients' fatigue might be explained by the presence of an enterovirus, it is not associated with all or even most CFS/ME patients. As such, serologic test, polymerase chain reaction examination of muscle biopsy specimens and other methods aimed at detecting enterovirus infections are not useful in the diagnosis of CFS/ME.

Retroviruses: One published account reported evidence that certain DNA sequences could be detected in white blood cells of CFS/ME patients by using a technique known as the polymerase chain reaction, or PCR. Several efforts to repeat this study under blinded conditions were unsuccessful. Additional efforts indicate that none of the identified retroviruses are associated with CFS/ME. PCR analysis for human retrovirus DNA is not useful for the diagnosis of CFS/ME.

Human herpesvirus 6: A report suggested that human herpesvirus type 6 (HHV-6), and in particular actively replicating HHV-6 may be associated with CFS/ME. Subsequent efforts to confirm this association have however been unsuccessful. In addition, HHV-6 is an extremely common infection and is present in nearly 100% of humans by the age of three years. It is, therefore, not useful as a diagnostic marker for CFS/ME.

Candida albicans: Like HHV-6 this yeast is so common in humans, that it is virtually ever-present. There is no evidence that there is a causal association between *Candida albicans* and CFS/ME. It is, therefore, not useful as a diagnostic marker.

4.5.3 Immunological tests

Natural killer (NK) cell assays: Some studies have reported a trend among CFS/ME patients to have reduced NK cell activity and/or reduced NK cell numbers. Some studies have, however, failed to demonstrate any relationship between NK cell activity and CFS/ME. Even those that have demonstrated a trend did not observe differences between CFS/ME patients and controls that were sufficient to permit the use of NK cell assays as a diagnostic tool for CFS/ME, and there were individual CFS/ME patients within all the studies who exhibited apparently normal NK cell function and numbers. As such, NK cell assays have no value as a diagnostic marker for CFS/ME.

Cytokine assays: Various reports have suggested that elevated levels of certain immune system cytokines are associated with CFS/ME. Findings among various research groups are, however, inconsistent. No differences between CFS/ME sufferers and controls were sufficiently large to be diagnostic, and there were some CFS/ME patients in the research who had no such elevations in cytokine. No cytokine has been identified to date that serves as a useful diagnostic marker for CFS/ME.

Cell marker assays: At least one study has observed an elevation in the number of T cells expressing activation markers among the more severely ill CFS/ME patients. This work has, however, not been confirmed and no such trend has been observed in other studies. As such, no set of immune cell markers has yet been identified that serves as a diagnostic tool for CFS.

4.5.4 Neurological/Imaging tests

Abnormal neurological signs are not consistently reported in most patients with CFS/ME. The initial reports of inflammation of the brain, spinal cord or muscles have not been confirmed. Imaging studies using CT or magnetic

resonance scans can demonstrate detailed brain structure but do not provide information about brain functions. There are reports within the literature of white matter changes but these are variable and non-specific. Furthermore, such imaging techniques are prone to misinterpretation if there are subtle differences in brain structure.

Functional imaging of various types (functional magnetic resonance (fMRI), SPECT, and PET) are relatively new techniques to have been developed. Studies from other conditions have demonstrated the many difficulties in interpreting abnormalities – particularly in determining whether or not such suspected abnormalities are primary or secondary phenomena [6]. Imaging tests should not, therefore, be performed as a diagnostic technique for CFS.

4.5.5 Other tests

Tilt table test: This test involves strapping the patient to a table that can be tilted at various angles. The patient's blood pressure is measured, sometimes before and after administration of medication that hastens the heartbeat, at several angles of inclination and declination. In one study most CFS/ME patients were found to exhibit a marked decrease in blood pressure in the tilt table test. There is, however, insufficient information and the Tilt Table test should not be used as a diagnostic technique for CFS/ME.

4.5.6 Summary

One of the key issues surrounding the management of people with CFS/ME is the difficulty surrounding diagnosis. Sufferers often experience a lack of belief and a slowness to recognise the illness. In addition many of the symptoms of CFS/ME may overlap with other common syndromes, such as fibromyalgia and IBS. A diagnostic test with a high sensitivity and a high specificity would, therefore, benefit patients and doctors. This remains problematic, however, due to uncertain aetiology and the lack of specific disease markers. Diagnosis is currently based on the recognition of symptoms together with the exclusion of alternative conditions. Thus, a positive diagnosis is usually made from clinical history, a physical and psychological examination and laboratory tests. The only laboratory tests that are currently recommended for the routine evaluation of people with fatigue are aimed at detecting alternative medical conditions. The utility of undertaking theoretical and novel diagnostic tests is limited. This statement is reflected in most of the documents reference in this report. The Working Group report to the CMO, for example, states that whilst specialised tests may be required to exclude particular conditions that are suggested by a combination of symptoms (for example, blood markers of rheumatic diseases) “tests used in research, such as specialist neuroimaging, do not currently seem necessary as part of routine care” [1]

The Royal Australasian College of Physicians clinical practice guidelines, outlined the tests recommended in the evaluation of people with CFS/ME and those which “have no basis in evidence and are not recommended” (Box 2) [5]

Recommended*

- Full blood count and film
- Erythrocyte sedimentation rate
- Urea, electrolyte and creatinine levels
- Serum calcium and phosphate levels
- Liver function tests
- Thyroid-stimulating hormone level
- Urinalysis for protein, blood and sugar

Not recommended **

Serological tests for:

- Epstein-Barr virus
- Enteroviruses
- Lyme disease in Australia
- Tests of immunity, including T lymphocyte subset measurements and functional assays
- Urinary protein metabolite screening
- Neuroimaging studies, including magnetic resonance imaging or radionuclide studies
- Autoantibody assays or
- Serum creatinine kinase

* - tests to exclude other diagnoses may be performed if indicated by the clinical evaluation

** - available evidence indicates that these tests have no role in standard lab evaluation of people with CFS.

Box 2. Laboratory investigations for the evaluation of chronic fatigue

A further indication of the lack of utility associated with undertaking novel diagnostic tests is provided by the MRC research strategy[6]. They state that “in view of the probable multiplicity of potential causal factors, and the widely disparate findings reported, that studies investigating causal pathways and mechanisms whilst having merit, would not have the same immediate impact on increasing understanding of CFS/ME, nor reducing the suffering of patients. This is not to say that such studies should be abandoned, rather that it is not an essential pre-requisite to identify triggers and causal pathways in order to undertake research on CFS/ME” [6]. Without further research into the causal pathways of CFS/ME, the utility of conducting novel diagnostic tests is likely to remain limited.

In the short-term the MRC CFS/ME Research Advisory Board consider that the research community should be encouraged to develop high quality research proposals for funding that address key issues of CFS/ME research that are amenable for study at the present time: case definition; understanding symptomatology and new approaches to management.

5. Ongoing developments/research

As a result of the Working Group report to the CMO, there are a number of ongoing developments/research which may, in the future, further contribute to the debate of novel diagnostic tests for CFS/ME.

Firstly, the Working Group report has informed the External Reference Groups developing the two National Service Frameworks (NSFs) for both children's services and adults with long-term conditions. The NSFs will address some of the generic issues affecting the management of illness in childhood and adolescence and long-term medical conditions in adults.

Secondly, the MRC published a Research Strategy for CFS/ME in May 2003, as a direct response to the publication of the Working Group report to the CMO. The research strategy aims to provide a framework for advancing the understanding of the illness and patient care. It sets out key priorities for future investigation, offers guidance on research methods and emphasises the importance of the continuing involvement of people with CFS/ME, their carers and the groups representing them [6]. There have been two initiatives in response to the MRC research strategy. One has been a highlight notice to the research community welcoming high quality proposals across the entire spectrum of CFS/ME research. The other was a scientific meeting to discuss the potential for epidemiological studies in the UK [15]. In addition, the MRC is funding two clinical trials to assess the effectiveness of various types of non-drug treatment for patients with CFS/ME [16].

Thirdly, clinical guidelines for the diagnosis and management of CFS/ME will be developed by NICE. This is likely to be published 2006-07.

Fourthly, in May 2003 it was announced by the government that there was to be a cash injection of £8.5 million for services specifically designed for people with CFS/ME. The aim of this money is to develop services where none previously existed. The first phase of development commenced in April 2004 with a further phase planned in 2005 with the intention that funding would be then built into PCT allocations in 2006.

The first phase of investment has seen money allocated towards the development of specialist centres. The location of these new CFS/ME services are in Newcastle, Leeds, Liverpool, Manchester, Sheffield, Birmingham/West Midlands, East Midlands, East Anglia, North London (St. Bartholomew), Surrey (Sutton), Bath/Bristol, Cornwall/Devon. The centres and local teams will champion and support the development of local services to improve the care and treatment of the many people with CFS/ME.

Led by local CFS/ME specialists, the centres will improve the overall care of patients with CFS/ME by:

- Providing access to specialist assessment, diagnosis and advice on treating the condition
- Developing education and training resources for health professionals to improve the knowledge and skills of staff

- Supporting clinical research into the causes and treatment of CFS/ME.

Two local support teams spread throughout the country will provide support to those adjusting to and coping with CFS/ME by:

- Providing specialist rehabilitation programmes for patients to help increase energy and activity levels
- Developing a network of local domiciliary services (health, education, and social services) for those more severely affected who may be house-bound or bed-bound
- Supporting GPs and other health professionals and in partnership with local self-help groups develop expert patient and self-management initiatives [16].

APPENDIX 1

The various case definitions for CFS/ME.

<p>US Centre for Disease Control and Prevention 1988 (CFS) (Holmes 1988)</p>	<p>6 months duration of fatigue Functional activity – 50% decrease in activity 6 or 8 symptoms required; physical signs sometimes required Neuropsychiatric symptoms – may be present New onset required Exclusions: extensive list of physical causes, psychosis, bipolar disorder, substance abuse</p>
<p>US Centres for Disease control and Prevention, 1994 (CFS) (Fukuda, 1994)</p>	<p>6 months duration of fatigue Substantial functional impairment 4 symptoms required cognitive or neuropsychiatric symptoms may be present New onset required Exclusions: clinically important medical conditions, melancholic depression, substance abuse, bipolar disorder, psychosis, eating disorders</p>
<p>Australia 1990 (CFS) (Lloyd)</p>	<p>6 months duration of fatigue Substantial functional impairment – disruption of daily activities Postexertional fatigue No symptoms specified Cognitive or neuropsychiatric symptoms required New onset not required Exclusion: Known physical causes, psychosis, bipolar disorder, substance abuse, eating disorder.</p>
<p>UK, 1991 “Oxford criteria” (CFS) (Sharpe)</p>	<p>6 months duration of fatigue Disabling functional impairment – affects physical and mental functioning No symptoms specified Cognitive or neuropsychiatric symptoms – may be present Definite onset required. Exclusions – known physical causes, psychosis, bipolar disorder, eating disorder, organic brain disease, substance abuse. Other psychiatric disorders (depressive illness, anxiety disorders) are not reasons for exclusion.</p>
<p>London, 1990 (ME) (derived from Dowsett and Ramsey)</p>	<p>Complaint of general or local muscular fatigue following minimal exertion with prolonged recovery time. Neurological disturbance, especially of cognitive, autonomic, and sensory functions Variable involvement of cardiac and other systems, a prolonged relapsing course Syndrome commonly initiated by respiratory and/or</p>

	gastrointestinal infection but an insidious or more dramatic onset after neurological, cardiac or endocrine disability.
WHO, 1994	The WHO's International Classification of Diseases provides a system of categories for international systematic recording. These are not diagnostic criteria and are not used by clinicians as such. The current version, ICD-10, includes categories for Neurasthenia/Fatigue syndrome and for post-viral fatigue syndrome/Benign Myalgic Encephalomyelitis.

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See also:

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