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Article in *Journal of Chronic Fatigue Syndrome* · December 2011

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## The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study

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■ The complexities of the chronic fatigue syndrome and the methodologic problems associated with its study indicate the need for a comprehensive, systematic, and integrated approach to the evaluation, classification, and study of persons with this condition and other fatiguing illnesses. We propose a conceptual framework and a set of guidelines that provide such an approach. Our guidelines include recommendations for the clinical evaluation of fatigued persons, a revised case definition of the chronic fatigue syndrome, and a strategy for subgrouping fatigued persons in formal investigations.

*Ann Intern Med.* 1994;121:953-959.

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We have developed a conceptual framework and a set of research guidelines for use in studies of the chronic fatigue syndrome. The guidelines cover the clinical and laboratory evaluation of persons with unexplained fatigue; the identification of underlying conditions that may explain the presence of chronic fatigue; revised criteria for defining cases of the chronic fatigue syndrome; and a strategy for dividing the chronic fatigue syndrome and other unexplained cases of chronic fatigue into subgroups.

### Background

The chronic fatigue syndrome is a clinically defined condition (1-4) characterized by severe disabling fatigue and a combination of symptoms that prominently features self-reported impairments in concentration and short-term memory, sleep disturbances, and musculoskeletal pain. Diagnosis of the chronic fatigue syndrome can be made only after alternative medical and psychiatric causes of chronic fatiguing illness have been excluded. No pathognomonic signs or diagnostic tests for this condition have been validated in scientific studies (5-7); moreover, no definitive treatments for it exist (8). Recent longitudinal studies suggest that some persons affected by the chronic fatigue syndrome improve with time but that most remain functionally impaired for several years (9, 10).

### Issues in Chronic Fatigue Syndrome Research

The central issue in chronic fatigue syndrome research is whether the chronic fatigue syndrome or any subset of it is a pathologically discrete entity, as opposed to a debilitating but nonspecific condition shared by many different entities. Resolution of this issue depends on whether clinical, epidemiologic, and pathophysiologic features convincingly distinguish the chronic fatigue syndrome from other illnesses.

Clarification of the relation between the chronic fatigue syndrome and the neuropsychiatric syndromes is particularly important. The latter disorders are potentially the most important source of confounding in studies of chronic fatigue syndrome. Somatoform disorders, anxiety disorders, major depression, and other symptomatically defined syndromes can manifest severe fatigue and several somatic and psychological symptoms and are diagnosed more frequently in populations affected by chronic fatigue (11-13) and the chronic fatigue syndrome (14, 15) than in the general population.

The extent to which the features of the chronic fatigue syndrome are generic features of chronic fatigue and deconditioning due to physical inactivity common to a diverse group of illnesses (16, 17) must also be established.

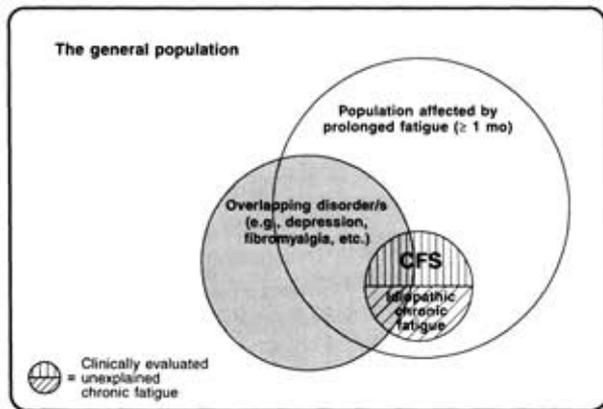
### A Conceptual Framework for Studying the Chronic Fatigue Syndrome

In the United States, 24% of the general adult population has had fatigue lasting 2 weeks or longer; 59% to 64% of these persons report that their fatigue has no medical cause (18, 19). In one study, 24% of patients in primary care clinics reported having had prolonged fatigue ( $\geq 1$  month) (20). In many persons with prolonged fatigue, fatigue persists beyond 6 months (defined as chronic fatigue) (21, 22).

We propose a conceptual framework (Figure 1) to guide the development of studies relevant to the chronic fatigue syndrome. In this framework, in which the chronic fatigue syndrome is considered a subset of prolonged fatigue ( $\geq 1$  month), epidemiologic studies of populations defined by prolonged or chronic fatigue can be used to search for illness patterns consistent with the chronic fatigue syndrome. Such studies, which differ from case-control and cohort studies based on predetermined criteria for the chronic fatigue syndrome, will also produce much-needed clinical and laboratory background information.

This framework also clarifies the need to compare populations defined by the chronic fatigue syndrome with several other populations in case-control and cohort studies. The most important comparison populations are those

\*For a listing of members of the Study Group, see Appendix.



**Figure 1.** A conceptual framework of abnormally fatigued populations, including those with the chronic fatigue syndrome (CFS) and overlapping disorders.

defined by overlapping disorders, by prolonged fatigue, and by forms of chronic fatigue that do not meet criteria for the chronic fatigue syndrome. Controls drawn exclusively from healthy populations are inadequate to confirm the specificity of chronic fatigue syndrome-associated abnormalities.

#### Need for Revised Criteria To Define the Chronic Fatigue Syndrome

The possibility that chronic fatigue syndrome study populations have been selected or defined in substantially different ways has made it difficult to interpret conflicting laboratory findings related to the chronic fatigue syndrome (23). For example, the North American chronic fatigue syndrome working case definition (1) has been inconsistently applied by researchers (24). This case definition is frequently modified in practice because some of the criteria are difficult to interpret or to comply with (25) and because opinions differ about the classification of chronic fatigue cases preceded by a history of psychiatric illnesses (26, 27).

Current criteria for the chronic fatigue syndrome also do not appear to define a distinct group of cases (28; Reyes M, et al. Unpublished data). For example, participants in the Centers for Disease Control and Prevention (CDC) chronic fatigue syndrome surveillance system (29) who met the chronic fatigue syndrome case definition did not substantially differ by demographic characteristics, symptoms, and other illness features from those who did not meet the definition (except by criteria used to place patients into one of our predetermined surveillance classification categories [Reyes M, et al. Unpublished data]). These findings indicate that additional subgrouping or stratification of study cases into more homogeneous groups is necessary for comparative studies.

#### Need for Clinical Evaluation Standards

Our experience suggests that fatigued persons often receive either inadequate or excessive medical evaluations. In the CDC chronic fatigue syndrome surveillance system, all participants were clinically evaluated by a primary physician before enrollment. Subsequently, 18%

were found to have a preexisting medical condition that plausibly accounted for their chronic fatiguing illness (Reyes M, et al. Unpublished data). These medical conditions were identified either from a single battery of routine laboratory tests done on blood specimens obtained at enrollment or from review of available medical records.

We believe that inappropriate tests are often used to diagnose the chronic fatigue syndrome in chronically fatigued persons. This practice should be discouraged.

#### Need for a Comprehensive and Integrated Approach

The complexities of the chronic fatigue syndrome and the existence of several obstacles to our understanding of it make a comprehensive and integrated approach to the study of the chronic fatigue syndrome and similar illnesses desirable. The purpose of the following proposed guidelines (Figure 2) is to facilitate such an approach.

#### Guidelines for the Clinical Evaluation and Study of the Chronic Fatigue Syndrome and Other Illnesses Associated with Unexplained Chronic Fatigue

##### Definition and Clinical Evaluation of Prolonged Fatigue and Chronic Fatigue

Prolonged fatigue is defined as self-reported, persistent fatigue lasting 1 month or longer. Chronic fatigue is defined as self-reported persistent or relapsing fatigue lasting 6 or more consecutive months.

The presence of prolonged or chronic fatigue requires clinical evaluation to identify underlying or contributing conditions that require treatment. Further diagnosis or classification of chronic fatigue cases cannot be made without such an evaluation. The following items should be included in the clinical evaluation.

1. A thorough history that covers medical and psychosocial circumstances at the onset of fatigue; depression or other psychiatric disorders; episodes of medically unexplained symptoms; alcohol or other substance abuse; and current use of prescription and over-the-counter medications and food supplements.

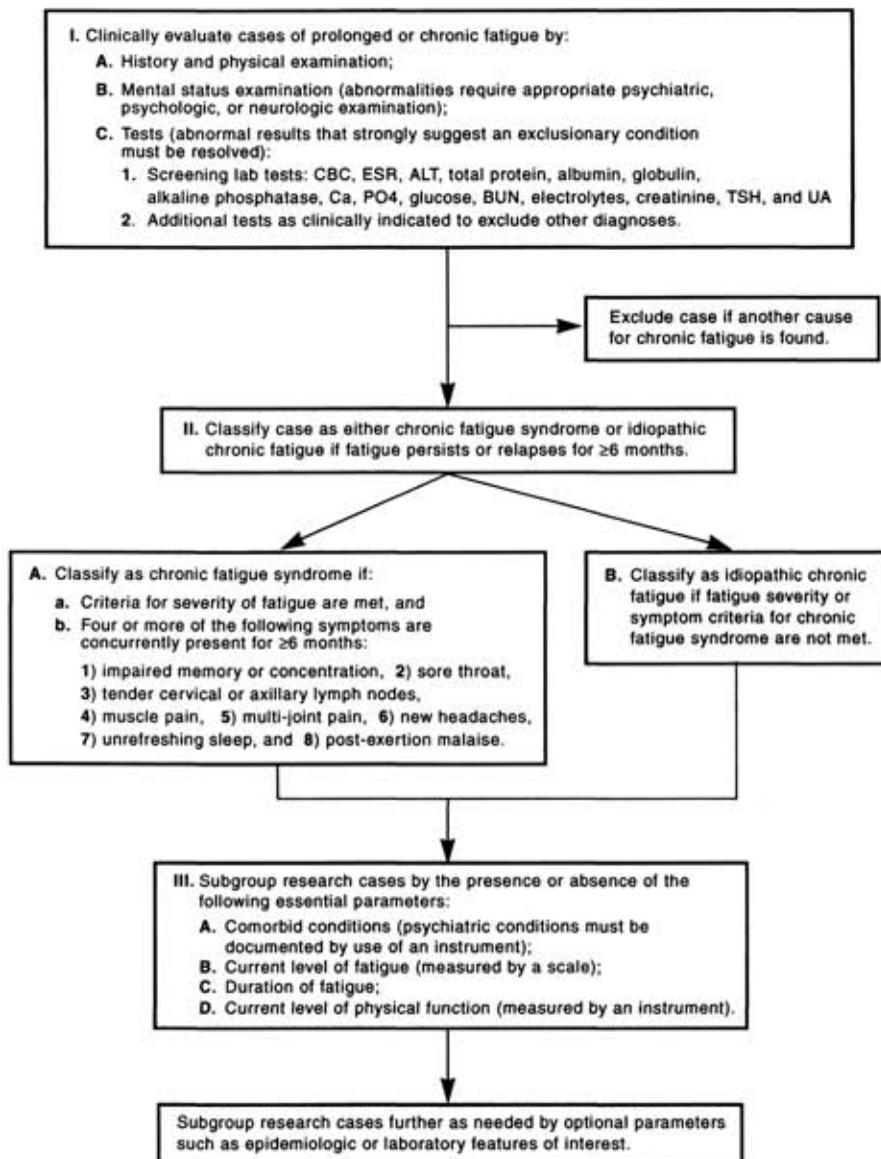
2. A mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Particular attention should be directed toward current symptoms of depression or anxiety, self-destructive thoughts, and observable signs such as psychomotor retardation. Evidence of a psychiatric or neurologic disorder requires that an appropriate psychiatric, psychological, or neurologic evaluation be done.

3. A thorough physical examination.

4. A minimum battery of laboratory screening tests including complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis.

Routinely doing other screening tests for all patients has no known value (20, 30). However, further tests may be indicated on an individual basis to confirm or exclude another diagnosis, such as multiple sclerosis. In these

**Figure 2. Evaluation and classification of unexplained chronic fatigue.** ALT = alanine aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ESR = erythrocyte sedimentation rate; PO<sub>4</sub> = phosphorus; TSH = thyroid-stimulating hormone; UA = urinalysis.



cases, additional tests or procedures should be done according to accepted clinical standards.

The use of tests to diagnose the chronic fatigue syndrome (rather than to exclude other diagnostic possibilities) should be done only in the setting of protocol-based research. The fact that such tests are investigational and do not aid in diagnosis or management should be explained to the patient.

In clinical practice, no additional tests, including laboratory tests and neuroimaging studies, can be recommended for the specific purpose of diagnosing the chronic fatigue syndrome. Tests should be directed toward confirming or excluding other etiologic possibilities. Examples of specific tests that do not confirm or exclude the diagnosis of the chronic fatigue syndrome include serologic tests for Epstein-Barr virus, retroviruses, human herpesvirus 6, enteroviruses, and *Candida albicans*; tests of immunologic function, including cell population and function studies; and imaging studies, including magnetic resonance imaging scans and radionuclide scans (such as single-photon emission computed tomography and positron emission tomography) of the head.

### Conditions That Explain Chronic Fatigue

The following conditions exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any active medical condition that may explain the presence of chronic fatigue (31), such as untreated hypothyroidism, sleep apnea, and narcolepsy, and iatrogenic conditions such as side effects of medication.

2. Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies and unresolved cases of hepatitis B or C virus infection.

3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa.

4. Alcohol or other substance abuse within 2 years before the onset of the chronic fatigue and at any time afterward.

5. Severe obesity (32, 33) as defined by a body mass index [body mass index = weight in kilograms/(height in meters)<sup>2</sup>] equal to or greater than 45.

Any unexplained physical examination finding or laboratory or imaging test abnormality that strongly suggests the presence of an exclusionary condition must be resolved before further classification.

#### Conditions That Do Not Adequately Explain Chronic Fatigue

The following conditions do not exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.

3. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptomatic sequelae.

4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate to strongly support a diagnosis of a discrete connective tissue disorder without other laboratory or clinical evidence.

#### Major Classification Categories: Chronic Fatigue Syndrome and Idiopathic Chronic Fatigue

Clinically evaluated, unexplained cases of chronic fatigue can be separated into either the chronic fatigue syndrome or idiopathic chronic fatigue on the basis of the following criteria.

A case of the chronic fatigue syndrome is defined by the presence of the following: 1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and 2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain, multijoint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours.

The method used (for example, a predetermined checklist developed by the investigator or spontaneous reporting by the study participant) to establish the presence of these and any other symptoms should be specified.

A case of idiopathic chronic fatigue is defined as clinically evaluated, unexplained chronic fatigue that fails to meet criteria for the chronic fatigue syndrome. The reasons for failing to meet the criteria should be specified.

#### Subgrouping and Stratification of Major Classification Categories

In formal studies, cases of the chronic fatigue syndrome and idiopathic chronic fatigue should be subgrouped before analysis or stratified during analysis by the presence or absence of essential variables, which should be routinely established in all studies. Further subgrouping by optional variables can be done according to specific research interests.

#### Essential Subgrouping Variables

1. Any clinically important coexisting medical or neuropsychiatric condition that does not explain the chronic fatigue. The presence or absence, classification, and timing of onset of neuropsychiatric conditions should be established using published or freely available instruments, such as the Composite International Diagnostic Instrument (34), the National Institute of Mental Health Diagnostic Interview Schedule (35), and the Structured Clinical Interview for DSM-III(R) (36).

2. Current level of fatigue, including subjective or performance aspects. These levels should be measured using published or widely available instruments. Examples include instruments by Schwartz and colleagues (37), Piper and colleagues (38), Krupp and colleagues (39), Chalder and colleagues (40), and Vercoulen and colleagues (41).

3. Total duration of fatigue.

4. Current level of overall functional performance as measured by published or widely available instruments, such as the Medical Outcomes Study Short Form 36 (42) and the Sickness Impact Profile (43).

#### Optional Subgrouping Variables

Examples of optional variables include:

1. Epidemiologic or laboratory features of specific interest to researchers. Examples include laboratory documentation or self-reported history of an infectious illness at the onset of fatiguing illness, a history of rapid onset of illness, or the presence or level of a particular immunologic marker.

2. Measurements of physical function quantified by means such as treadmill testing or motion-sensing devices.

#### Discussion

Several general points must be appreciated if these guidelines are to be used as intended. First, the overall purpose of the proposed conceptual framework and guidelines is to foster a more systematic and comprehensive approach toward the collection of data about the chronic fatigue syndrome and similar illnesses. As such,

these tools are intended for use as standard references. However, none of the components, including the revised case definition of the chronic fatigue syndrome, can be considered definitive. These research tools will evolve as new knowledge is gained. Second, none of the provisions in these guidelines, especially the definition of idiopathic chronic fatigue and subgroups of the chronic fatigue syndrome, establish new clinical entities. Rather, these definitions were designed to facilitate comparative studies. Finally, general reference to these guidelines should not be substituted for clear and detailed methodologic descriptions when reporting studies. The lack of detailed information about the sources, selection, and evaluation of study participants (including controls), case definitions, and measurement techniques in reports of chronic fatigue syndrome research has contributed substantially to our current difficulties in interpreting research findings.

Several specific points about the clinical evaluation are worth emphasizing. The primary purpose of clinically evaluating a person with unexplained fatigue is to identify and treat any underlying and contributing factors. Such an evaluation should begin, whenever possible, before 6 months have elapsed. Because the particulars of any clinical evaluation will vary from patient to patient, our recommendations have been limited to those aspects of clinical evaluation that can be universally applied to all patients. With regard to the clinical psychiatric evaluation of fatigued persons, we consider a mental status examination to be the minimal acceptable level of assessment. Although a structured psychiatric evaluation of all patients with fatigue is highly desirable, we recognize the practical difficulties of implementing such a recommendation. Diagnosis of the chronic fatigue syndrome should not impede the treatment of coexisting disorders, notably depression.

Many conditions that are primary causes of chronic fatigue preclude the diagnosis of the chronic fatigue syndrome or idiopathic chronic fatigue. We presented principles for identifying such exclusionary conditions rather than listing them because of the range and complexity of human illnesses. In some instances, however, we identified specific exclusionary conditions. The presence of severe obesity makes the diagnosis of unexplained symptoms, such as fatigue or joint pains, extremely difficult. We distinguished between psychiatric conditions for pragmatic reasons. It is difficult to interpret symptoms typical of the chronic fatigue syndrome in the setting of illnesses such as major psychotic depression or schizophrenia. More importantly, care of these persons should focus on their chronic psychiatric disorder. On the other hand, we did not use other psychiatric disorders, such as anxiety disorders and less severe forms of depression, as a basis for exclusion. Such psychiatric conditions are highly prevalent in persons with chronic fatigue and the chronic fatigue syndrome, and the exclusion of persons with these conditions would substantially hinder efforts to clarify the role that psychiatric disorders have in fatiguing illnesses. This is a particularly important issue to resolve. These parts of the guidelines concur with the recommendation by a 1991 National Institutes of Health workshop (24) that chronic fatigue cases preceded by some, but not all, psychiatric syndromes can be classified as the chronic fatigue syndrome.

The revised case definition for the chronic fatigue syndrome is modeled on the 1988 chronic fatigue syndrome working case definition (1). The purpose of our revisions was to address some of the criticisms (25) of that case definition and to facilitate a more systematic collection of data internationally. We dropped all physical signs from our inclusion criteria because we agreed that their presence had been unreliably documented in past studies. The required number of symptoms was decreased from 8 to 4 and the list of symptoms was decreased from 11 to 8 because we agreed that multiple symptom criteria had increased the restrictiveness of the 1988 chronic fatigue syndrome working case definition without increasing the homogeneity of cases (Reyes M, et al. Unpublished data). Whether to retain any symptom criteria other than chronic fatigue generated the most disagreement among the authors. Disagreement occurred between those who favored a more restrictive approach (using several symptom criteria), as was done in the 1988 chronic fatigue syndrome working case definition, and those who favored a broader definition of chronic fatigue syndrome (using fewer symptom criteria) as was done in the Australian (3) and British (4) chronic fatigue syndrome case definitions. Those favoring multiple symptoms argued that use of multiple symptoms best reflected the empiric clinical sense of the chronic fatigue syndrome as a distinct entity. Others argued that no symptoms have been shown to be specific for the chronic fatigue syndrome (28) and that some studies suggest that a requirement for multiple symptoms biases the selection of cases toward those with psychiatric disorders (28, 44). Disagreement over this particular issue underscores the need to establish specific features of the chronic fatigue syndrome and the validity of any chronic fatigue syndrome case definition.

Developing an operational definition of fatigue was a problem because the concept of fatigue itself is unclear (45, 46). In our conception of the chronic fatigue syndrome, the symptom of fatigue refers to severe mental and physical exhaustion, which differs from somnolence or lack of motivation and which is not attributable to exertion or diagnosable disease. We retained the requirement of 6 months' duration of fatigue to facilitate comparison with earlier cases of the chronic fatigue syndrome. The requirement for an "average daily activity below 50%" was eliminated because this level of impairment is difficult to verify.

We defined the condition of "idiopathic chronic fatigue" to focus attention on the need to clarify how other forms of unexplained chronic fatigue are related to the chronic fatigue syndrome.

Our strategy for subgrouping major classification categories depends on the data made available from standardized evaluations of patients with chronic fatigue. Subgrouping by essential variables will encourage the collection of a body of core data. Additional subgrouping by optional variables will allow researchers considerable flexibility in defining specific subgroups to answer specific research questions.

The name "chronic fatigue syndrome" is the final issue that we wish to address. We sympathize with those who are concerned that this name may trivialize this illness. The impairments associated with chronic fatigue syndrome are not trivial. However, we believe that changing

the name without adequate scientific justification will lead to confusion and will substantially undermine the progress that has been made in focusing public, clinical, and research attention on this illness. We support changing the name when more is known about the underlying pathophysiologic process or processes associated with the chronic fatigue syndrome and chronic fatigue.

## Appendix

The following are the other members of the International Chronic Fatigue Syndrome Study Group: National Institutes of Health, Bethesda, Maryland: Ann Schluenderberg, ScD; University of Colorado, Denver, Colorado: James F. Jones, MD; Prince Henry Hospital and University of New South Wales, Sydney, Australia: Andrew R. Lloyd, MD, FRACP; King's College School of Medicine and Dentistry, London, United Kingdom: Simon Wessely, MRCP, MRC Psych; Polyclinic Medical Center and Pennsylvania State College of Medicine, Harrisburg, Pennsylvania: Nelson M. Gantz, MD; Texas A & M University Health Science Center and Scott & White Memorial Hospital, Temple, Texas: Gary P. Holmes, MD; University of Washington Medical Center, Seattle, Washington: Dedra Buchwald, MD; University of Toronto, Toronto, Canada: Susan Abbey, MD, FRCP(C); University of California, San Francisco, San Francisco, California, and Alta Bates Hospital, Berkeley, California: Jonathan Rest, MD; University of California, San Francisco, San Francisco, California: Jay A. Levy, MD; Food and Drug Administration, Rockville, Maryland: Heidi Jolson, MD, MPH; Lake Tahoe Medical Center, Incline Village, Nevada: Daniel L. Peterson, MD; University Hospital Nijmegen, Nijmegen, the Netherlands: Jan H.M.M. Vercoulen, PhD; Centro Regionale di Riferimento Oncologico, Aviano, Italy: Umberto Tirelli, MD; Karolinska Institute at Huddinge University Hospital, Stockholm, Sweden: Birgitta Even-gard, MD; New Jersey Medical School, Newark, New Jersey: Benjamin H. Natelson, MD; Centers for Disease Control and Prevention, Atlanta, Georgia: Lea Steele, Michele Reyes, and William C. Reeves, MD.

**Acknowledgments:** The authors thank Carla Arpino, Judy Basso, Lyria Boast, Janet K. Dale, Karen Ezrine, Marya Grambs, K. Kimberly Kenney, Teruo Kitani, David Klonoff, Dorothy Knight, Gerhard R.F. Krueger, Hirohiko Kuratsune, Gudrun Lindh, Lars Lindquist, Lisa Livens, Alison Mawle, David McCluskey, John O'Connor, Orvalene Prewitt, Bonnie Randall, Karen B. Schmaling, Scott Schmid, John Stewart, Lars Wahlstrom, Denis Wakefield, and Andrew Wilson.

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