

## Cancer-Related Fatigue: The Scale of the Problem

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**Key Words.** Cancer • Fatigue • Quality of life • Depression • Anxiety • Prevalence

### ABSTRACT

Fatigue is one of the most common and debilitating symptoms experienced by patients with cancer. Cancer-related fatigue (CRF) is characterized by feelings of tiredness, weakness, and lack of energy, and is distinct from the “normal” drowsiness experienced by healthy individuals in that it is not relieved by rest or sleep. It occurs both as a consequence of the cancer itself and as a side effect of cancer treatment, although the precise underlying pathophysiology is largely unknown. CRF may be an early symptom of malignant disease and is reported by as many as 40% of patients at diagnosis. Virtually all patients expect fatigue from cancer therapy. Up to 90% of patients treated with radiation and up to 80% of those treated with chemotherapy experience fatigue. CRF continues for months and even years

following completion of treatment in approximately one third of the patients with cancer. The impact of CRF on a patient’s quality of life (QoL), particularly in relation to physical functioning and the ability to perform activities of daily living, is both profound and pervasive. In addition, CRF is associated with considerable psychological distress and can impose a significant financial burden by limiting a patient’s ability to work. These effects can extend to caregivers and family members, who may also have to reduce their working capacity in order to provide additional care for a patient with CRF. This paper examines the prevalence of CRF and explores the impact of this distressing symptom on patients’ functioning and QoL. *The Oncologist* 2007;12(suppl 1):4–10

Disclosure of potential conflicts of interest is found at the end of this article.

### INTRODUCTION

Fatigue is one of the most prevalent symptoms experienced by cancer patients. It has been reported to occur in a majority of patients across a wide range of cancer types [1–3]. The impact of cancer-related fatigue (CRF) on a patient’s ability to function is considerable; hence, this symptom is among the most distressing of all those reported by patients. CRF can persist for months or even years after the completion of cancer treatment. As the life expectancy of people with cancer increases, the burden associated with CRF grows [4–8]. CRF also affects cancer treatment. It may compromise the timing or completion of

treatment regimens, either because fatigue is a dose-limiting adverse effect or because it reduces the patient’s willingness to adhere to treatment.

Clinicians, patients, family members, and researchers are increasingly recognizing that CRF represents a significant consequence of cancer and its treatment that requires clinical attention and intervention. CRF has been accepted as a diagnosis in the International Classification of Diseases, Tenth Revision [9], and clinical practice guidelines for its management have been formulated by the National Institutes of Health and the National Comprehensive Cancer Network (NCCN) [10,11].

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This paper examines the prevalence of CRF and explores its impact on patients' functioning and quality of life (QoL).

### Definition of Cancer-Related Fatigue

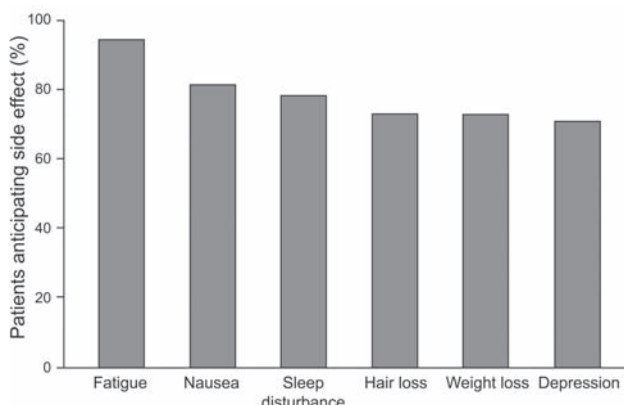
Cancer-related fatigue can be defined as a "persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning" [10]. It is characterized by feelings of tiredness, weakness, and lack of energy. CRF is distinct from the typical tiredness that most people experience as a result of normal daily life in that it is not relieved by rest or sleep, nor does it correspond to the patient's level of exertion [12,13].

### CANCER-RELATED FATIGUE IS PREVALENT

The American Cancer Society estimates that over 1.3 million individuals were diagnosed with cancer in 2005 and a similar number of new cases are expected in 2006 [14,15]. Fatigue is one of the most frequently anticipated adverse effects of cancer treatment; we have shown that 95% of patients who are scheduled to receive chemotherapy or radiotherapy expect to experience some degree of fatigue during their treatment (Fig. 1) [16].

### Patients with a Variety of Cancers Experience Fatigue

Reported incidence rates for CRF in the clinical trial setting tend to be in the range of 70%–80% [17]. Variation in reported rates appears to be related to the type of cancer, treatments, and method of assessment [18]. For example, estimates for the incidence of CRF during treatment have been reported to vary from 37% to 78% for patients with lung cancer [19,20], from 28% to 91% for those with breast



**Figure 1.** Side effects of treatment anticipated by patients scheduled to receive chemotherapy or radiotherapy. Based on data from Hofman M, Morrow GR, Roscoe JA et al. Cancer patients' expectations of experiencing treatment-related side effects: A University of Rochester Cancer Center–Community Clinical Oncology Program study of 938 patients from community practices. *Cancer* 2004;101:851–857.

cancer [21,22], and as low as 15% for patients with prostate cancer [23,24]. Forlenza and colleagues used the Swedish Twin Registry to determine the likelihood of CRF according to diagnosis among patients who were also registered in the Swedish Cancer Registry [25]. They found that patients with lung or prostate carcinoma were most likely to report fatigue of more than 6 months' duration. Moreover, patients with lung carcinoma, prostate carcinoma, or melanoma were most likely to report fatigue with some level of functional impairment (Fig. 2).

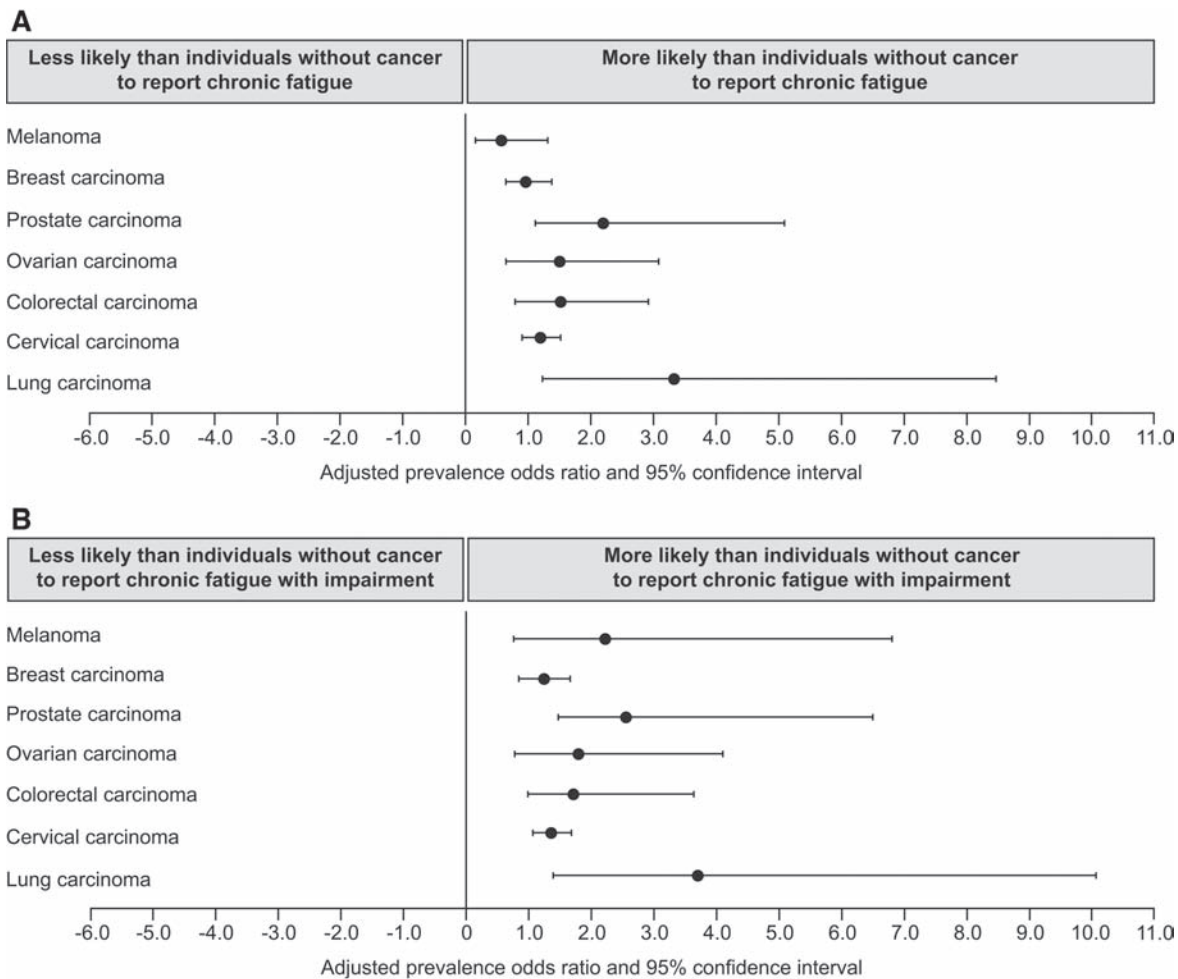
Our recent studies, with sample sizes of several hundred consecutive patients, have shown that >80% of outpatients receiving chemotherapy or radiotherapy reported some degree of CRF as assessed using the Fatigue Symptom Inventory (Fig. 3) ([26] and G.R. Morrow et al., manuscript in preparation). For example, in a subset of patients with breast cancer who were receiving radiotherapy, fatigue was the most commonly experienced side effect, with 84% of patients reporting fatigue, compared with 75% reporting pain and 25% reporting nausea [27]. Fatigue has also been reported as a side effect of virtually all other forms of cancer treatment, including stem cell or bone marrow transplantation, hormonal therapy, and treatment with biologic response modifiers [28].

### Fatigue Occurs from Before Diagnosis to Beyond Treatment Completion

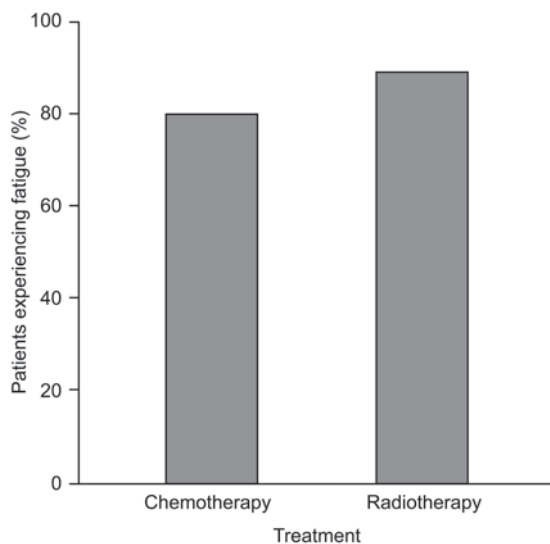
Little information is available concerning the incidence of fatigue prior to diagnosis. However, CRF has been reported throughout the course of malignant disease: from diagnosis, during therapy, and for months to years after completion of treatment while patients are in clinical remission [29,30]. Hofman and coworkers found that, of patients surveyed to examine their expectations of cancer therapy, over 50% reported some degree of fatigue, pain, sleep problems, depression, or memory loss prior to initiation of their treatment [16]. Curt and coworkers conducted a telephone survey in order to evaluate the prevalence and duration of fatigue in 379 patients with cancer who had undergone chemotherapy [31]. They found that 76% had experienced fatigue for at least a few days a month during their last course of chemotherapy, compared with 54% who experienced nausea, 23% who experienced depression, and 20% who experienced pain (Fig. 4). They also noted that more than half of the patients experienced fatigue at least once a week and 30% of the patients experienced fatigue on a daily basis.

### Fatigue Often Persists for Years in Cancer Survivors

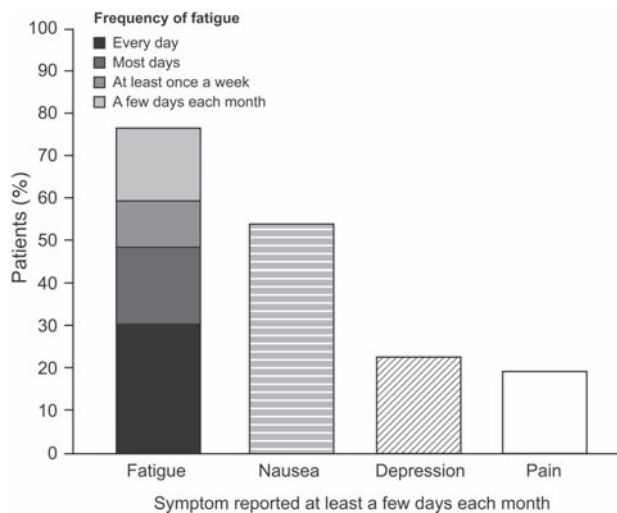
Whichever therapy they receive, the patient's expectation is that CRF will diminish following completion of treatment. For perhaps one third of the patients with cancer, it



**Figure 2.** Likelihood of reporting chronic fatigue (A) and chronic fatigue with impairment (B) among patients with cancer listed in a national registry, compared with individuals without cancer. Based on data from Forlenza MJ, Hall P, Lichtenstein P et al. Epidemiology of cancer-related fatigue in the Swedish Twin Registry. *Cancer* 2005;104:2022–2031.



**Figure 3.** Prevalence of fatigue, measured using the Fatigue Symptom Inventory, in patients receiving radiotherapy ( $n = 1,129$ ) or chemotherapy ( $n = 760$ ) for cancer (G.R. Morrow et al., manuscript in preparation).



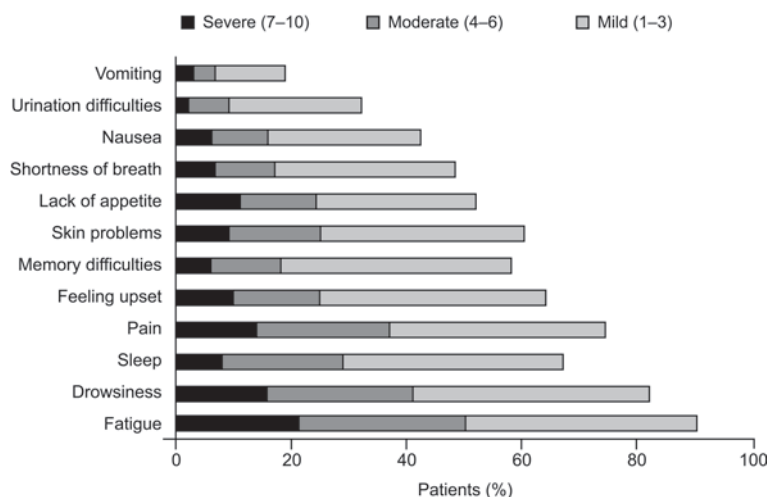
**Figure 4.** Frequency of side effects experienced by patients ( $n = 379$ ) undergoing chemotherapy. Based on data from Curt GA, Breitbart W, Cella D et al. Impact of cancer-related fatigue on the lives of patients: New findings from the Fatigue Coalition. *The Oncologist* 2000;5:353–360.

may persist for months or even years [29,30,32]. At present, the most comprehensive data on the persistence of fatigue come from studies of survivors of breast cancer. A recent study of 763 women who survived breast cancer found that 35% still reported fatigue 1–5 years after completion of their treatment, and 34% reported fatigue 5–10 years after treatment completion [33]. Of the women included in this survey, 21% reported fatigue at both assessment points, illustrating the persistence of this debilitating symptom in a significant proportion of cancer survivors [33]. It has been hypothesized that some type of chronic inflammatory processes may contribute to the persistent fatigue experienced by survivors of breast cancer [34]. Further research is now needed to establish the persistence of CRF among survivors of other malignancies and to explore the underlying causes of persistent CRF.

**THE FATIGUE REPORTED BY PATIENTS WITH CANCER IS SEVERE**

The severity of CRF over time—like the symptom itself—depends on many factors, including the treatment regimen, assessment technique, and patient population. In general, however, the severity of CRF following chemotherapy peaks within 4 or 5 days of completion of treatment and gradually lessens over time, although it never recedes to pretreatment levels [30,35]. CRF is reported in around 80% of patients undergoing radiotherapy, and a number of studies have found that the severity of the fatigue experienced by such patients gradually increases over the course of treatment [20,36–38]. In a detailed study of the incidence and severity of side effects during the course of radiation therapy, fatigue was the most prevalent and the most severe symptom reported by patients (Fig. 5) [26] and G.R. Morrow et al., manuscript in preparation).

**Figure 5.** Prevalence and intensity of side effects experienced by patients during radiotherapy. Reprinted from Hickok JT, Morrow GR, Roscoe JA et al. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. *J Pain Symptom Manage* 2005;30:433–442, with permission from The U.S. Cancer Pain Relief Committee.



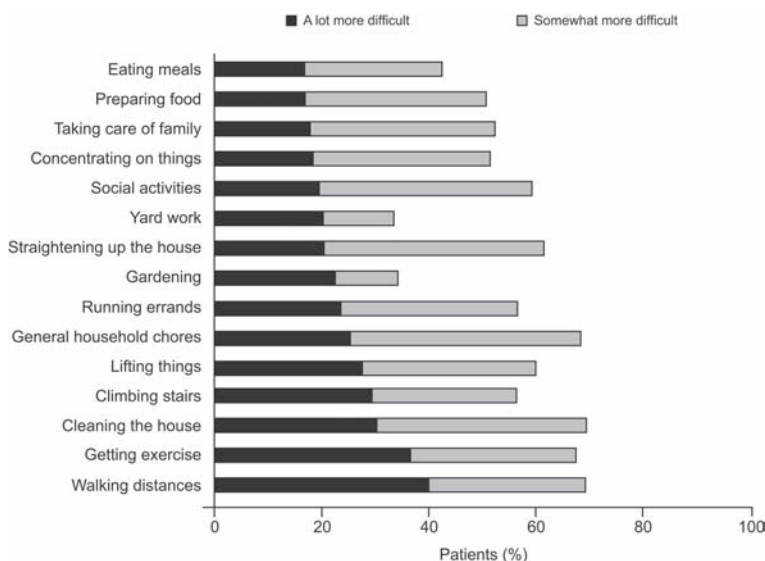
**CANCER-RELATED FATIGUE HAS A PROFOUND IMPACT ON PATIENTS’ LIVES**

Not only is CRF the symptom most frequently anticipated and reported by cancer patients [12], it is also widely rated as one of the most distressing, both during and after treatment. Indeed, CRF has been rated as more troublesome and to have a greater negative impact on patients’ daily activities and QoL than other cancer-related symptoms, including pain, depression, and nausea [39–41].

**Impact of Cancer-Related Fatigue on Physical Functioning, Activities of Daily Living, and QoL**

The impact of CRF on the ability to perform activities of daily living is both profound and pervasive. In a study of 379 patients with cancer and a history of chemotherapy, almost all patients with fatigue (91%) felt that it prevented a “normal” life and 88% felt that their fatigue had changed their daily routine [31]. Patients with fatigue reported significant impairment in their ability to complete a variety of activities of daily living, including preparing food, cleaning the house, light lifting, and social activities with friends and family (Fig. 6) [42]. These impairments are likely to be a direct result of the impact of fatigue on the patients’ physical functioning. Brown and coworkers used an objective measure of physical functioning—chair-rise time—to assess the impact of fatigue and found that patients with greater fatigue had poorer physical functioning [43]. More recently, Mallinson and colleagues used the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale and the self-reported Physical Function subscale of the Medical Outcomes Study Short-form (36-item) Health Survey, a widely used QoL instrument, and found an inverse correlation between self-reported fatigue and physical functioning [44].

**Figure 6.** Impact of fatigue on usual activities in patients with cancer and a history of chemotherapy ( $n = 301$ ). Adapted from Crawford J, Gabilove JL. Therapeutic Options for Anemia and Fatigue. Medscape Oncology 2000. Available at <http://oncology.medscape.com/Medscape/oncology/TreatmentUpdate/2000/tu02/public/toc-tu02.html>, with permission from Medscape Portals Inc. (<http://www.medscape.com/viewprogram/583> © 2000, Medscape Portals, Inc.)



Studies in patients with a range of cancer diagnoses have reported the expected negative correlation between the incidence of CRF and patients' QoL [7,36,45–48]. In their study of fatigue, psychological distress, and functional status among women receiving radiotherapy for uterine cancer, Ahlberg and coworkers found highly statistically significant negative correlations between general fatigue and multiple domains of QoL, including physical, role, emotional, cognitive, and social functioning (all  $p < .001$ , except social functioning  $p = .002$ ) [36]. They further demonstrated that physical, role, and cognitive functioning remained highly negatively correlated with general fatigue over time.

### The Psychological and Emotional Impact of Cancer-Related Fatigue

Several studies have highlighted a link between CRF and increased levels of depression, anxiety, and mood disturbance [5,32,49,50]. These psychological symptoms can affect a patient's ability to perform activities of daily living, including self-care, and may even have a negative impact on treatment outcomes by reducing survival times [51]. While psychological distress has been shown to be a weak predictor of the levels of post-treatment fatigue, any causal relationship remains unclear [7,52].

In their evaluation of the prevalence and impact of CRF, Curt and coworkers found that fatigue had a profound emotional effect on patients, with the majority (90%) reporting a loss of emotional control, 74% reporting feelings of isolation and solitude, and 72% reporting feelings of dejection (Table 1) [31]. Tchekmedyian and colleagues found that, among 249 patients with lung cancer who were anemic, improvements in fatigue were significantly associated with improvements in depres-

sion and anxiety ( $p < .001$ ), suggesting that interventions to improve fatigue might have the additional benefit of reducing psychological distress [53].

### Economic Consequences of Cancer-Related Fatigue

Cancer-related fatigue has been shown to have a significant effect on employment and financial status. Curt and coworkers reported that, of 177 patients currently employed, 77% lost at least 1 day at work as a result of fatigue, with over 75% forced to change their conditions of employment as a result of the fatigue they experienced [31]. The economic impact was not limited to the patients themselves but also extended to caregivers and family members, many of whom worked fewer hours as a result of providing care. One fifth of the patients needed to employ someone to help with household chores, such as cleaning, which incurred additional financial costs [31]. Berndt and coworkers reported that improvements in fatigue were associated with gains in productive time as well as an enhanced ability to perform

**Table 1.** The impact of cancer-related fatigue on emotional health in patients ( $n = 301$ ) undergoing treatment for cancer

Aspect reported in at least 50% of patients	Patients (%)
Having to push yourself to do things	77
Decreased motivation or interest in usual activities	62
Sadness, frustration, or irritability because of fatigue	53
Diminished interest in normal activities	51
Mental exhaustion	51

From Curt GA, Breitbart W, Cella D et al. Impact of cancer-related fatigue on the lives of patients: New findings from the Fatigue Coalition. *The Oncologist* 2000;5:353–360.

daily activities [54]. This relationship further supports the need for, and potential benefits of, active interventions to manage fatigue in cancer patients.

### Cancer-Related Fatigue and Survival

There is some research support for the speculation that CRF may have an impact on survival. Mormont and coworkers confirmed a negative relationship between fatigue and levels of daytime activity and reported a fivefold lower survival, poorer QoL, and more fatigue among patients with altered circadian activity levels in a study of 200 patients with metastatic colorectal cancer [55].

### CONCLUSIONS

Cancer-related fatigue is a highly prevalent and distressing symptom experienced by the majority of patients both during treatment for cancer and in the period following completion of treatment. CRF profoundly affects patients' abilities to perform activities associated with daily living and limits their personal and social roles within their family and community, resulting in a significant decrement in overall QoL. CRF is also associated with significant levels of psychological distress, and it imposes a financial burden by limiting a patient's

ability to work effectively. This economic effect can extend to caregivers and family members, who may have to reduce their working hours in order to provide care for a patient with CRF.

The underlying causes of CRF are poorly understood and further research is warranted in order to develop effective, patient-centered management strategies and to improve QoL and other outcomes. Effective interventions to reduce CRF—both during and following treatment—are urgently needed and have the potential to improve physical functioning, QoL, emotional and psychological health, and to relieve some of the financial burden that a diagnosis of cancer can bring.

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### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

G.R.M. has acted as a consultant for MGI Pharma and Cephalon.

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