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Cancer-Related and Treatment-Related Fatigue

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Abstract

Fatigue is a distressing and persistent symptom for patients with gynecological cancer and for survivors. Debilitating cancer-related fatigue (CRF) is produced by both the disease and its treatment. Although awareness and study of CRF have grown in recent years, consistent assessment has not been a priority in routine medical practice. The pathophysiological mechanisms that induce CRF remain unclear, and effective pharmacological interventions have yet to be established. Based on the literature and our own research results, this review focuses on recent progress toward understanding the nature and causes of CRF and on several promising treatment modalities.

Given the prevalence and severity of CRF in the gynecological cancer patient population, establishing standardized fatigue measurement and management methods in routine clinical oncology care is of utmost importance. Whether CRF has an underlying inflammatory cause is still hypothetical, however, and no mechanism-driven symptom intervention is currently in clinical use, even though the development of such interventions would provide patients with greater symptom control. Advancing translational and clinical fatigue research will require anatomical pathway studies and well-designed clinical investigations that focus on the development of mechanism-driven interventions based on physiological–behavioral fatigue research, implementation of guidelines for experimental designs, and discovery of biomarkers identifying individuals at high risk for CRF. Validated patient-reported outcomes measures are an essential component of such clinical studies. Because numerous subscales, unidimensional measures, and multidimensional measures exist, clinicians and researchers should consider individual circumstances, good clinical practice, and research goals as guides for choosing the most appropriate fatigue measurement tool. Additionally, education about CRF should be made available to all patients and their caregivers, as accurate and age-appropriate information about conditions like CRF can alleviate much of the stress and anxiety brought on by poor communication about this distressing condition.

Keywords

cancer-related fatigue; gynecological cancer; patient-reported outcomes; Brief Fatigue Inventory

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Introduction

Most epidemiological studies indicate that the fatigue caused by cancer and its treatment occurs more pervasively, persistently, and profoundly than any other symptom [1]. Fatigue is also the most prevalent symptom for cancer survivors who have no evidence of active disease [2,3]. For patients with gynecological cancer, cancer-related fatigue (CRF) has been well documented as an adverse event by clinicians in clinical trials of new drugs [4,5] and during standard intraperitoneal chemotherapy [6]. CRF was the most prevalent symptom (reported by 93% of patients) in a qualitative study of ovarian cancer [7], and severe fatigue (rated 7–10 on a 0–10 scale) was found in 20% of patients during the validation study for the MD Anderson Symptom Inventory ovarian cancer module [8].

The pathophysiological mechanisms underlying the development of CRF remain unclear despite much research, and effective pharmacological interventions have yet to be established. Given the prevalence and severity of CRF in the gynecological cancer patient population, however, establishing standardized measurement and management methods in routine clinical oncology care is of utmost importance. This review focuses on recent progress toward understanding the nature and causes of CRF and on several promising treatment modalities.

The clinical characteristics of fatigue

Various attempts have been made to characterize fatigue. The ASCPRO (Assessing the Symptoms of Cancer using Patient-Reported Outcomes) working group defined CRF as the “perception of unusual tiredness that varies in pattern and severity and has a negative impact on ability to function in people who have or have had cancer” [9]. The National Comprehensive Cancer Network (NCCN) practice guidelines for clinical management of fatigue define it as “a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning” [10]. ASCPRO further characterized CRF as physical, subjective, temporal, emotional, cognitive, unusual, and affecting the patient's ability to function [9]. Fatigue has also been described by word-terms such as weariness, exhaustion, lassitude, weakness, malaise, discomfort, and impatience, or as the inability to perform aspects of normal functioning.

However one may define it, CRF negatively impacts a patient's daily functioning and diminishes quality of life. CRF lasts longer than typical fatigue and is more severe and unrelenting. It can be so overwhelming that a patient may request a “chemo holiday” (a lessened dose in order to recover from severe symptom burden) or may even elect to discontinue therapy altogether. In either case, curative treatment may be compromised.

The NCCN guidelines attribute the causes of CRF to both the cancer and the cancer therapy [10]. Consequently, CRF can occur at any point along the disease trajectory. The combination of cancer-related and treatment-related factors affecting CRF include disease progression, acute or late response to cancer therapy, and other medical and psychological conditions associated with chronic illness.

Disease-related fatigue or unusual tiredness is often the first symptom that patients notice before they are diagnosed with cancer [11]. Fatigue can also herald disease progression: in a study of elderly patients, fatigue was more severe in those with late-stage disease than in those with early-stage disease [12]. Fatigue and poor appetite are hallmark symptoms for cachexia in terminally ill patients. High fatigue is a strong independent predictor of survival and adds to traditional prognostic markers such as performance status, age, sex, and tumor grade [11,13].

Cancer treatment is well known to produce CRF and to worsen existing fatigue [14]. A history of chemotherapy was independently associated with severe CRF in patients with various types of advanced cancer [15]. Chemotherapy induces various toxicities, such as hematological, gastrointestinal-tract, and neural toxicities, that may be significant factors in the development of severe fatigue. Fatigue, in turn, can become a dose-limiting factor during chemotherapy. Because such toxicities are expected by both treatment teams and the patients themselves, and because effective fatigue interventions are lacking, patients often accept fatigue as the price to be paid for achieving a cure.

Cancer surgery can also cause CRF in the immediate postoperative period, although this fatigue can often be alleviated by increased analgesia [16]. Dynamically increasing fatigue has been reported to be the most severe symptom associated with accumulating radiation dose during radiotherapy or concurrent chemoradiation therapy; the trajectory of fatigue development often parallels the development of other symptoms, such as pain, disturbed sleep, poor appetite, and drowsiness [14].

Cancer survivors who have completed therapy and have no evidence of active disease still may not be free from symptoms. In a large population-based study [3], moderate to severe fatigue (rated 4 on a 0–10 scale) that interfered with daily functioning was reported by 29% of survivors. Poor performance status (Eastern Cooperative Oncology Group performance status 1; odds ratio, 3.48) and a history of depression (odds ratio, 2.21) were associated with moderate to severe fatigue in survivors. Higher percentages of short-term survivors (<5 years) versus long-term (≥5 years) survivors reported moderate to severe fatigue in the breast cancer cohort (38% vs 18%, respectively; $P = .001$) and the colorectal cancer cohort (23% vs 43%, $P = .067$); no significant difference was found for the prostate cancer cohort (23% vs 18%). Moderate to severe fatigue was equally prevalent in long-term survivors by sex (18% in both breast cancer and prostate cancer cohorts). A survey of 1-year cancer survivors revealed that fatigue was among the 3 most-negative symptoms (along with depression and pain) among 67 symptoms affecting health-related quality of life [17].

What causes CRF?

Currently, there is no accepted pathophysiological evidence to explain whether a constellation of mechanisms or a centrally mediated disorder causes CRF. To understand the anatomical pathway of fatigue, translational work, including brain neuroimaging studies in both humans and animal models, along with further investigation into the potential shared mechanisms and interventions for neurological disease-associated fatigue (such as that seen in chronic fatigue syndrome, multiple sclerosis, chronic HIV infection, and Parkinson's

disease) and CRF, is urgently needed. The origins of fatigue in multiple sclerosis suggest that a specific dysfunction or involvement of the basal ganglia contributes to fatigue [18].

Although the underlying etiology of fatigue is not yet fully understood, several working hypotheses suggest possible mechanisms for this complex phenomenon.

The inflammation hypothesis

Patients with cancer undergoing aggressive therapy or with advanced disease often experience a cluster severe symptoms led by fatigue. Development of moderate to severe fatigue along with other sickness symptoms, such as pain, distress, poor appetite, drowsiness, and disturbed sleep, provides a rationale for studying the role of inflammation as a common mechanism underlying the production of multiple symptoms, including fatigue.

The hypothesis that activation of the proinflammatory cytokine network induces fatigue has been under investigation since the 1990s. Dysregulated inflammation and its toxic downstream effects are believed to constitute a significant biological basis for CRF and other symptoms [11,19,20]. Preclinical research on immune-to-brain communication pathways in the peripheral immune system indicates that proinflammatory cytokines, primarily interleukin (IL)-1 β and tumor necrosis factor (TNF)- α , send signals to the brain that promote sickness behaviors, including fatigue, disturbed sleep, and depressive symptoms, in vulnerable individuals. The neuroanatomy of cytokine-induced depression focuses on brain circuits, with evidence of decreased baseline activity in the frontal and temporal cortices and the insula and increased activity in the cerebellum and subcortical and limbic regions [21].

Susceptibility to fatigue is affected by a complex interplay with the etiological agent (eg, cancer treatment, infections, centrally acting drugs). Studies of genomic encoding for fatigue are now beginning to explore the increased activity of proinflammatory transcription factors as contributors to fatigue [22,23]. A study of breast cancer survivors with persistent fatigue found increased expression of inflammation-related genes, particularly those responsive to the proinflammatory nuclear factor- κ B transcription control pathway, together with a decreased expression of glucocorticoid-dependent anti-inflammatory genes [24].

IL-6 and TNF- α have been associated with persistent fatigue *in vivo* and *in vitro* [25] and with activation of innate immune cells and T-cells. In a quantitative review, CRF was associated with increased circulating levels of IL-6, IL-1 receptor antagonist, and neopterin [26]. TNF- α signaling has been associated with postchemotherapy fatigue in patients with early-stage breast cancer [27]. A temporal association was found during aggressive chemoradiation therapy between serum or plasma inflammatory markers and the development of fatigue and a cluster of other sickness symptoms (pain, disturbed sleep, drowsiness, and poor appetite) that affect physical functioning in patients with cancer [28]. Inflammatory processes associated with tumor growth can cause abnormalities in energy metabolism and inhibit muscle function, indicating that elevated levels of plasma IL-6 [29] and C-reactive protein [30] may be related to increased levels of fatigue seen in terminally ill patients with cancer. Activation of the tryptophan-degrading enzyme indoleamine 2,3-

dioxygenase generates neurotoxic metabolites [31]. Studies of anti-inflammatory treatments to improve fatigue in cancer patients or survivors, such as TNF- α antagonists [32] and yoga [33], are providing increasing evidence for a translational approach to effective mechanism-driven symptom intervention.

Other hypotheses

Proinflammatory cytokines may act independently to produce CRF or may overlap or work synergistically with other mechanisms that act either directly or indirectly on the brain, such as vagal-afferent activation hypothalamic–pituitary–adrenal axis disruption, serotonin dysregulation, growth-factor activation, and circadian rhythm modulation [11,34]. Disruption in metabolic activity by cancer or its treatment (such as the disrupted metabolism of adenosine triphosphate, a major source of energy for skeletal-muscle contraction [11]) also has been hypothesized as a potential cause of CRF. Abnormalities in energy metabolism may be related to increased energy need (the hypermetabolic state that can accompany tumor growth, infection, fever, or surgery), decreased substrates (eg, anemia, hypoxemia of any cause, poor nutrition), or abnormal accumulation of muscle metabolites (eg, lactate) that impair intermediate metabolism or normal muscle functioning. Immobility and lack of exercise may also reduce the efficiency of neuromuscular functioning. Fatigue in patients and survivors might also be related to acute sickness conditions, chronic comorbidities or unhealthy status, psychological/psychiatric conditions, or long-term use of central nervous system stimulating/sedating medications (eg, opioids).

There is lack of consistency in the independent effects of these factors on fatigue, and their interactions with cancer and various therapies may be complicated. Longitudinal studies have promoted a better understanding of how CRF fluctuates according to different triggers and critical moderating factors, which should ultimately advance efforts to develop methods of mechanism-driven symptom intervention and prevention.

Measurement methods

CRF can cause observable behavioral manifestations and decreases in performance, and it is frequently accompanied by other visible symptoms. Most fatigue documentation is based on clinician observation reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Although adverse symptom-event reporting is a vital aspect of clinical trials and drug labeling to ensure patient safety and inform risk–benefit decision making, CRF itself is a subjective experience that cannot be directly measured by an observer—and all the more so because of its multifactorial nature and the fact that agreement among clinicians reporting adverse symptom events is moderate at best [35].

The current understanding is that a validated fatigue-assessment process based on an individual's self-report is feasible and reliable, such that subjective patient-reported outcomes (PROs) have become the standard method for assessing dimensions of fatigue. The US Food and Drug Administration (FDA) encourages investigators to use standardized, psychometrically validated PRO measures in clinical research for symptom intervention [36]. Such tools are essential for evaluating the treatment and management of CRF and for conducting translational mechanism studies and epidemiological studies with fatigue as a

primary outcome. Further, online patient self-reporting is a feasible long-term strategy for toxicity symptom monitoring during chemotherapy, even among patients with advanced cancer and high symptom burden. In short, whereas longitudinal clinician-rated CTCAE assessments may better predict unfavorable clinical events, PROs better reflect daily health status [37].

Qualitative studies have informed our understanding of the nature of fatigue and the meaning to patients with cancer of such concepts as “tired,” “fatigued,” and “exhausted” [38]. Quantitative studies have further defined fatigue in terms of severity and interference with daily functioning and have differentiated among fatigue severity (mild, moderate, severe) levels. For example, the Brief Fatigue Inventory measures patients fatigue severity and fatigue-related interference with functioning during the past 24 hours. On a 0–10 scale, a worst-fatigue rating of 6 was associated with moderate to severe (4) interference with patient functioning in all aspects of daily life [1,39].

Existing validated fatigue measures typically assess severity, frequency, and the degree to which fatigue interferes with daily life. These results should be integrated, on a patient-by-patient basis, with factors such as the quality, temporal pattern, and history of the fatigue and expectations associated with disease phase and treatment status. The assessment process should also integrate potential etiologies, cancer treatment, and current systemic disorders, which should help to identify treatable causes of fatigue.

CRF assessment tools

No single standardized PRO fatigue measure based on FDA guidance has been adopted broadly. Many fatigue-assessment tools have been developed over the years for use in patients with either cancer or neurological or systemic disorders [40], yet half of these were used only once. These tools vary in their construction, the number of items assessed, and in the type of scale used, from visual analog scales on which patients mark fatigue severity along a line, to numerical rating scales in which patients rate fatigue severity on a numbered scale with a verbal anchor at each end (eg, 0 = “no fatigue” and 10 = “fatigue as bad as you can imagine”). The selection of an appropriate fatigue tool will depend on a number of considerations, such as the goals of the research or clinical use, the measurement model needed for any planned statistical analyses, how well a given tool has performed in the past, evidence of its psychometric validity, and how frequently it will need to be administered [9]. Some of these considerations are detailed below.

Tools for measuring persistent CRF should be both practical and psychometrically sound. They should present a reasonable recall period, use easily understood terms, incorporate easy-to-use scales and standardized rules for administration and scoring, and be sensitive to change over time. Instruments to be used in multinational studies should undergo linguistic and cross-cultural validation [41].

Fatigue assessment tools can be either unidimensional or multidimensional. Current research has demonstrated that CRF is sufficiently unidimensional to be measured as such [42]. Unidimensional measures can be used to determine whether more-comprehensive clinical

examination is needed and, when used in research or clinical trials, can provide enough data to track changes in fatigue both over time and in response to treatment.

Unidimensional measures can be single-item tools, like the widely used NCCN patient-reported fatigue-intensity rating [10] or the “fatigue at its worst” item from the Brief Fatigue Inventory [1], which uses a 0–10 numeric scale. The CTCAE uses a 5-point Likert scale rated by medical staff. Unidimensional measures for CRF may have multiple items, as do the Brief Fatigue Inventory [1] and the Fatigue Severity Scale [43]. Multiple-item unidimensional measures with good reliability, such as the Brief Fatigue Inventory, the Patient-Reported Outcomes Measurement Information System (PROMIS), and selected items from the European Organization for Research and Treatment of Cancer QLQ-C30 [44], can generate usable results even when a small percentage of responses are missing. These tools can be used as a rapid screening tool or a continual-monitoring variable in clinical practice.

Multidimensional measures may distinguish between physical and mental fatigue and can measure responses in affective functioning and activity. The Multidimensional Fatigue Inventory is a commonly used measure of fatigue, and its general fatigue subscale can serve as a global index of fatigue severity [45]. Some multidimensional scales are too long for very ill patients to complete or too complicated in their wording for translation.

Interpretation of CRF assessment results

The severity of fatigue may be the most informative indicator of the need for intervention. Thus, CRF can be an important outcome measure in drug trials and clinical practice, and standardized PRO assessment of fatigue may provide reliable information for managing this common and debilitating symptom. The use of fatigue categorizations such as mild, moderate, and severe may provide a clinically meaningful indicator for determining whether a fatigue intervention is effective. The best example of fatigue severity delineated in this manner is the NCCN practice guidelines [46]. An empirical study supported the categories of fatigue on a 0–10 severity scale as mild (1–3), moderate (4–6), and severe (7–10) [3].

Health problems related to high levels of fatigue have been studied because of the need for proactive assessment and development of tailored interventions. In a study in breast cancer patients who responded to the Brief Fatigue Inventory [47], more-exhausted patients reported significantly higher perceived stress, anxiety, depression, pain, and sleep disturbance, and lower quality of life. Functional impairment or interference has been shown to increase as fatigue worsened [39], similar to results from pain studies [48,49].

Worsening fatigue maybe related to baseline high fatigue or to patient characteristics such as sex, disease status, performance status, recent cancer treatment, history of depression, and comorbidity [50]. In a large multicenter study of patients with various cancer types under active treatment, moderate to severe fatigue was related to using strong opioids, 5% weight loss within the past 6 months, using >10 medications, and having lung cancer. For survivors, moderate to severe fatigue was related to poor performance status and a history of depression [3].

Interventions

Unlike opioids for severe pain and antiemetic drugs for nausea/vomiting, no single effective intervention exists for severe fatigue. General supportive care for CRF in patients and survivors include those developed by the NCCN [46,51] and the Oncology Nursing Society. The guidelines propose a treatment algorithm in which patients are evaluated regularly for fatigue, using a brief screening instrument, and are treated as indicated by their fatigue level once it causes distress or interferes with daily activities or functioning. Current CRF management strategies tend to focus on patient/family education and counseling, physical activity and other behavioral interventions, psychostimulants, and treatment of contributing factors, such as pain, emotional distress, sleep disturbance, anemia, and hypothyroidism [52].

Despite continuing methodological limitations (such as the placebo effect noticed in short-term fatigue treatment trials) [53], the frequency of reports on the efficacy of both pharmacological and nonpharmacological treatments for fatigue is increasing.

Psychostimulants

Preliminary evidence for the use of psychostimulants to treat CRF was summarized in a 2011 meta-analysis of 5 placebo-controlled trials, wherein psychostimulants consistently showed a small but favorable result of improvement in fatigue [54]. Clinical trials with larger samples are needed, however, to make conclusive recommendations and to rule out placebo effects.

The psychostimulant methylphenidate directly stimulates adrenergic receptors and indirectly causes the release of dopamine and norepinephrine from presynaptic terminals. Given in dosages of 10–20 mg daily, it is generally well tolerated by cancer patients. In a systematic review and meta-analysis, Gong et al. [55] showed that methylphenidate maintained a superior effect with long-term use (more than 4 weeks), indicating that this agent may overcome placebo effect. Insomnia and agitation are the common side effects that need to be monitored, but these are mostly reversible with discontinuation of the treatment. Paulsen et al. [56] have shown that patients with advanced cancer treated with opioids may benefit from short-term use of this agent to manage fatigue. Modafinil, a central nervous system stimulant, is a well-tolerated and potentially effective augmenting agent for patients with fatigue and sleepiness who are partial responders to selective serotonin reuptake inhibitors. However, results from clinical studies of modafinil for managing CRF have been inconsistent, such that insufficient evidence exists to support prescribing it for that purpose. A Phase III trial reported that modafinil significantly benefited patients undergoing chemotherapy who had severe fatigue at baseline [57], whereas no reduction in fatigue level was observed in a 4-week, randomized multicenter trial in a cohort of patients with advanced lung cancer [58].

Antidepressants

In the belief that fatigue and depression might share pathophysiological characteristics, some researchers have used antidepressants to treat fatigue in depressed cancer patients. The

antidepressant paroxetine produced a significant reduction in depressive symptoms but not in fatigue [59]; however, Roscoe et al. [60] reported a more favorable outcome from a double-blind placebo-controlled trial. Patients with sleep difficulties and depression may benefit from antidepressants such as nortriptyline and amitriptyline, which have sedative qualities. Bupropion may improve CRF because of its ability to increase dopaminergic neurotransmission [61].

Complementary alternative therapy

Many patients use herbal and supplemental preparations to cope with CRF. A study of unexplained chronic fatigue reported that the alternative treatments coenzyme Q10, dehydroepiandrosterone, and ginseng were the most helpful in ameliorating fatigue. Research into American ginseng in patients with CRF has indicated that patients receiving the largest doses showed the most improvement in overall energy levels and overall mental, physical, spiritual, and emotional well-being [62]. Guarana (*Paullinia cupana*) is a plant native to the Amazon basin that has energy-enhancing and tonic properties. These effects are thought to be mainly due to the methylxanthine present in the plant's seeds. Chinese herbal medicine and acupuncture have not been thoroughly studied, but trends toward effective and safe use have been seen in randomized clinical trials to treat CRF [63]. Patients using herbal treatments should exercise caution because of possible profound drug interactions.

Despite the difficulty of conducting double-blinded trials of complementary alternative medicines, preliminary evidence supports the potential efficacy of integrative approaches in the treatment of cancer fatigue. A mind–body intervention may include such approaches as relaxation, mindfulness-based stress reduction, medical Qigong, massage, healing touch, Reiki, and combined-modality interventions such as aromatherapy, lavender foot soak, and reflexology [64]. Yoga showed beneficial effects in a randomized study of breast cancer patients undergoing adjuvant radiotherapy [33].

Psychological interventions

Interest has been growing in the role of cognitive behavioral therapy, psychoeducational therapy, and supportive expressive therapy, including support groups, counseling, and journal writing for CRF management in patients and survivors [51]. A systematic review and meta-analysis in 119 clinical studies with fatigue-related primary or secondary outcomes found small to moderate, but significant and clinically meaningful, effect sizes for psychological interventions for fatigue [65]. Another study reported a small to medium effect size for 18 psychosocial interventions (support-group therapy and individual psychotherapy) that provided education, coping strategy programs, tailored behavioral interventions, and professionally or self-administered stress-management training [66].

Physical activity

Exercise may be an effective way to manage CRF both during and after treatment, although the effect sizes found in a meta-analysis of 22 studies were small [67]. In a meta-analysis of 9 studies of the effects of aerobic or resistance exercise on CRF for women receiving adjuvant therapy for breast cancer [68], exercise appeared to improve physical fitness and, as a result, to improve day-to-day functioning. Another systematic review and meta-analysis

found moderate, but significant and clinically meaningful, effect sizes for exercise interventions for fatigue [65]. The exercises in these studies varied by type (walking, cycling, swimming, resistance exercise, combined exercise), intensity (with most programs aiming for 50%–90% of the estimated maximal oxygen consumption rate, from twice a day to twice per week), degree of supervision, and duration (from 2 weeks to 1 year).

Survivors with moderate to severe fatigue should be encouraged to maintain adequate levels of physical activity. In summarizing 12 randomized, controlled clinical trials, Mustian et al. [69] remarked that exercise is safe for and well tolerated by cancer survivors. Structured rehabilitation programs have generated significant and sustained improvement in chronic fatigue, especially in cancer survivors, although it is necessary to base the program on the patient's current energy level and stage along the treatment trajectory. In a large cohort of breast cancer survivors, a better postdiagnosis diet and adherence to physical activity recommendations was significantly related to lower fatigue [70].

Conclusion

CRF is a distressing and persistent symptom for both patients and survivors. Debilitating CRF can be produced by the cancer or by its treatment, especially in patients in active therapy. Although awareness and study of this symptom have grown in recent years, consistent assessment has not been a priority in routine medical practice. That CRF may have an underlying inflammatory mechanism is still a hypothesis, and no mechanism-driven symptom intervention is currently in clinical use.

Advancing research into and clinical management of CRF will require well-designed clinical trials of fatigue interventions, which in turn will require reliable and valid measures that assess widely accepted dimensions of CRF, both for screening and for use in trials. Because numerous subscales, unidimensional measures, and multidimensional measures exist, clinicians and researchers should consider individual circumstances, good clinical practice, and research goals as guides for choosing the most appropriate fatigue measurement tool.

The development of mechanism-driven fatigue interventions from physiological–behavioral fatigue research, implementation of guidelines for experimental designs, and discovery of biomarkers to identify high-risk individuals would provide patients with greater symptom control. In addition, education about CRF should be made available to all patients and their caregivers, as accurate and age-appropriate information about conditions like CRF can alleviate much of the stress and anxiety brought on by poor communication about this distressing condition.

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