There are over 14 million survivors of cancer living in the United States alone and tens of millions more worldwide, with this population expected to nearly double in the next decade. The successes of prevention, early detection, and better therapies have led to an emerging understanding of the substantial medical and psychosocial issues for this growing population that must be tackled for individuals and from the health care system and societal perspectives.

The major components of survivorship care include (1) surveillance for recurrence and new primary cancers, including consideration of genetic risk predisposition; (2) prevention, monitoring for, and management of long-term and late effects of cancer and cancer treatment, including medical and psychosocial issues; (3) counseling and assistance for optimizing health behaviors; and (4) coordination of care to assure that patients receive the appropriate evidence-based follow-up care from the appropriate provider at the right times.2,3 Increasing awareness and delivery of this care in a patient-centered, proactive manner in our already overburdened health system has proven to be quite a challenge. This is, in part, because standardizing the care for survivors of cancer poses unique and substantial hurdles. Although individual patients have varying and diverse needs in all medical settings, cancer comprises myriad diseases necessitating a wide range of therapeutic interventions and associated risks in follow-up with diverse recommendations for care. Tailored proactive survivorship care planning is one potential solution to this issue, yet the resources, efforts, changes in standard conventions of care required, and the limited data demonstrating their value have limited their uptake to date.4,6

Another major and related issue is that cancer research to date has predominantly focused on improving disease control and cure rates. Relatively little dedicated research has centered on survivorship concerns. And much of the available data to inform the care of survivors has been observational from therapeutic clinical trials without patient-reported outcomes or from large databases with little granularity. Further, there have been few prospective studies, limited intervention research, and even fewer randomized trials of interventions to improve care and outcomes for survivors. Thus, the sparse evidence base to guide the care of survivors has generally led to heterogeneous follow-up and care concerning most issues for cancer survivors. And even in the few settings where enough data exists to inform evidence-based, systematic guidelines, they are not routinely followed.7

Finally, survivorship care in its infancy has suffered from a prior lack of prioritization.8 Just like the treatment of most cancers, a one size fits all approach does not work for cancer survivorship care. Most recently, risk-based care has been advocated for targeting the appropriate care to individual patients, from the appropriate provider, at the most optimal times in the cancer care trajectory.9 To address these needs, researchers, clinicians, and advocates worldwide have been working to define cancer survivors’ needs and determine how to optimally deliver the care to meet them. Formalized in 2011, the American Society of Clinical Oncology’s (ASCO’s) Survivorship Committee aims to deliver high-quality survivorship care to enhance patients’ long-term health by managing concerns related to cancer treatment and survivorship.10 The committee offers educational opportunities and clinical guidance on survivorship care, including an array of guidelines focused on specific survivorship concerns,
including anxiety, depression, and fatigue. In addition to this growing body of guidelines, the ASCO Cancer Survivorship Compendium is a repository of tools and resources to enable oncology providers to implement or improve survivorship care within their practices. This manuscript highlights two of the first guidelines that have emerged from the dedicated work of ASCO’s Survivorship and Clinical Practice Guidelines Committees, surrounding fatigue, anxiety, and depression as targetable, treatable symptoms that are highly prevalent in cancer survivors.

CANCER-RELATED FATIGUE GUIDELINES
Fatigue is one of the most common and distressing symptoms of people undergoing cancer treatment. In addition to fatigue during treatment, approximately one-third of patients will go on to experience persistent fatigue for months or years following the completion of their treatment. As part of a larger effort to address symptom management and quality-of-life issues in post-treatment cancer survivors, ASCO’s Cancer Survivorship Committee organized an expert panel charged with formulating a new clinical practice guideline or endorsing or adapting an existing guideline for screening, assessment, and management of post-treatment fatigue in survivors of adult-onset cancers.

The panel began by searching literature to determine whether guidelines existed that it could endorse or adapt. Based on the search and prespecified evaluation criteria, the panel chose to adapt a 2011 pan-Canadian practice guideline for screening, assessment, and care of cancer-related fatigue. This guideline was also informed by recommendations from the Oncology Nursing Society (ONS) and the National Comprehensive Cancer Network (NCCN). The panel also considered two NCCN guidelines that had been created or updated since 2009. The resulting adapted guideline was published in the Journal of Clinical Oncology in 2014. The ASCO-adapted guideline is organized into an algorithm that specifies recommendations for screening, comprehensive and focused assessment, laboratory evaluation, treatment care options, and ongoing monitoring and follow-up.

Overview of the Clinical Algorithm for Cancer-Related Fatigue
Screening. The primary recommendations for screening are to screen all patients for fatigue at their initial visit, at appropriate intervals during and following treatment, and as clinically indicated; and to screen using brief self-report measures with established cutoff scores. One recommended way to screen is through use of a simple 0-to-10 numeric rating scale (0, no fatigue; 10, worst fatigue imaginable), where mild fatigue is indicated by scores of 1 to 3, moderate fatigue is indicated by scores of 4 to 6, and severe fatigue is indicated by scores of 7 to 10. The guideline further recommends that patients who report moderate to severe fatigue undergo a comprehensive and focused assessment.

Comprehensive and focused assessment. The primary recommendations for comprehensive and focused assessment are to conduct a focused fatigue history that evaluates the various features of the patient’s experience of fatigue (e.g., associated or alleviating factors); to consider the possibility of disease recurrence; and, in the absence of disease recurrence, to assess treatable factors that may be contributing to fatigue (e.g., comorbidities, medications, nutritional issues). When conducting this assessment, the primary clinical team must decide when referral to an appropriately trained professional (e.g., cardiologist) is needed. Laboratory evaluations may also play a role in a comprehensive and focused assessment based on the presence of other symptoms and the onset and severity of fatigue. Possible laboratory evaluations include a complete blood cell count with differential and a comprehensive metabolic panel.

Treatment and care options. Regardless of the reported level of fatigue, the guideline recommends that all patients be offered education about fatigue after treatment (e.g., information about the difference between fatigue that is normal in most individuals following exertion or lack of sleep and cancer-related fatigue) and advice about general strategies to help manage fatigue (e.g., self-monitoring of fatigue). These issues may be further confounded in our aging population, including patients with cancer, and therefore cancer survivors as well. For patients reporting moderate or severe fatigue, the guideline first recommends treating contributing factors identified as part of the comprehensive and focused assessment. For example, the assessment may suggest that the patient’s fatigue can be addressed by treating their sleep problem or pain problem. Beyond this action, the guideline indicates that patients with moderate to severe fatigue may benefit from physical activity, psychosocial, mind-body, or pharmacologic interventions. At present, there are no clear standards for selecting among these interventions to treat an individual patient, and research is needed about how best to prioritize, sequence, and link the available treatment options. The guideline contains specific recommendations for each type of intervention based on a review of existing guidelines and a re-
cent literature review. Readers may also wish to review a recent ONS update on evidence-based interventions for cancer-related fatigue.19

Ongoing monitoring and follow-up. For patients who received treatment for fatigue, the guideline recommends that they be observed and re-evaluated regularly to determine whether treatment has been effective or needs to be readdressed. For patients who did not receive treatment for fatigue, the guideline recommends promotion of ongoing self-monitoring and screening at follow-up visits since fatigue can still emerge as a late effect.

Challenges and Opportunities for Implementing the Cancer-Related Fatigue Guideline

Many of the challenges in implementing this guideline will be similar to those identified for the broader challenge of implementing survivorship care plans. One important issue is the significant time and resources required to develop care plans.10 Proposed solutions for this problem included development of automated, programmable applications to expedite the process.10 Another important issue is health care providers’ concern that they possess insufficient knowledge of cancer survivor issues to adequately address them.20 Efforts to address this issue should include dissemination of the guideline and related information in formats and forums desired by providers. With regard to the current guideline, ASCO University recently posted a brief web-based educational program summarizing the recommendations.21 Other challenges more specific to fatigue include the lack of documentation about fatigue levels and the lack of supportive care referrals for providing interventions for fatigue. Documentation can potentially be improved by introducing routine symptom screening using electronic methods (e.g., computer kiosks or tablets) that deliver the information collected immediately to clinicians for review and action.22 Finally, referrals can be facilitated by identifying in-house or community resources that can provide relevant interventions. Also, it may be possible to deliver certain interventions to patients remotely via the Internet.23

ANXIETY AND DEPRESSION GUIDELINES

ASCO provided practice recommendations adapted from the Pan-Canadian guideline on Screening, Assessment, and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer,24 which addressed the optimum screening, assessment, and psychosocial-supportive care interventions for adults with cancer who are identified as experiencing symptoms of depression and/or anxiety.

The ASCO panel underscores that health care practitioners implementing the guideline recommendations should first identify the available resources in their institution and community for the treatment of anxiety and depressive anxiety symptoms. The availability and accessibility of supportive care services for all are important in preventing or reducing the severity of symptoms of psychopathology. As a minimum, practitioners should verify with their institution or local hospital the preferred pathway for care of an individual who may present with a psychologic or psychiatric emergency. Presented first are the recommendations applicable to both anxiety and depressive symptom presentations, followed by the considerations unique to each.

General Recommendations

Screening. All patients should be screened for psychologic symptoms at their initial visit, at appropriate intervals, and as clinically indicated, especially with changes in disease status (e.g., post-treatment, recurrence, progression) and when there is a transition to palliative and end-of-life care. Screening should be done using valid and reliable measures of anxiety or depressive symptoms that feature reportable scores (dimensions) that are clinically meaningful (established cutoffs). A phased screening and assessment that does not rely simply on a symptom count from the screening measure is recommended. Consider the need to use culturally sensitive measures. Tailor further assessment or treatment for those with learning disabilities or cognitive impairments.

Identification or determination of the presence or absence of pertinent history or risk factors is important for interpretation of the screen and decision making for subsequent follow-up assessment. Other concerns that may become evident with screening, such as risk of harm to self and/or others, severe anxiety or agitation, or the presence of psychosis or confusion (delirium) requires referral to a psychiatrist, psychologist, physician, or equivalently trained professional for emergency evaluation. Facilitate a safe environment and one-to-one observation, and initiate appropriate harm-reduction interventions to reduce risk of harm to self and/or others.

Follow-up assessment. When moderate-to-severe or severe symptomatology is detected through screening, individuals should have a diagnostic assessment to identify the nature and extent of the symptoms and the presence or absence of anxiety disorder(s) or mood disorders. The clinical team must decide when referral to a psychiatrist, psychologist, or equivalently trained professional is needed for diagnostic assessment. The clinical team should share responsibility for assessments, designating those who are expected to conduct assessments as per scope of practice. If a patient needs a referral for the treatment of anxiety or depression, discuss with the patient the reason(s) for and anticipated benefits from the referral. Further, the clinical team should subsequently determine the patient’s compliance with the referral.

Treatment. Medical (e.g., unrelieved symptoms such as pain and fatigue, or delirium brought on by infection or electrolyte imbalance) or substance abuse causes of anxiety or
Special Considerations: Depressive Symptoms and Mood Disorders
Screening for symptoms. The Patient Health Questionnaire-9 (PHQ-9) is recommended for depression screening. The first two items assess for the classic symptoms of low mood and anhedonia. If a patient endorses either item (or both) as occurring for more than half of the time or nearly every day within the past 2 weeks (i.e., a score of ≥ 2), he or she should complete the remaining items of the PHQ-9. It is estimated that 25% to 30% of patients would need to complete the remaining items. The traditional cutoff for the PHQ-9 is 10 or greater. The panel’s recommended cutoff score of 8 or greater is based on study of the diagnostic accuracy of the PHQ-9 with cancer outpatients. A meta-analysis by Manea et al also supports the 8 or greater cutoff score. As suggested for screening, it is important to determine the associated sociodemographic, psychiatric or health comorbidities, or social impairments, if any, and the duration that depressive symptoms have been present.

Follow-up assessment. If moderate-to-severe or severe symptomatology is detected, individuals should have a diagnostic assessment to identify the nature and extent of the depressive symptoms and the presence or absence of a mood disorder. The assessment should also identify the severity of cancer symptoms (e.g., fatigue), possible stressors, and risk factors for depression.

Treatment for mood disorders. It is recommended to use a stepped care model and tailor intervention recommendations based on variables such as the following:

- Current symptomatology level and presence or absence of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis.
- Level of functional impairment in major life areas.
- Presence or absence of risk factors.
- History of and response to previous treatments for depression.
- Patient preference.
- Persistence of symptoms following receipt of an initial course of depression treatment.

For severe levels of depressive symptoms or a diagnosed mood disorder, use pharmacologic, psychologic (e.g., psychotherapy, psychoeducational therapy, cognitive-behavioral therapy, and exercise) or combined treatment delivered by appropriately trained individuals. Depressive disorders have special characteristics. Many individuals (50% to 60%) with a diagnosed depressive disorder will have a comorbid anxiety disorder, with generalized anxiety being the most prevalent. If an individual has comorbid anxiety symptoms or disorder(s), the route is usually to treat the depression first. Also, some people have depression that does not respond to an initial course of treatment.

Follow-up and reassessment. Persons with depressive symptoms commonly lack the motivation necessary to follow through on referrals and/or to comply with treatment recommendations. With this in mind, on a biweekly or monthly basis until symptoms have remitted, consider the following:

- Assess follow through and compliance with individual or group psychologic or psychosocial referrals, as well as satisfaction with these services.
- Assess compliance with any pharmacologic treatment, patient concerns about side effects, and satisfaction with the treatment’s symptom relief.
- If compliance is poor, assess and construct a plan to circumvent obstacles to compliance or discuss alternative interventions that present fewer obstacles.
- After 8 weeks of treatment, if symptom reduction and satisfaction with treatment are poor despite good compliance, alter the treatment course (e.g., add a pharmacologic intervention to a psychologic, change the specific medication, refer to individual psychotherapy if group therapy has not proved helpful).

Special Considerations: Anxiety Symptoms and Disorders
Screening for symptoms. Anxiety disorders include specific phobias and social phobia, panic and agoraphobia, generalized anxiety disorder (GAD), obsessive compulsive disorder, and post-traumatic stress disorder. It is recommended that patients be assessed for generalized anxiety disorder, as it is the most prevalent of all anxiety disorders and commonly co-morbid with others, primarily mood disorders or other anxiety disorders (e.g., social anxiety disorder).

The GAD-7 scale is also recommended. Patients with GAD do not necessarily present with symptoms of anxiety. The pathognomonic GAD symptom—multiple excessive worries—may present as concerns or fears. Whereas cancer worries may be common for many, GAD worry or fear may be disproportionate to actual cancer-related risk (e.g., excessive fear of recurrence, worry about multiple symptoms, or symptoms not associated with current disease or treatments). Importantly, an individual with GAD has
worry about a range of other noncancer topics and areas of his or her life.

**Follow-up assessment.** The assessment should identify signs and symptoms of anxiety (e.g., panic attacks, trembling, sweating, tachypnea, tachycardia, palpitations, sweaty palms), severity of symptoms, possible stressors (e.g., impaired daily living), risk factors, and times of vulnerability and should also explore underlying problems or causes. If a patient has severe symptoms of anxiety following the further assessment, when possible, confirm an anxiety disorder diagnosis before initiating any treatment options (e.g., DSM-5, which may require making a referral).

**Treatment for anxiety disorders.** For a patient with moderate anxiety, the primary oncology team may choose to manage the concerns using typical supportive care management. In addition, the team can use a stepped care model to tailor any additional intervention recommendations based on variables such as the following:
- Current symptomatology level and presence or absence of DSM-5 diagnoses.
- Level of functional impairment in major life areas.
- Presence or absence of risk factors.
- Chronicity of GAD and response to previous treatments, if any.
- Patient preference.

If anxiolytic therapy is used, patients should be informed of the side effect profiles of the medications, tolerability of treatment (including the potential for interaction with other current medications), response to prior treatment, and patient preference. Patients should be warned of any potential harm or adverse effects—particularly about the long-term use of benzodiazepines in the treatment of anxiety. These medications carry an increased risk of abuse and dependence and are associated with side effects including cognitive impairment. As a consequence, use of these medications should be time limited in accordance with established psychiatric guidelines.

**Follow-up and reassessment.** Because cautiousness and a tendency to avoid threatening stimuli are cardinal features of anxiety pathology, persons with symptoms of anxiety commonly do not follow through on referrals or treatment recommendations. With this in mind, the mental health professional or other member of the clinical team managing the patient’s anxiety should assess the following on a monthly basis or until symptoms have subsided:
- Follow through and compliance with individual or group psychologic or psychosocial referrals, as well as satisfaction with the treatment.
- Compliance with and pharmacologic treatment, patient’s concerns about side effects, and satisfaction with the symptom relief provided by the treatment.

If medications are used, consider tapering if symptoms are under control and if the primary environmental sources of anxiety are no longer present. Longer periods of tapering are often necessary with benzodiazepines, particularly with potent or rapidly eliminated medications.

If compliance is poor, assess and construct a plan to circumvent obstacles to compliance, or discuss alternative interventions that present fewer obstacles. After 8 weeks of treatment, if symptom reduction and satisfaction with treatment are poor despite good compliance, alter the treatment course.

**SUMMARY OF ANXIETY AND DEPRESSION GUIDELINES**

As noted in the 2008 Institute of Medicine report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, and confirmed in a recent report, the psychologic needs of patients with cancer are not being addressed, posing a serious problem for U.S. health care. If psychologic needs are not addressed, regardless of when they arise, they then predict later stress and anxiety, depressive symptoms, low quality of life, and increased side effects with treatment and more physical symptoms. Alternatively, treatment for either anxiety or depression can successfully address issues such as these and has the potential to reduce the risk of recurrence or cancer death.

Overall, mood disorders are associated with lower quality of life and soaring health care costs. Patients with cancer who are depressed worry about their disease (70%), relationships with friends (77%), the well-being of family members (74%), and finances (63%), and the sequelae of this includes more symptom distress and maladaptive coping among others. Depression in particular is associated with heightened risk for premature mortality (recurrence risk = 1.22–1.39) and cancer death (recurrence risk = 1.18). Two studies have now documented increased rates of suicide among populations of long-term survivors of breast and testicular cancer.

Anxiety is the most common mental health issue for long-term cancer survivors. Heightened anxiety is associated with increased side effects and symptoms and poorer physical functioning. Worry, the hallmark of GAD, can be multifocal with content shifting over time from treatment concerns to physical symptoms and limitations. Be it stress, anxiety, or worry, all are related to important neuroendocrine changes, which may account, in part, for the poorer survival among patients with cancer who have heightened stress.

The majority of patients with cancer do well, manifesting remarkable resilience at diagnosis, treatment, and thereafter. Regardless of the timing and circumstances by which any psychiatric comorbidity may arise, patients can experience enormous emotional, interpersonal, and financial costs, and providers and the health care system alike can encounter economic consequences when depressive and anxiety disorders are not treated. Screening and early, efficacious treatment for those manifesting significant symptoms of anxiety or depression holds the potential to reduce the human cost of cancer, not only for patients and survivors but also for those who care for and about them.
Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Institutional relationships are marked “Inst.” Relationships marked “U” are uncompensated.


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