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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Survivorship

Version 2.2021 — July 1, 2021

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ε Epidemiology
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NCCN Survivorship Panel Members
NCCN Survivorship Sub-Committee Members
Summary of the Guidelines Updates

General Survivorship Principles

- Definition of Survivorship & Standards for Survivorship Care (SURV-1)
- General Principles of the Survivorship Guidelines (SURV-2)
- Screening for Subsequent New Primary Cancers (SURV-3)
- Familial/Genetic Risk Assessment Considerations For Subsequent Primary Cancers (SURV-4)
- Assessment By Health Care Provider at Regular Intervals (SURV-5)
- Survivorship Assessment (SURV-A)
- Survivorship Resources For Health Care Professionals And Patients (SURV-B)
- See Principles of Screening for Treatment-Related Subsequent Primary Cancers (See SURV-C)

Preventive Health

- Healthy Lifestyles (HL-1)
  - Physical Activity (SPA-1)
  - Nutrition and Weight Managment (SNWM-1)
  - Supplement Use (SSUP-1)
- Immunizations and Infections (SIMIN-1)

Late Effects/Long-Term Psychosocial and Physical Problems

- Cardiovascular Disease Risk Assessment (SCVD-1)
- Anthracycline-Induced Cardiac Toxicity (SCARDIO-1)
- Anxiety, Depression, Trauma, and Distress (SANXDE-1)
- Cognitive Function (SCF-1)
- Fatigue (SFAT-1)
- Lymphedema (SLYMPH-1)
- Hormone-Related Symptoms (SMP-1)
- Pain (SPAIN-1)
- Sexual Function (SSF-1)
  - Female Treatment Options (SSF-2)
  - Male Treatment Options (SSF-3)
- Sleep Disorders (SSD-1)
- Employment and Return to Work (SWORK-1)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2021 of the NCCN Guidelines for Survivorship from Version 1.2021 include:

SANXDE-E First-Line Antidepressants for Depression or Anxiety in Adults Table
- **Erratum: Under "Usual Starting Dose per Day Total (mg)," the mirtazapine 150 mg dose was added in error. The mirtazapine dose has been changed to 15 mg.**

Updates in Version 1.2021 of the NCCN Guidelines for Survivorship from Version 2.2020 include:

GENERAL CHANGES
- **New algorithm added for Employment and Return to Work (SWORK-1)**

GENERAL SURVIVORSHIP PRINCIPLES
- **The 2021 updates for the following algorithms are in progress.**
  - **Definition of Survivorship/Standards for Survivorship Care (SURV-1)**
  - **General Principles of the Survivorship Guidelines (SURV-2)**

SURV-3 Screening for Subsequent New Primary Cancers
- **This page was extensively revised.**
- **Recommendations on this page regarding familial assessment consideration that impact screening were moved to a new page for: "*Familial/Genetic Risk Assessment Considerations For Subsequent Primary Cancers*" (SURV-4)**

SURV-A Survivorship Assessment (Patient Version)
- **Survivorship Concerns (Changes also made for the Provider Key on SURV-A 2 of 2)**
  - **Cardiac Toxicity changed to *Cardiac Health***
  - ***Employment/Return to Work* added**
    - **New question added, *Do you have concerns about how cancer and/or cancer therapy has affected your ability to work? YES/NO***

SURV-B Survivorship Resources for Health Care Professionals and Patients
- **The following resources were added:**
  - **Legal and Employment Issues**
    - **The ADA National Network https://adata.org**
    - **Job Accommodation Network (JAN) www.askjan.org**
    - **National Cancer Legal Services Network (NCLSN) www.nclsn.org**
    - **Social Security Administration https://www.ssa.gov/disability**
  - **Suicide Prevention and Other Psychosocial Issues**
    - ***Pocket SAFE-T Card* https://adaa.org/sites/default/files/SMA09-4432.pdf**

SURV-C Principles of Screening for Treatment-Related Subsequent Primary Cancers
- **This is a new section that provides cancer screening recommendations for subsequent primary cancers based on the the survivor's prior treatment exposures.**

PREVENTIVE HEALTH
- **The 2021 updates for the following algorithms are in progress.**
  - **Healthy Lifestyles (HL-1)**
    - **Physical Activity (SPA-1)**
    - **Nutrition and Weight Management (SNWM-1)**
    - **Supplement Use (SSUP-1)**
  - **Immunizations and Infections (SIMIN-1)**

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LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Cardiovascular Disease Risk Assessment

- The 2021 updates for this algorithm are in progress. (SCVD-1)

Anthracycline-Induced Cardiac Toxicity

- The 2021 updates for this algorithm are in progress. (SCARDIO-1)

Anxiety, Depression, Trauma, and Distress

General

- "Substance abuse" changed to "Substance *use disorder*" or "Substance *use*" throughout the algorithms as appropriate.

SANXDE-1

- Second bullet; Fourth arrow sub-bullet: Revised to, "Monitor distress, especially at times of *new diagnoses,* transitions in care..."
  - Revised, "...when they are feeling increased distress, anxiety, or depression. ~~See DIS-A from NCCN Guidelines for Distress Management~~." *(See NCCN Guidelines for Distress Managment)*
  - New diamond sub-bullet added, "*Screening for anxiety, depression, trauma, and distress should be a part of routine care. The panel recommends using validated measures such as the PHQ-9 for depression, GAD-7 for anxiety, PC-PTSD-5 for trauma (See Trauma Screening (SANXDE-D), NCCN Distress Thermometer Screening Tool (See DIS-A) or PROMIS measures for distress.*"
- Third bullet; Second sub-bullet revised: "... or obsessive compulsive disorders. *Diagnosis and management of these disorders should be done by a mental health professional (See NCCN Guidelines for Distress Managment).*"

SANXDE-2

- Columnn heading revised to Screening: Anxiety, ~~And~~ Depression, *And Trauma*
- Screening questions revised to include trauma:
  - *Trauma screening*
    - ◊ *had nightmares or thoughts about your cancer or treatment when you did not want to?*
    - ◊ *tried hard not to think about events related to your cancer or went out of your way to avoid situations that reminded you of those events?*
- Second column: New pathway added for *Trauma (one or both symptoms screened "yes") and impact on quality of life.*

SANXDE-3

- First column: Revised, Substance Abuse/Dependence to "Substance *Use Disorder*".

SANXDE-4

- Screening: Post-Traumatic Stress Symptoms or Disorder (PTSD)
  - Bullet added: S*creen for PTSD symptoms using PC-PTSD-5 (See Trauma Screening [SANXDE-D])*
- Diagnosis: Consider PTSD removed
- Footnote removed: The following additional tools may be used for screening: Primary Care PTSD Screen (PC-PTSD), 4 items, http://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp; or full screening with the 20-item PTSD Checklist for DSM-5 (PCL-5), intended for use by qualified health professionals with advanced graduate training in psychological diagnostic assessment: http://www.ptsd.va.gov/professional/assessment/documents/ptsd_trauma_assessments.asp.

SANXDE-6

- Screening: Adjustment Disorder/Distress: Revised, Distress that interferes with the ability to cope, *sleep disturbance, difficulty concentrating,or difficulty with relationships*

SANXDE-7

- Evaluation
  - Medical Factors (H&P Exam); General review: History of *childhood or adult* trauma *prior to or after cancer diagnosis*.

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LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Anxiety, Depression, Trauma, and Distress

SANXDE-8 Management and Treatment

- Nonpharmacologic Interventions
  - For all survivors
    - ◊ Second arrow sub-bullet: Revised, "Provide reassurance that symptoms of worry, stress, *fear of recurrence*, anxiety..."
    - ◊ Fourth arrow sub-bullet: Revised, "... Consider referral to social work services, ~~or~~ patient navigator, *and/or financial navigator* (if available)..."
  - For adjustment disorder or distress without safety risk, mania, or psychosis
    - ◊ Specified algorithm pages *DIS-10* and *DIS-17* from the NCCN Distress Management Guidelines.
    - ◊ Refer to a therapist...
      - – Diamond sub-bullet revised: Cognitive behavioral therapy (CBT) (eg, mindfulness, behavioral activation, structured CBT ~~groups, digital modalities~~) *can be effective for distress, fear of recurrence, trauma symptoms, insomnia, or other symptoms related to distress and can be delivered as individual therapy in structured groups, or with digital modalities (category 1).*
      - – Diamond sub-bullet removed: Psychological or social factors interfering with prescribed care
    - ◊ Arrow sub-bullet revised: "Consider *referral for* integrative therapies..."
- New footnote added: *For additional resources,* See SURV-B 4 of 4.

SANXDE-9 Management and Treatment

- Pharmacologic Interventions
  - This page was extensively revised.

SANXDE-A
1 of 3 Safety Evaluation

- Danger to Self or Others or Inability to Care for Self
  - Psychosocial risk factors revised
    - ◊ "Personality ~~dysfunction~~ *disorder* or bipolar disorder..."
    - ◊ Added: *New trauma or change in major stress or trauma*
  - Medical risk factors: Added *Substance use disorder*
- Consider Protective Factors to Balance with Risks
  - Psychosocial protective factors: Revised, "Responsibility to/*bonds with* family, *pets,* or others...
  - Footnote a revised to include *SAFE-T Card*.

2 of 3

- Acute (Urgent/Emergent) Interventions:
  - Lower risk pathway: Bullet revised, "~~For suicide hotline information~~ *Provide contact information for local crisis hotlines or counselors*..."
  - Elevated risk pathway; Emergency intervention: Bullet revised, "Evaluate availability of firearms, weapons, *medications,* and *other potentially lethal methods of suicide and* arrange to..."

SANXDE-B Risk Factors for PTSD

- Physical; New arrow sub-bullet added: *Unrelieved chronic pain or physical dysfunction*

SANXDE-C Principles of Pharmacologic Interventions

- Special Pharmacologic Considerations for Concomitant Problems
  - Fatigue: Added *Consider bright light therapy*
- Caveats
  - *Monitor for serotonin toxicity with use of any serotonergic agent*
  - *Monitor for anticholinergic effects that can worsen cognition and other side effects (eg, dry mouth or other mucosa)*
  - *Recommend using non-CYP2D6– or non-CYP3A4–inhibiting options when possible.*
  - Use psychotropics with cytochrome P450 interactions with caution in survivors taking tamoxifen *or other medications metabolized through CYP2D6 or CYP3A4 pathways*
  - Nefazodone removed from the list of psychotropics.
- Footnote a revised: "*Evidence generally does not support the clinical significance of the inhibitory activity of SSRIs, SNRIs, or other antidepressants on tamoxifen's or other CYP2D6- or CYP3A4-metabolized agent's anticancer effects in terms of increased recurrence or mortality rates. However, pharmacokinetic/pharmacogenetic studies do indicate reduced availability of endoxifen in lower CYP2D6 metabolizers taking tamoxifen.* SSRIs, and in particular paroxetine..."
- Footnote b is new: *Antidepressants that are strong CYP3A4 inhibitors or inducers may interact with some cancer prevention or maintenance drugs other than tamoxifen, such as tyrosine kinase inhibitors, monoclonal antibodies, or mTOR inhibitors.*
- References were added.

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LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Anxiety, Depression, Trauma, and Distress---continued

SANXDE-D Trauma Screening

- This is a new section that provides trauma screening questions and recommendations for subsequent follow-up assessment.

SANXDE-E First-Line Antidepressants for Depression or Anxiety in Adults

- This is a new table that includes drugs, doses, side effect severity profile, CYP450 interactions and caution notes.

Cognitive Function

- The 2021 updates for this algorithm are in progress. (SCF-1)

Fatigue

SFAT-1 Considerations for Fatigue in Cancer Survivor

- First bullet
  - First arrow sub-bullet revised: "Receipt of chemotherapy, ~~and~~ radiation, *endocrine, targeted, and/or cellular therapies* are ~~both~~ predisposing factors for cancer-related fatigue..."
  - Second arrow sub-bullet revised: "The time-course of fatigue is unique to the survivor and his or her treatment plan~~, but some general principles apply. Mild to moderate fatigue is common in cancer survivors who undergo chemotherapy and/or radiation; mild to moderate fatigue lasting up to one year can occur in a proportion of cancer survivors~~. *However, many cancer survivors report that fatigue may be a disruptive symptom months or years after treatment ends*.
- The following bullets were added
  - *Fatigue is a subjective experience that should be systematically assessed using patient self-reports and other sources of data for cancer survivors in the months and years after diagnosis.*
  - *Patients and family/caregiver(s) should be informed that management of fatigue is an integral part of total health care and that fatigue can persist following treatment.*
  - *Medical care contracts should include reimbursement for the management of fatigue.*
  - *Disability insurance should include coverage for the continuing effects of fatigue.*
  - *Referral to rehabilitation services including physical therapy, occupational therapy and physical medicine should be considered for survivors with fatigue in the months and years after cancer diagnosis*.
- Footnote was removed and placed into the algorithm above: See the NCCN Guidelines for Cancer-Related Fatigue.

SFAT-2 Screening

- None to mild (0-3) pathway: Added, E*ducation and counseling on general strategies for management of fatigue with an emphasis on continued surveillance*.

SFAT-3 Primary Evaluation Fatigue Score Moderate or Severe (4-10)

- Assessment of treatable contributing factors;
  - Under Comorbidities, several bullets were condensed to "Organ dysfuction" and changed to new footnote "c" *Cardiac, endocrine (eg, hypothyroidism, hypogonadism, adrenal insufficiency), gastrointestinal pulmonary, renal, and/or hepatic dysfunction*.
  - *Physical inactivity or sedentary behavior* added.

SFAT-5 Interventions For Cancer Survivors

- Patient/Family Education and Counseling
  - Energy ~~conservation~~ *prioritization*
    - ◊ *Plan and* pace *activities*
- Other Interventions
  - CBT for ~~sleep~~ *insomnia*
  - *Bright white light therapy*
  - *Massage therapy (category 1)*
- Footnote h is new: *Bright white light therapy of 10,000 lux is most frequently self-administered in the early morning for 30-90 minutes. Timing needs to be adjusted for those who sleep during the day. Johnson J, et al. J CA Survivorship 2018, 12(2):206-215.*

Lymphedema

- The 2021 updates for this algorithm are in progress. (SLYMPH-1)

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LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Hormone-Related Symptoms

SMP-1 Principles of Menopause Symptom Management in Female Survivors

- Title revised, Principles of Menopause *Symptom* Management in Female Survivors
- Menopause
  - First bullet revised: Many survivors may experience symptoms ~~without meeting the definition of menopause~~ *whether or not they have ovarian function*.
  - Second bullet revised: "...serial estradiol levels may be useful to confirm ~~post-~~ *current* menopausal status."
  - Peri- or pre-menopausal survivors; Second arrow sub-bullet revised: Survivors who have become amenorrheic and are sexually active *with a male partner* should be counseled on the need for contraception to prevent unintended pregnancy if they do not meet the definition of menopause. *Menopause is defined as no menses for one year in the absence of prior chemotherapy or tamoxifen use, or no menses after surgical removal of all ovarian tissue*.
  - Bullet removed and added into bullet noted above: Menopause is defined as no menses for one year in the absence of prior chemotherapy or tamoxifen use, or no menses after surgical removal of all ovarian tissue.
- Treatment Options for Vasomotor Symptoms
  - Hormonal therapies
    - ◊ Revised "Hormonal therapies (*relatively* contraindicated..." (Also for SMP-2)
    - ◊ Removed: Custom-compounded bioidentical hormone therapy is not recommended (contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk) (See SMP-B)

SMP-3 (Females and Males)

- Workup/Assessment: Rule out other ~~causes of menopausal symptoms~~ *etiologies* (ie, thyroid disease, diabetes)

SMP-4 Vasomotor symptoms (Females)

- Treatment for Vasomotor Symptoms
  - Order of the bullets revised
  - New bullet added, *Non-hormonal pharmacologic treatments*
    - ◊ Arrow sub-bullet revised: Categories include antidepressants, anti-convulsants, neuropathic pain relievers, ~~and~~ certain anti-hypertensives, *and certain antimuscarinic anticholinergic agents*
- Footnote regarding "Compounds with limited evidence of safety and efficacy" was removed. Parts of the footnote were used for new footnote "l": *Data are limited on the effectiveness and safety of phytoestrogens, botanicals, and dietary supplements in survivors of some cancers. The panel consensus is that the efficacy and safety data for these treatments are too limited to make a recommendation for use (See Discussion)."*
- Footnote i revised: MHT is *generally* contraindicated in survivors of hormonally mediated cancers. *Custom-compounded bioidentical hormone therapy is not recommended. There is a lack of data supporting claims that custom-compounded bioidentical hormones are a safer and more effective alternative to standard hormone therapies. In fact, they may be harmful*.

SMP-5 Vaginal dryness (Female)

- Treatment: *Hyaluronic acid (category 2B)* added as a non-hormonal treatment.
- Footnote n is new: *Recommend as first-line therapy if vaginal dryness is not too severe*.
- Footnote "r" revised: *Vaginal* DHEA should be used with caution in survivors with a history of ~~estrogen-dependent~~ *hormonally mediated* cancers *because safety in this population is unknown*.

SMP-6 ADT-Related Symptoms (Male)

- Footnote regarding "Compounds with limited evidence of safety and efficacy" was removed. Parts of the footnote were used for new footnote "t": *Data are limited on the effectiveness and safety of phytoestrogens, botanicals, vitamin E, and dietary supplements in survivors of some cancers. The panel consensus is that the efficacy and safety data for these treatments are too limited to make a recommendation for use (See Discussion)*.

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LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Hormone-Related Symptoms---continued

SMP-A Non-Hormonal Pharmacologic Treatments and Dosing

- New drug class added to table: *Antimuscarinic anticholinergic*
  - *Oxybutynin* recommendations added.
- Footnote d revised: CYP2D6. *Evidence generally does not support the clinical significance of the inhibitory activity of SSRIs, SNRIs, or other antidepressants on tamoxifen's or other CYP2D6- or CYP3A4-metabolized agent's anticancer effects in terms of increased recurrence or mortality rates. However, pharmacokinetic/pharmacogenetic studies do indicate reduced availability of endoxifen in lower CYP2D6 metabolizers taking tamoxifen*. SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6.

SMP-B Principles of Menopausal Hormone Therapy Use in Survivors (Females)

- Second bullet; General recommendations...: Arrow sub-bullet removed: Custom-compounded bioidentical hormone therapy; There is a lack of data supporting claims that custom-compounded bioidentical hormones are a safer and more effective alternative to standard hormone therapies. In fact, they may be harmful.
- Fifth bullet revised: "*Relative* contraindications for MHT in cancer survivors..."
- First arrow sub-bullet: "History of hormonally mediated cancers *(high-risk endometrial and most breast)*"

PAIN

SPAIN-1 General Principles of Pain Management

- First bullet; First arrow sub-bullet revised: "...differential diagnosis should include cancer recurrence *or progressive disease*."
- Third bullet: New arrow sub-bullet added: *Non-cancer pain in cancer survivors should be treated congruent with pain diagnosis, with opioids remaining the last resort. Consider referring to primary care service for management of non-cancer pain*.
- Sixth bullet revised: "Physical modalities (heat, cold, massage, *acupuncture*, physical therapy..."

SPAIN-2 Principles of Opioid Use in Long-Term Survivors

- New bullet added: *Provide survivor and caregiver education on safe opioid use, storage, and disposal*.
- Fourth bullet: Removed arrow sub-bullet, Discussion of gradual tapering should be routine.
- Seventh bullet revised: "Monitor for aberrant drug-taking behaviors *and for signs of substance use disorder*..." and following arrow sub-bullets added
  - *Verbalize concerns to the survivor and refer to pain, palliative care, physiatry, and/or substance use disorder/mental health specialists.*
  - *Engage caregivers or people living with the survivor if possible.*
- Footnote "a' is new: *Aberrant behaviors may include family member using drugs prescribed to the survivor.*

SPAIN-3 Universal Screening

- New pathway added: *Pain unrelated to cancer*

SPAIN-4 Neuropathic pain

- Treatment
  - General measures
    - ◊ Revised, *Non-opioids*/Adjuvant analgesics (Also for SPAIN-5)
    - ◊ Local therapies; Pharmacologic therapies: *Diclofenac topical gel* added.
  - Bullet revised: "*For moderate or severe pain,* opioids and dual-action opioid agonist/noradrenaline reuptake inhibitor..."
  - Bullet revised: ~~For refractory pain,~~ Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, *integrative services,* and/or palliative care *as appropriate.* (Also for SPAIN-5)
- New footnotes added
  - *Scrambler therapy can be considered. Loprinzi C, et al. Support Care Cancer 2020;28(3):1183-1197.*
  - *Initiating opioids in cancer survivors should be carefully considered after failure of other interventions.*
- Footnote d: Reference updated.

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LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

PAIN--continued

SPAIN-5 Chronic Pain Syndrome

- **Treatment: Bullet revised: "*For moderate or severe pain,* opioids..."**
- **Last column header revised: ~~Treatment~~ *Additional Interventions***
  - **For post-mastectomy or post-thoracotomy syndrome, new recommendations added**
    - ◊ ***Physical therapy or structured exercise***
    - ◊ ***Possible botulinum toxin injection***
- **Footnote f is new: *Initiating opioids in cancer survivors should be carefully considered after failure of other interventions.***

SPAIN-6 Myalgias, Arthralgias

- **Treatment: The order of the pharmacologic recommendations was revised.**

SPAIN-7 Skeletal Pain

- **Treatment**
  - **For chronic vertebral compression, added *Consider medial branch blocks and radiofrequency ablation for post-compression arthritic pain*.**
  - **For avascular necrosis, added**
    - ◊ ***Joint replacement as clinically indicated***
    - ◊ ***Nerve ablation evaluation and bracing for patients who are not joint replacement candidates***

SPAIN-8 Myofascial Pain

- **Treatment: New bullet added, *For muscle cramps or spasms, check electrolytes, calcium and magnesium levels, and hydration status.* This recommendation was previously a footnote.**

Sexual Function

- **The 2021 updates for this algorithm are in progress. (SSF-1)**

Sleep Disorders

- **The 2021 updates for this algorithm are in progress. (SSD-1)**

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General Survivorship Principles

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DEFINITION OF SURVIVORSHIP

- **An individual is considered a cancer survivor from the time of diagnosis, during and immediately after treatment, and through the balance of his or her life. Family members, friends, and caregivers are also affected by cancer.[a]**
- **These guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer have on the adult survivor. This includes the potential impact on health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.**
- **These guidelines are applicable to survivors across the continuum of care, including those on endocrine therapy, with chronic cancers (eg, metastatic disease), and long-term survivors.**

STANDARDS FOR SURVIVORSHIP CARE[b]

Care of the cancer survivor should include:

1. **Prevention of new and recurrent cancers and other late effects**
2. **Surveillance for cancer spread or recurrence, and screening for subsequent primary cancers (SURV-3)[c]**
3. **Assessment of late psychosocial, physical, and immunologic effects**
4. **Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns)**
5. **Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met**
6. **Planning for ongoing survivorship care:[d]**
   - ◊ **Information on treatment received including all surgeries, radiation therapy, and systemic therapies**
   - ◊ **Information regarding follow-up care, surveillance, and screening recommendations**
   - ◊ **Information on post-treatment needs, including information regarding acute, late, and long-term treatment-related side effects and health risks when possible (See NCCN Guidelines for Treatment of Cancer by Site)**
   - ◊ **Delineation regarding roles of oncologists, primary care physicians (PCPs), and subspecialty care physicians in long-term care and the timing of transfer of care if appropriate**
   - ◊ **Healthy behavior recommendations (See HL-1)**
   - ◊ **Periodic assessment of ongoing needs and identification of appropriate resources**

[a]Adapted with permission from the National Coalition for Cancer Survivorship as shown in the National Cancer Institute's Office of Cancer Survivorship Definitions web page, available at https://cancercontrol.cancer.gov/ocs/statistics/index.html#definition-survivorship.

[b]From Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council 2006. Available at: http://www.nap.edu/catalog/11468.html.

[c]Surveillance testing (eg, labwork, imaging, other studies) should be based on cancer diagnosis and individualized patient risk. A small excess risk of cancer has been linked to frequent radiographic imaging. Surveillance testing should be performed as per NCCN Guidelines for Treatment of Cancer by Site. Additional labwork, imaging, or other studies to evaluate for recurrence should be based on clinical presentation and judgment.

[d]Commission on Cancer: Optimal Resources for Cancer Care (2020 Standards): https://www.facs.org/-/media/files/quality-programs/cancer/coc/optimal_resources_for_cancer_care_2020_standards.ashx.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GENERAL PRINCIPLES OF THE SURVIVORSHIP GUIDELINES

- These guidelines are focused on options to maintain and enhance wellness in cancer survivors, including those who are enduring ongoing treatment, those who have completed cancer treatment, and those in clinical remission.
  (Also see the NCCN Guidelines for Supportive Care Table of Contents)
- These guidelines are designed to provide a framework for the general survivorship care and management of potential long-term and/or late effects of cancer and its treatment that survivors may experience.
- The NCCN Guidelines for Survivorship should be used as a supplement to the follow-up recommendations within the disease-specific guidelines. See the NCCN Guidelines for Treatment of Cancer by Site and NCCN Guidelines for Palliative Care for recommendations regarding metastatic disease.
- These guidelines provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment, and are intended for health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in both the oncology and primary care practices.
- These guidelines, with the appropriate disease-specific guideline, provide a framework for the coordination of care between the survivor's health care providers to insure that needs are appropriately addressed.
- The panel does not assume that all survivorship issues will be addressed at every visit. The panel recommends periodic screening assessments and appropriate follow-up care as clinically indicated.
- Referral to other health care disciplines/providers or community resources may be used to address several indications or identified issues with one intervention (eg, rehabilitation for fatigue, depression, and pain).
- For survivorship issues related to younger populations, also see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology and the Children's Oncology Group Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (www.survivorshipguidelines.org).
- For survivors treated with immunotherapy, ongoing surveillance for immune-mediated toxicities is warranted. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

The 2021 update for the algorithm is in progress.

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SCREENING FOR SUBSEQUENT NEW PRIMARY CANCERS

- **Subsequent new primary malignant neoplasms may occur in survivors years after treatment when the survivor's oncologist may no longer be involved in the survivor's care.**
- **The overall cancer rate in survivors is higher than in the general population. This increased risk is due to genetic susceptibilities (eg, hereditary cancer syndromes) and/or family history, shared etiologic exposures (eg, smoking, environmental exposures, health behaviors, HPV), and mutagenic effects of cancer treatment. Health behaviors should be modified as possible (eg, smoking cessation, weight management) to decrease the risk of subsequent malignancies.**
- **Healthy lifestyle and behavioral counseling are important to reduce risk factors that may contribute to subsequent cancers (See HL-1).**
- **Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents. For recommendations for screening considerations, See Principles of Screening for Treatment-Related Subsequent Primary Cancers (See SURV-C).**
- **Screening for subsequent primary cancers should be a shared responsibility between primary and oncology care physicians (See the NCCN Guidelines for Detection, Prevention, and Risk Reduction Table of Contents).**
- **Evidence suggests that excess lifetime radiation exposure from CT imaging may be associated with a mildly increased risk of developing a radiation-associated cancer. Use of radiologic studies to screen for recurrent cancer should be based on diagnosis and evidence that early detection of recurrence will improve cancer-related outcomes. Recommendations for surveillance imaging modality and frequency can be found in the NCCN Guidelines for Treatment of Cancer by Site.**
- **For familial assessment considerations that impact screening, see SURV-4.**

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FAMILIAL/GENETIC RISK ASSESSMENT CONSIDERATIONS FOR SUBSEQUENT PRIMARY CANCERS

- **Periodic updating of family cancer history (when known) is recommended to reassess hereditary risk, as it should not be assumed that all cancer survivors were assessed at diagnosis. Genetic testing guidelines and knowledge about hereditary cancer risk evolve over time and new family diagnoses may occur making periodic assessment important.**
- **Comprehensive family history including any prior genetic testing is the first step in genetic risk assessment.**
- **Genetic risk assessment by a cancer genetic professional is appropriate for certain breast cancer survivors, all survivors of epithelial ovarian cancer, survivors of colorectal or endometrial cancer diagnosed at age 50 or younger, survivors of high-grade prostate cancer, or survivors of pancreatic cancer with or without genetic testing as appropriate. Many other survivors of rare cancers, cancers diagnosed at young ages, multiple primary cancers, or those with one or more relatives with the same or related cancers are also candidates for risk assessment per guidelines from NCCN and other expert groups. Genetic testing is recommended for appropriate survivors based on results of the risk assessment.**
  - **Criteria for formal genetic risk assessment and/or testing, and for management of patients with known germline mutations linked to an increased risk for cancer can be found in the following NCCN Guidelines:**
    - **NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**
    - **NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
    - **NCCN Guidelines for Gastric Cancer**
    - **NCCN Guidelines for Neuroendocrine and Adrenal Tumors**
    - **NCCN Guidelines for Thyroid Carcinoma**
    - **NCCN Guidelines for Prostate Cancer**
    - **NCCN Guidelines for Melanoma: Cutaneous**
  - **Genetic testing with multigene panels should be reconsidered in those with prior negative tests with limited sets of genes.**
- **Consider referral to genetic counseling services for risk assessment and/or testing if the survivor has not had a comprehensive evaluation at time of their diagnosis.**
- **Genetic testing may also provide opportunities to identify and reduce risks in relatives of cancer survivors.**

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ASSESSMENT BY HEALTH CARE PROVIDER (ONCOLOGY OR PRIMARY CARE) AT REGULAR INTERVALS

- **A periodic assessment at least annually is recommended for all survivors to determine any needs and necessary interventions. For sample assessment, see SURV-A.[e]**
- **Shared coordinated care between the oncology, primary care, and subspecialty care providers is encouraged. Depending on the cancer type and stage of disease, transition of care to a PCP may be done when deemed clinically appropriate with referral back to oncologic care as needed.**
- **Care providers are also encouraged to assess the following at regular intervals:**
  1. **Current disease status**
  2. **Functional/performance status**
  3. **Medication use (including over-the-counter [OTC] medications and supplements)**
  4. **Comorbidities**
  5. **Prior cancer treatment history and modalities used**
  6. **Family history**
  7. **Psychosocial factors**
  8. **Assess weight and health behaviors that can modify cancer and comorbidity risk (including tobacco/alcohol use)**
  9. **See NCCN Guidelines for Treatment of Cancer by Site for disease-specific recommendations for surveillance/follow-up**

The 2021 update for this algorithm is in progress.

[e]This is a sample assessment tool. While this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment. Validation of the best way to assess survivorship issues is ongoing.

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SURVIVORSHIP ASSESSMENT (Patient Version)
Please answer the following questions:

Survivorship Concerns	Survivorship Care Survey
Cardiac Health	1. Do you have shortness of breath or chest pain after physical activities (eg, climbing stairs) or exercise? Yes/No 2. Do you have shortness of breath when lying flat, wake up at night needing to get air, or have persistent leg swelling? Yes/No
Anxiety, Depression, Trauma, and Distress	3. In the past two weeks, have you been bothered more than half the days by little interest or pleasure in doing things? Yes/No 4. In the past two weeks, have you been bothered more than half the days by feeling down, depressed, or hopeless? Yes/No 5. Has stress, worry, or being nervous, tense, or irritable interfered with your life? Yes/No
Cognitive Function	6. Do you have difficulties with multitasking or paying attention? Yes/No 7. Do you have difficulties with remembering things? Yes/No 8. Does your thinking seem slow? Yes/No
Fatigue	9. Do you feel persistent fatigue despite a good night's sleep? Yes/No 10. Does fatigue interfere with your usual activities? Yes/No 11. How would you rate your fatigue on a scale of 0 (none) to 10 (extreme) over the past week? 0–10
Lymphedema	12. Since your cancer treatment, have you had any swelling, fatigue, heaviness, or fullness on the same side as your treatment that has not gone away? Yes/No
Hormone-Related Symptoms	13. Have you been bothered by hot flashes/night sweats? Yes/No 14. Have you been bothered by other hormone-related symptoms (ex, vaginal dryness, incontinence)? Yes/No
Pain	15. Are you having any pain? Yes/No 16. How would you rate your pain on a scale of 0 (none) to 10 (extreme) over the past month? 0–10
Sexual Function	17. Do you have any concerns regarding your sexual function, sexual activity, sexual relationships, or sex life? Yes/No 18. Are these concerns causing you distress? Yes/No
Sleep Disorder	19. Are you having problems falling asleep, staying asleep, or waking up too early? Yes/No 20. Are you experiencing excessive sleepiness (ie, sleepiness or falling asleep in inappropriate situations or sleeping more during a 24-hour period than in the past)? Yes/No 21. Have you been told that you snore frequently or that you stop breathing during sleep? Yes/No
Healthy Lifestyle	22. Do you engage in regular physical activity or exercise, such as brisk walking, jogging, weight/resistance training, bicycling, swimming, etc.? Yes/No ▸ 22a. If you answered "Yes," how often? 23. Excluding white potatoes, do you eat at least 2½ cups of fruits and/or vegetables each day? Yes/No 24. Do you have concerns about your weight? Yes/No 25. Do you take vitamins or other supplements? Yes/No
Immunizations and Infections	26. Have you received your flu vaccine this flu season? Yes/No 27. Are you up to date on your vaccines? Yes/No/Don't know
Emplyoment/ Return to Work	28. Do you have concerns about how cancer and/or cancer therapy has affected your ability to work? YES/NO

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SURVIVORSHIP ASSESSMENT[a]
(Provider Key)

Based on the survivor's answers to the assessment questions, refer to the detailed recommendations indicated below:

Survivorship Concerns	Survivorship Care Survey	Provider Key
Cardiac Health	Questions 1–2	If YES to any question, refer to SCVD-1
Anxiety, Depression, Trauma and Distress	Questions 3–5	If YES to any question, refer to SANXDE-1
Cognitive Function	Questions 6–8	If YES to any question, refer to SCF-1
Fatigue	Questions 9–11	If YES to either question 9 or 10, or a rating of >3 to question 11, refer to SFAT-1
Lymphedema	Questions 12	If YES to question 12, refer to SLYMPH-1
Hormone-Related Symptoms	Questions 13–14	If YES to any question, refer to SMP-1
Pain	Questions 15–16	If YES to question 15 and a rating of >4 to question 16, refer to SPAIN-1
Sexual Function	Questions 17–18	If YES to any question, refer to SSF-1
Sleep Disorder	Questions 19–21	If YES to any question, refer to SSD-1
Healthy Lifestyle	Questions 22–25	If NO to question 22 or 23, or YES to question 24, OR if question 22a is less than 3 times per week, OR if BMI not in the healthy range, refer to HL-1 If YES to question 25, refer SSUP-1
Immunizations and Infections	Questions 26–27	If NO to question 26, or NO or DON'T KNOW to question 27, refer to SIMIN-1
Employment and Return to Work	Question 28	If YES to any question 28, refer to SWORK-1

[a]This is a sample assessment tool. While this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment. Validation of the best way to assess survivorship issues is ongoing.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS[a]

General Online Information	
National Coalition for Cancer Survivorship (NCCS)	http://www.canceradvocacy.org/
American Association for Cancer Research (AACR)	http://www.aacr.org
American Cancer Society (ACS) • Survivorship information • Cancer Survivors Network • National Cancer Survivorship Resource Center • Physical side effects information, including sexual function	http://www.cancer.org/index http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index http://csn.cancer.org/ http://www.cancer.org/SurvivorshipCenter http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/index
American Institute for Cancer Research (AICR): Survivorship information • Survivorship information • Nutrition, physical activity, weight management	http://www.aicr.org/patients-survivors/
American Society of Clinical Oncology (ASCO) • Survivorship information for patients • Tools and resources for oncology providers	http://www.cancer.net/survivorship https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/survivorship/survivorship-compendium
Cancer Care: Free, professional support services for anyone affected by cancer	www.cancercare.org
Centers for Disease Control and Prevention: Survivorship information	https://www.cdc.gov/cancer/survivors/index.htm
Leukemia & Lymphoma Society: Survivorship information	http://www.lls.org/diseaseinformation/managingyourcancer/survivorship/
LIVESTRONG	http://www.livestrong.org/
National Cancer Institute: Cancer Survivorship Research • Springboard Beyond Cancer, Facing Forward series, designed to educate cancer survivors, family members, and health care providers about the challenges associated with life after cancer treatment	http://survivorship.cancer.gov https://survivorship.cancer.gov/springboard http://cancercontrol.cancer.gov/ocs/resources/ffseries.html
National Comprehensive Cancer Network (NCCN) • Life After Cancer: Patient and Caregiver Resources and Information	http://www.nccn.org/index.asp http://www.nccn.org/patients/resources/life_after_cancer/
MedlinePlus: Current accurate information by cancer site	http://www.nlm.nih.gov/medlineplus/cancers.html
Oncology Nursing Society: Putting Evidence Into Practice	https://www.ons.org/explore-entrance
Help Lines	
American Cancer Society	1.800.227.2345 http://www.cancer.org
American Psychosocial Oncology Society	1.866.276.7443 http://apos-society.org/
Cancer Support Community	1.888.793.9355 http://www.cancersupportcommunity.org/
LIVESTRONG SurvivorCare	1.855.220.7777
National Cancer Institute's Cancer Information Service	1.800.4.CANCER
National Suicide Prevention Lifeline	1-800-273-TALK http://suicidepreventionlifeline.org

[a]There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS[a] (continued)

Other Survivorship Guidelines	
Children's Oncology Group: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers	http://www.survivorshipguidelines.org/
Survivorship Care Planning	
ASCO Cancer Treatment Summaries	http://www.cancer.net/survivorship/follow-care-after-cancer-treatment/asco-cancer-treatment-and-survivorship-care-plans
Integrative Therapies	
Memorial Sloan Kettering Cancer Center's Herbs website	https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs
National Center for Complementary and Integrative Resources for Health Care Providers	https://nccih.nih.gov/health/providers
Legal and Employment Issues	
Americans with Disabilities Act	www.ada.gov
The ADA National Network	https://adata.org
ASCO Cancer.net: Working When You Have Cancer: An Expert Q&A	https://www.cancer.net/blog/2018-12/working-when-you-have-cancer-expert-qa
Cancer and Careers: Patient information about working and dealing with cancer	http://www.cancerandcareers.org/en
Cancer Legal Resource Center	https://thedrlc.org/cancer/
Job Accommodation Network (JAN)	www.askjan.org
National Cancer Institute: Going Back to Work	https://www.cancer.gov/about-cancer/coping/day-to-day/back-to-work
National Coalition for Cancer Survivorship (NCCS) Employment Rights • "Employment Rights, "Working It Out" • "What Cancer Survivors Need To Know About Health Insurance"	http://www.canceradvocacy.org/resources/employment-rights/ https://canceradvocacy.org/wp-content/uploads/Working_It_Out.pdf https://canceradvocacy.org/wp-content/uploads/2013/01/Health-Insurance.pdf
ACS: • Understanding Health Insurance • Returning to Work After Cancer Treatment	https://www.cancer.org/treatment/finding-and-paying-for-treatment/understanding-health-insurance.html https://www.cancer.org/treatment/finding-and-paying-for-treatment/understanding-financial-and-legal-matters/working-during-and-after-treatment/returning-to-work-after-cancer-treatment.html
Social Security Administration	https://www.ssa.gov/disability

[a]There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

Continued

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS[a] (continued)

Information About LGBTQ Individuals with Cancer	
CDC Lesbian, Gay, Bisexual, and Transgender Health	https://www.cdc.gov/lgbthealth/index.htm
National LGBT Cancer Network	https://cancer-network.org/
Menopause and Sexual Health	
The North American Menopause Society	http://www.menopause.org
American College of Obstetricians and Gynecologists (ACOG)	https://www.acog.org/
International Society for the Study of Women's Sexual Health (ISSWSH)	https://www.isswsh.org/
Physical Activity	
American Cancer Society • Nutrition and Physical Activity Guidelines for Cancer Survivors, Patient Page • "Physical Activity and the Cancer Patient" guide	http://onlinelibrary.wiley.com/doi/10.3322/caac.21146/pdf http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingactive/physical-activity-and-the-cancer-patient
American College of Sports Medicine: ACSM ProFinder: Search for Certified Professionals	https://www.acsm.org/get-stay-certified/find-a-pro
Cancer Supportive and Survivorship Care: Exercise: A Cancer Survivor's Tool For Wellness	http://www.cancersupportivecare.com/whyexercise.html
LIVESTRONG at the YMCA	http://www.livestrong.org/YMCA
SilverSneakers: A program that helps older adults live healthy, active lifestyles	https://www.silversneakers.com/

[a]There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS[a] (continued)

Nutrition and Weight Management	
ASCO Obesity and Cancer Toolkit	https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/obesity-cancer
Cancer Nutrition Consortium: Nutritional Guidance & Support	https://www.cancernutrition.org/
LIVESTRONG MyPlate Calorie Tracker	http://www.livestrong.com/myplate
National Heart, Lung, and Blood Institute • Guideline for the Management of Overweight and Obesity in Adults • 3 Steps to Initiate Discussion About Weight Management With Your Patients	 http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/obesity-evidence-review http://www.nhlbi.nih.gov/health/prof/heart/obesity/aim_kit/steps.pdf
National Institute of Diabetes and Digestive Kidney Diseases Body Weight Planner	https://www.niddk.nih.gov/health-information/weight-management/body-weight-planner?dkrd=hispt0903
New American Plate	http://www.aicr.org/new-american-plate
Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics	http://www.oncologynutrition.org/
Cardiovascular Health	
American Heart Association/American Stroke Association Tools	https://millionhearts.hhs.gov/tools-protocols/tools.html
CardioOnc.org (database of cancer drugs and cardiac toxicities)	http://cardioonc.org/providers/
Oral and Dental Health	
National Institute of Dental and Craniofacial Research: Oral Complications of Cancer Treatment	http://www.nidcr.nih.gov/oralhealth/Topics/CancerTreatment/OralComplicationsCancerOral.htm

[a]There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS[a] (continued)

Sleep Disorders	
National Cancer Institute Sleep Disorders (PDQ®)–Health Professional Version	https://www.cancer.gov/about-cancer/treatment/side-effects/sleep-disorders-hp-pdq
Smoking Cessation	
American Cancer Society: Smoking cessation support	http://www.cancer.org/healthy/stayawayfromtobacco/index
ASCO: Tobacco Cessation and Control Resources	https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control
North American Quitline Consortium	http://map.naquitline.org/
U.S. Federal Government: Smoking cessation support	http://www.smokefree.gov/
Suicide Prevention and Other Psychosocial Issues	
Veterans Affairs/Department of Defense Practice Guidelines: Assessment and Management of Patients at Risk for Suicide	https://www.healthquality.va.gov/guidelines/MH/srb/VASuicidePreventionPocketGuidePRINT508FINAL.pdf
NCCN Guidelines for Patients: Distress	https://www.nccn.org/patients/guidelines/distress/index.html
Anxiety and Depression Association of America • Mobile app • Pocket SAFE-T Card	https://adaa.org/ https://adaa.org/finding-help/mobile-apps https://adaa.org/sites/default/files/SMA09-4432.pdf
Substance Abuse and Mental Health Services Administration	https://www.samhsa.gov/find-treatment

[a]There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

- **As part of screening and early detection for subsequent primary cancers, history and physical exam are recommended at least annually.**
- **Also see the NCCN Guidelines for Adolescent and Young Adult Oncology and other NCCN Guidelines as referenced. For adult survivors of pediatric cancer, please reference the Children's Oncology Group Long-Term Follow Up Guidelines.**

Treatment-Related Subsequent Primary Cancers by Treatment Exposure

Treatment exposure (and body part affected, where noted)	Increased subsequent primary cancer risk	Screening and Early Detection Recommendations	Comments
Radiation Therapy, including Total Body Irradiation (TBI)			
Cranial	Meningiomas	Imaging as clinically indicated	
	Skin cancer	Consider annual skin exam and/or dermatology referral	Counsel on sun safety and regular use of sunscreen (at least SPF 30)
Head and Neck	Mucosal head and neck cancer	Annual head and neck exam and/or otolaryngology referral	Counsel on avoidance of tobacco and heavy alcohol use
	Thyroid cancer	Annual neck exam	Neck ultrasound as clinically indicated
	Skin cancer	Consider annual skin exam and/or dermatology referral	Counsel on sun safety and regular use of sunscreen (at least SPF 30)
	Salivary gland cancers	Imaging as clinically indicated	
	Soft tissues sarcomas	Imaging as clinically indicated	
Mantle/chest	Breast cancer (female)	Breast MRI and mammogram annually, starting at age 30 or 8 years after radiation, whichever occurs last, for exposure ≥10 Gy and under 30 years old. See also NCCN Guidelines for Breast Cancer Screening and Diagnosis	• Risk starts to increase at about 8 years after exposure • Consider chemoprevention options (see NCCN Guidelines for Breast Cancer Risk Reduction)
	Skin cancer	Consider annual skin exam and/or dermatology referral	Counsel on sun safety and regular use of sunscreen (at least SPF 30)
	Soft tissue sarcomas	Imaging as clinically indicated	
	Lung Cancer	Consider imaging as clinically indicated	• Smoking substantially increases risk. For smokers and former smokers: ▸ Counsel on tobacco cessation as indicated ▸ Consider spiral CT scan or referral to lung cancer screening clinic for shared decision making if screening criteria met (see NCCN Guidelines for Lung Cancer Screening) ▸ For survivors not meeting lung cancer screening criteria (especially survivors of Hodgkin lymphoma), consider chest imaging as clinically indicated

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PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

Treatment-Related Subsequent Primary Cancers by Treatment Exposure

Treatment exposure (and body part affected, where noted)	Increased subsequent primary cancer risk	Screening and Early Detection Recommendations	Comments
Radiation Therapy, including Total Body Irradiation (TBI)--Continued			
Abdomen/flank/pelvic	Colorectal cancer	Colorectal cancer screening starting at age 30 or 5 years after radiation, whichever occurs last, for exposure ≥20 Gy[a]	Repeat colorectal cancer screening based on findings, in consultation with primary care, gastroenterologist, or oncologist
	Skin cancer	Consider annual skin exam and/or dermatology referral	Counsel on sun safety and regular use of sunscreen (at least SPF 30)
	Soft tissue sarcomas	Imaging as clinically indicated	
Extremities	Skin cancer	Consider annual skin exam and/or dermatology referral	Counsel on sun safety and regular use of sunscreen (at least SPF 30)
	Soft tissue sarcomas	Imaging as clinically indicated	

[a]These recommendations are based on data from the treatment of children and adolescents as well as emerging data regarding the rising incidence of colorectal cancer in younger adults within the general population.

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PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

Treatment-Related Subsequent Primary Cancers by Treatment Exposure

Treatment exposure (and body part affected, where noted)	Increased subsequent primary cancer risk	Screening and Early Detection Recommendations	Comments
Transplant Conditioning Therapy (RT or chemotherapy)			
Hematopoietic Stem Cell Transplantation	• May increase the risk for a variety of hematologic or solid tumor cancers, including skin cancer, MDS/AML, liver cancer, cervical cancer, oral cancer • May increase the risk for lymphoproliferative disorders	• CBC as clinically indicated • Adhere to age appropriate cancer screening recommendations • Consider annual skin exam and/or dermatology referral	• Chronic GVHD may increase the risk of certain subsequent malignancies[1,2] • Counsel on sun safety and regular use of sunscreen (at least SPF 30) • Counsel on importance of regular dental checkups
Systemic Therapy			
Alkylating agents, anthracyclines, epipodophyllotoxins	Hematologic malignancies (eg, AML)	CBC as clinically indicated	
Alkylating agents	Bladder Cancer	Urine cytology as clinically indicated	When given in combination with pelvic radiation, risk is increased
Tamoxifen	Uterine Cancer	Assess vaginal pain or bleeding annually; If abnormal uterine bleeding, referral to gynecology for consideration of transvaginal U/S and biopsy	Risk is increased for postmenopausal women on therapy compared with premenopausal women
PARP Inhibitors	MDS; AML	CBC as clinically indicated	MDS and AML are rare; usually after long-term treatment[3]

[1]Gunduz M, et al. Clin Transplant 2017;31.
[2]Rambhia PH, et al. J Am Acad Dermatol 2018;79:378-380 e373.
[3]LaFargue CJ, et al. Lancet Oncol. 2019 Jan; 20(1): e15–e28.

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Preventive Health

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GENERAL PRINCIPLES OF HEALTHY LIFESTYLES

- **Healthy lifestyle habits have been associated with improved overall health and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.**
- **All survivors should be encouraged to achieve and maintain a healthy lifestyle. At a minimum all survivors should be encouraged to:**
  - **Achieve and maintain a healthy body weight throughout life (SNWM-2).**
  - **Engage in physical activity (eg, exercise, taking the stairs, parking in the back of parking lot) daily (SPA-1).**
  - **Maintain a healthy diet high in vegetables, fruits, and whole grains and low in excess sugars, fried foods, and red and processed meat (SNWM-1).**
  - **Minimize alcohol intake (SNWM-1).**
  - **Avoid use or stop using cigarette/tobacco products. (See NCCN Guidelines for Smoking Cessation)**
  - **Practice sun safety.**
    - ◊ **Utilize a sunscreen with an SPF of at least 30 that protects against UVA and UVB rays and is water resistant.**
    - ◊ **Apply sunscreen generously and reapply every 2 hours or after swimming/excessive sweating.**
    - ◊ **Consider using physical barriers whenever possible (ie, hats, shirts with sleeves, avoiding direct sun during peak hours).**
    - ◊ **Avoid tanning beds.**
  - **Ensure adequate amount of sleep (SSD-1).**
  - **Follow up with PCP regularly.**
    - ◊ **Adhere to age-appropriate and treatment-associated health screening, preventive measures (SIMIN-1), and cancer screening recommendations (See NCCN Guidelines for Detection, Prevention, & Risk Reduction).**
- **Obtain nutrients from food sources rather than relying on dietary supplements. Routine use of dietary supplements is not recommended for the purposes of cancer control. (SSUP-1)**
- **Set incremental goals for diet, physical activity, and weight management.**
- **Clinicians should assess individual and community-level barriers to meeting the healthy lifestyle recommendations and support patients in developing strategies to overcome challenges.**

The 2021 update for this algorithm is in progress.

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GENERAL PRINCIPLES OF PHYSICAL ACTIVITY

- **Physical activity and exercise recommendations should be tailored to individual survivor's abilities and preferences**
- **Physical activity for cancer survivors:[a]**
  - **Overall volume of weekly activity should be at least 150–300 minutes of moderate-intensity[b] activity or 75 minutes of vigorous-intensity[b] activity or equivalent combination spread out over the course of the week.**
  - **Two to three sessions per week of strength/resistance training that include major muscle groups (See SPA-A)**
  - **Stretch major muscle groups at least two days per week on days that other exercises are performed**
- **Engage in general physical activity daily (eg, taking the stairs, parking in the back of parking lot)**
  - **Physical activity includes exercise, daily routine activities, and recreational activities**
- **Avoid prolonged sedentary behavior (eg, sitting for long periods)**

Preview update for this algorithm in progress.

[a]Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:243-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine & Science in Sports & Exercise 2010;42:1409-1426. Available at: http://journals.lww.com/acsm-msse/Fulltext/2010/07000/American_College_of_Sports_Medicine_Roundtable_on.23.aspx.

[b]Light physical activity: No noticeable change in breathing pattern; Moderate exercise: Can talk, but not sing; Vigorous exercise: Can say a few words without stopping to catch a breath (See Examples of Physical Activity [SPA-B]).

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PHYSICAL ACTIVITY ASSESSMENT

Ask about prior and current participation in physical activity and assess level of current physical activity at regular intervals

→

Focused clinical evaluation
- Weight/BMI
- Blood pressure
- Functional status
- Assess baseline level of activity prior to diagnosis and current level of activity[c]
- Barriers to physical activity as assessed by survivor
  - Environmental (home, gym access, outdoor space)
  - Financial
  - Physical limits
  - Time/competing demands
  - Social support
  - Stress
- Review of systems
- Disease status
- Nutritional status

Assessment of treatable contributing factors
- Pain
- Fatigue
- Emotional distress
- Nutritional deficits/imbalance
- Medications/side effects

→

Assessment of comorbidities and treatment effects as appropriate:
- Cardiovascular disease (including cardiomyopathy)
- Pulmonary disease
- Arthritis/musculoskeletal issues
- Lymphedema
- Peripheral neuropathy
- Bone health/bone strength (including presence of bone metastases)
- Incontinence or bowel/bladder symptoms
- Presence of stoma or ostomy
- Fall risk assessment
- Need for assistive devices (cane, walker, brace, etc.)
- History or presence of anemia/thrombocytopenia
- Steroid myopathy

→

Determine risk level for exercise-induced adverse events
(See SPA-3)

[c]Ask patient about duration, intensity, and frequency of activity. For example, see Godin G and Shepard RJ. Godin Leisure-Time Exercise questionnaire. Medicine and Science in Sports and Exercise 1997; 29 June Supplement: S36-S38. (https://journals.lww.com/acsm-msse/Fulltext/1997/06001/Godin_Leisure_Time_Exercise_Questionnaire.9.aspx)

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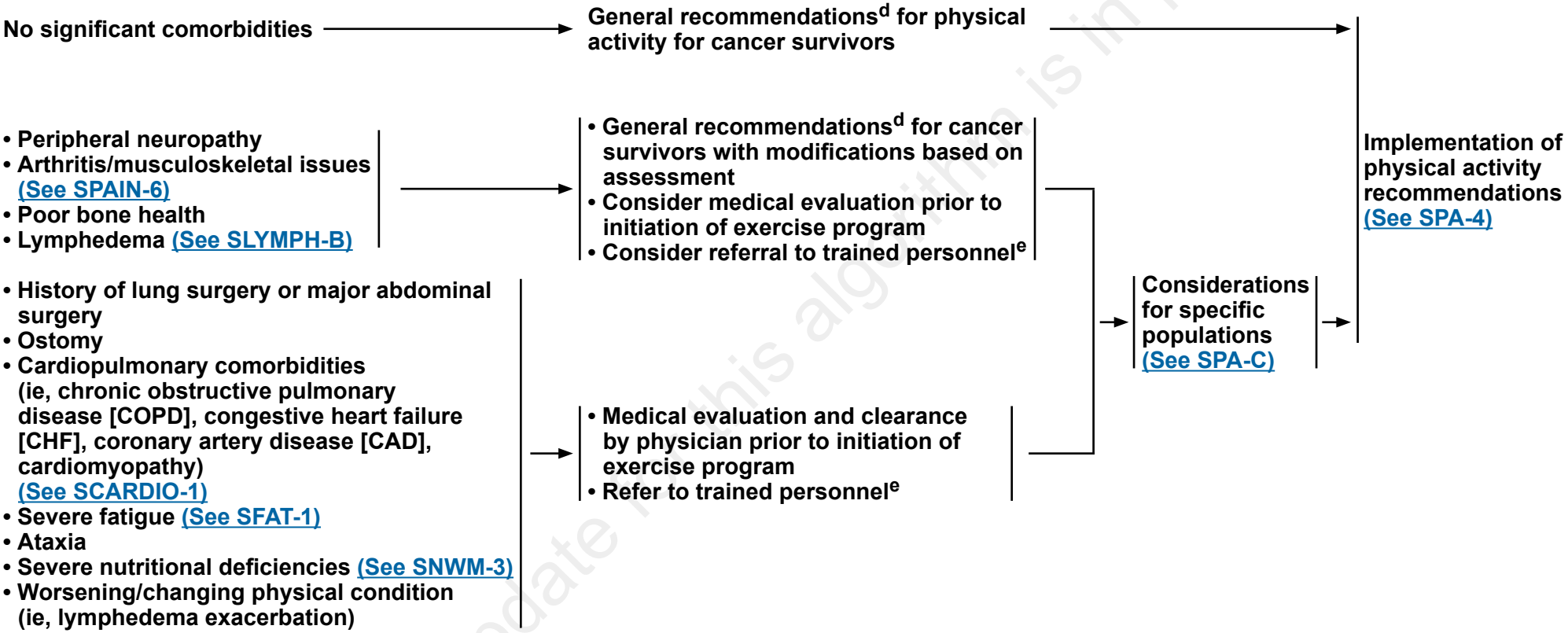
RISK ASSESSMENT FOR PHYSICAL ACTIVITY-INDUCED ADVERSE EVENTS



[d] See General Principles of Physical Activity (SPA-1).

[e] Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://www.acsm.org/get-stay-certified] and American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

The 2021 update of this algorithm is in progress.

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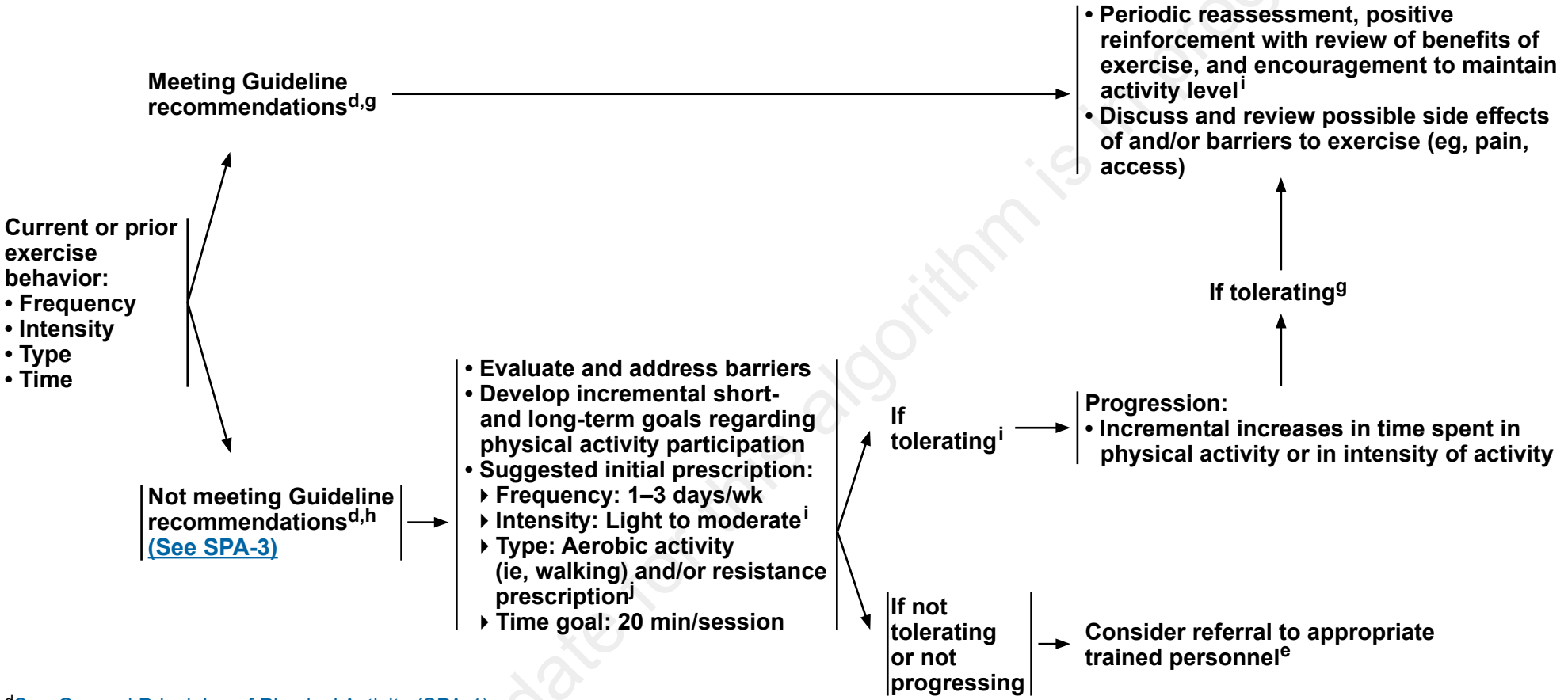
IMPLEMENTATION OF RECOMMENDATIONS[f]



[d] See General Principles of Physical Activity (SPA-1).

[e] Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://www.acsm.org/get-stay-certified] and American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

[f] Reproduced and adapted with permission from Jones LW, Eves ND, Peppercorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol 2010;11:914-916.

[g] If tolerating minimum guideline recommendations, consider encouragement of variation within exercise program or physical activities.

[h] Patients with comorbidities may need additional evaluation before doing more rigorous activity.

[i] See Examples of Physical Activity and Strategies to Increase Physical Activity (SPA-B).

[j] See Guidance for Resistance Training Recommendations (SPA-A).

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GUIDANCE FOR RESISTANCE TRAINING RECOMMENDATIONS

- **Health benefits of resistance training include improvement in muscle strength and endurance, improvements in functional status, and maintenance/improvement in bone density.**
- **Core and strength training is important to maintain balance and minimize fall risk.**
- **All major muscle groups (chest, shoulders, arms, back, core, and legs) should be incorporated into a resistance training program.**
- **Resistance training prescription**
  - **Frequency: 2–3 times/wk with adequate rest between sessions**
  - **Intensity: 2–3 sets of 10–15 repetitions per set; consider increasing weight amount as tolerated when 3 sets of 10–15 repetitions becomes easy**
  - **Rest: 2- to 3-minute rest period between sets and exercises**
  - **For survivors who wish to start resistance training, refer to trained personnel or exercise specialist if available.[a]**
- **Utilize weight amount that would allow for performance of 10–15 repetitions.**
- **For survivors at risk for or with lymphedema, See SLYMPH-B.**

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[a]Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://www.acsm.org/get-stay-certified] and American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

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NCCN Guidelines Version 2.2021
Survivorship: Physical Activity

NCCN Guidelines Index
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Discussion

EXAMPLES OF PHYSICAL ACTIVITY		
Light Exercise[a] **(No noticeable change in breathing pattern)** **• Leisurely biking at 5 miles/hour or less** **• Activity-promoting video game** **• Light housework (light sweeping, dusting)** **• Bowling** **• Playing catch** **• Slow walking** **• Child care** **• Yoga** **• Tai chi**	**Moderate Exercise[b]** **(Can talk, but not sing)** **• Ballroom/line dancing** **• Biking on level ground or with few hills** **• General gardening** **• Baseball, softball, volleyball** **• Doubles tennis** **• Using a manual wheelchair** **• Brisk walking** **• Water aerobics** **• Yoga** **• Pilates**	**Vigorous Exercise[b]** **(Can say a few words without stopping to catch a breath)** **• Aerobic/Fast dancing** **• Biking faster than 10 miles/hour** **• Heavy gardening** **• Hiking uphill** **• Jumping rope** **• Martial arts** **• Race walking, jogging, running** **• Running sports (basketball, hockey, soccer)** **• Swimming (fast pace or laps)** **• Singles tennis** **• Stair climbing** **• High-intensity yoga**

STRATEGIES TO INCREASE PHYSICAL ACTIVITY
• Physician recommendation
• Referral to trained personnel or exercise specialist if available **• Supervised exercise program or classes**
• Telephone counseling
• Motivational interviewing[c]
• Evaluate readiness to change, importance of change, self-efficacy
• Cancer survivor-specific print materials **(See SURV-B 2 of 2)**
• Set short- and long-term goals
• Consider use of pedometer or wearable fitness tracker to monitor activity goals (eg, obtain 10,000 steps per day)
• Encourage social support (exercise buddy, group)

[a]From the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/phy_act.htm) and the Compendium of Physical Activities (https://sites.google.com/site/compendiumofphysicalactivities).
[b]Reproduced and adapted from U.S. Department of Health and Human Services. Move Your Way. Washington, DC: U.S. Department of Health and Human Services. https://health.gov/moveyourway. Accessed March 16, 2020.
[c]Consider referral to trained personnel.

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CONSIDERATIONS FOR SPECIFIC POPULATIONS[a]

- **Established lymphedema:**
  - **For workup and treatment of established lymphedema (See SLYMPH-3)**
  - **For considerations regarding physical activity in survivors with established lymphedema (See SLYMPH-B)**

- **Ostomy users:[1]**
  - **Empty ostomy bag before engaging in exercise**
  - **Weight lifting/resistance exercises should start with low resistance and progress slowly under the guidance of trained exercise professionals[b]**
  - **Modify core exercises to minimize excess intra-abdominal pressure and avoid Valsalva maneuvers, as ostomy survivors may be at risk for parastomal hernias.**
  - **Use ostomy protector when engaging in contact sports or where there is a risk of a trauma to the ostomy.**
  - **Discuss hydration strategies prior to, during, and after physical activity in survivors with ileostomies, as dehydration is possible given ostomy placement and output.**

- **Peripheral neuropathy:**
  - **Stability, balance, and gait should be assessed before engaging in exercise; consider balance training as indicated**
  - **Consider alternative aerobic exercise (stationary biking, water aerobics) rather than walking if neuropathy affects stability**
  - **Resistance training recommendations:**
    - ◊ **Monitor discomfort in hands when using hand-held weights**
    - ◊ **Consider using dumbbells with soft/rubber coating, and/or wear padded gloves (eg, cycling gloves)**
    - ◊ **Consider resistance training machines**

The 2021 update for this algorithm is in progress.

Footnotes

[a]When possible, survivors in these populations should initiate an exercise program under supervision by trained personnel.

[b]Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://www.acsm.org/get-stay-certified] or American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

References

[1]Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: Consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc 2019;51:2375-2390.

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GENERAL PRINCIPLES OF NUTRITION

- **Assess dietary pattern for daily intake of fruits, vegetables, and unrefined grains, as well as red and processed meats, alcohol, and processed foods or beverages with added fats and/or sugars.**
- **Assess eating and snacking habits, including portion size, frequency of eating out, timing of meals, and use of added fats and/or sugars to foods or beverages.**
- **All survivors should be encouraged to:**
  - **Make informed choices about food to ensure variety and adequate nutrient intake.**
  - **Limit red meat intake to <18 oz per week and avoid processed meat.**
  - **Limit refined sugars and processed foods.**
  - **Eat a diet that is at least 50% plant-based, with the majority of food being vegetables, fruit, and whole grains.[a,b]**
  - **Track calorie intake.**
    - ◊ **Self-monitoring of caloric intake has been shown to be an effective strategy for weight management.**
  - **Minimize alcohol intake.**
    - ◊ **Limit intake to no more than one drink per day for a woman and two drinks per day for a man.[c,d]**
    - ◊ **Alcohol is high in calories, leads to poorer food choices, and is associated with elevated risk for several cancers.**
- **For patients desiring further recommendations for dietary guidelines**
  - **Consider referral to a dietitian or nutritionist.**
  - **The USDA approximate food plate volumes (www.choosemyplate.gov) are:**
    - ◊ **Vegetables and fruits should comprise half the volume of food on the plate**
    - ◊ **Vegetables: 30% of plate; fruits 20% of plate**
    - ◊ **Whole grains: 30% of plate**
    - ◊ **Protein: 20% of plate**
- **Recommended sources of dietary components:**
  - **Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and fatty fish[e]**
  - **Carbohydrates: fruits, vegetables, whole grains, and legumes**
  - **Protein: poultry, fish, legumes, low-fat dairy foods, and nuts**
- **Currently there is no consensus either refuting or supporting the role of soy foods in cancer control. Thus, moderate consumption (3 or fewer servings per day) of soy foods is considered prudent.**

[a]Recommendation for healthy food portion sizes can be found on the American Institute of Cancer Research (AICR) New American Plate website (https://www.aicr.org/cancer-prevention/food-facts/aicrs-new-american-plate/) as well as the USDA "Choose My Plate" website www.choosemyplate.gov.
[b]Encourage the use of healthy recipes from resources such as the American Cancer Society's "Find Healthy Recipes" website: http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/maindishes/index.
[c]Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full.
[d]There are some cancers for which survivors should abstain from alcohol. These include liver, esophageal, kidney, and head and neck cancers.
[e]These foods are high in calories and should be limited if overweight or obesity is an issue.

Note: All recommendations are category 2A unless otherwise indicated.
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GENERAL PRINCIPLES OF WEIGHT MANAGEMENT

- **All survivors should be encouraged to achieve and maintain a normal body mass index (BMI) and strive for metabolic health.**
  - **Weight gain should be a priority for underweight survivors. (See SNWM-4)**
  - **Weight loss should be a priority for overweight/obese survivors.**
    - ◊ **Weight gain after cancer diagnosis and treatment is common and can exacerbate risk for functional decline, comorbidity, and possibly cancer recurrence or death, and can reduce quality of life.**
  - **Weight maintenance should be a priority for normal weight survivors.**
- **In conjunction with primary care, survivors should be assessed for metabolic health and body composition independently of BMI.**
- **Providers should discuss strategies for weight management.**
  - ◊ **Practice portion control.**
  - ◊ **Make informed food choices through routine evaluation of food labels.**
  - ◊ **Incorporate physical activity, particularly strength training, to assure optimal lean body mass (SPA-1).**
  - ◊ **Track weight, diet, calories, and physical activity routines (eg, journaling, mobile-phone apps).**
- **Referrals to registered dietitians, especially those who are Certified Specialists in Oncology Nutrition (CSO) and members of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics, should be considered.[f]**
- **There is no current evidence to support the use of weight loss supplements in cancer survivors.**

The 2021 update for this algorithm is in progress.

[f]Many hospitals employ CSOs and those in private practice can be accessed via the Academy of Nutrition and Dietetics locator at www.eatright.org.

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NUTRITION AND WEIGHT MANAGEMENT ASSESSMENT[g]

- Evaluate weight status based on BMI criteria[h]
- Evaluate involuntary weight change[i]

→

Clinical evaluation:

- Assess current dietary and physical activity habits and ask about:
  - Daily food intake and eating habits
  - Physical activity habits
  - Willingness to address weight (if necessary) and past strategies used to change[j]
  - Barriers to nutrition and weight management:
    - ◊ Access to healthful, nutrient-dense foods
    - ◊ Financial and socioeconomic issues
    - ◊ Time
  - Appetite and changes in eating patterns

→

Assess treatment effects and medical issues:

- Effects of treatment
  - GI dysmotility
  - Swallowing issues/ dysphagia
  - Dysgeusia/change in taste
  - Oropharyngeal anatomic changes
  - Bowel dysfunction
  - Digestive enzyme insufficiency
  - GI tract reconstruction/ anastomoses
- Comorbidities:
  - Cardiovascular disease
  - Diabetes
  - Renal disease
  - Liver disease
  - Mood disorders (eg, anxiety and depression)
  - Thyroid dysfunction
  - GI disease
- Medication use
- Dental health
- Supplement use
- Psychosocial distress and fear of recurrence

INTERVENTIONS

→

- Discuss "General Principles of Nutrition" (See SNWM-1)
- Discuss "General Principles of Weight Management" (See SNWM-2)
- Discuss "General Principles of Physical Activity" (See SPA-1)

→

Additional Nutrition and Weight Management Interventions (See SNWM-4)

[g]Coordination with primary care physicians and other involved providers is recommended.
[h]The following BMI calculator from the Centers for Disease Control and Prevention may be used: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html.
BMI is calculated using the following formula: weight in pounds (lbs) X 703 / height in inches squared. The weight categories are as follows: Underweight (BMI <18.5 kg/m^2), Normal weight (BMI 18.5–24.9 kg/m^2), Overweight (BMI 25–29.9 kg/m^2), Obese (BMI ≥30 kg/m^2).
[i]Consider workup for disease recurrence in the setting of cachexia or signifcant involuntary weight loss/gain >5% within 3 months.
[j]For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/obesity-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.

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GOAL	ADDITIONAL NUTRITION AND WEIGHT MANAGEMENT INTERVENTIONS[g,j]
Weight gain[k] →	• Discuss increasing frequency of feeding • Discuss avoiding fluid intake with meals • Encourage foods that are both high in calories and nutrient-dense (eg, avocados, nuts) • Manage contributing treatment effects and risk factors as clinically indicated ▸ Dental health and risk factors for poor oral intake ▸ Swallowing disorder, taste/smell disorders, and GI motility as appropriate ▸ Offer smoking cessation assistance as appropriate (See NCCN Guidelines for Smoking Cessation) ▸ Contributing psychosocial factors (See SANXDE-1) ▸ Barriers to food access and preparation such as living too far from grocery store, lack of transportation, or lack of abilities to prepare food • Consider referral to dietitian for individualized counseling
Weight maintenance →	• Reinforce maintenance of normal body weight throughout lifetime • Monitor weight weekly • Limit foods that are high in calories, particular those that provide relatively few nutrients such as sugar-sweetened beverages and foods with high amounts fo fats and sugars • Practice portion control through plate and serving size awareness
Weight loss[k] →	• Manage contributing treatment effects and risk factors as clinically indicated ▸ Contributing psychosocial factors, including depression (See SANXDE-1) ▸ Barriers to healthy food access such as living too far from grocery store, lack of transportation, or lack of abilities to prepare food • Refer to community resources or PCP • Refer to dietitian or weight management programs for individualized help as needed[k] • Consider evaluation for bariatric surgery or pharmacologic therapy[m] as appropriate (if obese or morbidly obese) • Monitor weight daily • Recommend weight loss of no more than 2 lbs per week and no more than 1 lb per week in survivors older than 64 years • Limit foods that are high in calories, particularly those with relatively few nutrients such as sugar-sweetened beverages and foods with high amounts of fat and sugars • Substitute high-calorie foods with low-calorie, nutrient-dense foods such as water-rich/low-starch vegetables, broth-based soups, whole grains, fresh fruits for desserts, and beverages such as water, unsweetened tea, and black coffee. • Practice portion control by using smaller plates and restricting intake to one serving

[g]Coordination with primary care physicians and other involved providers is recommended.
[j]For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/obesity-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.
[k]Modification of diet and dietary components should be done on an individual basis.
[l]Strongly consider for survivors with negligible weight loss from diet and exercise interventions.
[m]The safety and efficacy of these drugs in cancer survivors is unknown. Lifestyle modifications are preferred over pharmacologic therapy.

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GENERAL PRINCIPLES OF SUPPLEMENT USE

- **Supplement use is not recommended for most survivors, except in instances of documented deficiencies, inadequate diet, or comorbid indications (eg, osteoporosis, ophthamologic disorders, cirrhosis).**
- **Little data exist to support the use of vitamins or other dietary supplements for the purposes of cancer control, recurrence, or prevention.**
- **Taking vitamin supplements does not replace the need for adhering to a healthy diet. All efforts should be made to obtain nutrients from dietary intake.[a]**
- **Providers should assess supplement use at regular intervals. Ask about reasons for supplement use and supplement ingredients.[b]**
- **Refer survivors using multiple and/or or unfamiliar supplements to a registered nutritionist/dietitian, preferably one with oncology credentials.**
- **Survivors of certain cancers are at risk for vitamin deficiencies based on their cancer treatment. Deficiencies should be assessed and repleted as needed (for example, See GAST-I 2 of 3 from the NCCN Guidelines for Gastric Cancer).**

The 2021 update for this algorithm is in progress.

[a]Referral to registered dietitians, especially those who are Certified Specialists in Oncology Nutrition (CSO) , should be considered for guidance in supplement use, if deemed necessary.
[b]Consider use of available resources for information on supplements (See SURV-B 2 of 3).

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GENERAL PRINCIPLES OF IMMUNIZATIONS

- **These principles apply to cancer survivors, including those with hematologic or solid tumor malignancies and those post transplant.**
- **Clinicians should consider and encourage the administration of inactivated vaccines (eg, influenza) or vaccines made of purified antigens (eg, pneumococcus), bacterial components (eg, diphtheria-tetanus-pertussis), or genetically engineered recombinant antigens (eg, hepatitis B) in all cancer and transplant survivors. In the absence of known harm, administration of inactivated vaccines with the hope of achieving some protection may be worthwhile. The usual doses and schedules are recommended.[a,b,c]**
  - **Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf**
- **Vaccines as a strategy to prevent infection represents a unique challenge in cancer and transplant survivors. Vaccines may not trigger protective immune responses in actively immunocompromised individuals or in survivors with residual immune deficits. In addition, certain vaccines such as those that are live attenuated (eg, zoster, MMR) are contraindicated in actively immunosuppressed individuals because of a proven or theoretical increased risk of prolonged shedding and disease from the live organism present in the vaccine; other live attenuated vaccines might also be contraindicated in survivors' close contacts. When other vaccine options exist, they should be preferred over live attenuated vaccines in survivors (eg, recombinant zoster vaccine).**
- **Ideally, clinicians should have administered all indicated vaccines to patients before initiation of cancer treatment (if possible, at least 2 weeks before cancer treatment).[e]**
  - **Inactivated or recombinant vaccines should be administered 2 or more weeks before cancer treatment and 3 or more months after cancer chemotherapy. While this schedule is preferred, the inactivated influenza vaccine can be administered during cancer treatment.**
  - **Live viral vaccines[d] can be administered 4 or more weeks before cancer treatment or 3 or more months after cancer chemotherapy, but consultation with an infectious disease specialist or physician familiar with vaccination in survivors and/or patients with cancer is strongly recommended.**
- **In survivors who received anti–B-cell antibody therapy, vaccination should be delayed for at least 6 months after chemotherapy and the last dose of such therapy.**

[a]National Center for Immunization and Respiratory Diseases. General recommendations on immunization — recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21293327.
[b]Also see: Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:133-135.
[c]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[d]See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors or In Close Contacts of Immunocompromised Survivors (SIMIN-A).
[e]Cancer treatment includes chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, and splenectomy.

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RISK ASSESSMENT AND SCREENING

Risk factors for infections:
- Underlying disease
- Post-splenectomy
- Prior chemotherapy
- Monoclonal antibodies (eg, rituximab, alemtuzumab)
- Prior radiation
- Corticosteroids
- Prior cellular therapies
  - Hematopoietic cell transplantation (HCT)[f]
  - CAR T-cell therapy
- Prior/current exposure to endemic infections or epidemics
- Blood transfusion history

→

INTERVENTIONS

- Education on infection prevention practices
  - Safe pet care/avoidance of zoonosis[g]
  - Travel precautions[h]
  - Gardening precautions[i]
  - Proper hand hygiene[j]
- Vaccines[d,k]
  - Assess overall immune system viability and history of allergic reactions to vaccines
    - ◊ Baseline white blood cell count (WBC) should be adequate before starting vaccinations, unless elevated due to disease status
    - ◊ Patient should not be on immunosuppressive drugs[l] or chemotherapy
    - ◊ Ongoing infection should not be present
- Antimicrobial prophylaxis
  (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)

→ See SIMIN-3

[d] See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors or In Close Contacts of Immunocompromised Survivors (SIMIN-A).

[f] HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

[g] Safe pet care tips include washing hands with soap and running water after handling animal feces. If possible, survivors at high risk for immune suppression should avoid direct contact with animal feces and other bodily secretions. Survivors with elevated risk of infection and those who are immunocompromised are at higher risk for zoonoses and should use extra caution.

[h] Travel precautions include education on the need for pre-travel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections. Travelers may find useful information at https://wwwnc.cdc.gov/travel/yellowbook/2020/travelers-with-additional-considerations/immunocompromised-travelers or by consulting a travel clinic.

[i] Examples of gardening precautions include:
- Wearing gloves to avoid skin cuts/punctures that could have delayed healing and to avoid thorns that can have fungus or staphylococcus/streptococcus.
- Wearing a protective mask to avoid spores. (For guidelines on physical activity, see [SPA-1])

[j] For proper hand hygiene, see the Centers for Disease Control and Prevention (CDC) "Clean Handwashing: Clean Hands Save Lives" campaign https://www.cdc.gov/handwashing/.

[k] For dosing and schedule, See General Principles of Vaccines in Cancer Survivors (SIMIN-B).

[l] Patients should not be on immunosuppressive drugs including ≥0.5 mg/kg of prednisone or equivalent, or greater than a combination of two immunosuppressive medications given concurrently.

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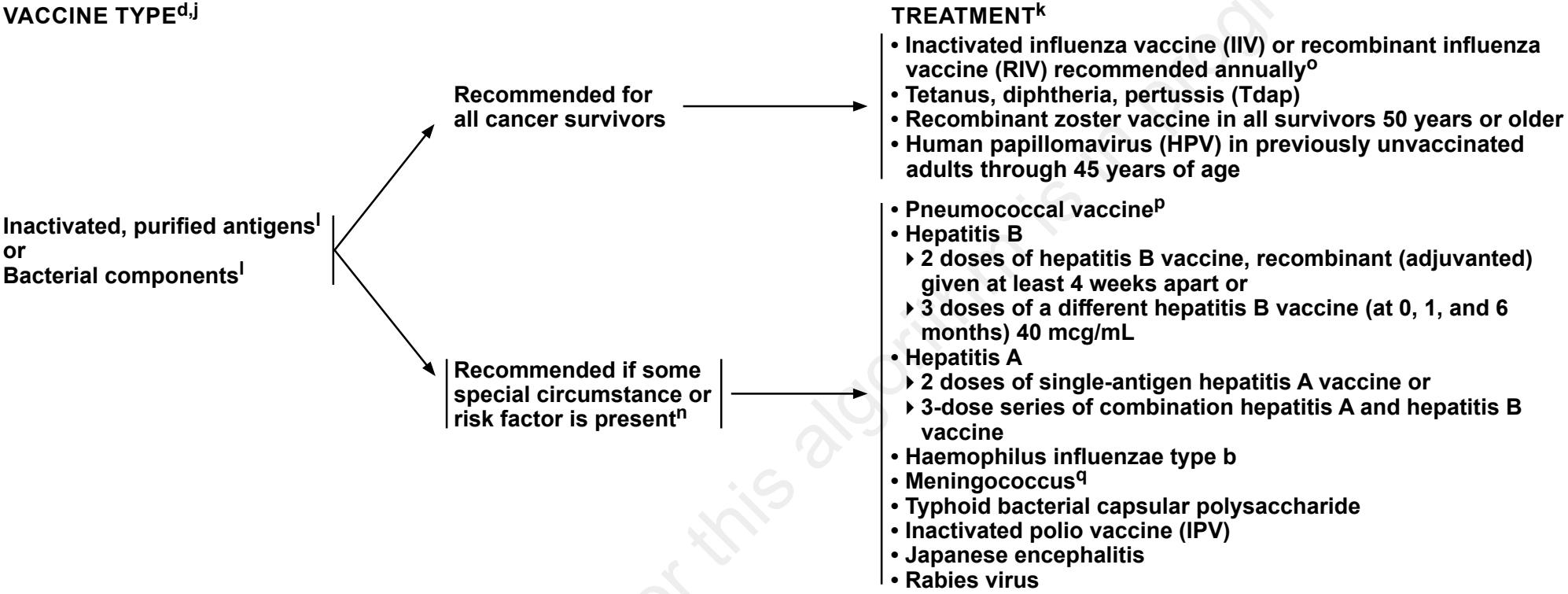

[d] See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors or In Close Contacts of Immunocompromised Survivors (SIMIN-A).

[k] For dosing and schedule, See General Principles of Vaccines in Cancer Survivors (SIMIN-B).

[m] Inactivated or purified antigens or bacterial components should be administered beginning at least 3 months after chemotherapy or radiation therapy and 6 months after HCT (a dose of inactivated influenza vaccine can be given as early as 4 months after HCT, but a second dose should be considered in this situation).

[n] These vaccines should be considered if there are unique circumstances such as functional or anatomic asplenia or in patient's lifestyle, upcoming travel, or local epidemic or risks that merit their use. Please consult with an infectious disease or travel medicine specialist. Vaccination precautions for survivors who had hematopoietic cell transplant can be found on SIMIN-B (2 of 3).

[o] See Principles of Influenza Vaccine(s) (SIMIN-C).

[p] PCV-13 and PPSV-23 are recommended for adults 65 years or older and for younger adults who are immunocompromised (ie, HCT and functional or anatomic asplenia) or for lung cancer survivors or those who had lung resection. [Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: Updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:1069-1075; and Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-819.]

[q] Recommended in high-risk patients or those with functional or anatomic asplenia. Committee on Infectious Diseases. Recommendations for serogroup B meningococcal vaccine for persons 10 years and older. Pediatrics 2016;138.

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VACCINES CONTRAINDICATED OR TO BE USED WITH CAUTION IN ACTIVELY IMMUNOCOMPROMISED SURVIVORS OR TO BE USED WITH CAUTION IN CLOSE CONTACTS OF IMMUNOCOMPROMISED SURVIVORS[1]
Live attenuated vaccines[a]
• Measles, mumps, rubella (MMR)
• Varicella zoster[b,c,d]
• Oral typhoid
• Yellow fever
• Rotavirus[e]

The 2021 version for this algorithm is in progress.

Footnotes

[a]Severe complications have followed vaccination with live attenuated vaccines among immunocompromised patients. They should not be offered to an actively immunocompromised or transplant survivor or their close contacts, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist. If a live attenuated vaccine is inadvertently administered to a survivor's close contact, close contact with the survivor should be avoided for 2 to 6 weeks following vaccination depending on the type of administered vaccine.

[b]A new recombinant zoster vaccine has become available in the United States and should be considered the preferred zoster vaccine for cancer survivors. For additional recommendations regarding zoster vaccine, see Principles of Zoster (Shingles) Vaccine Use in Cancer or Transplant Survivors (SIMIN-D).

[c]Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of varicella or zoster vaccine, until the lesions clear.

[d]There are 3 vaccines that contain live attenuated varicella zoster virus: Varicella Virus Vaccine Live (VAR) is a single-antigen vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older; Measles, Mumps, Rubella and Varicella Virus Vaccine Live (MMRV) is indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age; and Zoster Vaccine Live (ZVL) is indicated for prevention of herpes zoster (shingles) in individuals 50 years of age and older.

[e]Immunocompromised survivors should avoid handling diapers of children who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.

References

[1]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Non-Transplant Survivors[1,2]

- **These principles apply to survivors of hematologic or solid tumor malignancies except those receiving anti–B-cell antibodies.[a]**

- **The following vaccines can be administered to cancer survivors:**
  - **Influenza vaccine annually (See Principles of Influenza Vaccine(s) SIMIN-C)**
  - **Pneumococcal vaccine**
    - ◊ **Recommended for adults 65 years or older and for younger adults who are immunocompromised1**
    - ◊ **13-valent pneumococcal conjugate vaccine (PCV13) x 1 dose if never vaccinated against pneumococcus**
    - ◊ **23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks after the indicated dose(s) of PCV13.**
    - ◊ **For those who received PPSV23, PCV13 should be administered ≥1 year after the last PPSV23 dose.**
    - ◊ **A second dose of PPSV23 is recommended 5 years after the first dose for immunocompromised survivors and those with functional or anatomic asplenia.**
  - **Tetanus, diphtheria, pertussis vaccine (Td/Tdap):**
    - ◊ **Administer a one-time dose of Tdap to adults younger than 65 years of age who have not received Tdap previously or for whom vaccine status is unknown to replace one of the 10-year Td boosters (substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years). Otherwise administer Td booster every 10 years.**
    - ◊ **Consider administering a Tdap booster every 5 years.**
  - **Human papillomavirus (HPV) vaccine in adult survivors through age 45 years. For dosing and schedules see https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html**

Version 2021 update for this algorithm is in progress.

Footnotes

[a] In survivors who received anti–B-cell antibody therapy, the above vaccines can be given, but should be delayed for at least 6 months after chemotherapy and the last dose of such therapy.

References

[1] Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-819 https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm

[2] Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:133-135.

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Note: All recommendations are category 2A unless otherwise indicated.
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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Survivors Who Had Cellular Therapy (ie, HCT, CAR T-cell therapy)[b,3]

- For infection concerns and recommended prophylaxis for immune-targeted agents, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
- Influenza vaccine annually
  (See Principles of Influenza Vaccine(s) SIMIN-C)
  - One dose should be administered annually to all cancer survivors starting 6 months after HCT and starting 4 months after if there is a community outbreak of influenza as defined by the local health department.
- Pneumococcal vaccine
  - Three doses (1 month apart) of PCV13 should be administered 3–6 months after HCT.
  - At 12 months after HCT, 1 dose of PPSV23 should be given provided the patient does not have chronic graft-versus-host disease (GVHD).
  - For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HCT.
- Haemophilus influenzae type b (Hib) vaccine
  - Three doses of Hib vaccine should be administered 6–12 months after HCT.
- Meningococcal conjugate vaccine quadrivalent (MCV4)
  - The MCV4 vaccine may be considered in outbreak situations or in endemic areas.
  - The MCV4 vaccine is appropriate for splenectomized/functional asplenia survivors
- Tetanus, diphtheria, pertussis vaccination[4]
  - Three doses of DTaP vaccine should be administered 6–12 months after HCT (administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second). This three-dose regimen should be followed by Td boosters every 10 years.
  - Alternatively, one dose of Tdap and 2 doses of DT or one dose of Tdap and 2 doses of Td can be given.
- Hepatitis B (HepB) vaccine
  - Two doses of HepB vaccine, recombinant (adjuvanted) given at least 4 weeks apart or three doses of HepB vaccine should be administered 6–12 months after HCT.
  - 3 doses of a different hepatitis B vaccine (at 0, 1, and 6 months) 40 mcg/mL
  - If a postvaccination anti-hepatitis B surface antigen (anti-HBsAg) concentration of ≥10 mIU/mL is not obtained, a second series of HepB vaccine is recommended.
  - 1st dose of HepB vaccine (after which anti-HBs is tested) using high dose (40 µg) should be administered.
- Inactivated polio vaccine (IPV)
  - Three doses of IPV vaccine should be administered 6–12 months after HCT
- Human papillomavirus (HPV) vaccine
  - Administration of 3 doses of HPV vaccine 6–12 months after HCT for adult survivors through age 45 years.
- Live viral vaccines should not be administered to HCT survivors with active GVHD or ongoing immunosuppression. They should only be administered to HCT survivors without active GVHD or ongoing immunosuppression following consultation with an infectious diseases specialist.
  - Measles, mumps, rubella (MMR) vaccine
    - ◊ MMR vaccine should be avoided within 4 weeks before HCT.
    - ◊ A 2-dose series of MMR vaccine should be administered to measles-seronegative adolescents and adults 24 months after HCT in patients with neither chronic GVHD nor ongoing immunosuppression and 8–11 months after the last dose of immune globulin intravenous (IGIV).
  - Zoster vaccine (VAR)
    - ◊ The new recombinant zoster vaccine is recommended, but the VAR vaccine may be used if patients have normal immunity and recombinant zoster is not available. (see SIMIN-D)
    - ◊ A 2-dose series of recombinant zoster vaccine or VAR should be administered 24 months after HCT to varicella-seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of IGIV.

Footnotes
[b]HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

References
[3]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318. https://www.ncbi.nlm.nih.gov/pubmed/24421306.

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS	
Vaccines Considered Safe for Cancer and Transplant Survivors and Close Contacts[c]	
Inactivated or purified antigens or bacterial components[d] • Influenza: inactivated influenza virus vaccine[e] ▸ Trivalent (IIV3), standard dose ▸ Trivalent (IIV3), high dose ▸ Quadrivalent (IIV4), standard dose • Pneumococcus: ▸ Pneumococcal conjugate vaccine (PCV) ▸ PPSV • Meningococcus: ▸ Quadrivalent meningococcal conjugate vaccine (MCV4: serotypes A, C, W, Y) ▸ Meningococcal vaccine (serotype B)[3] • Tetanus, diphtheria, pertussis (Td/Tdap) • Hepatitis A • Haemophilus influenzae type b	**Recombinant viral antigens** • Hepatitis B • Human papillomavirus (HPV) • Recombinant trivalent influenza vaccine (RIV3)[e] • Zoster (RZV)

Footnotes

[c]Ideally, clinicians should have administered all indicated vaccines to patients at least 2 weeks before initiation of cancer treatment (ie, chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, splenectomy).

[d]For patients traveling to endemic countries, vaccines such as typhoid bacterial capsular polysaccharide, inactivated polio vaccine (IPV), Japanese encephalitis, and rabies virus are recommended by the Centers for Disease Control and Prevention (www.cdc.gov).

[e]Administration of the flu vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2019-20 influenza season. MMWR Recomm Rep 2019;68:1-21.

References

[3]Folaranmi T, Rubin L, Martin SW, Patel M, MacNeil JR; Centers for Disease Control (CDC). Use of serogroup B meningococcal vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep 2015 Jun 12;64(22):608-612.

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PRINCIPLES OF INFLUENZA VACCINE(S)[1,2]

- **Annual influenza vaccination is recommended[2] for all cancer and transplant survivors. Live attenuated influenza vaccines should be avoided in these individuals unless they have been cleared to do so by an infectious disease specialist or physician familiar with vaccination in this population.**
- **For a summary of recommendations for prevention and control of influenza with vaccines see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6713402/**
- **Components of the influenza vaccine are determined each year by the World Health Organization (WHO) according to reports of the most common influenza viruses that are likely to circulate that year.**
- **Influenza vaccines can be inactivated or recombinant. They may contain standard or higher doses of the antigen. They can be trivalent or quadrivalent.**

Preferred Vaccines

- **Inactivated influenza vaccine**
  - **Trivalent (IIV3), standard dose**
  - **Trivalent (IIV3), high dose**
  - **Quadrivalent (IIV4), standard dose**
- **Recombinant influenza vaccine[a]**
  - **Trivalent (RIV3)**
  - **Quadrivalent (RIV4)**

To date, there is no evidence that one vaccine is superior to any other vaccine.

The 2021 update for this algorithm is in progress.

Footnotes

[a]Administration of the flu vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2019-20 influenza season. MMWR Recomm Rep 2019;68:1-21.

References

[1]Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:133-135.

[2]Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2019-20 influenza season. MMWR Recomm Rep 2019;68:1-21.

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PRINCIPLES OF ZOSTER (SHINGLES) VACCINE USE IN CANCER OR TRANSPLANT SURVIVORS[1,2]

Recombinant zoster vaccine (Preferred)

- **A new recombinant zoster vaccine has become available in the United States. The recombinant vaccine is the preferred zoster vaccine for cancer survivors, and is recommended for survivors aged 50 years and older.**
- **In survivors who have previously received the live attentuated zoster vaccine, immunization with recombinant zoster vaccine should be considered. The recombinant vaccine should not be given less than 2 mo after receiving the live attenuated vaccine.**

Live attenuated zoster vaccine

- **Although the recombinant zoster vaccine is preferred, the live attenuated zoster vaccine can be given if the recombinant vaccine is unavailable or access to the recombinant vaccine is an issue.**
- **Live attenuated zoster vaccine may be considered in survivors with a history of solid tumors or leukemia whose disease is in remission, who have restored their immunocompetence, and who have not received chemotherapy or radiation for at least 3 months.**
- **If live attenuated zoster vaccine is given prior to starting therapy, it should be administered at least 4 weeks prior to the first dose of immunosuppressive therapy.[2]**
- **The vaccine can be administered to select immunocompetent survivors regardless of whether they report a prior episode of herpes zoster.[a]**
- **Licensed antiviral medications active against members of the herpes virus family (eg, acyclovir, famciclovir, valacyclovir, valganciclovir) might interfere with replication of the live, varicella zoster virus (VZV)-based zoster vaccine.[b]**
- **A single dose of live attenuated zoster vaccine is recommended for cancer or transplant survivors 60 years of age and older assuming that active or ongoing immunodeficiency is not present and that there is no history of cellular immunodeficiency.**
  - **For survivors aged 50–59 years, live attenuated zoster vaccination should be considered in those with a history of varicella or zoster infection or VZV seropositive with no previous doses of varicella vaccine.**
- **Live attenuated zoster vaccine should be avoided:**
  - **in patients with lymphomas, other malignant neoplasms affecting the bone marrow or lymphatic system, or a history of cellular immunodeficiency;**
  - **in patients on immunosuppressive therapy, including high-dose corticosteroids (>20 mg/day of prednisone or equivalent) lasting 2 or more weeks; and**
  - **in patients undergoing or with history of HCT. The experience of HCT recipients with VZV-containing vaccines (eg, zoster vaccine) is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation in patients without active GVHD or enhanced immunosuppression.**

Footnotes

[a]Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing postherpetic neuralgia (PHN, a common complication of zoster that results in chronic, often debilitating pain that can last months or even years), or to treat ongoing PHN. Before routine administration of zoster vaccine, it is not necessary to ask patients about their history of varicella (chickenpox) or to conduct serologic testing for varicella immunity. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103-108.

[b]Survivors taking chronic acyclovir, famciclovir, valacyclovir, or valganciclovir should discontinue these medications at least 24 hours before administration of zoster vaccine. These medications should not be used for at least 2 weeks after vaccination, by which time the immunologic effect should be established.

References

[1]Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103-108. https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm

[2]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.

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Late Effects/Long-Term Psychosocial and Physical Problems

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PRINCIPLES OF CARDIOVASCULAR DISEASE RISK ASSESSMENT

- **Cardiovascular disease (CVD) remains a leading cause of death in cancer survivors. The risk of CVD-related death varies with years from diagnosis, with most survivors being at greatest risk 5 or more years after diagnosis and completion of curative therapy.**
- **Shared risk factors for both cancer and CVD (ie, smoking, poor health behaviors) contribute to the development of CVD and structural heart disease or heart failure, a concept that becomes especially relevant to cancer survivors. Attention and counseling regarding shared risk factors may improve cancer- and cardiovascular-related outcomes.**
- **Cancer treatments (cytotoxic and targeted systemic therapies,a radiation therapy) can result in diverse cardiovascular issues, including cardiomyopathy, hypertension, hyperlipidemia, cardiac arrhythmia, myocardial infarction, and cerebrovascular accidents. Survivors treated with anthracyclines may be at increased risk for heart failure. (See SCARDIO-1)**
- **Most cardiovascular diseases (such as atherosclerosis) develop over time as a result of well-defined risk factors such as hypertension, hyperlipidemia, tobacco abuse, obesity and diabetes. Control of these risk factors can decrease the risk of subsequent cardiovascular events.**
- **Survivors should be assessed throughout the survivorship continuum for:**
  - **Pre-existing and emerging CVD (eg, coronary artery disease [CAD], congestive heart failuree [CHF], peripheral vascular disease, arrhythmias including atrial fibrillation) and CVD risk factors (eg, hypertension, dislipidemia, obesity, cigarette/tobacco use, diabetes mellitus), with intervention for modifiable risk factors as necessary**
  - **Cancer treatment history (eg, regimen/dose,[a] radiation field)**
  - **Diet and exercise habits, cigarette/tobacco use**
- **Tools exist to help quantify atherosclerotic CVD (ASCVD) risk (eg, ASCVD risk score[b]).**
- **Survivors should be counseled on any increased risk of CVD they may have based on prior treatment, comorbidity, or CVD risk factors and on the ABCDEs of CVD Prevention. (See Table 1 on SCVD-2)**
- **Cooperation and shared care with primary care providers, and cardiovascular specialists as needed, is key to optimizing cardiac and vascular outcomes in cancer survivors.**
- **Consider referral to cardio-oncology or a cardiology specialist for high-risk survivors.**

[a]HER2-directed therapy, VEGF signaling pathway inhibitors, cisplatin, anthracyclines with or without taxanes, and androgen deprivation therapy are CVD risk factors.
[b]The ASCVD Risk Estimator Plus from the American College of Cardiology is available at http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/.

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PRINCIPLES OF CARDIOVASCULAR DISEASE RISK ASSESSMENT

Table 1: ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors[c]	
A	• Awareness of risks and presentation of heart disease • Assessment of cardiovascular disease and cardiovascular risk • Aspirin use as appropriate (indicated for secondary prevention; clinician-survivor discussion required for primary prevention with careful weighing of benefits and risks)
B	• Blood pressure monitoring/management (with clinician-survivor discussion regarding the use of hypertension treatment and blood pressure goals)
C	• Cholesterol assessment/management (with clinician-survivor discussion regarding the use of statin therapy for primary prevention and lipid profile goals) • Cigarette/tobacco cessation (See NCCN Guidelines for Smoking Cessation)
D	• Diet and weight management (See SNWM-1) • Dose (cumulative) of anthracyclines and/or radiation to heart • Diabetes mellitus prevention/treatment
E	• Exercise (See SPA-1) • Echocardiogram and/or EKG based on individual risk

[c]Adapted with permission from Montazeri K, Unitt C, et al. ABCDE Steps to Prevent Heart Disease in Breast Cancer Survivors. Circulation 2014;130:e157-e159.

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PRINCIPLES OF ANTHRACYCLINE-INDUCED CARDIAC TOXICITY

- **Cancer treatments can result in diverse cardiovascular issues (See SCVD-1). This algorithm focuses specifically on heart failure or cardiomyopathy that may arise from anthracycline therapy. Other systemic therapies may also cause cardiomyopathy (eg, HER2-targeted therapies), and some of the concepts presented in these recommendations may apply to these other cardiomyopathies.**
- **Anthracycline-induced heart failure may take years or even decades to manifest. Data suggest that signs of cardiac dysfunction can be seen prior to the development of symptoms. If detected early, anthracycline-induced heart failure may be responsive to cardioprotective medications, although prospective studies evaluating these medications are lacking.**
- **Survivors may have risk factors that predispose them to heart failure. Some survivors may have structural heart disease (such survivors are considered to have Stage B heart failure) even if they have no actual symptoms. A history of anthracycline exposure is a risk factor that predisposes survivors to cardiac disease.[a] (See SCARDIO-3).**
- **Having a history of anthracycline exposure plus additional cardiovascular risk factors increases the risk of developing cardiomyopathy and heart failure. It is encouraged that such survivors should have heart failure risk factors, including hypertension, dyslipidemia, and diabetes addressed in coordination with primary care.**
- **The risk for cardiovascular problems varies greatly depending on the type of anthracycline used and the cumulative dose received.**
- **For this algorithm, the panel has placed an emphasis on early recognition and prevention of clinical heart failure, as well as early treatment of patients at risk with appropriate cardioprotective medications to prevent cardiac remodeling over time. Therefore, for high-risk survivors, the panel emphasizes the need for a thorough clinical screening for heart failure within one year after completion of anthracycline therapy.**

The 2021 update for this algorithm is in progress.

[a]Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-e239.

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INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical (H&P)
  - Assess for signs and symptoms of heart failure[b,c]
  - Assess patient's ability to perform routine and desired activities of daily living (ADLs)
  - Look for signs of volume overload
- Review medications, alcohol use, and other substance use
- Review oncologic history
  - Review total cumulative dose of anthracycline
  - Other systemic therapy and/or chest radiation therapy
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - High cumulative anthracycline dose (ie, cumulative doxorubicin dose at or higher than 250 mg/m^2 or equivalent)
  - Low-normal LVEF (50%–54%) at baseline
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], baseline evidence of structural heart disease)
  - Smoking
  - Obesity

→

- Cardiovascular risk factor management (see SCVD-1)[d]
- Consider two-dimensional echocardiogram (ECHO) with doppler flow study within 1 year after completion of anthracycline therapy for survivors with[c,e,f]
  - High cumulative anthracycline dose
  - Low cumulative anthracycline dose and 1 or more heart failure risk factors

→

No evidence of structural heart disease, but symptomatic[b] →
- Workup for other causes of symptoms
- Referral to other specialties (eg, pulmonology or cardiology)

No evidence of structural heart disease and asymptomatic
or
No ECHO performed and asymptomatic → See Stage A (SCARDIO-3)

Evidence of structural heart disease (asymptomatic or symptomatic[b]):
- Left ventricular (LV) dysfunction
- LV hypertrophy
- Valvular disease
- LV dilatation and/or wall thinning

→ Determine stage of cardiomyopathy (heart failure) (See SCARDIO-3)

[b]Signs and symptoms of heart failure include: shortness of breath or chest pain after physical activity or exercise, shortness of breath when sleeping, waking up at night due to shortness of breath, and swelling in the legs.
[c]Patients with symptoms of heart failure should undergo an echocardiogram.
[d]Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[e]Referral to cardiologist/cardio-oncologist if there are echocardiographic abnormalities.
[f]For survivors of certain cancer types, longer-term cardiovascular surveillance may be needed. Please see the NCCN Guidelines for Treatment of Cancer by Site for specific monitoring recommendations.

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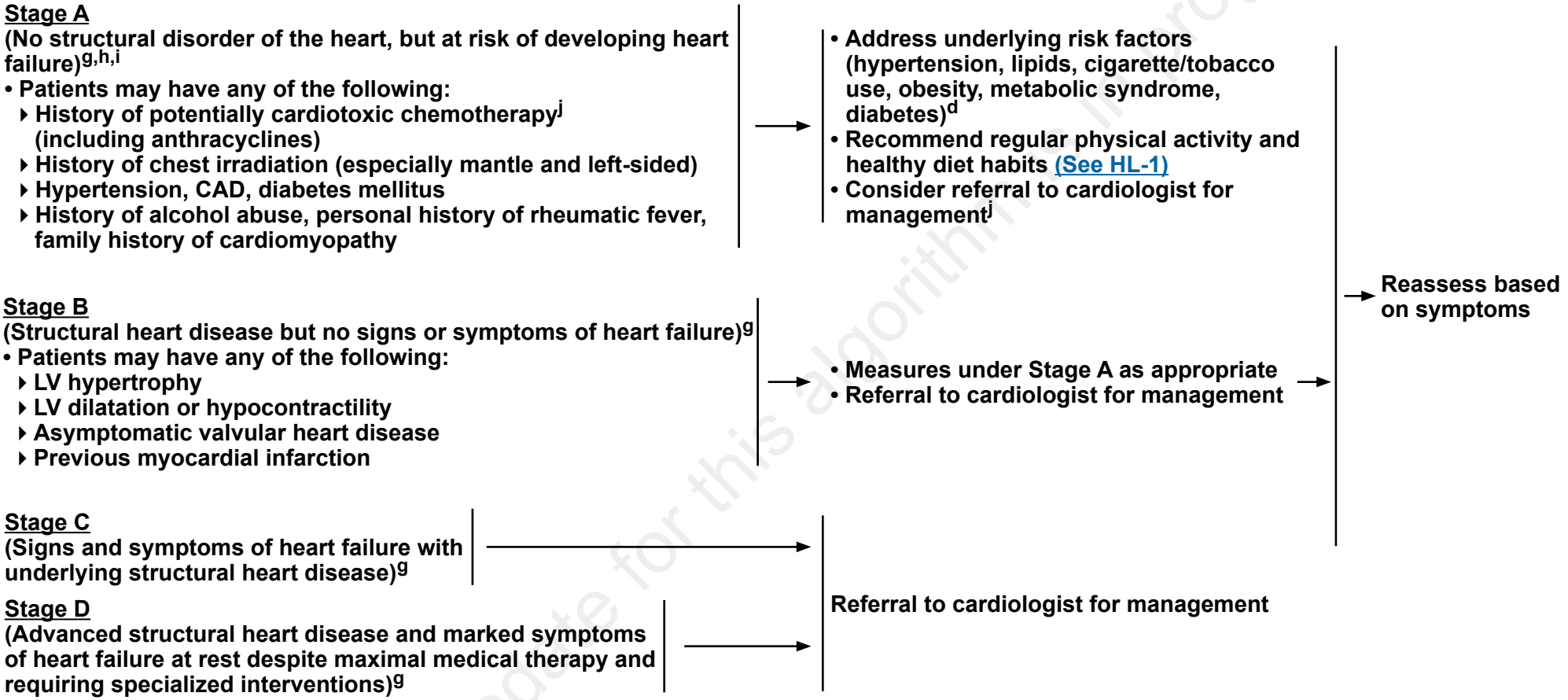

[d]Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[g]Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the Amercian College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240-e327.
[h]Consider use of biomarkers in select patients at high risk for heart failure (Stage A) (See Discussion).
[i]Any patient who has received potentially cardiotoxic chemotherapy and/or chest radiation (and specifically anthracycline-based chemotherapy) should be considered Stage A cardiomyopathy.
[j]For a list of potentially cardiotoxic chemotherapy agents, see Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. N Eng J Med 2016;375:1457-1467.
[k]Consider referral to a cardiologist, especially if additional anthracycline therapy or other cardiotoxic treatment is needed.

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GENERAL PRINCIPLES OF ANXIETY, DEPRESSION, TRAUMA, AND DISTRESS

- **The NCCN Guidelines for Distress Management define distress as "a multifactorial unpleasant emotional experience of a psychological (ie, cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment." The NCCN Guidelines for Survivorship complement the NCCN Guidelines for Distress Management.**

- **Survivors of cancer and its treatment are at elevated risk for mental health issues such as fear of recurrence, distress, anxiety, and depression that may persist for many years after diagnosis.[a]**
  - **Fear of recurrence can lead to increased symptoms when surveillance testing or follow-up appointments are scheduled and increased anxiety when physical symptoms occur that may or may not be similar to those experienced during the cancer diagnosis.**
  - **Medical, psychosocial, environmental, and psychiatric health factors may affect the mood of cancer survivors and need to be considered when screening for distress, anxiety, and depression in survivors and deciding on treatment. (See SANXDE-6)**
  - **Recurrent worry, fear, thoughts, or images related to cancer events should be distinguished from obsessive compulsive disorders. Repetitive, persisting thoughts, images, or behaviors or mental acts that a person is compelled to perform, aimed at reducing intense anxiety or preventing a dreaded event require psychiatric referral for evaluation and treatment.**
  - **Monitor distress, especially at times of new diagnoses, transitions in care, cancer surveillance, significant loss, other major life events, and with social isolation.**
    - ◊ **Patients may not appear to be distressed and should be encouraged to inform their health care provider when they are feeling increased distress, anxiety, or depression. See NCCN Distress Thermometer Screening Tool (See DIS-A)**
    - ◊ **Screening for anxiety, depression, trauma, and distress should be a part of routine care. The panel recommends using validated measures such as the PHQ-9 for depression, GAD-7 for anxiety, PC-PTSD-5 for trauma (Also see Trauma Screening [SANXDE-D]), NCCN Distress Thermometer Screening Tool (See DIS-A) or PROMIS measures.**
  - **Clinical assessments should include and evaluate psychosocial aspects of a survivor's background, including trauma (See SANXDE-7)**

- **This algorithm is intended for oncologists and other health care providers to screen for distress, anxiety, and depression in cancer survivors, to provide steps for addressing these concerns with survivors, and to facilitate decisions about referral to specialists.**
  - **The algorithm is not intended as a psychiatric diagnosis and treatment tool.**
  - **The algorithm focuses on more common mood disorders after cancer;. It does not screen or address treatment for psychiatric conditions such as bipolar disorders, schizophrenia, personality disorders, or obsessive compulsive disorders. Diagnosis and management of these disorders should be done by a mental health professional (See NCCN Guidelines for Distress Management).**

- **Decisions about treatment and referral will depend on the acuteness of onset of symptoms, their intensity, and safety of the survivor and others. (See SANXDE-6 and SANXDE-A)**

[a]Lu D, Andersson TM, Fall K, et al. Clinical diagnosis of mental disorders immediately before and after cancer diagnosis: a nationwide matched cohort study in sweden. JAMA Oncol 2016;1188-1196.

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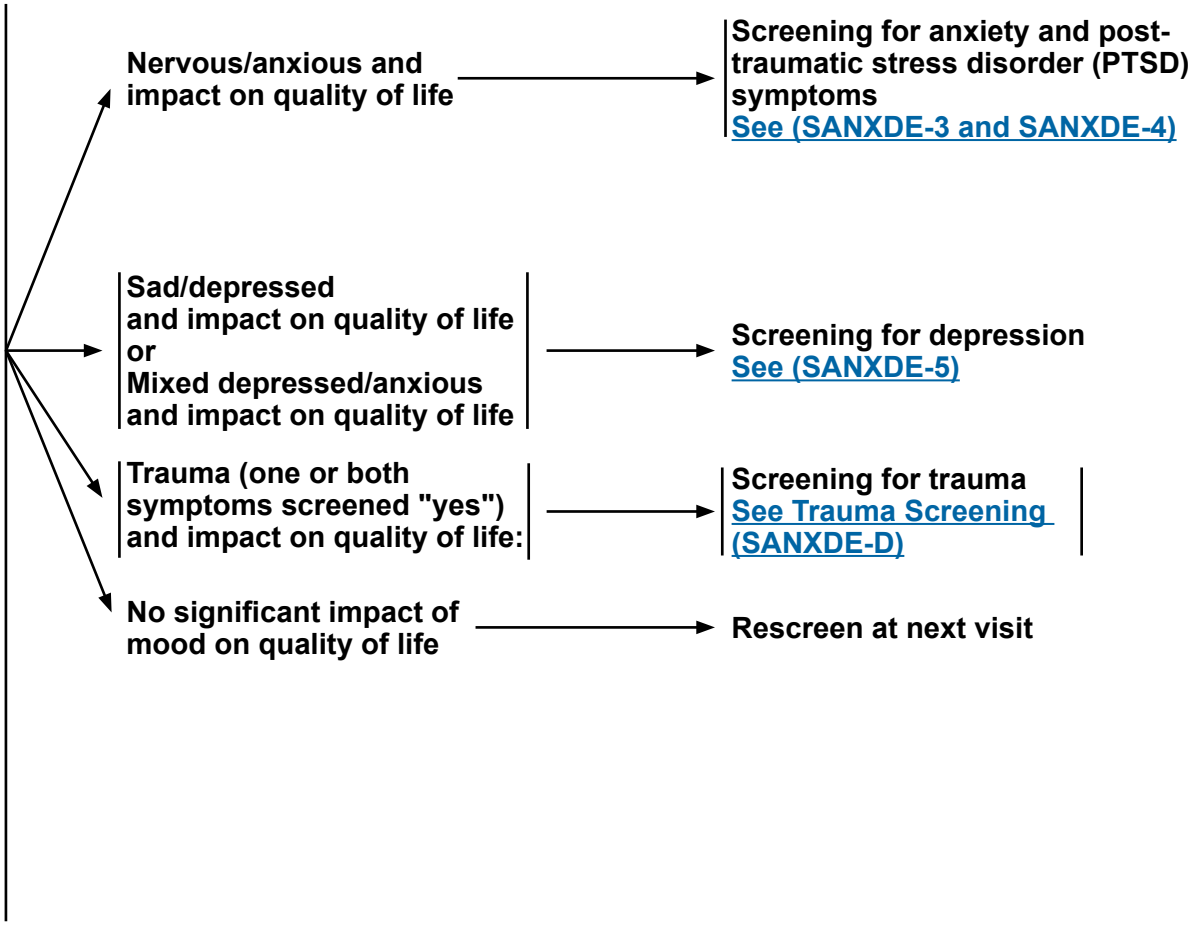
SCREENING: ANXIETY, DEPRESSION, AND TRAUMA

Screening questions[b] to be asked at regular intervals, especially when there is a change in clinical status or treatment, or patient presents with multiple somatic complaints:[c]

- **In the past two weeks, on more days than not have you:**
  - **Nervous/anxious**
    - ◊ **had worries or fears related to your cancer?**
    - ◊ **felt nervous, or worried about other things?**
    - ◊ **had trouble controlling your worry?**
  - **Sad/depressed**
    - ◊ **had less interest or enjoyment in activities than usual?**
    - ◊ **felt sad or depressed?**
  - **Trauma screening**
    - ◊ **had nightmares or thoughts about your cancer or treatment when you did not want to?**
    - ◊ **tried hard not to think about events related to your cancer or went out of your way to avoid situations that reminded you of those events?**
- **Additional screening for impact of mood on quality of life if "Yes" to any of the above:**
  - **had difficulty functioning or withdrawn from daily activities because of these (above-mentioned) feelings or problems?**
  - **had trouble sleeping (eg, staying asleep, falling asleep, getting too much sleep)?[b]**
  - **had difficulty concentrating?[b]**



[b]A positive response to any of the questions should result in further assessment. However, if a patient has an isolated problem with sleep or concentration in the absence of other symptoms, see (SSD-1) or (SCF-1).

[c]If the NCCN Distress Thermometer is used as a primary screening tool, these questions would follow for those survivors with an elevated level of distress.

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SCREENING: ANXIETY AND PANIC[d]

Anxiety
Excessive anxiety and worry that is difficult to control and ≥3 of the following:
- **Restless or on edge**
- **Easily fatigued**
- **Difficulty concentrating or mind going blank**
- **Irritability**
- **Muscle tension**
- **Sleep disturbance**

Panic
Sudden intense fear or discomfort that peaks within minutes and ≥4 of the following:[e]
- **Palpitations, pounding heart**
- **Sweating**
- **Trembling or shaking**
- **Sensations of shortness of breath or smothering**
- **Chest pain or discomfort**
- **Nausea or abdominal distress**
- **Feeling dizzy, lightheaded, unsteady**
- **Chills or heat sensations**
- **Paresthesias (numbness or tingling)**
- **Feelings of unreality or being detached from oneself**
- **Fear of losing control**
- **Fear of dying**

DIAGNOSIS

≥3 symptoms and persisting more than 6 months: Consider general anxiety disorder, PTSD symptoms, or adjustment disorder → **Safety evaluation[g]** → **See Evaluation (SANXDE-7) or Refer to mental health services for evaluation and treatment[h]**

<3 symptoms and/or persisting less than 6 months: Adjustment disorder[f] with anxious or mixed mood or Other anxiety disorder → **See Screening (SANXDE-6)**

Panic disorder → **Safety evaluation[g]** → **See Evaluation (SANXDE-7) or Refer to mental health services for evaluation and treatment[h]**

[d]The following additional tools may be used for individual intensive screening for a specific problem: Anxiety GAD-7; Panic: Brief Patient Health Questionnaire, item 2 a-e. Both tools can be found at http://www.phqscreeners.com.
[e]Consideration should be taken for evaluation of other medical causes to rule out alternative etiologies.
[f]Development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). [American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.]
[g]See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[h]Psychiatrist, psychologist, advanced practice clinician, and/or social worker.

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SCREENING: POST-TRAUMATIC STRESS SYMPTOMS OR DISORDER (PTSD)[i,j]

- **Screen for PTSD symptoms using PC-PTSD-5**
  See Trauma Screening (SANXDE-D)
- **Assess risk factors for PTSD (See SANXDE-B)**
- **Diagnosis of PTSD requires symptoms from each of the following 4 categories**
  - **Exposure to traumatic events (eg, cancer diagnosis, treatment)[k] and the following symptoms that cause clinically significant distress or impairment in social interactions, capacity to work, or other functioning for more than 1 month:**
    - ◊ **Re-experiencing: repeated, disturbing memories, dreams, or flashbacks (minimum 1 symptom)**
    - ◊ **Persistent avoidance: avoidance of distressing memories, thoughts, feelings, or external reminders of the cancer experience (minimum 1 symptom)**
    - ◊ **Negative alterations in mood or cognition: exaggerated negative beliefs about oneself or the world, feeling detached or estranged from others, lack of positive emotions, feelings of fear, horror, anger, guilt, or shame (minimum 2 symptoms)**
    - ◊ **Arousal: hypervigilance (being super alert or watchful or on guard), difficulty concentrating, sleep disturbance, aggressiveness, risky or self-destructive behavior (minimum 2 symptoms)**

DIAGNOSIS

→ **• Post-traumatic stress symptoms impacting quality of life**
• Consider adjustment disorder/distress (see SANXDE-6)

→ **Safety evaluation[g]**

→ **See Evaluation (SANXDE-7)**
or
Refer to mental health services for evaluation and treatment[h]

[g] See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[h] Psychiatrist, psychologist, advanced practice clinician, and/or social worker.
[i] For a complete list of screening symptoms review the American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
[j] Also See Risk Factors for PTSD (SANXDE-B).
[k] Person may directly experience the traumatic event, witness the event, learn of the event occurring to a close family member or friend, or experience repeated or extreme exposure to aversive details of the trauma. Life-threatening illness or cancer or debilitating medical condition is not necessarily a traumatic event, but may be in some cases. A history of PTSD prior to a cancer diagnosis increases risk for symptoms of PTSD to be associated with cancer treatment if experiences remind the survivor of a prior traumatic event. A future trauma may also evoke traumatic cancer memories increasing post-traumatic stress symptoms.

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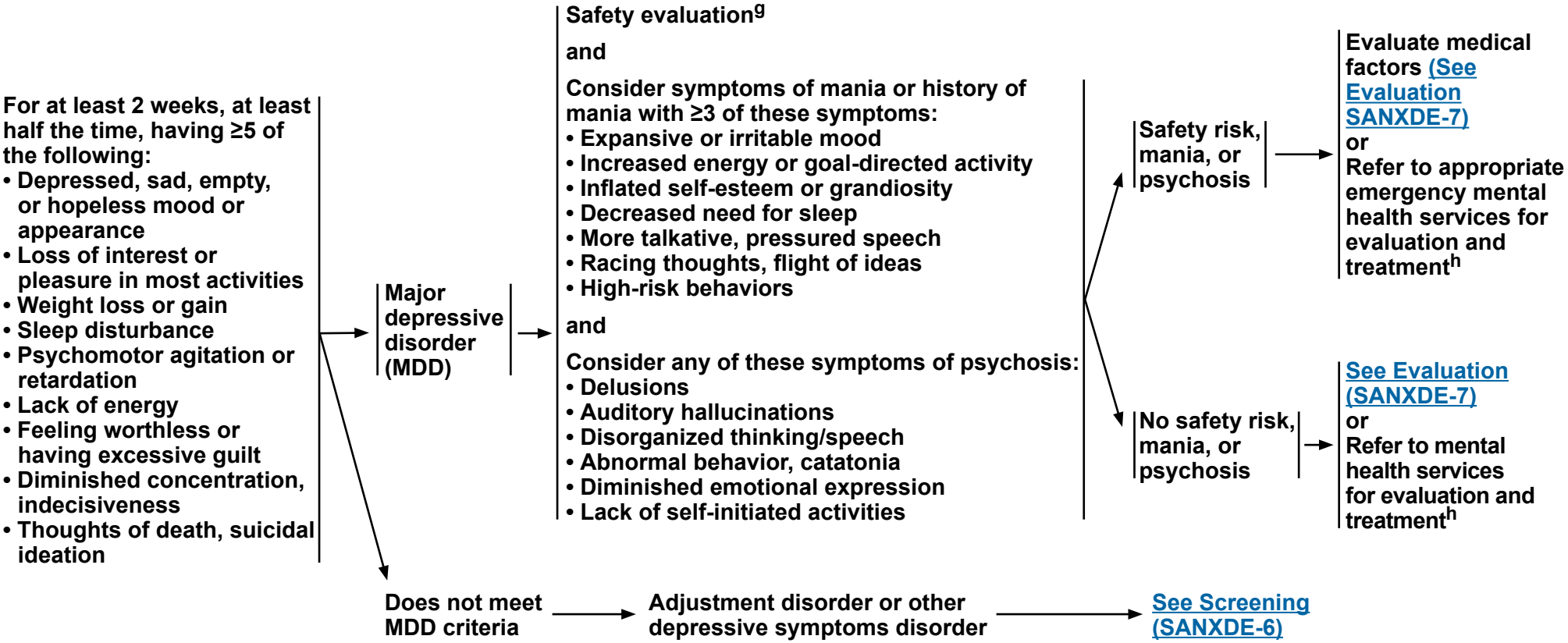
SCREENING: DEPRESSION[i,l,m] DIAGNOSIS



[g] See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[h] Psychiatrist, psychologist, advanced practice clinician, and/or social worker.
[i] For a complete list of screening symptoms review the American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
[l] The following additional tools may be used for individual intensive screening for a specific problem: Screening Tools: PHQ-9 or PHQ-2. The PHQ-2 is comprised of the first two items of the PHQ-9 and can be used as an initial depression screening. If the patient responds affirmatively to either of these two items, the remaining 7 items are asked. (Available at: www.phqscreeners.com and http://www.commonwealthfund.org/usr_doc/PHQ2.pdf).
[m] When screening, also take into consideration a survivor's cultural differences at presentation (eg, somatization as expression of emotional distress).

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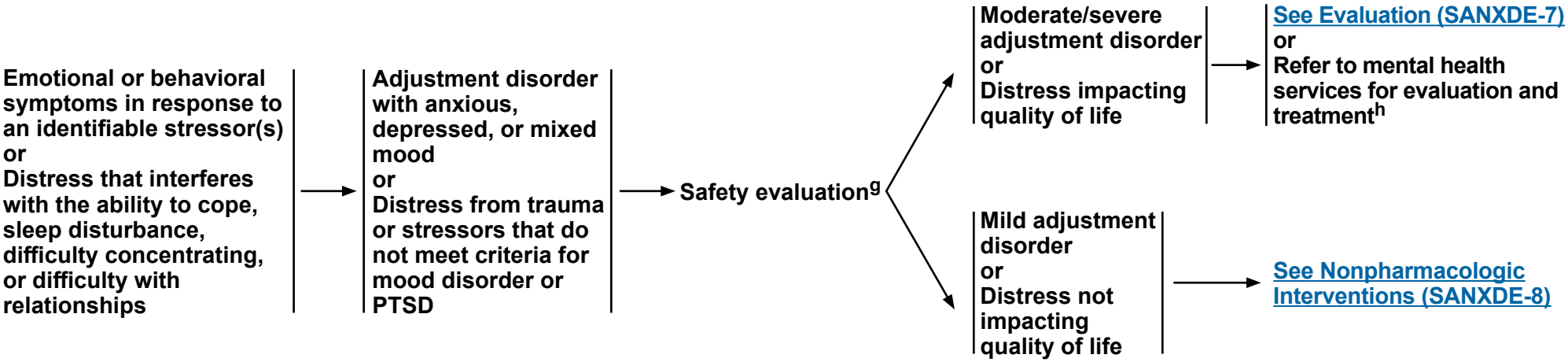
SCREENING: ADJUSTMENT DISORDER/DISTRESS[i,n]

DIAGNOSIS



[g] See Safety Evaluation for Anxiety and Depression (SANXDE-A).
[h] Psychiatrist, psychologist, advanced practice clinician, and/or social worker.
[i] For a complete list of screening symptoms review the American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
[n] The following additional tool may be used for screening distress level: NCCN Distress Thermometer Screening Tool [DIS-A]. A score of ≥4 indicates moderate/severe distress: "On a scale of 0–10 how much distress have you been experiencing in the past week, including today with 0 = No Distress and 10 = Extreme Distress?"

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EVALUATION: ANXIETY, DEPRESSION, TRAUMA, AND DISTRESS[o]

Medical Factors (H&P Exam)

- General review:
  - Illness status/progression
  - Medication changes/side effects
  - Presence of new or poorly controlled symptoms (ie, pain, nausea, constipation)
  - Status of coexisiting medical conditions
  - Substance use disorder
  - History of prior major depression, anxiety disorder, or suicide attempt
  - History of childhood or adult trauma prior to or after cancer diagnosis
  - Fatigue level (See SFAT-1)
  - Functional status
  - Current coping strategies
  - Sexual function (See SSF-1)
  - Infertility
  - Other medical factors including cognitive function (See SCF-1)
- Laboratory studies to consider:
  - Metabolic studies
  - Infection workup
  - Anemia with underlying deficiencies
  - Endocrine/hormonal status
- Other studies as clinically indicated:
  - Neurologic:
    - ◊ Central nervous system (CNS) imaging
    - ◊ Neuropsychological testing
  - Cardiac: electrocardiogram (EKG), ECHO, stress test (See SCARDIO-1)
  - Pulmonary function tests
  - Sleep evaluation (See SSD-1)

→

Psychiatric/Emotional Factors

- Symptom review based on the Survivorship Anxiety and Depression screening recommendations (See SANXDE-2 through SANXDE-6); evaluate for anticipation/fear of recurrence in the setting of:
  - Active surveillance by oncology team
  - New symptoms or findings suggestive of recurrence
  - Transitions in surveillance and care
- Consider other major psychiatric disorders

→

Social/External Factors

- Environmental stressors and non–cancer-related factors:
  - Social isolation, living alone
  - Family and caregiver conflicts, roles, and responsibilities
  - Spouse, intimate partner relationship
  - Financial problems and limited insurance coverage
  - Employment concerns
  - Limited access to medical care
  - Adolescents, younger adults, lack of connection with peers
  - History of abuse (ie, emotional, physical, sexual)
  - Spiritual, religious, or existential concerns
  - Other stresses

→

Management and Treatment (See SANXDE-8)
or
For mania, psychosis, extensive psychiatric history, or moderate to high safety risk
- Refer for psychiatric evaluation and treatment

[o]These are general factors/principles that affect anxiety, depression, trauma, distress, and adjustment that need to be considered when evaluating survivors.

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ANXIETY, DEPRESSION, TRAUMA, AND DISTRESS: MANAGEMENT AND TREATMENT

NONPHARMACOLOGIC INTERVENTIONS

- **For all survivors:**
  - Address treatable contributing factors
    - ◊ Pain, sleep disturbance, fatigue, toxic metabolic/endocrine/other medical comorbidities, substance use disorder
  - Provide reassurance that symptoms of worry, stress, fear of recurrene, anxiety, and depression are common problems among cancer survivors and that these symptoms can be treated
  - Provide support and education to patient and family regarding normal recovery phases after treatment, common stresses, distress and fears, and strategies for managing uncertainty and distress
  - Provide resources for social support networks and specific social, emotional, spiritual, intimacy, and practical problem needs, including online and mobile phone apps. Consider referral to social work services, patient navigator, and/or financial navigator (if available). (See SURV-B)
  - Develop a plan for regular physical activity and healthy nutrition. (See HL-1)

- **For adjustment disorder or distress without safety risk, mania, or psychosis (See DIS-10 and DIS-17 from the NCCN Guidelines for Distress Management):**
  - Refer to a therapist, preferably one with psycho-oncology training if available (ie, psychologist, psychiatrist, social worker, advanced practice clinician, licensed therapist):
    - ◊ Cognitive behavioral therapy (CBT) (eg, mindfulness, behavioral activation, structured CBT) can be effective for distress, fear of recurrence, trauma symptoms, insomnia, or other symptoms related to distress and can be delivered as individual therapy in structured groups, or with digital modalities (category 1)
    - ◊ Social work for complex social factors
    - ◊ Supportive normalizing of survivor's experience
    - ◊ Existential therapy related to values, meaning, and purpose in life
  - Consider referral to chaplain for spiritual support for religious conflict, concerns about death and afterlife, guilt, grief, and meaning and purpose in life
  - Consider referral for integrative therapies (ie, mindfulness meditation, imagery/hypnosis, yoga)
  - Consider referral for couples, family, caregiver, or relationship counseling/support

- **For moderate to severe intensity major depression, generalized anxiety, panic, or PTSD symptoms:**
  - Refer for evaluation and treatment by a mental health professional[h]
  - Consider pharmacologic and/or nonpharmacologic treatments

- **For substance used disorder:[p]**
  - Safety evaluation (SANXDE-A)
  - See DIS-21 from the NCCN Guidelines for Distress Management
  - Refer to substance use disorder specialist

- Reevaluate symptoms and function at next visit
- Revise referrals and interventions if symptoms are persistent or increased

Consider pharmacologic interventions (See SANXDE-9)

[h]Psychiatrist, psychologist, advanced practice clinician, and/or social worker.
[p]For additional resources, See SURV-B 4 of 4.

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ANXIETY, DEPRESSION, TRAUMA, AND DISTRESS: MANAGEMENT AND TREATMENT

PHARMACOLOGIC INTERVENTIONS[q]

- Consider referral to mental health professional[r]
- First-line treatment: (See SANXDE-C and SANXDE-E)
  - Selective serotonin reuptake inhibitors (SSRIs)
    - ◊ Consider for concomitant hot flashes
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs):
    - ◊ Consider for concomitant pain or neuropathic pain
    - ◊ Consider for concomitant hot flashes
  - Inform survivor of potential side effects
  - Counsel survivor that it may take up to 2 to 6 weeks at a therapeutic dose for SSRIs and SNRIs to take effect
  - Benzodiazepines (ie, clonazepam, lorazepam):
    - ◊ For acute anxiety relief or while waiting for antidepressant to take effect
    - ◊ Adjust dose once SSRIs or SNRIs are fully effective and symptoms are partially or completely abated
  - Counsel survivor that symptoms of withdrawal may occur should any of the above-mentioned medications be abruptly discontinued
    - ◊ Withdrawal symptoms may include restlessness, akathisia, GI upset, dizziness, tingling, sleep disruption
    - ◊ More common with venlafaxine, paroxetine
    - ◊ Withdrawal effects can be avoided with slow taper
    - ◊ Withdrawal effects may be life-threatening and may require a mental health specialist
- Medications not recommended as first-line treatments: tricyclics, tetracyclics, serotonin modulators, monoamine oxidase inhibitors

→

- Follow up with survivor by phone or visit about medication effects and mood in 2–4 weeks
- Reevaluate distress and function at next visit, within 4–8 weeks
- Monitor for increased suicidal thoughts or plans and other side effects
- Increase dose if within therapeutic dosing range and distress remains elevated and side effects are manageable
- Consider drug switch if there are adverse effects or side effects that impact adherence
- Refer to a prescribing mental health professional for diagnostic evaluation if distress is persistent, increased, or other mood change, or medication management is not stable and effective in 8–12 weeks

[q] See Principles of Pharmacologic Interventions (SANXDE-C).
[r] Psychiatrist, psychologist, advanced practice clinician.

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SAFETY EVALUATION[a]

DANGER TO SELF OR OTHERS OR INABILITY TO CARE FOR SELF

Consider at elevated risk if survivor:

Has an organized plan for suicide or homicide

OR

Has suicidal or homicidal thoughts and, based on clinical judgment, the survivor is at imminent risk of harm to self or others

- **Consider the following risk factors:**
  - **Psychosocial risk factors**
    - ◊ **Previous attempts at suicide or self-injury (eg, cutting or burning)**
    - ◊ **Personality disorder or bipolar disorder with impulsivity, irritation, agitation, or aggression**
    - ◊ **New trauma or change in major stress or trauma**
    - ◊ **Family history or other exposure to suicide**
    - ◊ **Isolation**
    - ◊ **Recent loss of important person or relationship breakdown**
    - ◊ **Depression**
    - ◊ **Loss of rational thinking**
    - ◊ **Fear of death or dying due to pain and suffering**
    - ◊ **Feeling hopeless or loss of control**
    - ◊ **Perceives self as a burden**
    - ◊ **Access to firearms/weapons**
    - ◊ **Financial instability**
    - ◊ **Alcohol or other substance use disorder**
  - **Demographic risk factors**
    - ◊ **Male**
    - ◊ **Age (especially young adults and older adults)**
    - ◊ **No spouse or live-in partner**
  - **Medical risk factors**
    - ◊ **Chronic illness/pain or recent change in health status**
    - ◊ **Non-adherence to treatment or difficulty making treatment decisions**
    - ◊ **Sleep disorder (See SSD-1)**
    - ◊ **Poor physical and emotional function, including disability**
    - ◊ **Access to potentially lethal medications (opioids, benzodiazepines, antidepressants)**
    - ◊ **Substance use disorder**

→

CONSIDER PROTECTIVE FACTORS TO BALANCE WITH RISKS:

- **Psychosocial protective factors**
  - **Personal resources that increase resilience, environmental support, or coping**
  - **Strong interpersonal bonds to family/ community**
  - **Reasonably safe and stable environment**
  - **Help seeking**
  - **Good impulse control and coping/problem-solving skills**
  - **Sense of belonging, sense of identity, and good self-esteem**
  - **Cultural, spiritual, and religious beliefs about the meaning and value of life**
  - **Identification of future goals**
  - **Identifies reasons for living**
  - **Responsibility to/bonds with family, pets or others; living with family**
  - **Supportive social network or family**
  - **Belief that suicide is immoral; high spirituality**
  - **Engaged in work or school**
  - **Engaged in enjoyable activities**
  - **Access to health care with support of ongoing medical and mental health relationships**
- **Demographic protective factors**
  - **Married, child-rearing responsibilities**
  - **Employed**

→ **Determine risk level (See SANXDE-A 2 of 3)**

[a]For further information on screening and responding to suicide risk, see https://www.healthquality.va.gov/guidelines/MH/srb/VASuicidePreventionPocketGuidePRINT508FINAL.pdf or SAFE-T Card: https://adaa.org/sites/default/files/SMA09-4432.pdf

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ACUTE (URGENT/EMERGENT) INTERVENTIONS

Lower risk based on:
- Suicidal ideation with no plan, no thoughts of danger to others
- Clinical judgment based on assessment of risk factors and protective factors

→

Develop safety plan with survivor and family
- Immediate referral for mental health evaluation based on urgency
- Regular follow-up and monitoring until psychiatric care is in place
- Address underlying conditions and risk factors
- Have survivor agree to contact a health care provider, call 911, or go to the nearest emergency room if suicidal thoughts increase or change
- Provide contact information for local crisis hotlines or counselors.

(See SURV-B)

Elevated risk of danger to self or others based on:
- Suicidal or homicidal thoughts with plan and/or with multiple other risk factors or
- Clinical judgment based on assessment of risk factors and protective factors
- Inability to care for self

→

Emergency intervention:
- Evaluate availability of firearms, weapons, medications, and other potentially lethal methods of suicide and arrange to have them secured
- If offsite and threat is to others or patient is agitated or threatening:
  - Call 911
    and/or identify caregiver who is with patient to take to emergency room or call 911 or follow state mental health emergency plan
- If onsite and patient becomes agitated or threatening:
  - Involve other staff/security, keep door open, call 911, and maintain direct observation of patient
  - Refer to emergency psychiatric evaluation procedures onsite
  - Identify and follow any state reporting or other requirements

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SAFETY EVALUATION	ACUTE (URGENT/EMERGENT) INTERVENTIONS
DANGER FOR ABUSE OR NEGLECT OF VULNERABLE PERSON (CHILD, ELDERLY, PERSON UNABLE TO CARE FOR SELF): • Self-report or observation of risk for or actual physical, sexual, health care, or financial abuse	→ Determine acuity, involve social work or emergency services, and follow mandatory reporting requirements • Refer to urgent social work or emergency room for full evaluation of risks and options • Follow state laws for reporting abuse
SUBSTANCE USE DISORDER • Self-report, caregiver/family report, or observation of misuse of medications or of altered mental status potentially related to drug or alcohol use	→ See Substance-Related and Addictive Disorders (DIS-21) section in the NCCN Guidelines for Distress Management

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RISK FACTORS FOR PTSD

- **Physical**
  - **Recurrence of cancer**
  - **Intensive treatment (eg, bone marrow/stem cell transplant, intensive care unit stay)**
  - **Unrelieved chronic pain or physical dysfunction**
  - **Advanced disease**
  - **Younger age**
- **Psychosocial**
  - **Exposure to previous trauma (eg, combat, sexual assault, major loss)**
  - **History of mental health issues prior to cancer**
  - **Poor coping skills (eg, using avoidance)**
  - **Lower income and/or less education**
  - **Less social support**
- **Significant change in life stressors including health, interpersonal, financial, and occupational**

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PRINCIPLES OF PHARMACOLOGIC INTERVENTIONS

Special Pharmacologic Considerations for Concomitant Problems:

- Substance use
  - Minimize use of benzodiazepines
  - Alternatives for sedation and acute anxiety are low-dose atypical neuroleptics (ie, olanzapine, quetiapine) or gabapentin
- Pain syndromes (eg, neuropathy) (See SPAIN-1)
  - SNRIs
  - Tricyclic antidepressants (TCAs)
    - ◊ Amitriptyline has sedating properties that may or may not be desirable
    - ◊ Nortriptyline and desipramine have the fewest side effects
- Fatigue (See SFAT-1)
  - Consider less-sedating antidepressants such as bupropion
  - Consider bright light therapy[1]
  - Evidence for psychostimulant effects for depression and fatigue are limited and mixed (See SFAT-5)
- Insomnia
  - See Sleep Disorders (See SSD-1)

Caveats (Also see SANXDE-E):

- Review side effects with patient, noting that some may be beneficial (sedation, arousal, or weight gain and appetite stimulation)
- Monitor QT interval on EKG at initiation and dose increases with neuroleptics and citalopram
- Monitor for serotonin toxicity with use of any serotonergic agent
- Monitor for anticholinergic effects that can worsen cognition and other side effects (eg, dry mouth or other mucosa)
- Blood pressure should be monitored with venlafaxine and treated appropriately
- Recommend using non-CYP2D6– or non-CYP3A4–inhibiting options when possible.[a]
- Use psychotropics with cytochrome P450 interactions with caution in survivors taking tamoxifen or other medications metabolized through CYP2D6 or CYP3A4 pathways[a,b] (See SANXDE-E)
  - Fluoxetine[a,2,3]
  - Paroxetine[a,2,3]
  - Sertraline[a,2,3]
  - Bupropion
  - Fluvoxamine
  - Duloxetine
  - Clomipramine
- Refer to specialist if first-line treatment fails or if there are complicating factors such as chronic pain or substance use disorder

Footnotes

[a]Evidence generally does not support the clinical significance of the inhibitory activity of SSRIs, SNRIs, or other antidepressants on tamoxifen's or other CYP2D6- or CYP3A4-metabolized agent's anticancer effects in terms of increased recurrence or mortality rates. However, pharmacokinetic/pharmacogenetic studies do indicate reduced availability of endoxifen in lower CYP2D6 metabolizers taking tamoxifen.[2,3] SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6.

[b]Antidepressants that are strong CYP3A4 inhibitors or inducers may interact with some cancer prevention or maintenance drugs other than tamoxifen, such as tyrosine kinase inhibitors, monoclonal antibodies, or mTOR inhibitors.

References

[1]Johnson JA, et al. J Cancer Surviv 2018;12:206-215.
[2]Haque R, et al. J Natl Cancer Inst 2015;108:djv337.
[3]Wedret JJ, et al. Ment Illn 2019;11:8115.

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TRAUMA SCREENING[1,2,3]

In the past two weeks, have you…

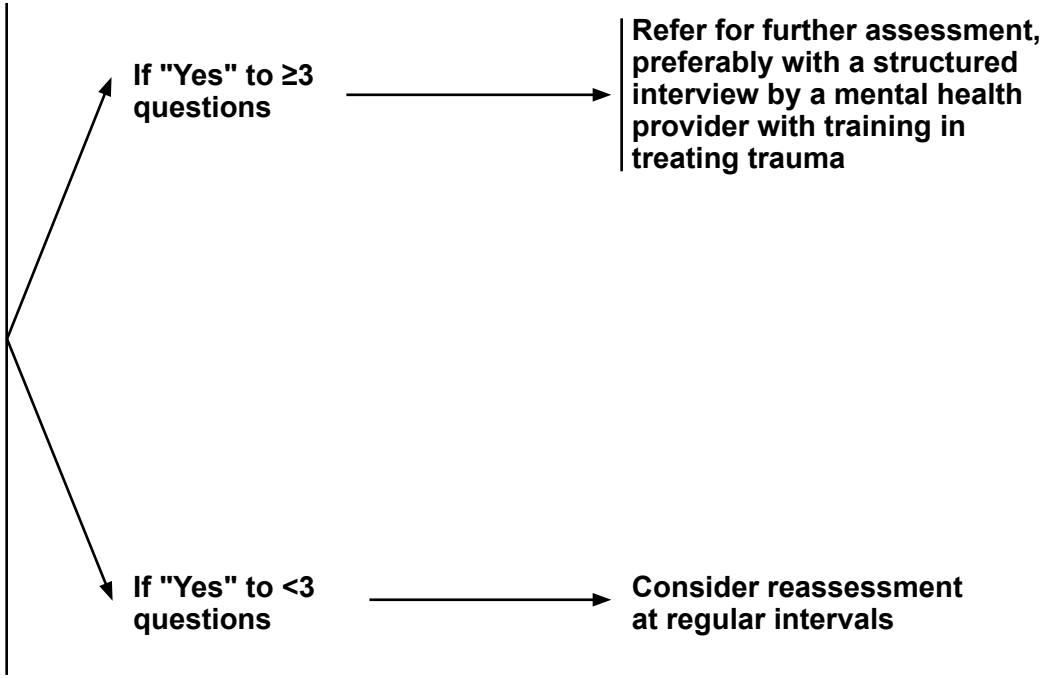
1. Had nightmares or thoughts about your cancer or treatment when you did not want to?
YES NO

2. Tried hard not to think about events related to your cancer or went out of your way to avoid situations that reminded you of those events?
YES NO

3. Been constantly on guard, watchful, or easily startled?
YES NO

4. Felt numb or detached from people, activities, or your surroundings?
YES NO

5. Felt guilty or unable to stop blaming yourself or others for events during your cancer treatment or any problems the event(s) may have caused?
YES NO



[1]Reproduced and adapted from Prins A, Bovin MJ, Kimerling R, et al. (2015). Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) [Measurement instrument]. Available at https://www.ptsd.va.gov.
[2]The PC-PTSD-5 is designed to identify individuals with probable PTSD. Available at https://www.ptsd.va.gov/professional/assessment/documents/pc-ptsd5-screen.pdf
[3]Prins A, et al. J Gen Intern Med 2016;31:1206-1211.

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First-Line Antidepressants for Depression or Anxiety in Adults[a,b]

Drug	Usual Starting Dose PER DAY TOTAL (mg)[b]	Extreme Dose Range PER DAY TOTAL (mg)	Severity of Side Effects[†] Scale: 0 = none; 1 = slight; 2 = low; 3 = moderate; 4 = high								CYP450 Interaction Modulator Potential[d]	Notes
			Antichol	Drowsiness	Insomnia/ agit	↓ BP	QTc	GI	↑ Weight	Sexual		
Selective serotonin reuptake inhibitors												
Citalopram	20	10–40[e]	0	0	1	1	1	1	1	3	CYP2D6 mild	Caution with imatinib. May prolong QTc at higher doses
Escitalopram	10	5–30	0	0	1	1	1	1	1	3	CYP2D6 mild	May prolong QTc at higher doses
Fluoxetine	20	10–80	0	0	2	1	1	1	0	3	CYP2D6 strong; CYP3A4 moderate	Caution with tamoxifen, imatinib; long half-life
Paroxetine	20	10–50	1	1	1	2	0–1	1	2	4	CYP2D6 strong	Caution with tamoxifen, tyrosine kinase inhibitors, and monoclonal antibodies (eg, imatinib)
Paroxetine CR	25	12.5–62.5	1	1	1	2	0–1	1	2	4	CYP2D6 strong	
Sertraline	50	25–300	0	0	2	1	0–1	2	1	3	CYP2D6 moderate; CYP3A4 moderate	Inhibits CYP2D6 only at high doses
Serotonin-norepinephrine reuptake inhibitor												
Desvenlafaxine[f,g]	50	50–400	0	0	1	0	0	2	0	1	CYP2D6 mild	
Duloxetine	30 to 60	30–120	0	0	1	0	0	2	0–1	1	CYP2D6 moderate	May improve neuropathic pain
Venlafaxine[g]	37.5–75	75–375	0	1	1	0	1	2	0	3	CYP2D6 mild	DOSING IS TWICE A DAY (**except** XR formulation) Withdrawal can occur more readily with short-acting preparation
Venlafaxine XR[g]	37.5	75–375	0	1	1	0	1	2	0–1	3	CYP2D6 mild	
Atypical agents												
Bupropion	200	100–450	0	0	2	0	1	1	0	0	CYP2D6 strong	DOSING IS TWICE A DAY (**except** XL 24 formulation) Caution with sorafenib, tamoxifen. Can be helpful for energizing; contraindicated if seizure history or bulimia; used for smoking-cessation
Bupropion SR 12 hr or XL 24 hr	150	150–400	0	0	1	0	1	1	0	0	CYP2D6 strong	
Mirtazapine	15	7.5–60	1	4	0	0	1	0	4	1	CYP2D6 mild	Safe with tamoxifen; may improve nausea, hot flashes, appetite, insomnia

[†]Antichol, anticholinergic; Insomnia/agit, insomnia/agitation; ↓ BP, orthostatic hypotension; QTc, QTc prolongation; GI, gastrointestinal; ↑ weight, weight gain; sexual, sexual dysfunction.
Note: All SSRIs and SNRIs are associated with transient nausea and gastrointestinal discomfort upon initiation or dose increase.

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Continued

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FOOTNOTES FOR FIRST-LINE ANTIDEPRESSANTS FOR DEPRESSION OR ANXIETY IN ADULTS

[a]Information extracted from:

- Simon G, Rush AJ. Unipolar major depression in adults: Choosing initial treatment. UpToDate, accessed 11/30/2020, https://www.uptodate.com/contents/unipolar-major-depression-in-adults-choosing-initial-treatment?search=antidepressants&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2.
- Caraci F, Crupi R, Drago F, Spina E. Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metab 2011;12:570-577.
- Mehta RD, Roth AJ. Psychiatric considerations in the oncology setting. CA Cancer J Clin 2015;65:300-314.
- Miguel C, Albuquerque E. Drug interaction in psycho-oncology: antidepressants and antineoplastics. Pharmacology 2011;88:333-339.
- Wedret JJ, Tu TG, Paul D, et al. Interactions between antidepressants, sleep aids and selected breast cancer therapy. Ment Illn 2019;11:8115.

[b]These recommendations do not apply to bipolar depression.

[c]Starting doses for elderly, those with renal or hepatic compromise, drug-sensitive survivors, or those with low body mass index may be half the usual starting dose.

[d]Hypericum extract (ie, St. John's wort) can reduce the plasma concentrations of tyrosine kinase inhibitors and monoclonal antibodies by inducing both CYP3A4 and P-glycoprotein (P-gp).

[e]Citalopram: maximum dose of 20 mg is recommended for those aged >60 years or those with hepatic insufficiency or if taking drugs with CYP3A4 metabolism or other interacting medications that can increase levels.

[f]Desvenlafaxine: no evidence that doses >50 mg per day provide any additional benefit.

[g]Desvenlafaxine and venlafaxine may cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.

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COGNITIVE FUNCTION FOLLOWING CANCER TREATMENT

General Principles

- **Growing evidence supports the validity of the patient-reported experience of cognitive dysfunction associated with cancer diagnosis and treatments.**
- **Neuropsychological testing and brain imaging have demonstrated abnormalities in patients diagnosed with and treated for cancer.**
- **Currently no effective brief screening tool for cancer-associated cognitive dysfunction has been identified. Existing diagnostic tools do not strongly correlate with patient reports of cognitive dysfunction. The Mini-Mental State Examination (MMSE®)[a] and similar screening tools lack adequate sensitivity for the more subtle decline in cognitive performance most commonly seen in cancer survivors.**
- **There is limited evidence to guide management of this condition.**
- **Patients benefit from validation of their symptom experience, a thorough evaluation of this concern and related issues, and education.**
- **Imaging studies may not be helpful, except to rule out structural abnormalities as indicated by high-risk illness, or focal neurologic deficits or comorbidities.**
- **Patients who report cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment (ie, depression, sleep disturbance, fatigue).**
- **These guidelines address cognitive function of survivors with non-CNS malignancies who did not have CNS-directed therapies.**

The 2021 update for this algorithm is in progress.

[a]Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

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COGNITIVE FUNCTION ASSESSMENT

Focused history:
- Focal neurologic deficits
- High risk or known metastatic disease/brain primary
- Onset, temporality
- Age (a risk factor for developing cognitive deficiency)
- Trajectory over time
- Cancer treatment history
- Prescription medications/OTC medications and supplements
- Education attainment
- Caregiver assessment of cognitive function
- Nature of impairments per patient; clarifying questions may include:
  - Do you have difficulty paying attention? Multitasking?
  - Do you frequently leave tasks incomplete?
  - Do you have difficulty finding words?
  - Do you have difficulty remembering things?
  - Do you need to use more prompts like notes or reminders than you used to?
  - Does it take you longer to think through problems; does your thinking seem slower?
  - Do you notice an impact on functional performance? Job performance?
- Assessment of medical history that may impact cognitive function

Assessment of contributing factors:
- Medications/side effects
- Emotional distress
  - Depression/anxiety (See SANXDE-1 and NCCN Guidelines for Distress Management)
- Symptom burden
  - Pain (See SPAIN-1)
  - Fatigue (See SFAT-1)
  - Sleep disturbance (See SSD-1)
- Comorbidities
- Use of alcohol and other agents that alter cognition
- New-onset vitamin deficiencies and endocrinopathies (eg, TSH, B_{12})

SPECIALIZED EVALUATION

Neuroimaging

See Cancer-Associated Cognitive Dysfunction Interventions (SCF-3)

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CANCER-ASSOCIATED COGNITIVE DYSFUNCTION INTERVENTIONS

Patient/Family Education and Counseling
- Validation of experience of cognitive dysfunction associated with cancer diagnosis and treatment
- Reassurance that cancer-associated cognitive dysfunction is often not a progressive neurologic disorder like progressive dementias[b]
- Support self-management and coping strategies

→

General Strategies for Management of Cancer-Associated Cognitive Dysfunction
- Teach enhanced organizational strategies (ie, using memory aids like notebooks and planners, keeping items in the same place, using reminder notes, smart phone technology)
- Encourage patients to do the most cognitively demanding tasks at the time of day when energy levels are highest
- Provide information about relaxation or stress management skills for daily use
- Recommend routine physical activity (See HL-1)
- Recommend limiting use of alcohol and other agents that alter cognition and sleep
- Consider meditation, yoga, mindfulness-based stress reduction, and cognitive training (ie, brain games)
- For older adults also see the cognitive function section of the NCCN Guidelines for Older Adult Oncology (OAO-F)
- Optimize management of:
  - Depression or emotional distress (See appropriate survivorship guidelines or NCCN Guidelines for Distress Management)
  - Sleep disturbance (See SSD-1)
  - Fatigue (See SFAT-1)
  - Contributing symptoms such as pain (See SPAIN-1)
  - Medical comorbidities

→ See Specific Interventions (SCF-4)

[b]Cognitive dysfunction may be progressive in survivors of CNS cancers or those who had CNS-directed therapies.

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CANCER-ASSOCIATED COGNITIVE DYSFUNCTION SPECIFIC INTERVENTIONS

FIRST-LINE INTERVENTIONS

- **Neuropsychological evaluation and recommendations**[c]
- **Cognitive rehabilitation**
  - **Occupational therapy**[d]
  - **Speech therapy**
  - **Neuropsychologist**
- **Psychotherapy**
- **Recommend routine physical activity** (See HL-1)

SECOND-LINE INTERVENTIONS

→ **Consider trial use of medications (methylphenidate, modafinil, or donepezil)**[e]

The 2021 update for this algorithm is in progress.

[c]Neuropsychological evaluation and intervention may be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.
[d]Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for an individual who notes the impact of specific functional limitations (ie, word finding, comprehension or task completion, quality-of-life or role expectations).
[e]Overall the evidence for these medications is lacking, but there may be some benefit in select survivors or certain clinical scenarios.

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DEFINITION OF CANCER-RELATED FATIGUE

- **Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. (See the NCCN Guidelines for Cancer-Related Fatigue.)**

CONSIDERATIONS FOR FATIGUE IN CANCER SURVIVORS

- **Fatigue is a common complaint in individuals undergoing cancer therapy and can be a persistent problem for some cancer survivors in the months and years after cancer diagnosis.**
  - **Receipt of chemotherapy, radiation, endocrine, targeted, and/or cellular therapies are predisposing factors for cancer-related fatigue, but it can be seen in some patients who are treated with surgery alone.**
  - **The time-course of fatigue is unique to the survivor and his or her treatment plan. However, many cancer survivors report that fatigue may be a disruptive symptom months or years after treatment ends.**
  - **Fatigue that initially presents months after the completion of adjuvant therapy or fatigue that worsens over this period warrants additional evaluation.**
- **Fatigue is a subjective experience that should be systematically assessed using patient self-reports and other sources of data for cancer survivors in the months and years after diagnosis.**
- **Patients and family/caregiver(s) should be informed that management of fatigue is an integral part of total health care and that fatigue can persist following treatment.**
- **Medical care contracts should include reimbursement for the management of fatigue.**
- **Disability insurance should include coverage for the continuing effects of fatigue.**
- **Referral to rehabilitation services including physical therapy, occupational therapy and physical medicine should be considered for survivors with fatigue in the months and years after cancer diagnosis.**
- **Also see the NCCN Guidelines for Cancer-Related Fatigue.**

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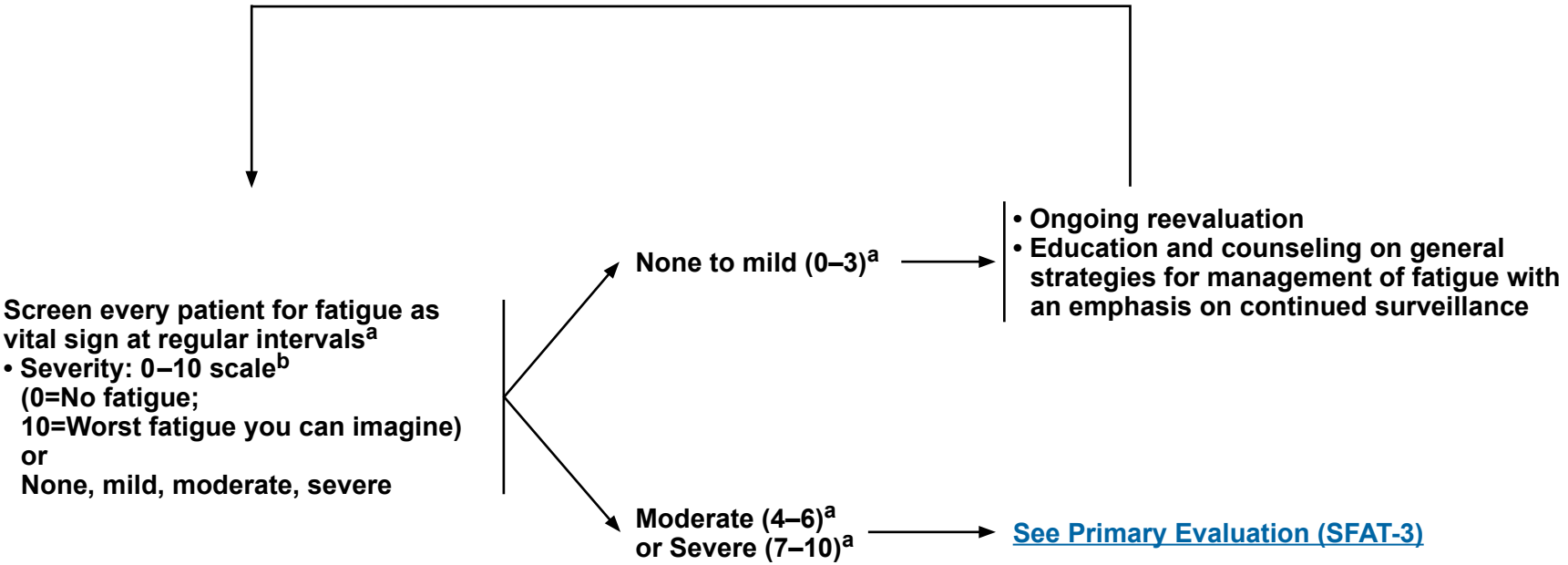
SCREENING



[a]Recommended screen and re-evaluation: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?"
[b]Butt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. J Pain Symptom Manage 2008;35:20-30.

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PRIMARY EVALUATION FATIGUE SCORE: MODERATE OR SEVERE (4–10)

H&P:

- Focused fatigue history
  - Onset, pattern, duration
  - Change over time
  - Associated or alleviating factors
  - Interference with function
- Evaluate disease status
  - Evaluate risk of recurrence based on stage, pathologic factors, and treatment history
  - Perform review of systems to determine if other symptoms substantiate suspicion for recurrence
- Assessment of treatable contributing factors:
  - Comorbidities
    - ◊ Alcohol/substance abuse
    - ◊ Organ dysfunction[c]
    - ◊ Infection
    - ◊ Anemia
    - ◊ Arthritis
  - Prescribed or OTC medications (eg, sleep aids, pain medications, antiemetics)
  - Emotional distress- screen for anxiety and depression (See SANXDE-1)
  - Sleep disturbance (eg, insomnia, sleep apnea, vasomotor symptoms, restless legs syndrome [RLS]) (See SSD-1)
  - Pain (See SPAIN-1)
  - Nutritional issues
    - ◊ Weight/caloric intake changes (See SNWM-1)
  - Deconditioning/loss of muscle mass
  - Physical inactivity or sedentary behavior

EVALUATION

Laboratory Evaluation:

- Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of fatigue
  - CBC with differential
    - ◊ Compare end-of-treatment hemoglobin/hematocrit with current values
    - ◊ Assess other cell lines (WBC and platelets)
  - Comprehensive metabolic panel
    - ◊ Assess electrolytes
    - ◊ Assess hepatic and renal function
  - Endocrine evaluation
    - ◊ TSH, especially in patients who have received prior head/neck, torso, or breast radiation
    - ◊ Consider more comprehensive evaluation or referral to specialist if other symptoms present
    - ◊ Cortisol stimulation test, if history of prolonged steroid use

Other Diagnostic Testing:

- Consider radiologic assessment only if high risk of disease recurrence OR if accompanying signs and symptoms suggest presence of metastatic disease
- Consider cardiac testing (ECHO) for patients treated with an anthracycline (See SCARDIO-1), trastuzumab, bevacizumab, other VEGF- or HER2-targeted therapy, or other therapy known to cause cardiac dysfunction
- Chest x-ray and oxygen saturation testing for pulmonary complaints[d]

→ See Treatment of Contributing Factors (SFAT-4)

[c]Cardiac, endocrine (eg, hypothyroidism, hypogonadism, adrenal insufficiency), gastrointestinal, pulmonary, renal, and/or hepatic dysfunction.
[d]Refer to a pulmonologist for pulmonary complaints.

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TREATMENT OF CONTRIBUTING FACTORS

- **Treat contributing factors:**
  - **Medications/side effects**
  - **Pain** (See SPAIN-1)
  - **Emotional distress** (See SANXDE-1) **and** NCCN Guidelines for Distress Management
  - **Anemia**
    - ◊ **Treat iron, B_{12}, folate deficiency, if present**
    - ◊ **Consider referral/further evaluation for anemia or cytopenias**
  - **Sleep disturbance** (See SSD-1)
  - **Nutritional deficit/imbalance**
  - **Comorbidities**

→ See Interventions for Cancer Survivors (SFAT-5)

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INTERVENTIONS FOR CANCER SURVIVORS

Patient/Family Education and Counseling

Provide information about patterns of fatigue during and after treatment
- Self-monitoring of fatigue levels
- Energy prioritization
  - Set priorities
  - Plan and pace activities
  - Schedule activities at times of peak energy

→

Physical Activity

- Maintain adequate levels of physical activity (category 1) (See SPA-1 and SPA-4)
- Survivors at higher risk of injury (eg, those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy or other comorbidities) should be referred to a physical therapist or exercise specialist
- Make use of local resources to help patients increase exercise (eg, aerobics, strength training, yoga)
  - Community exercise programs or classes, preferably those focused on cancer survivors
  - Exercise professional certified by the American College of Sports Medicine
  - For patients with fatigue interfering with function, consider referral to a physical therapist or physiatrist

→

Other Interventions[e]

- Psychosocial interventions (category 1)
  - CBT[f]/Behavioral therapy (category 1)
  - Mindfulness-based stress reduction (category 1)
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies (category 1)[g]
- Nutrition consultation
- CBT[f] for insomnia (category 1) (See SSD-1)
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene
- Acupuncture
- Bright white light therapy[h]
- Massage therapy (category 1)

→

Pharmacologic[i]

Consider psychostimulants[j] (methylphenidate[k]) after ruling out other causes of fatigue and failure of other interventions

[e]Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.
[f]A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment.
[g]Supportive expressive therapies (such as support groups, counseling, and journal writing) facilitate expression of emotion and foster support from one or more people.
[h]Bright white light therapy of 10,000 lux is most frequently self-administered in the early morning for 30-90 minutes. Timing needs to be adjusted for those who sleep during the day. Johnson J, et al. J CA Survivorship 2018, 12(2):206-215.
[i]Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients.
[j]Psychostimulants are at times used to treat cancer-related fatigue. A number of studies have evaluated their efficacy in the setting of active treatment and results have been mixed. There are extremely limited data regarding the use of these agents in the post-treatment setting.
[k]Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in patients with cancer.

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DEFINITION AND STAGES OF LYMPHEDEMA[a,b]

- **Definition: Lymphedema occurs when lymph fluid accumulates in the interstitial tissue, causing swelling of the limb or other areas such as the neck, trunk, or genitals. It is a common side effect of cancer treatment, occurring on the same side of the body as the cancer treatment, as a result of dysfunction of the lymphatic system.**
- **Stage 0 (latent/subclinical): Lymphatic dysfunction without swelling; subtle symptoms, such as a feeling of heaviness or fatigue in the limb, may be present.**
- **Stage 1 (spontaneously reversible): Accumulation of fluid and protein causing swelling; pitting edema may be evident; increased girth, heaviness, and/or stiffness of affected area. For the limbs, swelling is relieved with elevation.**
- **Stage 2 (irreversible): Spongy tissue consistency, with pitting edema that becomes less evident as swelling increases; tissue fibrosis causing hardness and increase in size. For the limbs, swelling is not relieved with elevation.**
- **Stage 3 (lymphostatic elephantiasis): Severe dry, scaly, thickened skin; increased swelling and girth of affected area; can be debilitating. In the limbs, fluid leakage and blisters are common.**

The 2021 update for this algorithm is in progress.

[a]National Cancer Institute Lymphedema (PDQ®)–Health Professional Version. https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq.

[b]International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology 2013;46:1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23930436.

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PRINCIPLES OF LYMPHEDEMA

- **Lymphedema is a potential side effect after the treatment of cancer resulting from damage to the lymphatic system. Lymphedema is most often diagnosed within 18 months of treatment; however, it can develop anytime in the life of the survivor. Depending on stage of diagnosis, lymphedema can be an acute or chronic condition.**
- **Swelling on the same side as the cancer treatment is a universal symptom of lymphedema. Additional initial symptoms may include sensation of heaviness, fatigue, fullness or tightness in the skin, or pain. Symptoms including decreased range of motion or strength and thickening of the skin may occur in later stages.[a]**
- **Survivors who had surgery or radiation to the axillary, supraclavicular, cervical, or inguinal lymph node system are at risk for the development of lymphedema. Sentinel node biopsy also increases the risk of lymphedema, although it poses less risk than complete dissection or radiation to the nodal group.**
- **Obesity (BMI >30 kg/m^2), localized infection, increased number of nodes removed, and higher initial extent of disease raise the risk of lymphedema development.**
- **Pretreatment limb measurement of both sides should be performed as a baseline for survivors with treatment-related or individual risk factors, preferably by a trained lymphedema specialist.**
- **Early detection/diagnosis is key for optimal lymphedema management because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment. Therefore, survivors should be told to inform their medical provider if subtle swelling or any other symptoms (eg, fullness, tightness, heaviness, pain) on the treated side are noted.**
- **Lymphedema may cause or exacerbate psychological distress (See SANXDE-1).**
- **Survivors at risk for lymphedema and those with lymphedema are at a higher risk of localized infection in the affected area. These infections can require hospitalization for IV antibiotics. Therefore, survivors with or at risk for lymphedema should be educated to inform their medical provider immediately for signs of infection in the affected area.**
- **Progressive weight training under supervision and physical activity are not associated with exacerbation or development of lymphedema.[c,d,e]**
- **Observational studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[f,g] In the absence of high-level data, however, the panel recommends that medical procedures such as venipuncture and blood pressure measurements be done on the non–at-risk arm/limb if possible.[h] If necessary, procedures may be done using the at-risk arm/limb. More research is needed to determine the effect of these procedures on the risk of lymphedema.**

[a]National Cancer Institute Lymphedema (PDQ®)–Health Professional Version https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq.
[c]Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426.
[d]Irwin M, ed. ACSM's Guide to Exercise and Cancer Survivorship. Champaign, IL: The American College of Sports Medicine; 2012.
[e]National Lymphedema Network. Position Paper: Exercise 2013. https://issuu.com/lymphnet/docs/exercise.
[f]Asdourian MS, Skolny MN, Brunelle C, et al. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. Lancet Oncol 2016;17:e392-405.
[g]Ahn S, Port ER. Lymphedema precautions: Time to abandon old practices? J Clin Oncol 2016;34:655-658.
[h]National Lymphedema Network. Position Paper: Lymphedema Risk Reduction Practices 2012 https://issuu.com/lymphnet/docs/risk_reduction.

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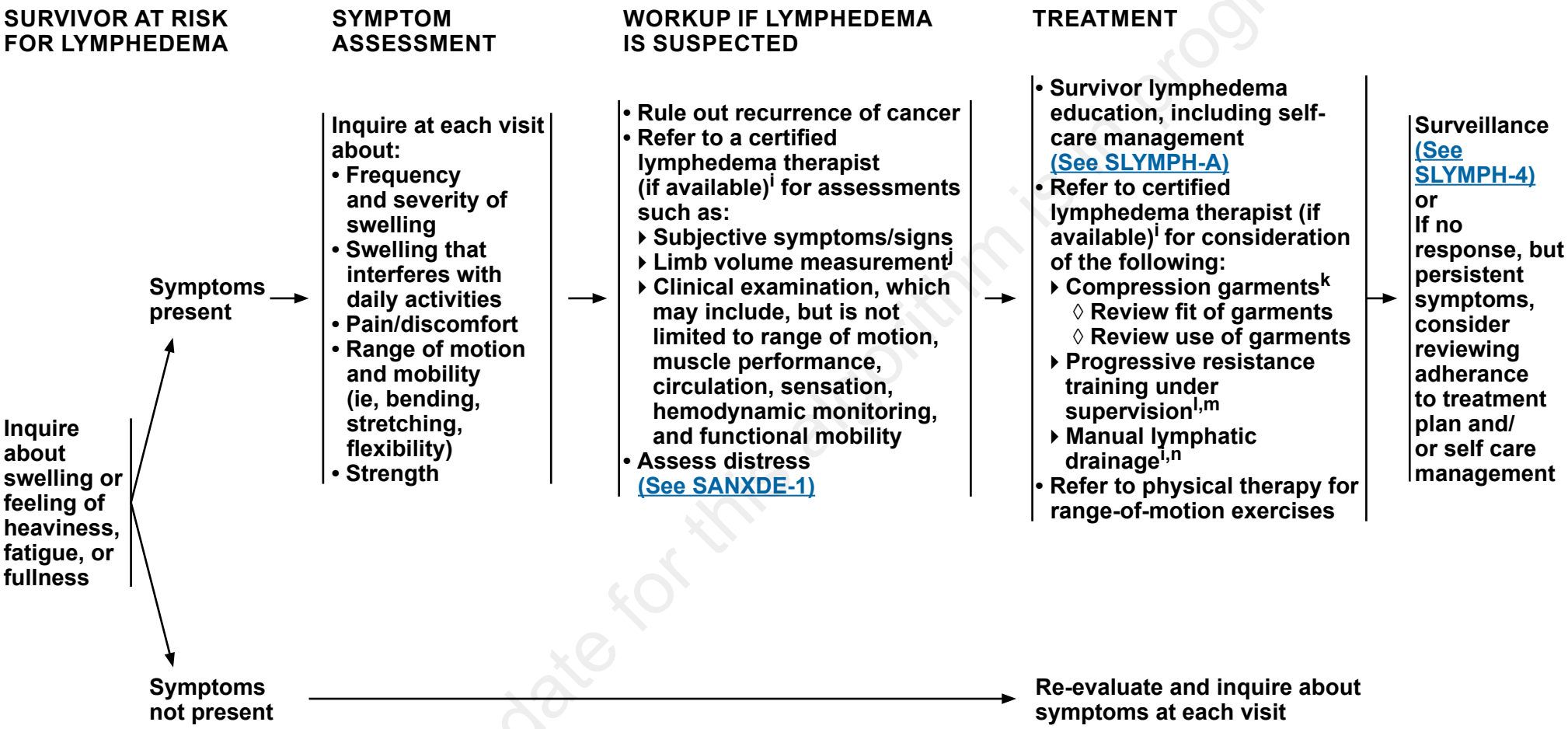

[i]Certified lymphedema therapists can be located using the following resource: https://www.clt-lana.org/search/therapists/.
[j]If baseline measurement is not available, measure unaffected contralateral limb as a reference.
[k]Compression garments should be prescribed. Optimally, they should be fitted and measured by a certified lymphedema therapist.
[l]If a certified therapist is not available, survivors with lymphedema can perform resistance training with a professional trainer who has knowledge of cancer-related physical activity principles. Weights should be slowly progressed as tolerated, and lymphedema should be evaluated periodically.
[m]See Principles of Physical Activity for Survivors with or At Risk for Lymphedema (SLYMPH-B).
[n]If a certified lymphedema therapist is not available, consider referral to appropriate provider for treatment.

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SURVEILLANCE

Follow-up with treatment team as clinically indicated

- **Inquire about fit and age of compression garments**
- **Replace compression garments as clinically indicated**
- **Check range of motion**
- **Inquire about performance of prescribed exercises**
- **Inquire about self-care management**
- **Continue survivor lymphedema education (See SLYMPH-A)**
- **Continue treatment as clinically indicated (See SLYMPH-3)**
- **Assess for distress (See SANXDE-1)**

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SURVIVOR LYMPHEDEMA EDUCATION

- **Survivors should be educated regarding:**
  - **Signs and symptoms of lymphedema and the importance of rapid reporting to the treatment team.**
  - **Signs and symptoms of infection (eg, redness, pain, skin streaking/warm to touch) in the affected area and the importance of rapid reporting to the treatment team.**
  - **Self-care management: Infection prevention measures,[a] risk reduction strategies,[b] maintenance of skin integrity on the affected side**
- **Survivors should also be informed that:**
  - **Progressive weight training under supervision and physical activity are not associated with exacerbation or development of lymphedema.[1,2,3] (See SLYMPH-B)**
    - ◊ **Progressive resistance training under supervision may improve lymphedema symptoms. However, caution is advised in this population, and survivors with or at risk for lymphedema should discuss physical activity plans with a lymphedema specialist before starting a program that involves strength or resistance training. (See SLYMPH-B)**
    - ◊ **Water exercise under supervision may be an option to consider after assessing any skin integrity and/or incision issues.[4]**
  - **Studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[5,6] However, medical procedures such as venipuncture and blood pressure measurements should be done on the non–at-risk arm/limb if possible.[7] If necessary, procedures may be done using the at-risk arm/limb.**

Footnotes

[a]Risk of infections can be reduced by safe pet care and gardening techniques (See SIMIN-2).

[b]For a complete list of lymphedema risk reduction practices, see the Position Statement from the National Lymphedema Network: https://issuu.com/lymphnet/docs/risk_reduction.

References

[1]Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426.

[2]Irwin M, ed. ACSM's Guide to Exercise and Cancer Survivorship. Champaign, IL: The American College of Sports Medicine; 2012.

[3]National Lymphedema Network. Position Paper: Exercise 2013. https://issuu.com/lymphnet/docs/exercise.

[4]Lindquist H, Enblom A. Water exercise compared to land exercise or standard care in female cancer survivors with secondary lymphedema. Lymphology 2015;48:64-79.

[5]Asdourian MS, Skolny MN, Brunelle C, et al. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. Lancet Oncol 2016;17:e392-405.

[6]Ahn S, Port ER. Lymphedema precautions: Time to abandon old practices? J Clin Oncol 2016;34:655-658.

[7]National Lymphedema Network. Position Paper: Lymphedema Risk Reduction Practices 2012 https://issuu.com/lymphnet/docs/risk_reduction.

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PRINCIPLES OF PHYSICAL ACTIVITY FOR SURVIVORS WITH OR AT RISK FOR LYMPHEDEMA

- **Lymphedema is not a contraindication for physical activity, and no special precautions are required if participating in cardiovascular/aerobic exercise or strength training of unaffected limbs.**
- **Continued full use of the extremity and range-of-motion exercises are encouraged to maintain strength and range of motion even in the presence of lymphedema.**
- **Progressive strength training:**
  - **Gradually increase resistance by smallest increment possible with monitoring.**
  - **Consider referral to lymphedema specialist for evaluation prior to starting a physical activity program that involves the affected or at-risk limb.**
  - **Compression garments may be required during training sessions.**
  - **When possible, survivors should work with trained exercise professionals[1] and initiate exercises involving affected body part only if lymphedema specialist or other appropriate health care provider determines that lymphedema is stable. Factors that may be considered include:**
    - ◊ **No need for lymphedema therapy within past 3 months**
    - ◊ **No recent limb infections requiring antibiotics**
    - ◊ **No change in limb circumference >10%**
    - ◊ **No change in ability to perform activities of daily living**
- **Survivors should undergo baseline and periodic evaluation for development or exacerbation of lymphedema.**
- **Survivors should stop exercise and see a lymphedema specialist if exacerbation of lymphedema occurs.**

[1]Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://www.acsm.org/get-stay-certified] or American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

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PRINCIPLES OF MENOPAUSE SYMPTOM MANAGEMENT IN FEMALE SURVIVORS

Menopause

- Many survivors may experience symptoms whether or not they have ovarian function.
- In female survivors with prior chemotherapy or pelvic radiation exposure or survivors on tamoxifen, serial estradiol levels may be useful to confirm current menopausal status.
- In non-cancer populations, primary ovarian insufficiency or early menopause may be associated with specific menopause-related health risks (see below). There are limited data in cancer survivors.
- Peri- or pre-menopausal survivors
  - For survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), and inhibin may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or those on tamoxifen, but alone are not reliable to ensure menopausal status.
  - Survivors who have become amenorrheic and are sexually active with a male partner should be counseled on the need for contraception to prevent unintended pregnancy if they do not meet the definition of menopause. Menopause is defined as no menses for one year in the absence of prior chemotherapy or tamoxifen use, or no menses after surgical removal of all ovarian tissue.

Menopausal Signs and Symptoms

- Vasomotor symptoms (ie, hot flashes/night sweats)
- Vaginal dryness
- Urogenital complaints
- Sexual dysfunction
- Sleep disturbance
- Mood disturbance and depression
- Cognitive dysfunction
- Arthralgias/myalgias
- Fatigue

Menopause-Related Health Risks

- Osteoporosis/bone fractures
- Cardiovascular disease
- Cognitive change
- Parkinson's disease

Treatment Options for Vasomotor Symptoms (See SMP-4)

- Non-hormonal options
  - Prescription alternatives (See SMP-A)
  - OTC options
  - Integrative therapies
  - Lifestyle modifications (See HL-1)
- Hormonal therapies (relatively contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk) (See SMP-B)
  - Combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus)
  - Tissue selective estrogen complexes (TSECs)[a]

[a]Novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen creating a TSEC.

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PRINCIPLES OF MANAGEMENT OF HORMONAL SYMPTOMS IN MALE SURVIVORS

- **Male survivors who have received radiation therapy, chemotherapy, or surgery for non-prostate malignancies may have hypogonadism and should be evaluated for biochemical evidence of hypogonadism (ie, testosterone free and total, LH, prolactin) and treated with testosterone for hormone-related symptoms.**
- **Male survivors of prostate cancer who have no evidence of recurrent disease may have symptoms of hypogonadism or have prior history of hypogonadism. These patients should be evaluated for biochemical evidence of hypogonadism. When to initiate treatment for low testosterone in prostate cancer survivors or resume treatments for men who had pre-existing hypogonadism is controversial and should be coordinated with the patient's primary cancer physician (ie, surgeon, oncologist, radiation oncologist).**
- **Androgen deprivation therapy (ADT) is the main therapeutic approach to metastatic prostate cancer, and may be used as adjuvant or neoadjuvant therapy in the treatment of prostate cancer.**
- **Male survivors who are receiving ADT may experience hormone-related symptoms and sexual dysfunction. These patients should not receive androgens (eg, testosterone).**
- **ADT-related symptoms and health risks:**
  - **Acute kidney injury**
  - **Anemia**
  - **Arthralgias/myalgias**
  - **Cardiovascular disease[b]**
    - ◊ **Prolongation of QT/QTc interval**
  - **Cognitive dysfunction**
  - **Decreased muscle (sarcopenia) and increased body fat**
  - **Decreased penile size**
  - **Mood disturbance and depression**
  - **Diabetes mellitus (new onset)**
    - ◊ **Reduced insulin sensitivity**
  - **Fatigue**
  - **Gynecomastia**
  - **Osteoporosis/bone fractures**
  - **Sexual dysfunction[c]**
  - **Sleep disturbance**
  - **Testicle atrophy**
  - **Thinning body hair[d]**
  - **Vasomotor symptoms (ie, hot flashes/night sweats)[e]**
  - **Venous thromboembolic disease**

Treatment Options for Vasomotor Symptoms (See SMP-6)

- **Non-hormonal options**
  - **Prescription alternatives (See SMP-A)**
  - **OTC options**
  - **Integrative therapies**
  - **Lifestyle modifications (See HL-1)**
- **Hormonal therapies (relatively contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk)**
  - **Androgens (eg, testosterone)**
    - ◊ **Contraindicated in males with carcinoma of the breast or known or suspected prostate cancer**
  - **Medroxyprogesterone acetate (a progestin)**
  - **Cyproterone acetate (an antiandrogen)**
  - **Estrogen (eg, diethylstilbestrol)**

[b]In males, ADT may increase cardiovascular morbidity and mortality, notably in the first 6 months of therapy and in men with two or more prior cardiovascular events. An increase in serum LDL cholesterol, HDL cholesterol, and triglycerides may also be seen.
[c]ADT-related sexual dysfunction includes loss of libido, loss of nocturnal and morning erections, and varying degrees of erectile dysfunction.
[d]Although facial and body hair decrease, some bald men may have some regrowth of scalp hair.
[e]Hot flashes may be associated with nausea and sweating and may occur during sleep.

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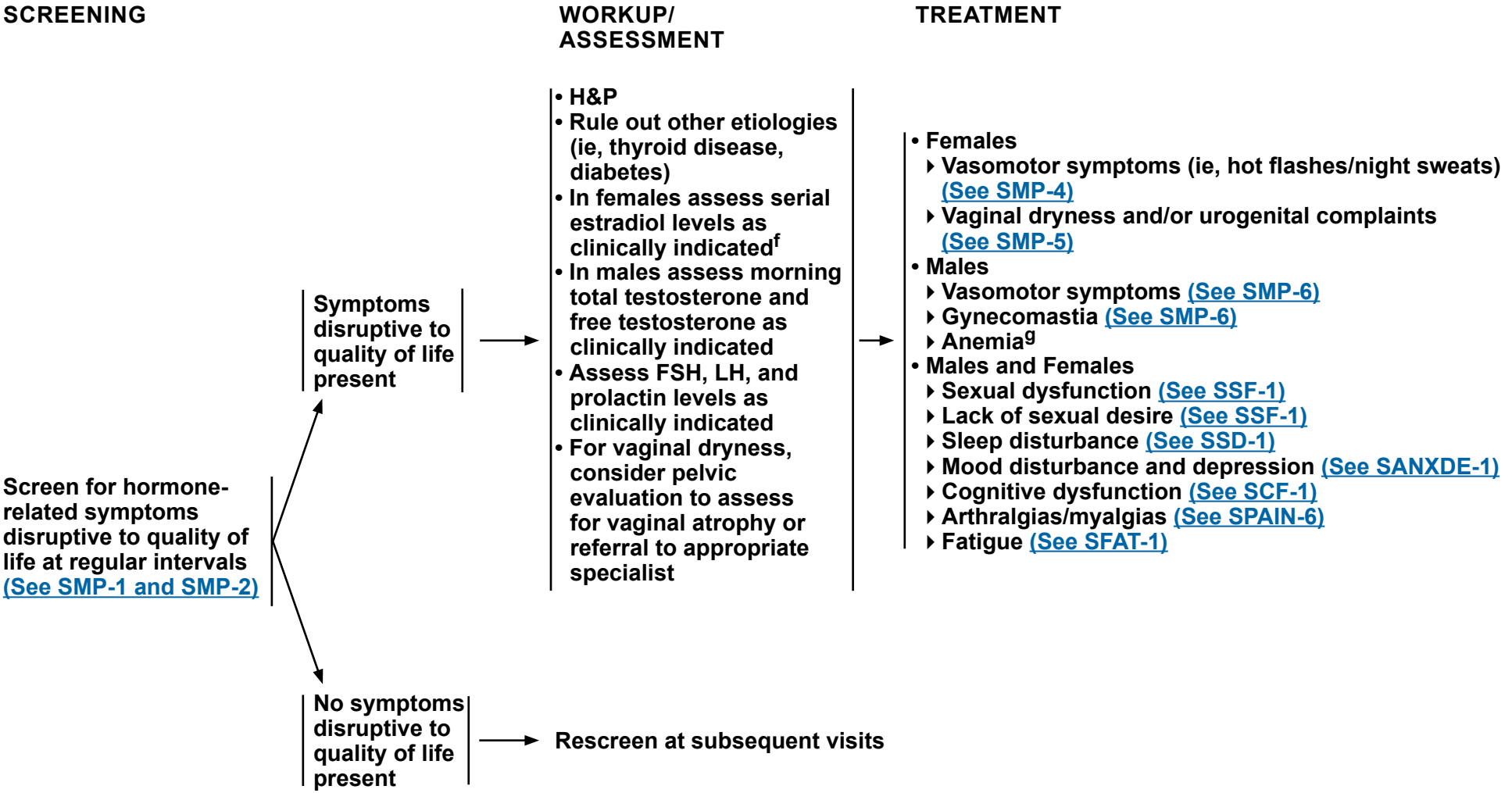

[f]For peri- or pre-menopausal female survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including FSH, AMH, and inhibin may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or those on tamoxifen, but alone are not reliable to ensure menopausal status.

[g]ADT-associated anemia is generally responsive to blood transfusions and erythropoietin and should be treated as per the NCCN Guidelines for Hematopoietic Growth Factors.

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MENOPAUSE SYMPTOM	TREATMENT
Vasomotor symptoms (ie, hot flashes/night sweats) disruptive to quality of life in females	• **Menopausal hormone therapy (MHT) or other hormonal therapies in appropriate candidates[h,i] with referral to appropriate specialist for MHT dosing and management** • **Non-hormonal pharmacologic treatments[j]** ▸ **Categories include antidepressants,[k] anti-convulsants, neuropathic pain relievers, certain anti-hypertensives, and certain antimuscarinic anticholinergic agents** • **Non-pharmacologic treatments[l]** ▸ **Weight loss if overweight or obese (See SNWM-1)** ▸ **Acupuncture** ▸ **Exercise/physical activity (See SPA-1)** ▸ **Lifestyle modifications[m] (See HL-1)** ▸ **Integrative therapies including CBT, yoga, and hypnosis**

[h] See Principles of Menopausal Hormone Therapy (MHT) Use In Survivors (Females) (SMP-B).
[i] MHT is generally contraindicated in survivors of hormonally mediated cancers. Custom-compounded bioidentical hormone therapy is not recommended. There is a lack of data supporting claims that custom-compounded bioidentical hormones are a safer and more effective alternative to standard hormone therapies. In fact, they may be harmful.
[j] See Non-Hormonal Pharmacologic Treatments and Dosing (SMP-A).
[k] Lower doses of antidepressants are often effective if the intent is to treat hot flashes (See SMP-A).
[l] Data are limited on the effectiveness and safety of phytoestrogens, botanicals, and dietary supplements in survivors of some cancers. The panel consensus is that the efficacy and safety data for these treatments are too limited to make a recommendation for use (See Discussion).
[m] Drinking alcohol may cause hot flashes in males/females. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake.

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MENOPAUSE SYMPTOM	TREATMENT
Vaginal dryness	• Non-hormonal treatments[n] ‣ Vaginal moisturizers, vaginal gels, hyaluronic acid (category 2B), oils (category 2B) • Lubricants for sexual activity[o] • Local estrogen treatment[p] (ie, rings, suppositories, creams) (category 2B) ‣ Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories. Therefore, if estrogen-based treatment is warranted, rings and suppositories are preferred over creams for survivors of hormonally sensitive tumors. • Other topical hormones[p] (ie, testosterone,[q] DHEA[r]) • Consider referral to appropriate specialist for management • For vaginal pain or discomfort, see SSF-2
Urogenital complaints (females)	• Local estrogen treatment[p] • Referral to appropriate specialist for management

[n]Recommend as first-line therapy if vaginal dryness is not too severe.
[o]Survivors should be cautioned that some lubricants may be irritating to the area of application.
[p]Vaginal estrogen and vaginal testosterone preparations can be used in managing vaginal atrophy, but safety has not been established for use in patients with or survivors of estrogen-dependent cancers.
[q]Although compounded testosterone vaginal creams are often used, there is a lack of data showing efficacy or safety in cancer survivors.
[r]Vaginal DHEA should be used with caution in survivors with a history of hormonally mediated cancers because safety in this population is unknown.

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ADT-RELATED SYMPTOMS	TREATMENT
Vasomotor symptoms (ie, hot flashes/night sweats) disruptive to quality of life in males	• Modification to ADT (See NCCN Guidelines for Prostate Cancer) • Pharmacologic treatments ▸ Hormonal therapy in appropriate candidates[s] with referral to appropriate specialist for dosing and management ◊ Medroxyprogesterone ◊ Cyproterone acetate ◊ Estrogen (eg, diethylstilbestrol) ▸ Non-hormonal therapies[k] ◊ Venlafaxine ◊ Gabapentin • Non-pharmacologic treatments[t] ▸ Acupuncture ▸ Exercise/physical activity (See SPA-1) ▸ Lifestyle modifications[m] (See HL-1) ▸ CBT ▸ Weight loss if overweight or obese (See SNWM-1)
Gynecomastia	• Prophylactic radiation (must be delivered prior to development of breast tissues) • Tamoxifen • Reduction mammoplasty

[k] See Non-Hormonal Pharmacologic Treatments and Dosing (SMP-A).
[m] Drinking alcohol may cause hot flashes in males/females. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake.
[s] Testosterone is contraindicated in males with carcinoma of the breast or known or suspected prostate cancer.
[t] Data are limited on the effectiveness and safety of phytoestrogens, botanicals, vitamin E, and dietary supplements in survivors of some cancers. The panel consensus is that the efficacy and safety data for these treatments are too limited to make a recommendation for use (See Discussion).

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NON-HORMONAL PHARMACOLOGIC TREATMENTS AND DOSING[a]

Class	Drug	Commonly Used Daily Dose for Managment of Vasomotor Symptoms	Comments (For maximum benefit, may increase to higher doses after a week as tolerated)
Antidepressants[b]	Venlafaxine[c] (SNRI) (preferred)	75 mg	Start at lowest dose possible (25 mg or 37.5 mg) and increase as tolerated
	Desvenlafaxine (SNRI)	100 mg	Start at lowest dose possible (25 mg or 50 mg) and increase as tolerated
	Escitalopram (SSRI)	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated
	Citalopram (SSRI)	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated
	Sertraline (SSRI)[d]	50 mg	• Start at lowest dose possible (25 mg) and increase as tolerated • Limited data on effectiveness • Use with caution for survivors on tamoxifen
	Paroxetine (SSRI)[d]	Low-dose 7.5 mg or Standard paroxetine short acting up to 20 mg, controlled release up to 25 mg	• Low-dose (7.5 mg) paroxetine is the only FDA-approved alternative to hormones for hot flashes • Use with caution for survivors on tamoxifen
	Fluoxetine (SSRI)[d]	20 mg	• Start at lowest dose possible (10 mg) and increase as tolerated • Limited data on effectiveness • Use with caution for survivors on tamoxifen
Anti-convulsant	Gabapentin[c] (preferred)	900 mg (typically 300 mg 3 times a day)	• Start at lowest dose possible (100 mg or 300 mg) and increase as tolerated • Consider starting at night time as this drug tends to cause sedation
	Pregabalin	150–300 mg	Start at lowest dose possible (25 mg) and increase as tolerated
Alpha-agonist hypertensive	Clonidine	0.1 mg (oral or transdermal)	Transdermal preparations may have fewer side effects
Antimuscarinic anticholinergic	Oxybutynin	5–10 mg	Start with 5 mg, typically used for overactive bladder (OAB) and may cause urinary retention along with other anticholinergic side effects

[a]For long-term care or maintenance and/or if lack of response, consider referral to appropriate health care specialist. A gradual tapering of dose rather than an abrupt discontinuation of drug is recommended when discontinuing these treatments.

[b]Anticipated clinical response of SSRIs/SNRIs for hormone-related symptoms tends to be more rapid than the typical response for depression. For additional information, See First-Line Antidepressants for Depression or Anxiety in Adults (SANXDE-E).

[c]Venlafaxine and gabapentin have been studied for the treatment of hormone-related symptoms in males, but data are limited. The other therapies have been used but not tested in males.

[d]Evidence generally does not support the clinical significance of the inhibitory activity of SSRIs, SNRIs, or other antidepressants on tamoxifen's or other CYP2D6- or CYP3A4-metabolized agent's anticancer effects in terms of increased recurrence or mortality rates. However, pharmacokinetic/pharmacogenetic studies do indicate reduced availability of endoxifen in lower CYP2D6 metabolizers taking tamoxifen. SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6.

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PRINCIPLES OF MENOPAUSAL HORMONE THERAPY (MHT) USE IN SURVIVORS (FEMALES)

- **MHT is the most effective therapy for management of vasomotor symptoms.**

- **General recommendations are to use the lowest dose possible to control symptoms.**
  - **Combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus)**
    - ◊ **Formulations of hormones include oral, transdermal, vaginal ring, and intrauterine device.**
  - **The TSEC conjugated estrogens/bazedoxifene is FDA approved for treating menopausal symptoms in healthy post-menopausal women.**
    - ◊ **These drugs are contraindicated in survivors of hormonally dependent cancers.**

- **If MHT is used, refer to appropriate specialist for MHT dosing and management.**

- **For young cancer survivors experiencing menopause at an early age, consider oral contraceptives or MHT for symptom relief and potential cardiac and bone benefits as long as not contraindicated.**

- **Relative contraindications for MHT in cancer survivors mirror those for the general population and include:**
  - **History of hormonally mediated cancers (high-risk endometrial and most breast)**
  - **History of abnormal vaginal bleeding**
  - **Active or recent history of thromboembolic event**
  - **Pregnancy**
  - **Active liver disease**

- **Caution in:**
  - **Survivors with coronary heart disease or hypertension**
  - **Survivors at increased genetic risk for cancers**
  - **Current smokers, especially if older than 35 years**

- **Approach to treatment should be individualized based on risks and benefits.**

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GENERAL PRINCIPLES OF PAIN MANAGEMENT

- **Comprehensive pain assessment should be done to determine the etiology of the pain.**
  - **If the pain is new and acute, differential diagnosis should include cancer recurrence or progressive disease.**
  - **If the pain is chronic, a specific cancer pain syndrome should be identified if possible.**
- **Conduct a discussion with the patient and family regarding realistic treatment goals, including improvement in functionality as well as pain relief.**
- **Opioid treatment is sometimes necessary, and the lowest appropriate dose should be used for the shortest amount of time, if possible. Adjuvant medications should be used in addition to the opioids if indicated.**
  - **Non-cancer pain in cancer survivors should be treated congruent with pain diagnosis, with opioids remaining the last resort. Consider referring to primary care service for management of non-cancer pain.**
- **Non-opioids are appropriate as primary therapy for many pain syndromes.**
- **Non-pharmacologic interventions can be used as the sole treatment for pain, or as adjuncts to pharmacologic therapy.**
- **Physical modalities (heat, cold, massage, acupuncture, physical therapy, or occupational therapy) are useful and should be considered for some pain syndromes.**
- **Use a multimodality approach to pain management if warranted, and if those resources are available.**
- **Psychological support of the survivor with chronic pain is necessary, and referral to psychosocial services should be considered for survivors in distress. (See SANXDE-1)**
- **Consider referral to a specialist for patients who might benefit from further pain interventions. This could include referral to interventional pain, physical medicine and rehabilitation, palliative care, urology, gynecology, orthopedic surgery, gastroenterology, or other appropriate consultants.**
- **The panel acknowledges the legalization of medical marijuana for various conditions in multiple states. However, there are presently not enough data to make any guideline recommendations regarding use in cancer survivors.**
- **Also see the NCCN Guidelines for Adult Cancer Pain.**

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PRINCIPLES OF OPIOID USE IN LONG-TERM SURVIVORS

- **When opioids are appropriate and necessary, establish treatment goals with survivors and caregivers and use the lowest effective opioid dose for the shortest period of time possible.**
- **Provide survivor and caregiver education on safe opioid use, storage, and disposal.**
- **Functional outcomes are important measures for patients on opioid therapy. The expected outcome (ie, improvement in function and/or pain) should be clearly discussed with survivors and caregivers, agreed upon, and documented upon initiation and continuation of chronic therapy.**
- **Re-evaluate the effectiveness and necessity of opioids on a regular basis.**
  - **If the expected outcome is not achieved, other treatment alternatives should be considered. If opioids are no longer appropriate, recommend gradual tapering of opioids to help avoid symptoms of withdrawal.**
- **Consider establishing pain treatment agreements (See PAIN-L of the NCCN Guidelines for Adult Cancer Pain).**
- **Address medical-related issues due to chronic or high-dose opioids.**
  - **Endocrine/hypopituitary abnormalities**
    - ◊ **Testosterone deficiency**
  - **Management of opioid adverse effects (ie, constipation, nausea, pruritus, delirium, motor and cognitive impairment, respiratory depression, sedation) (See PAIN-F of the NCCN Guidelines for Adult Cancer Pain)**
- **Monitor for aberrant drug-taking behaviors[a] and for signs of substance use disorder. (See PAIN-E 6 of 13 of the NCCN Guidelines for Adult Cancer Pain)**
  - **Verbalize concerns to the survivor and refer to pain, palliative care, physiatry, and/or substance use disorder/mental health specialists.**
  - **Engage caregivers or people living with the survivor if possible.**
- **The panel endorses the ASCO Policy Brief on Opioid Therapy and Access to Treatment (2016), particularly as it relates to weighing the risks/benefits of opioid treatment.**

[a]Aberrant behaviors may include family member using drugs prescribed to the survivor.

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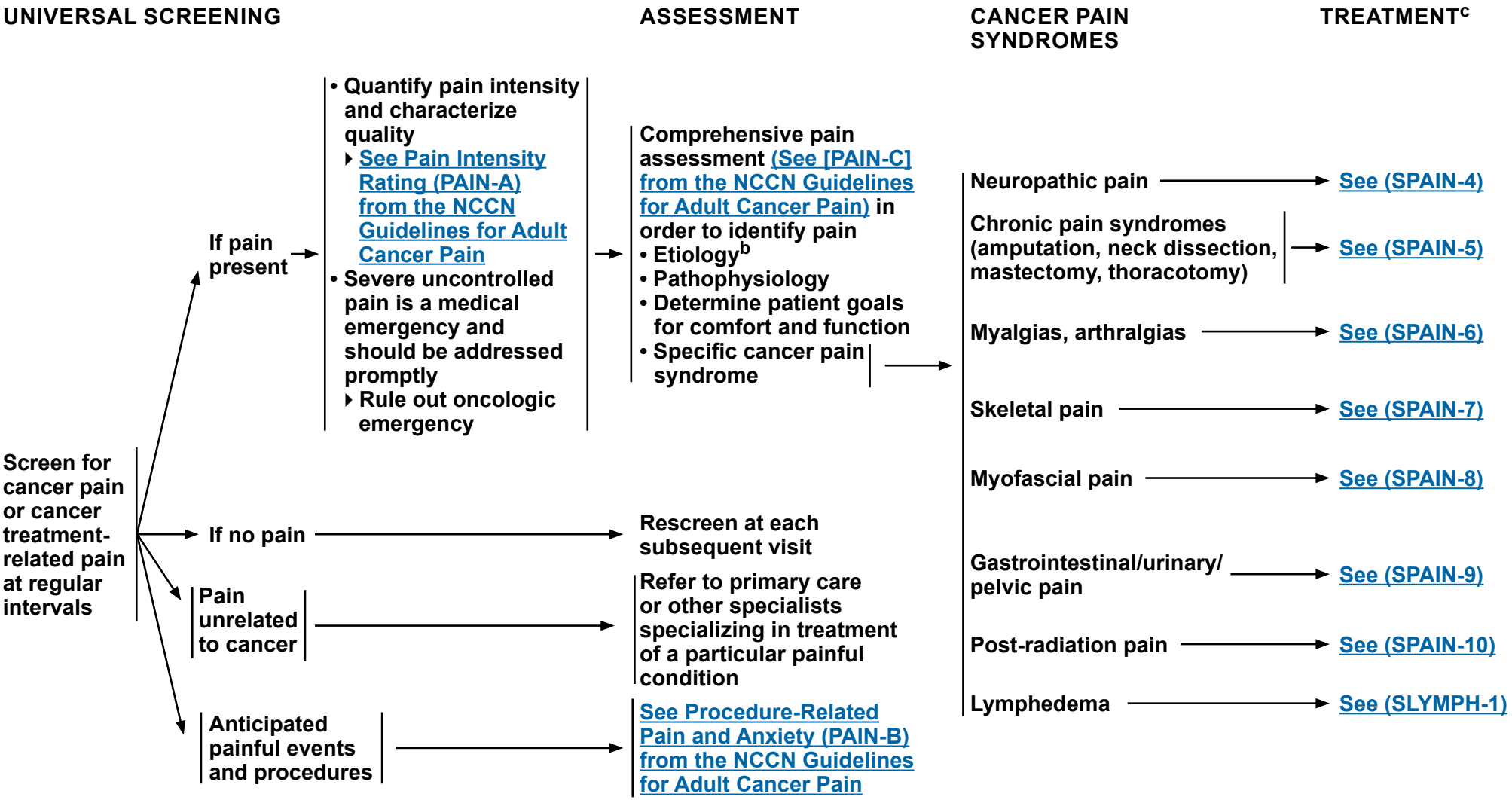
NCCN Guidelines Version 2.2021
Survivorship: Pain



[b]Referral to primary care physician for non-cancer treatment-related workup and pain management (ie, rheumatoid arthritis) and consider the possibility of pain due to cancer recurrence.

[c]See General Principles of Pain Management (SPAIN-1).

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CANCER PAIN SYNDROME	TREATMENT
Neuropathic pain[d] • Paresthesias (tingling or prickling) • Shooting, "electrical" • Numbness	• General measures: ‣ Non-opioid/Adjuvant analgesics (See [PAIN-G] from the NCCN Guidelines for Adult Cancer Pain) ◊ SNRIs ◊ Anticonvulsants ◊ TCAs ‣ CBT and psychosocial support (See [PAIN-H] from the NCCN Guidelines for Adult Cancer Pain) ◊ Consider hypnosis ‣ Local therapies ◊ Pharmacologic therapies – Topical patches (ie, lidoderm, capsaicin) – Compounded creams (eg, lidocaine, baclofen, ketamine, and amitriptyline combined) – Diclofenac topical gel ◊ Non-pharmacologic therapies – Heat – Ice – Acupuncture – Transcutaneous electrical nerve stimulation (TENS) unit • For moderate or severe pain, opioids and dual-action opioid agonist/noradrenaline reuptake inhibitor[e,f] See (PAIN-3, PAIN-4, and PAIN-5) from the NCCN Guidelines for Adult Cancer Pain • Consider referral to pain management services, interventional specialist,[g] physical therapy, physical medicine and rehabilitation, integrative services, and/or palliative care as appropriate

[d]Also see NCCN Guidelines for Adult Cancer Pain and Loprinzi CL, et al. J Clin Oncol 2020;38:3325-3348.
[e]See Principles of Opioid Use in Long-Term Survivors (SPAIN-2).
[f]Initiating opioids in cancer survivors should be carefully considered after failure of other interventions.
[g]Scrambler therapy can be considered. Loprinzi C, et al. Support Care Cancer 2020;28(3):1183-1197.

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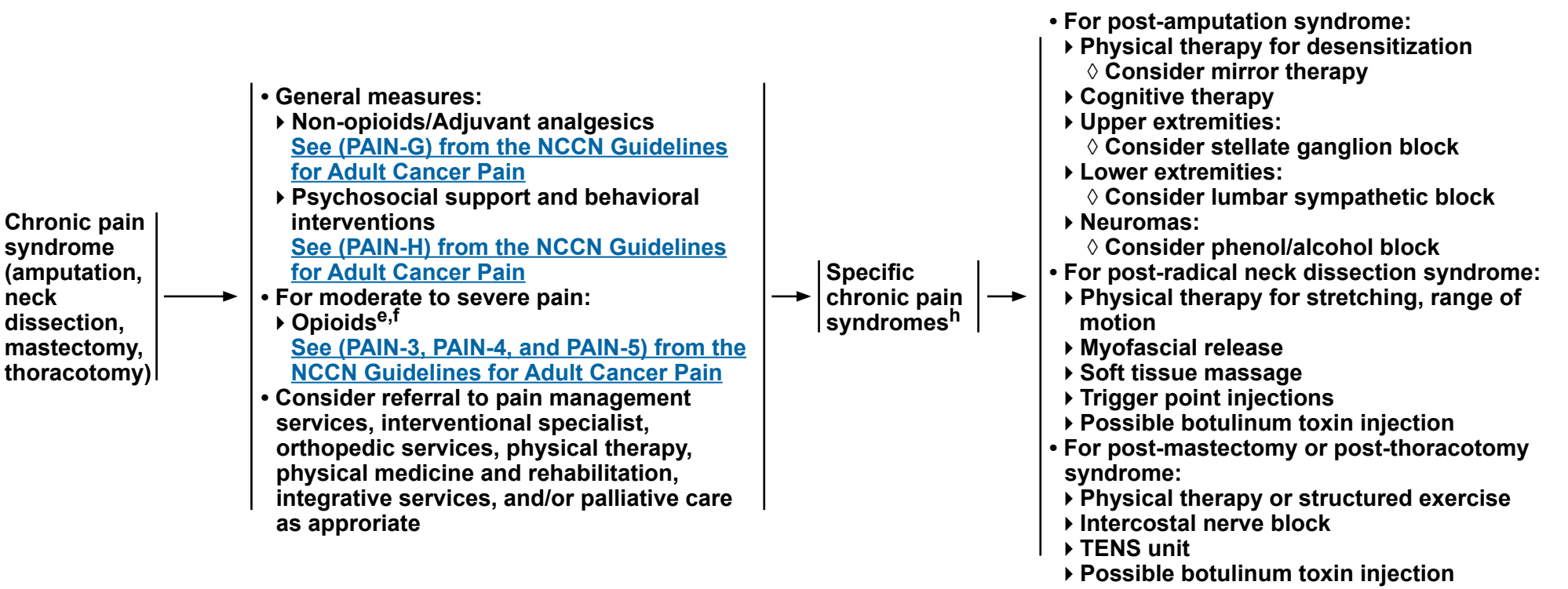

[e] See Principles of Opioid Use in Long-Term Survivors (SPAIN-2).
[f] Initiating opioids in cancer survivors should be carefully considered after failure of other interventions
[h] There are other postoperative pain syndromes and many treatment measures can be used across syndromes. Also consider referral to appropriate specialist.

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CANCER PAIN SYNDROME	TREATMENT
Myalgias, Arthralgias	• Nonpharmacologic ▸ Physical activity (category 1 for aromatase inhibitor [AI]-induced arthralgia) ▸ Heat (ie, paraffin wax, hot pack) ▸ Cold pack ▸ Aquatic therapy ▸ Ultrasonic stimulation[i] ▸ Massage ▸ Acupuncture (category 1 for AI-induced arthralgia) ▸ Yoga • Pharmacologic[j] ▸ SNRIs (category 1 for AI-induced arthralgia) ▸ TCAs ▸ Anticonvulsant drugs (ie, gabapentin, pregabalin) ▸ Acetaminophen ▸ COX-2 inhibitors ▸ Nonsteroidal anti-inflammatory drugs (NSAIDs) ▸ Muscle relaxants • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, orthopedic services, and/or palliative care

[i]Ultrasonic stimulation is a type of heat treatment that can penetrate directly to the bone and should be used with caution. It is not recommended for patients with multiple myeloma or bone metastases.
[j]Consider switching to an alternative AI or tamoxifen for AI-induced arthralgia.

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CANCER PAIN SYNDROME

Skeletal pain[k] →

TREATMENT

- **For vertebral compression:**
  - **General measures:**
    - ◊ **Bisphosphonates or other antiresorptive medications if appropriate**
    - ◊ **NSAIDs**
    - ◊ **Muscle relaxants**
    - ◊ **Consider vertebral augmentation (ie, vertebroplasty, kyphoplasty)**
    - ◊ **Acetaminophen**
    - ◊ **COX-2 inhibitors**
  - **Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, orthopedic services, and/or palliative care**
  - **For acute vertebral compression:**
    - ◊ **Opioids[e,f]**
    - ◊ **Bracing (ie, thoracolumbar sacral orthosis [TLSO], Jewett brace)**
    - ◊ **Limited bedrest**
    - ◊ **Weight-bearing exercises when pain improves**
    - ◊ **Physical therapy**
  - **For chronic vertebral compression:**
    - ◊ **Weight-bearing exercises**
    - ◊ **Physical therapy – thoracic and lumbar stabilization exercises**
    - ◊ **Consider medial branch blocks and radiofrequency ablation for post-compression arthritic pain**
- **For avascular necrosis:**
  - **Physical therapy – based on weight-bearing and range-of-motion restrictions**
  - **Opioids[e]**
  - **Muscle relaxants if myofascial component**
  - **Core decompression**
  - **Joint replacement as clinically indicated**
  - **Nerve ablation evaluation and bracing for patients who are not joint replacement candidates**
- **For osteonecrosis of the jaw:**
  - **Referral to oral surgeon**
  - **Anti-convulsants**
  - **SNRIs**
  - **Opioids[e]**

[e]See Principles of Opioid Use in Long-Term Survivors (SPAIN-2).
[k]For skeletal metastases and/or bone pain, see (PAIN-D) from the NCCN Guidelines for Adult Cancer Pain. Consider orthopedic/surgical referral.

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CANCER PAIN SYNDROME	TREATMENT
Myofascial pain	• Nonpharmacologic ▸ Physical activity ▸ Range-of-motion exercises ▸ Strengthening exercises ▸ Soft tissue/myofascial release massage ▸ Ultrasonic stimulation[i] ▸ Acupuncture or acupressure • Pharmacologic ▸ Topical ointments (ketamine) and patches (ie, lidocaine, capsaicin) ▸ NSAIDs ▸ Anticonvulsant drugs ▸ SNRIs ▸ Acetaminophen ▸ COX-2 inhibitors • For muscle cramps or spasms, check electrolytes, calcium and magnesium levels, and hydration status • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, and/or palliative care for services such as trigger point injections

[i]Ultrasonic stimulation is a type of heat treatment that can penetrate directly to the bone and should be used with caution. It is not recommended for patients with multiple myeloma or bone metastases.

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CANCER PAIN SYNDROME	TREATMENT
Gastrointestinal/urinary/pelvic pain →	• For gastrointestinal pain (abdominal pain/cramping): ▸ Adequate hydration ▸ Consider referral to gastroenterologist • For chronic pelvic pain:[m] ▸ Consider referral to specialist in pelvic floor pain such as urologist, gynecologist, or physical medicine and rehabilitation ▸ Consider physical therapy for pelvic floor exercises ▸ Adequate hydration ▸ Bowel regimen ▸ Dorsal column stimulation for chronic cystitis and chronic pelvic pain • For dyspareunia: (See SSF-2) ▸ Consider referral to gynecologist or sexual health specialist • For refractory gastrointestinal/urinary/pelvic pain: ▸ Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, and/or palliative care

[m]Multidisciplinary treatment for chronic pelvic pain is preferred if available.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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CANCER PAIN SYNDROME	TREATMENT
Post-radiation pain • Pain may be acute or appear months or years after radiation • Radiation may lead to scarring, adhesions, or fibrosis ▸ Differentiate fibrosis from recurrent tumor • Radiation to a localized area of the body (ie, head and neck, breast) may cause a chronic pain syndrome in that area	→ • Treat according to specific cancer pain syndrome guidelines, if appropriate (See SPAIN-3 for list of cancer pain syndromes) • Physical therapy • Pain medication (appropriate to the etiology) • Surgical lysis of adhesions may be indicated in extreme circumstances • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, orthopedic services, and/or palliative care for post-radiation pain including after stereotactic body RT (SBRT)

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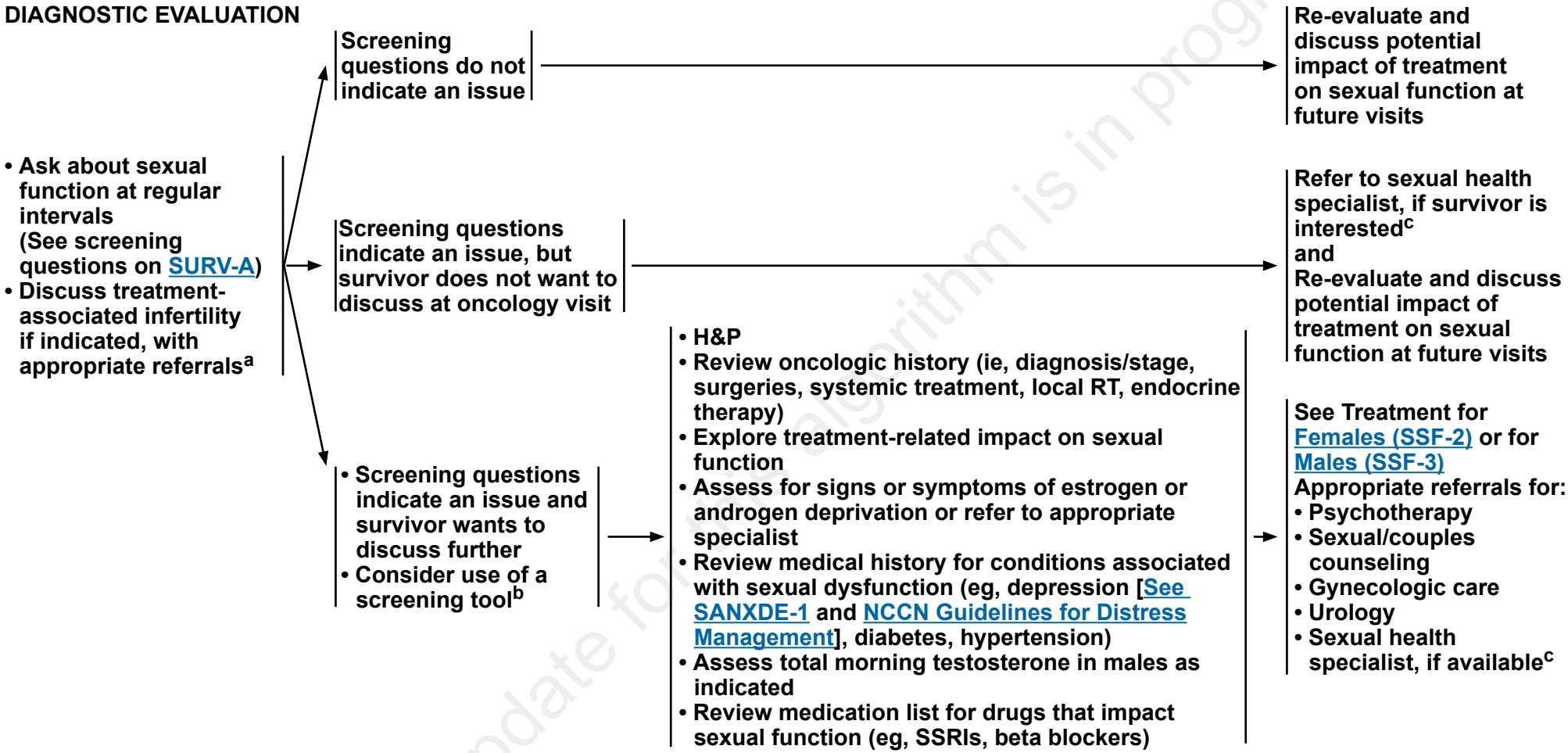
DIAGNOSTIC EVALUATION



[a]For information regarding fertility preservation for patients with cancer, see Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:2500-2510. http://www.ncbi.nlm.nih.gov/pubmed/23715580

[b]Several screening tools are available for both men and women. For women, options include the Brief Sexual Symptom Checklist for Women (SSF-A), Arizona Sexual Experience Scale (http://dx.doi.org/10.1080/009262300278623), and the Female Sexual Function Index (http://www.fsfiquestionnaire.com/). For men, the Sexual Health Inventory for Men (SHIM) (SSF-B), Sexual-Quality of Life-Men (http://dx.doi.org/10.1111/j.1743-6109.2007.00749.x), and the PROMIS Brief Function Profile-Male (http://www.assessmentcenter.net/) are examples.

[c]Sexual health specialists may come from a range of backgrounds, including primary care, gynecology, urology, oncology, psychology, and/or rehabilitation medicine. Whenever possible, survivor should be referred to an appropriate local resource for further sexual health evaluation.

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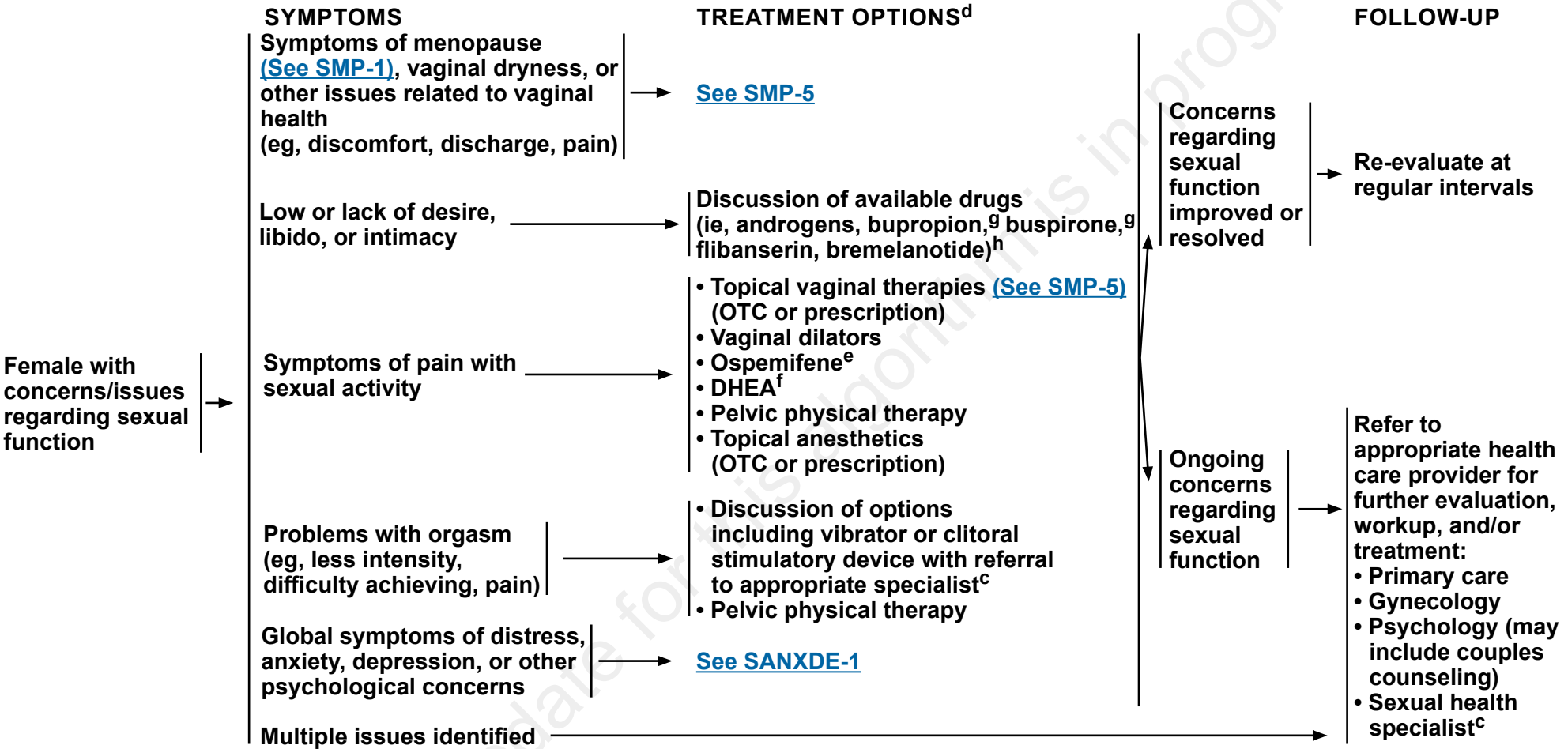

[c]Sexual health specialists may come from a range of backgrounds, including primary care, gynecology, urology, oncology, psychology, and/or rehabilitation medicine. Whenever possible, survivor should be referred to an appropriate local resource for further sexual health evaluation.
[d]Discuss risk/benefits of prescription medications if not contraindicated for cancer type or refer to appropriate health care provider (eg, sexual health specialist) for prescription and/or treatment as necessary.
[e]Currently ospemifene is contraindicated in survivors with a history of estrogen-dependent cancers.
[f]DHEA should be used with caution in survivors with a history of estrogen-dependent cancers.
[g]Bupropion and buspirone may be considered as off-label treatments for hypoactive sexual desire disorder, despite limited safety and efficacy data.
[h]There is a lack of data showing a benefit of sildenafil in women or of flibanserin and androgens in cancer survivors. In addition, there is a lack of safety data for the use of androgen-based therapy in survivors of hormonally mediated cancers.

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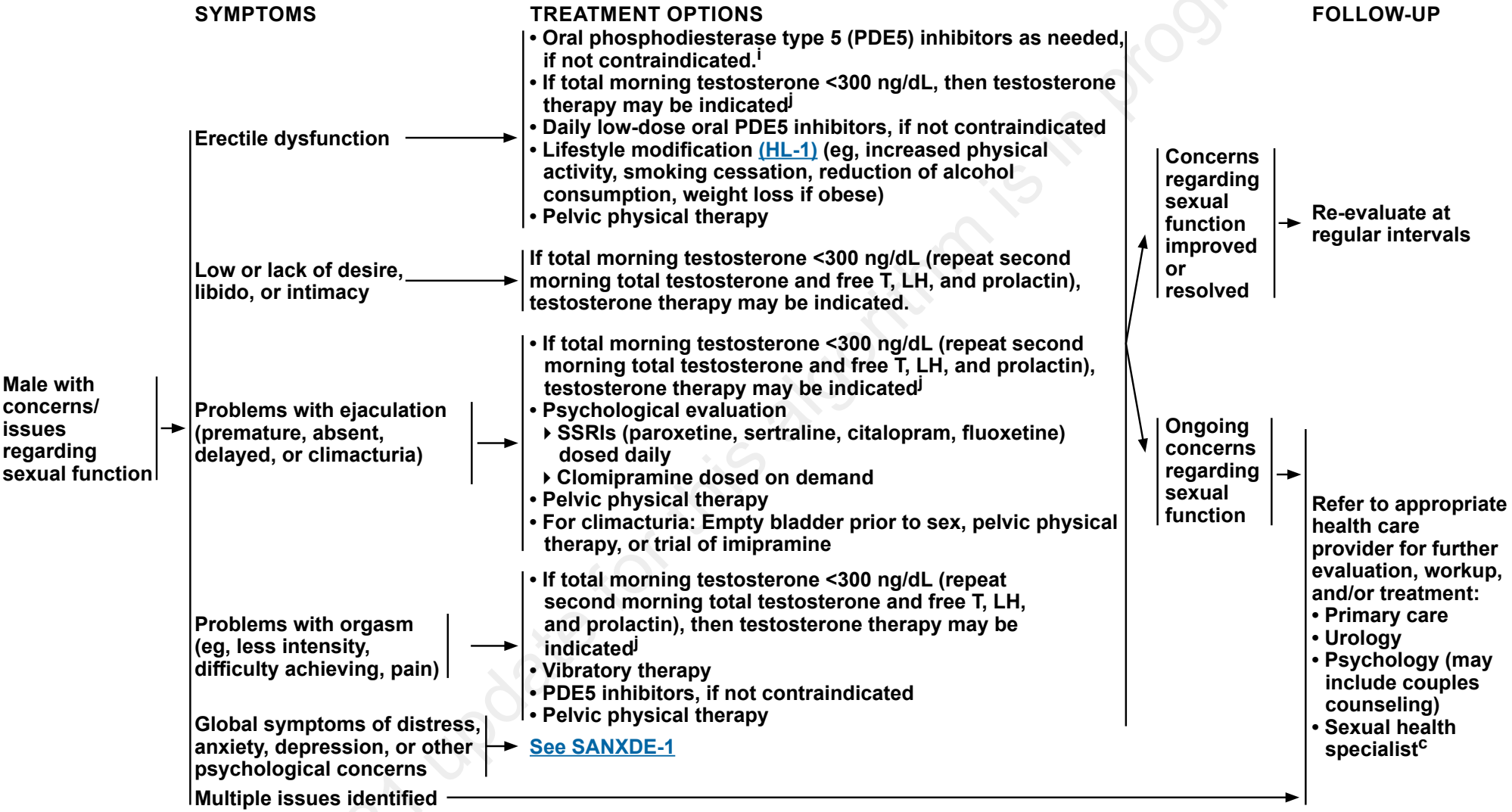
NCCN Guidelines Version 2.2021
Survivorship: Sexual Function (Male)



[c]Sexual health specialists may come from a range of backgrounds, including primary care, gynecology, urology, oncology, psychology, and/or rehabilitation medicine. Whenever possible, survivor should be referred to an appropriate local resource for further sexual health evaluation.
[i]Dosing should be titrated to optimal effect.
[j]Testosterone therapy should only be used if not contraindicated by primary oncologic diagnosis (eg, prostate cancer on active surveillance, prostate cancer under therapy with androgen deprivation).

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BRIEF SEXUAL SYMPTOM CHECKLIST FOR WOMEN[1]

Please answer the following questions about your overall sexual function:
1. Are you satisfied with your sexual function?

__ Yes __No
If no, please continue.

2. How long have you been dissatisfied with your sexual function?

3a. The problem(s) with your sexual function is:
(mark one or more)

__1 Problem with little or no interest in sex
__2 Problem with decreased genital sensation (feeling)
__3 Problem with decreased vaginal lubrication (dryness)
__4 Problem reaching orgasm
__5 Problem with pain during sex
__6 Other:

3b. Which problem is most bothersome? (circle)
1 2 3 4 5 6

4. Would you like to talk about it with your doctor?
__Yes __No

[1]Reprinted with permission from Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348.

Note: All recommendations are category 2A unless otherwise indicated.
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SEXUAL HEALTH INVENTORY FOR MEN (SHIM)[1]

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that best describes your own situation.

Please be sure that you select one and only one response for each question.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half The Time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half The Time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half The Time)	Almost Always or Always
	0	1	2	3	4	5

PROVIDER KEY: Add the numbers corresponding to questions 1-5.

TOTAL: _____

The SHIM further classifies ED severity with the following breakpoints: 1-7: Severe ED 8-11: Moderate ED 12-16: Mild to Moderate ED 17-21 Mild ED

[1]Reproduced and modified with permission from Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. Int J Impot Res 2005;17:307-319.

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SCREENING

Screening/assessment questions[a] to be asked at regular intervals, especially when there is a change in clinical status or treatment:

- **Are you having problems falling asleep, staying asleep, or waking up too early?**
- **Are you experiencing excessive sleepiness (sleepiness or falling asleep in inappropriate situations or sleeping more during a 24-hour period than in the past?)**
- **Have you been told that you snore frequently or stop breathing during sleep?**

No concerns for sleep disorder/disturbance → **Re-evaluate at subsequent visits/post therapy**

Concerns for sleep disorder/disturbance[b] →

H&P

- **Assessment of treatable or modifiable contributing factors:**
  - **Comorbidities**
    - ◊ **Alcohol and/or substance abuse**
    - ◊ **Obesity**
    - ◊ **Cardiac dysfunction**
    - ◊ **Respiratory disorders**
    - ◊ **Endocrine dysfunction (eg, hypothyroidism)**
    - ◊ **Anemia**
      - **Iron and ferritin levels**
    - ◊ **Emotional distress: screen for anxiety and depression (See SANXDE-1 and NCCN Guidelines for Distress Management)**
    - ◊ **Neurologic disorders including chemotherapy-induced peripheral neuropathy**
    - ◊ **Psychiatric disorders**
  - **Medications[c]**
  - **Vasomotor symptoms (see SMP-4 [females) and SMP-6 [males])**
  - **Review sleep/wake timing and/or sleep log/diary**
  - **Review caffeine intake**
  - **Review history of cancer treatments**
  - **Pain (See SPAIN-1)**
  - **Fatigue (See SFAT-1)**
  - **Shift work**
  - **Current coping strategies (eg, relaxation techniques, meditation)**

Insomnia symptoms (difficulty falling asleep staying asleep, or waking up too early):[d]
- **Duration >4 weeks**
- **Occurring at least 3 times per week**

→ **See SSD-2**

Sleep disturbance and/or excessive sleepiness[d]
- **Hypersomnias**
- **Obstructive sleep apnea[e]**
- **Restless legs syndrome (RLS)[e,f]**

→ **See SSD-3**

[a]The following additional tools may be used for individual intensive screening to assess sleep quality: PSQI https://www.sleep.pitt.edu/instruments/#psqi and PROMIS SLEEP http://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=183&Itemid=992.

[b]Patients may have more than one sleep disorder.

[c]Consider persistent use of sleep aids, pain medications, antiemetics, stimulants, antidepressants, anti-psychotics, sedative/hypnotics, opioids, over-the-counter sleep aids, or antihistamines.

[d]In the differential diagnosis of insomnia or excessive sleepiness symptoms, consider parasomnia or circadian rhythm sleep disorders and referral to a sleep specialist.

[e]Note that obstructive sleep apnea, RLS, circadian rhythm sleep disorders, and parasomnia may also present with symptoms of insomnia.

[f]RLS is also known as Willis-Ekbom disease.

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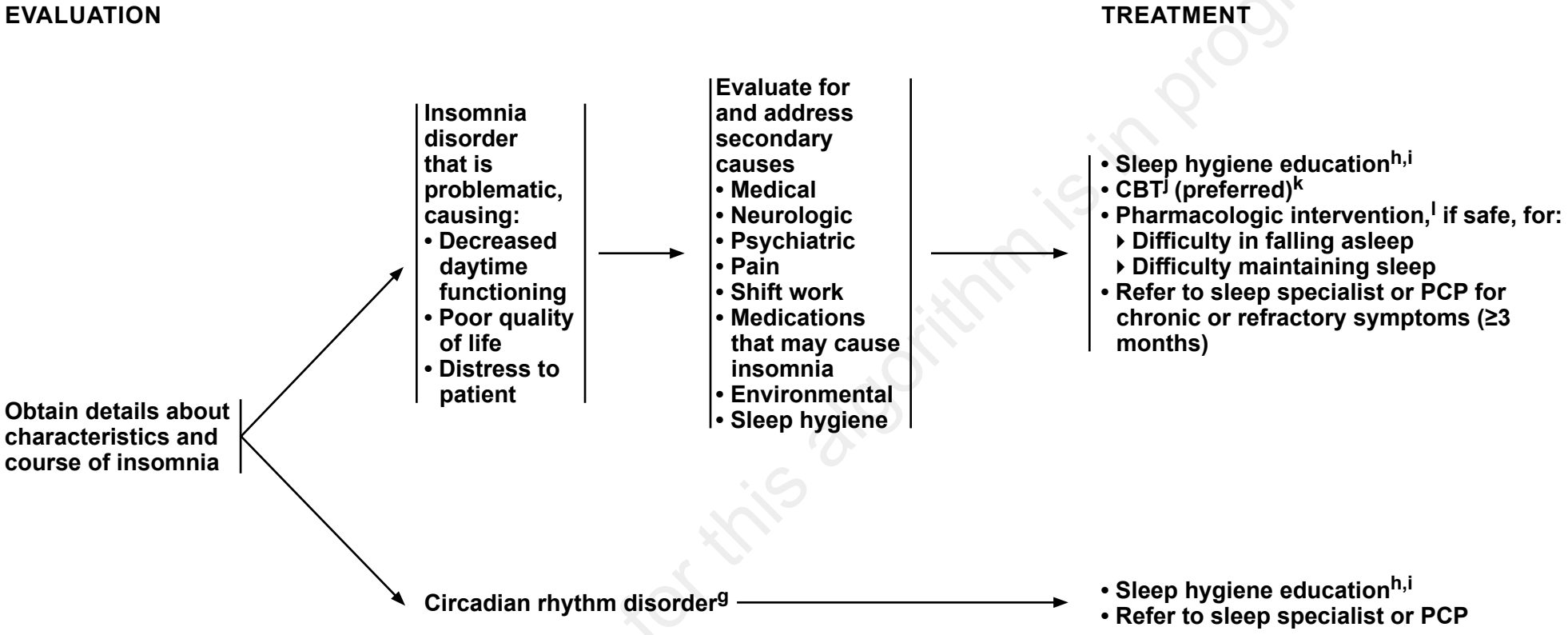

[g]Circadian rhythm disorder: A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to an alteration of the circadian timing system or to a misalignment with the sleep-wake schedule required by an individual's physical environment or social/work schedules.

[h]See General Sleep Hygiene Measures (SSD-A).

[i]Sleep hygiene alone has not been shown to be effective, but should be part of the initial treatment of all survivors with sleep disorders and as a prevention strategy for insomnia disorder. Sleep hygiene alone is not the recommended treatment for insomnia, but should be used in conjunction with other treatments such as CBT-I and/or pharmacotherapy.

[j]See Cognitive Behavioral Treatments (SSD-B).

[k]CBT is preferred over pharmacologic interventions as first-line therapy.

[l]See Principles for Choosing an FDA-Approved Hypnotic (SSD-C).

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NCCN Guidelines Version 2.2021
Survivorship: Sleep Disorders

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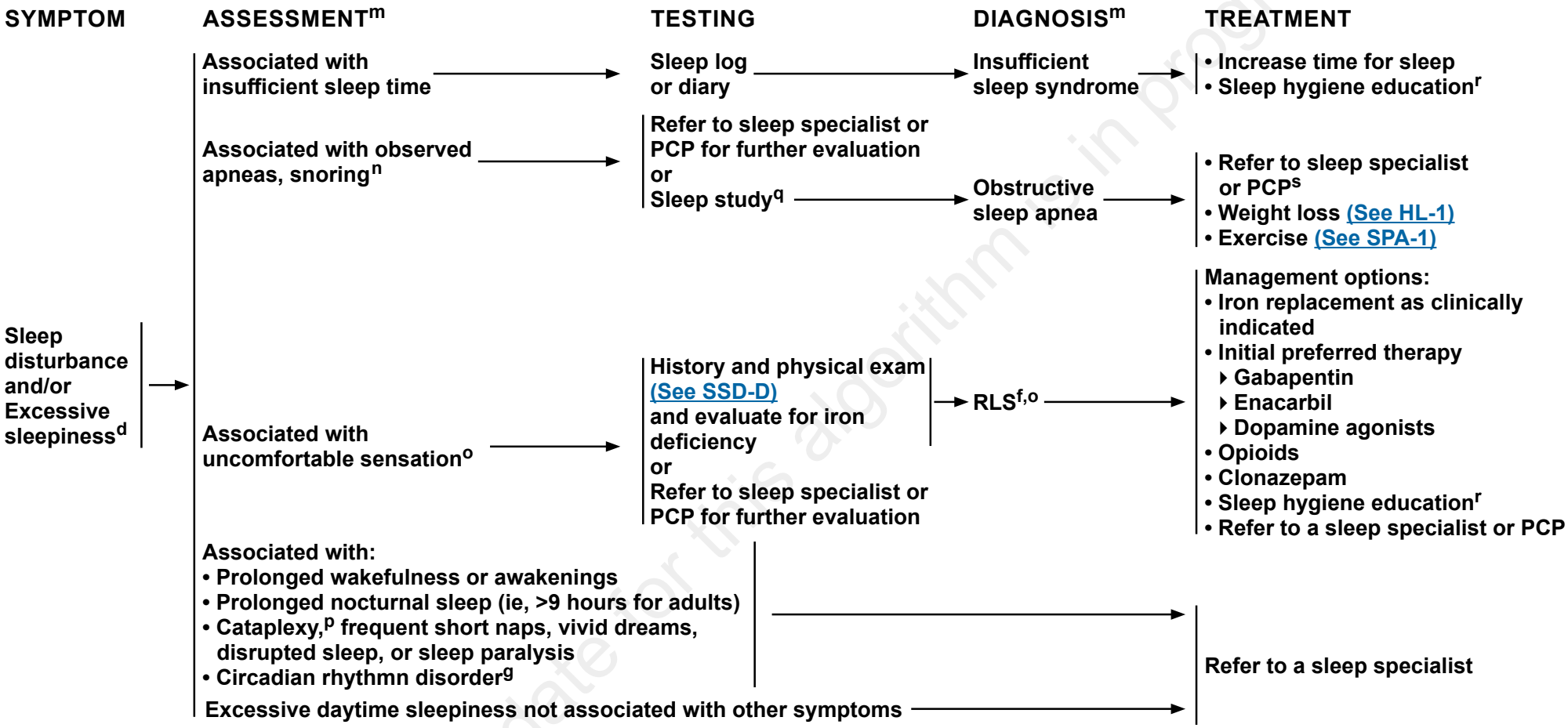

[d] In the differential diagnosis of insomnia or excessive sleepiness symptoms, consider parasomnia or circadian rhythm sleep disorders and referral to a sleep specialist.
[f] RLS is also known as Willis-Ekbom disease.
[g] Circadian rhythm disorder: A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to an alteration of the circadian timing system or to a misalignment with the sleep-wake schedule required by an individual's physical environment or social/work schedules.
[m] For other less frequent syndromes, refer to a sleep specialist.
[n] The following tools may be used to assess sleep apneas: STOP Questionnaire (Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812-821) and Berlin Questionnaire (http://sleepapnea.org/wp-content/uploads/2017/02/berlin-questionnaire.pdf).
[o] See Essential Diagnostic Criteria for Restless Legs Syndrome (SSD-D).
[p] Cataplexy: Sudden loss of muscle tone, typically triggered by strong emotions, such as laughter or anger. Cataplexy is the most specific diagnostic feature of narcolepsy.
[q] Sleep studies can be done as laboratory polysonography or as home sleep study. However, survivors with known cardiac disease or neurologic disease, who have used opiates for cancer-related pain, may not be good candidates for some home sleep tests.
[r] See General Sleep Hygiene Measures (SSD-A).
[s] The most common medical treatment for obstructive sleep apnea is continuous positive airway pressure (CPAP).

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GENERAL SLEEP HYGIENE MEASURES[1,2,3]

- **Maintain a regular bedtime and waketime every day.**
- **Engage in regular physical activity in the morning and/or afternoon (See SPA-1). Avoid moderate to strenuous physical activity within 3 hours of bed time.**
- **Increase exposure to bright light during the day.**
- **Reduce exposure to bright light (ie, computer, phone screens, light sources close to the eye) within a few hours before bedtime and during the night.**
- **Avoid heavy meals and limit fluid intake within 3 hours of bedtime.**
- **Avoid alcohol and nicotine too close to bedtime.**
- **Limit caffeine consumption and avoid caffeine consumption at least 4 hours before bedtime.**
- **Enhance sleep environment (dark, quiet room; comfortable temperature).**
- **Set aside a worry time before bedtime.**
- **Avoid looking at the clock when awake during the night.**
- **If necessary, limit to 1 short nap per day in the afternoon (no longer than 30 min).**
- **Turn off electronics and light-emitting sources at bedtime.**

The 2021 update for this algorithm is in progress.

[1]National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. 1998. NIH Publication. 98-4088.
[2]Kupfer DJ and Reynolds CF. Management of insomnia. N Engl J Med 1997;336:341-346.
[3]Lippmann S, Mazour I, Shahab H. Insomnia: therapeutic approach. South Med J. 2001;94:866-873.

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COGNITIVE BEHAVIORAL TREATMENTS[1]

Strategy	Goal
Stimulus control	Associate the bed/bedroom as a place for sleep or sexual activity only
Sleep restriction	Improve sleep continuity by: • Limiting time spent in bed[2] • Maintaining a regular sleep schedule by keeping a standard bedtime and wake time every day
Cognitive therapy[3] or internet-based cognitive behavioral therapy	Challenge survivor's maladapative beliefs and misconceptions about sleep disturbances
Relaxation training	• Reduce physiologic and cognitive arousal at bedtime • Techniques include progressive muscular relaxation, deep breathing, meditation, yoga, and biofeedback

The 2021 update for this algorithm is in progress.

[1]Data from Bootzin RR and Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992;53(suppl):37-41.
[2]Match total amount of time spent in bed to the actual amount of time spent sleeping (no less than 5 hours).
[3]Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep Med Rev 2016;27:20-28.

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PRINCIPLES FOR CHOOSING AN FDA-APPROVED HYPNOTIC:[1,2,3,4]

- **Does the patient have difficulty initiating or maintaining sleep?**
- **Does the patient have both sleep onset and sleep maintenance difficulty?**

AGENT	HELPS WITH SLEEP INITIATION	INCREASES TOTAL SLEEP TIME	INDICATED FOR SLEEP INITIATION AND MAINTENANCE
Zolpidem	+	+	–
Zolpidem CR	+	+	+
Zaleplon	+	–	–
Eszopiclone	+	+	+
Ramelteon	+	±	–
Temazepam	+	+	+
Doxepin (3–6 mg)	–	+	+
Suvorexant	+	+	+

[1]Data from the Physicians' Desk Reference (ed 66). Montvale, NJ: PDR Network, LLC; 2012.
[2]Inform patients that taking hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating).
[3]Other commonly used medications for insomnia include sedating medications such as antidepressants (ex, trazodone), antihistamines, atypical anti-pyschotics, other benzodiazepine receptor agonists, and nutritional/herbal supplements (ex, melatonin). They do not have an FDA-approved indication for the treatment of insomnia, and do not have enough data to be recommended for routine use.
[4]Most of these agents, with the exception of ramelteon, doxepin, and suvorexant, are benzodiazepine receptor agonists and can be associated with dependence, abuse, and withdrawal. Assessment for the continued need of hypnotics is recommended every 1–3 months.

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ESSENTIAL DIAGNOSTIC CRITERIA FOR RESTLESS LEGS SYNDROME[1]

- **An urge to move the legs usually accompanied by uncomfortable and unpleasant sensations in the legs, and sometimes the arms or other body parts.**
- **The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.**
- **The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.**
- **The symptoms are more pronounced in the evening or night or may only occur in the evening or night.**

IRON DEFICIENCY AND RESTLESS LEG SYNDROME

- **Iron deficiency is a secondary cause of RLS and can also exacerbate symptoms.**
- **Treatment with iron replacement in survivors with documented iron deficiency can improve symptoms.**
  - **Recommend taking iron replacement with vitamin C (eg, orange juice) to enhance the absorption of oral iron.**
  - **Goal ferritin level is 50–75 µg/L or until alleviation of symptoms.[2]**

The 2021 update for this algorithm is in progress.

[1]Reproduced with permission from Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-119.
[2]Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2016 Dec 13;87:2585-2593.

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GENERAL PRINCIPLES OF WORKING AND RETURNING TO WORK AFTER A CANCER DIAGNOSIS

- These recommendations related to working and returning to work apply to survivors who are post active treatment as well as persons living chronically with cancer. However, discussions about work are ideally best had before treatment begins so that treatment recommendations can take work needs into consideration if possible.
- Symptoms affecting work may wax and wane with a survivor's treatments or disease status, especially if they are living chronically with cancer or the consequences of cancer treatment. Some survivors might start and stop working more than once.
- Most existing literature focuses on unemployment and/or failure to return to work. However, underemployment and/or work limitations due to cancer or side effects are also common.
- Employment helps to protect survivors from financial toxicity, and at least in the United States, is frequently tied to health insurance access. This can be a main reason survivors work even when/if they are not fully recovered.
- Employment is an important source of personal interaction, normalcy, and social support. The psychosocial effects/advantages derived from work may include a sense of purpose, emotional well-being, link to identity, improved quality of life, connection with others, and distraction.
- Some populations are at increased risk for difficulties related to work (based on factors such as gender, age, race, ethnicity, cancer type, cancer stage, rural residence, educational attainment, etc). The increased difficulties in these populations are more likely for survivors with physically or cognitively demanding jobs or jobs with limited flexibility in scheduling or tasks. Additionally, patients with cancer may experience discrimination as a result of diagnosis/illness, and this may be a consideration for some individuals in decisions surrounding employment.
- Survivors should be offered information to help them understand their likely ability to work, take into account their finances and personal/family needs, and discuss potential work accommodations with their employers.
- Clinicians should regularly re-evaluate work-related concerns post active cancer treatment or for persons living chronically with cancer.
  - Periodically identify goals and barriers regarding work with survivor. (See SWORK-3)
  - A team approach may be needed. Consider early involvement of social work, primary care, physical therapy/occupational therapy, cancer rehabilitation, and/or career counseling services, if available.
  - Employment disability forms are not typically well-suited to cancer. However, clinicians should consider the survivor's needs for flexibility in tasks and hours, and other workplace accommodations as a starting point for filling out the necessary forms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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EVALUATION/ASSESSMENT

- Discuss survivor's concerns, needs, goals, and desires related to work
- Assess abilities required for job (eg, cognitive tasks, long periods of standing, use of hands)
- Assess barriers
  - Assess practical concerns regarding employment (eg, transportation, caregiving responsibilities, health insurance coverage, financial toxicity)
  - Assess treatable contributing symptoms:
    - ◊ Fatigue (See SFAT-1)
    - ◊ Pain/neuropathy (See SPAIN-1)
    - ◊ Musculoskeletal/neurologic issues (eg, joint/extremity mobility, deconditioning/ loss of muscle mass, sensory neuropathy)
    - ◊ Cognitive dysfunction (See SCF-1)
    - ◊ Anxiety, depression, distress (See SANXDE-1)
    - ◊ Vision/hearing changes
  - Assess comorbid conditions:
    - ◊ Organ dysfunction[a]
    - ◊ Hematologic dysfunction/Infection risk[b]
    - ◊ Alcohol/substance use

→

TREATMENT OF CONTRIBUTING FACTORS[c]

- Treat contributing symptoms
  - Fatigue (See SFAT-1)
  - Pain/neuropathy (See SPAIN-1)
  - Cognitive dysfunction (See SCF-1)
  - Anxiety, depression, distress (See SANXDE-1) and NCCN Guidelines for Distress Management
  - Musculoskeletal/neurologic issues
  - Vision/hearing
- Treat comorbidities

→ See Additional Interventions for Survivors (SWORK-3)

[a]Organ dysfunction resulting from cancer or cancer treatment that may most impact work include cardiac (see SCARDIO-1), pulmonary, and gastrointestinal.
[b]The majority of solid tumor survivors do not have an increased infection risk. However, infection risk should be assessed in post-transplant survivors.
[c]Treat contributing symptoms/comorbidities with appropriate pharmacologic interventions and/or referrals as needed.

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ADDITIONAL INTERVENTIONS FOR CANCER SURVIVORS

SURVIVOR/FAMILY EDUCATION AND COUNSELING

- Help survivor identify goals with regards to working and barriers to those goals
- Discuss coping strategies for the psychosocial impacts of cancer and cancer treatment
- Provide guidance about expected duration/ management of symptoms or comorbidities limiting employment and return to work
- Recommend that survivors find out about their employer's Human Resources (HR) policies
- Provide resources to understand options and communicate with employer
  (See SURV-B page 2 of 5)
  - Include community-based, national, and online career counseling resources

→

OTHER INTERVENTIONS

- Refer as appropriate:
  - Vocational/occupational rehabilitation specialist
  - Physical or occupational therapist
  - Psychologist
  - State vocational rehabilitative services
  - Neuropsychology evaluation
  - Social worker
  - Financial counselor
- Pharmacologic intervention for underlying causal symptom(s) as indicated (See SWORK-2)

→

Periodic re-evaluation (see SWORK-2)

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Discussion

This discussion corresponds to the NCCN Guidelines for Survivorship. Last updated on 07/14/2020.

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Overview

The number of cancer survivors in the United States increased from approximately 3 million in 1971 to more than 16.9 million in 2019.[1-3] This number is predicted to surpass 22 million by 2030.[3] This striking increase is generally attributed to rising cancer incidence rates (mainly resulting from an aging population), earlier detection, and better treatment.

Approximately 64% of survivors were 65 years of age or older in 2019.[3] Only 5% are younger than 40 years, and survivors of childhood cancer constitute between 0.5% and 3.0% of the survivor population.[4,5] In fact, an estimated 1 of every 5 persons older than 65 years is a cancer survivor. The most common cancer sites in the survivor population are breast, prostate, colon/rectum, and melanoma, together accounting for approximately 58% of survivors.[4] Approximately 64% of survivors were diagnosed 5 or more years ago, whereas 15% of survivors were diagnosed 20 or more years ago, and approximately 5% have survived 30 years or longer.[4]

Unfortunately, many of these cancer survivors experience physical and/or psychosocial late and/or long-term effects of cancer and its treatment, which can be severe, debilitating, and sometimes permanent. Survivors may be discharged from the care of their oncologist and feel isolated and scared. Furthermore, their primary care physicians (PCPs), who may now be responsible for their care, often do not know how best to care for the specific concerns and needs of cancer survivors.[6] ASCO's statement, "Achieving High-Quality Cancer Survivorship Care," cites a need for standardized, evidence-based practice guidelines for the management of treatment effects and health promotion of survivors.[7] ASCO, NCCN, ACS, and other groups that are working in parallel hope to provide this guidance.[8-12]

The NCCN Survivorship Panel is comprised of a multidisciplinary panel of experts that includes at least one oncologist, bone marrow transplant clinician, gynecologist, urologist, infectious disease specialist, cardiologist, PCP, psychologist, nutrition scientist, nurse, epidemiologist, social worker, and patient advocate. The panel has defined general principles of cancer survivorship to help guide the recommendations that form the basis for these guidelines.[13]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Survivorship, an electronic search of the PubMed database was performed to obtain key literature in the field of cancer survivorship, using the following search terms: (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("survivors"[MeSH Terms] OR "survivors"[All Fields] OR "survivor"[All Fields])) OR (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("survivorship"[All Fields])). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[14]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level

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evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

General Principles of These Guidelines

These NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer, including those in specialty cancer survivor clinics and primary care practices. These guidelines are focused on options to maintain and enhance wellness in cancer survivors who are receiving or have completed active therapy, including those receiving treatment for years, those who may be in remission, and those who are cured. These guidelines are designed to provide a framework for the management of long-term and/or late effects of cancer and its treatment. The guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer can have on the adult survivor's health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.

The panel acknowledges that there is a growing population of cancer survivors with chronic cancer. This group includes those with incurable disease who are receiving systemic therapy continuously and those who may be on treatment intermittently. Although these guidelines do not address the specific needs of survivors with chronic cancer (eg, psychosocial issues related to living for years with a terminal diagnosis and uncertainty about the future; how to handle comorbid conditions and disease prevention, screening, and treatment in the setting of limited life expectancy; managing discussions around new drugs and early-stage clinical trials),[15] many of the recommendations in these guidelines are relevant to this population (eg, those around fatigue, anxiety, depression). The panel emphasizes that these guidelines may be used to guide the management of all cancer survivors – not just those who have completed treatment, but also the population with chronic cancer.

These guidelines should be used as a supplement to the follow-up recommendations within the disease-specific guidelines (see NCCN Guidelines for Treatment of Cancer by Site, available at www.NCCN.org) and should provide a framework for the coordination of care between the survivor's health care providers to ensure that needs are appropriately addressed.

These guidelines are not intended to provide guidance for the care of survivors of childhood cancer (detailed guidelines for the care of childhood cancer survivors are available from the Children's Oncology Group at http://www.survivorshipguidelines.org/). For survivorship issues related to younger populations, please also see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at www.NCCN.org). For survivors treated with immunotherapy, ongoing surveillance for immune-mediated toxicities is warranted (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).

For this version of the NCCN Guidelines for Survivorship, the panel focused on the preventive health issues including healthy lifestyle behaviors, immunizations and prevention of infection, and cardiovascular disease (CVD) risk assessment and modification. The panel also focused on several common issues of survivors: 1) anthracycline-induced cardiac toxicity; 2) anxiety, depression, trauma, and distress; 3) cognitive decline; 4) fatigue; 5) lymphedema; 6) hormone-related symptoms; 7) pain; 8) female and male sexual dysfunction; and 9) sleep disorders. Additional topics will be addressed in subsequent updates.

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Cancer Survivors

The NIH adapted the definition of a cancer survivor from the National Coalition for Cancer Survivor and states: “An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. There are many types of survivors, including those living with cancer and those free of cancer. This term is meant to capture a population of those with a history of cancer rather than to provide a label that may or may not resonate with individuals.”[16]

The Effects of Cancer and Its Treatment

For some survivors, the consequences of cancer are minimal; these patients can return to a normal life after the completion of treatment. In fact, most cancer survivors report being in good general health and experience good to excellent quality of life.[17,18] Also, a survey of 659 survivors of breast, colorectal, and prostate cancers found that a majority do not suffer from psychologic morbidity or have a large number of unmet supportive care needs.[19,20] Other studies have similarly found that most survivors enjoy a high quality of life without a large number of cancer-related symptoms.[21,22]

However, many survivors do experience physical and/or psychosocial effects of cancer and its treatment.[23-25] Some sequelae become evident during anticancer treatment (long-term effects), whereas others may not manifest for months or years after active therapy (late effects). The problems can range from mild to severe, debilitating, or even life-threatening. Some problems are temporary or improve with time, whereas other problems are progressive or permanent. This topic has been well reviewed.[18,26]

A literature review suggests that at least 50% of survivors experience some late effects of cancer treatment.[26] The most common problems in cancer survivors are depression, pain, and fatigue.[27] The exact prevalence of various effects of cancer and its treatment are hard to quantify, because few studies have addressed these issues in a longitudinal fashion, comparing patients with and without a history of cancer to differentiate between the effects of cancer and the effects of aging.[18] In general, the prevalence of late effects in cancer survivors is believed to have increased over time, likely because anticancer interventions have become more complex and intense with combinations of surgery, radiation, chemotherapy, hormone therapy, and targeted biologics.[28]

Physical Effects

Physical effects of cancer and its treatment in cancer survivors include pain, musculoskeletal issues, fatigue, lack of stamina, urinary and bowel problems, lymphedema, premature menopause, cognitive deficits, diabetes, and sexual dysfunction.[18,29-32] The effects of cancer treatment on the heart and bone are also well known.[33-36] The type of physical effects depends mainly on the treatment received. For example, radiation to the pelvis can be associated with bowel, urinary, and sexual dysfunction and increased risk for subsequent primary malignancies.[37,38] The ACS Study of Cancer Survivors II found that 38% of survivors reported at least one unmet need in the physical domain (eg, pain, sexual dysfunction).[24]

Subsequent Primary Cancers

Importantly, the overall incidence of subsequent primary cancers in survivors is higher than in the general population because of genetic susceptibilities (eg, hereditary cancer syndromes), shared causative factors (eg, smoking, obesity, environmental exposures, human papillomavirus [HPV] infection), and/or the mutagenic effects of cancer treatment.[39-50] In fact, subsequent cancers accounted for 18% of all cancers diagnosed in the United States between 2009 and 2013.[51] Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.[52-58] These subsequent

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malignancies are especially well studied in long-term survivors of childhood cancers.[59-62] Studies by individual cancer type show that the incidence of subsequent unrelated cancers ranges from 2% in survivors of malignant lymphoma to 30% in survivors of small cell lung cancer (SCLC).[26] Another study of more than 2 million cancer survivors in the SEER database identified the highest risk for subsequent primary cancers in survivors of bladder cancer (34% at 20 years).[63] Overall, this study found that 8.1% of survivors of cancers diagnosed after age 18 years develop a subsequent malignancy within a mean follow-up of 7.1 years, with 55% of these survivors dying as a result of the subsequent cancer.

Screening for subsequent primary cancers should be a shared responsibility between primary and oncology care physicians (see the NCCN Guidelines for Detection, Prevention, & Risk Reduction, available at www.NCCN.org). In addition, lifestyle modifications that reduce the risk of subsequent primary cancers (eg, smoking cessation, physical activity, weight loss) should be encouraged.[64] Finally, referral to genetic risk assessment and/or testing should be considered for appropriate candidates, such as those with a cancer diagnosis at a young age or with multiple primary cancers, to identify those with a potential increased risk for subsequent malignancies.[65] Family cancer history should be periodically updated to reassess hereditary risk, because it should not be assumed that all cancer survivors were assessed at diagnosis. Genetic testing guidelines and knowledge about hereditary cancer risk evolve over time, and new family diagnoses may occur making periodic assessment important. Genetic risk assessment is appropriate for all survivors of breast cancer, epithelial ovarian cancer, high-grade prostate cancer, pancreatic cancer, and colorectal or endometrial cancer diagnosed at age 50 years or younger. Many other survivors of rare cancers, cancers diagnosed at young ages, multiple primary cancers, or those with one or more relatives with the same or related cancers are also candidates for risk assessment per guidelines from NCCN and other expert groups.

Genetic counseling and testing is recommended for appropriate survivors based on results of the risk assessment. Referral to genetic risk assessment and/or testing should be considered for appropriate candidates when available to identify those with an increased risk for subsequent malignancies. Genetic testing may also provide opportunities to identify and reduce risks in relatives of cancer survivors. Several NCCN Guidelines (available at www.NCCN.org) include criteria for genetic risk assessment and testing, and management recommendations for patients with known germline mutations linked to an increased risk for cancer, as listed above in these guidelines.

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Psychosocial Effects

Cancer can have positive effects on a significant portion of individuals, including strengthened relationships, a sense of gratitude or empowerment, and an increased appreciation for life.[66-72] Many survivors, however, experience psychologic distress after active treatment, and some experience a combination of positive and negative psychologic effects. Distress can result from the fear of recurrence or death or secondary to physical, social, or practical problems.[66,69,73] In fact, as many as 19% of survivors meet the criteria for post-traumatic stress disorder (PTSD).[66,69,74-76] Practical and social problems of survivors include issues surrounding employment, finances, and health and life insurance.[66,77-80]

Fear of Recurrence

As many as 70% of post-treatment cancer survivors report high levels of fear of cancer recurrence, which can cause significant and enduring distress.[69,81-84] In addition, caregivers report distress from fear of cancer recurrence in their loved one.[85] These fears and their associated distress may cause survivors and their caregivers to either avoid appropriate surveillance or to demand more intense surveillance than evidence supports.[84] In addition, survivors with high levels of fear of recurrence are more likely to be depressed and have a lower quality of life.[86]

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Employment Issues and Return to Work

Cancer and its treatment often have an adverse effect on work status, performance, and satisfaction.[87] Survivors often take long breaks from or even leave their jobs during treatment, and returning to work after cancer treatment can be critical to restoring normalcy to the lives of survivors. However, survivors may be left with disabilities or late/long-term effects that decrease their employment prospects or ability to perform at their previous levels. Several studies have shown that unemployment rates for survivors are higher than for the general population.[87-90] Furthermore, those survivors who do return to work often encounter difficulties, such as physical or cognitive limitations, fatigue, depression, anxiety, and perceived or real discrimination.[87,91,92]

Several studies have addressed factors that predict a delayed return to work.[93-99] For example, a French population-based study revealed that clinical factors, such as severity of the cancer, receipt of chemotherapy, or the experience of adverse effects, were associated with a delay in return to work.[97] In addition, a systematic review of cohort studies found that survivors who were older, had a lower education level, or had a lower income were less likely to return to work.[98] Another systematic review identified factors related to the person (eg, symptoms, coping, motivation), environmental supports (eg, family, workplace), and occupation (eg, type of work, job flexibility) that impacted successful return to work after cancer treatment.[100]

Some interventions to enhance return-to-work in cancer survivors have been studied (eg, psycho-education, physical training, vocational counseling), although additional research in this area is greatly needed.[101-104] Multidisciplinary interventions that combine vocational counseling with other elements (eg, patient education, patient counseling, behavioral training, physical exercises) may increase rates of return-to-work compared to usual care.

Financial Burden

The LIVESTRONG 2012 Survey found that approximately 33% of working-age survivors went into debt and 3% had filed for bankruptcy.[105] The ACS Study of Cancer Survivors II found that 20% of survivors reported unmet financial needs.[24] A study in Washington state found that patients with cancer have a 2.6-fold increased risk of bankruptcy.[106] In another study, 38% of patients with stage III colon cancer reported financial hardship resulting from cancer treatment, defined as accruing debt, selling or refinancing a home, borrowing money from friends or family, or experiencing a ≥20% decline in annual income.[107] Another study found that, in addition to the average >$16,000 excess economic burden that patients feel in the early phases of cancer treatment, survivors (>1 year from diagnosis) have an average annual excess economic burden that exceeds $4,000.[108,109] Much of this excess burden was because of excess medical expenditures. A more recent study found that the excess annual health care expenditures of cancer survivors averaged about $4400, and that the total mean annual direct health care expenditure for cancer survivors increased by about $1000 in the period from 2009 to 2010 to the period from 2015 to 2016.[109] Other recent studies also found that cancer survivors have greater out-of-pocket expenses and are more likely to experience material hardship than those without a history of cancer.[110,111] Younger cancer survivors seem to be particularly vulnerable to the financial effects of cancer.[111-113]

Clearly, with lost wages and increased expenses, the financial burden on many cancer survivors is great. Recent data suggest that patients belonging to racial and ethnic minorities are more likely to suffer financial hardship after cancer treatment.[114,115] Furthermore, the financial burden associated with cancer treatment and survivorship can lower health-related quality of life, increase psychologic distress, and impact adherence to prescribed medications.[116-119]

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Standards for Survivorship Care

In 2005, the Institute of Medicine (IOM) (now known as the National Academy of Medicine [NAM]) and the National Research Council compiled a report entitled, "From Cancer Patient to Cancer Survivor: Lost in Transition."[28] The NCCN Survivorship Panel adapted the essential components of survivorship care from the report:

1. Prevention of new and recurrent cancers and other late effects
2. Surveillance for cancer spread, recurrence, or subsequent cancers
3. Assessment of late psychosocial, physical, and immunologic effects
4. Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns)
5. Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met
6. Planning for ongoing survivorship care (see below)

In addition, the IOM report discusses the importance of policies that ensure access to and health insurance coverage for all aspects of survivorship care, including psychosocial services. Cancer survivors with untreated distress have poorer compliance with surveillance screenings and are less likely to exercise and quit smoking.[120] A 2008 IOM report, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs,"[121] concluded that psychosocial screening and care should be a part of the new standard for quality cancer care and should be integrated into routine care across the trajectory of cancer, which includes the period after active treatment. See the NCCN Guidelines for Distress Management (available at www.NCCN.org) and *Anxiety and Depression* below for recommendations on screening for and treating distress.

In September 2011, the LIVESTRONG Foundation convened a meeting of experts and stakeholders in the survivorship field to define essential elements of survivorship care. After 2 days of consensus building, the group agreed on the following elements that all medical settings must provide for cancer survivors, either directly or through referral (http://images.livestrong.org/downloads/flatfiles/what-we-do/our-approach/reports/ee/EssentialElementsBrief.pdf):

1. Survivorship care plan, psychosocial care plan, and treatment summary
2. Screening for new cancers and surveillance for recurrence
3. Care coordination strategy that addresses care coordination with PCPs and primary oncologists
4. Health promotion education
5. Symptom management and palliative care

The 2020 Commission on Cancer (CoC) of the American College of Surgeons' accreditation standards for hospital cancer programs (https://www.facs.org/quality-programs/cancer/coc/standards/2020) has a patient-centered focus that recommends and encourages, but does not require, the development and dissemination of a survivorship care plan for all patients completing primary therapy. The current standard requires the development and implementation of a survivorship program directed at meeting the ongoing needs of survivors treated with curative intent. More information can be found on its website.

Implementation of these standards for survivorship care has been challenging, and reasons for the difficulties have been described.[122-124] To move toward the goal of personalized pathways to ensure that all cancer survivors receive all essential components of care, an ACS-ASCO summit identified the following necessary strategies: 1) developing candidate care delivery models; 2) conducting implementation studies to model the effects of personalized follow-up care pathways on survivor outcomes, workforce and health care resources, and utilization and costs; 3) developing

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guidelines to inform the personalized care pathway delivery; and 4) identifying and filling research gaps.[123]

Models of Survivorship Care and the Role of Primary Care Providers

Various models have been proposed to facilitate the implementation of all the essential components of survivorship care for the growing population of post-treatment cancer survivors. These include survivorship clinics within academic or community cancer centers, community survivorship clinics run by primary care clinicians, and survivorship care in the primary care setting.[125-130] In each case, survivorship care is delivered by either physicians or by advanced practice clinicians such as nurse practitioners.[131] Each model has advantages and disadvantages, and no one model is clearly the best for all situations.

With the population of cancer survivors growing at a rapid pace, the demand for follow-up care is expected to increase. An increasing proportion of this care will likely be performed by primary care teams. In fact, a systematic review identified specific needs of cancer survivors in the primary care setting, including psychosocial needs, cancer/survivor information needs, and medical needs.[132] Because studies have shown that primary care providers often do not know how best to care for the specific concerns and needs of cancer survivors,[6,133-138] education for primary health care providers regarding appropriate survivorship care will be increasingly important.[139]

A study in the Netherlands found that patients with cancer 2 to 5 years after diagnosis increased their number of consultations with primary care compared with age- and sex-matched controls without cancer by 15% for colorectal cancer ($P < .05$), 24% for breast cancer ($P < .001$), and 33% for prostate cancer ($P < .001$).[140] These survivors also had more chronic conditions than controls. Although an American study using the SEER-Medicare database showed a smaller increase in primary care use by breast cancer survivors (10% increase in year 4 after diagnosis; $P < .05$),[141] these results show that PCPs are providing a substantial amount of survivorship care. In fact, according to IOM analyses of the 2001 and 2002 National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, approximately one-third of the more than 36 million cancer-related visits to physicians' offices were made to primary care.[28] Furthermore, a nationally representative survey by NCI and the ACS found that >50% of PCPs provide survivors with cancer-related follow-up care, often with co-management by oncologists.[142]

In a survey of survivors regarding their preferences for follow-up care, most participants said that the PCP should only provide care if the responsibility was shared with the oncologist.[143] One of the reasons commonly cited for this preference was that survivors believe their PCPs lack the needed expertise to deal with their specific issues. In addition, survivors cited a desire for continuity of care. Additional surveys of survivors of breast cancer in the United States and of survivors of breast, colorectal, and prostate cancer in the United Kingdom found similar preferences for oncologist-driven follow-up care over PCP follow-up care.[144,145] Importantly, however, two randomized trials comparing survivorship care administered by PCPs (provided guidelines outlining appropriate follow-up care) versus oncologists found no difference in disease-related outcomes, including survival.[146,147]

Survivorship Care Planning

Because primary care offices are in fact already caring for cancer survivors, it is critical for information to be shared between oncology and primary care teams. Good communication at the oncology/primary care interface may allow survivors to feel they have the continuity of care they desire.

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Some data suggest that treatment summaries and survivorship care plans lead to improvements in outcomes for survivors, such as having fewer emotional concerns and more often reporting that their needs have been met.[148,149] However, a randomized controlled trial of 408 survivors of breast cancer that assessed the effects of survivorship care plans found no differences on patient-reported outcomes, including cancer-specific distress, between patients who received a discharge visit and a care plan and those who received only a discharge visit.[150,151] Criticisms of this trial, including the relevance of its outcome measures, have been published.[152-154] Another trial randomized 221 survivors of stage I–III colorectal cancer to usual care or usual care plus a supportive care package that included a survivorship care plan, educational materials, a needs assessment, an end-of-treatment session, and three follow-up telephone calls.[155] No effects on distress, supportive care needs, or quality of life were seen, although survivors in the care plan group were more satisfied with their care. In addition, a trial in which 12 hospitals were randomized to usual care or to patient-tailored, automated survivorship care plans found that the receipt of a care plan was associated with an increase in symptoms, concern about illness, and emotional impact.[156] No differences in satisfaction with information or care were evident.

More recent population-targeted randomized controlled trials are lending some support for the benefits of survivorship care planning. One randomized controlled trial tested the role of survivorship care plans in 212 low-income, predominantly Latina survivors of stage 0–III breast cancer.[157] Survivors in the intervention group received the care plan with a treatment summary and a 1-hour counseling session with a trained, bilingual, bicultural nurse who encouraged patient empowerment; the care plan and treatment summary were also delivered to the health care providers of survivors in the intervention group. Patient-reported physician implementation of recommended survivorship care (eg, for depression, hot flashes), the primary trial outcome, was greater in the intervention group than in the usual care group (P = .003). Patient adherence to recommended survivorship care, the secondary outcome, was also greater for the intervention group, but did not reach statistical significance (P = .07). Whereas this trial provides support for the benefits of survivorship care plans, it is impossible to separate the effects of the care plan and the intensive counseling session, and the applicability of the findings to other populations is unknown. Another randomized controlled trial examined the efficacy of mailing a personalized survivorship care plan, which was designed with qualitative input of hematopoietic cell transplant survivors and briefly reviewed in a telehealth call by a trained non-professional.[149] The study randomized 458 hematopoietic cell transplant survivors 1 to 5 years after transplant to receive the survivorship care plan or delayed survivorship care plan. After 6 months, the survivorship-care-plan recipients reported reduced cancer-specific distress and improved general mental health, although they did not report higher levels of confidence in survivorship information when compared with the delayed care plan recipients as hypothesized. In this study, about two-thirds of survivors reported that they found the survivorship care plan useful in helping them understand their treatments and side effects, and helpful in managing their health. Another randomized trial found that a survivorship care plan, discussed in consultation with a physician who had received skills training, increased patient knowledge about their disease and increased adherence to certain health promotion recommendations.[158] A third trial did not see an increase in survivors' knowledge after provision of a survivorship care plan.[159] At this time, definitive data supporting the benefits of survivorship care plans are still insufficient.[160]

A survey that included a nationally representative sample of 1130 oncologists found that fewer than 5% of them provide a written survivorship care plan to survivors.[161] The survey also included 1020 PCPs, who were nine times more likely (95% CI, 5.74–14.82) to have survivorship discussions with survivors if they received a written care plan.

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More recent surveys have reported that 35% to 40% of survivors receive a written follow-up care plan and/or a written treatment summary.[162,163]

ASCO released a clinical expert statement on cancer survivorship care planning in 2014.[164] The group of experts identified barriers to the successful implementation of survivorship care planning (including the time it takes to complete one, the lack of reimbursement for doing so, and the uncertainty as to whose responsibility it is to prepare the plan) and revised the ASCO survivorship care plan template to help address some of these barriers. In addition, a pilot study assessed the use of electronic health records (EHRs) to reduce the time and effort involved with creating care plans.[165] Although many plan elements required manual entry by the oncologist, the median time to complete the plans was only 3 minutes (range 2–12 minutes). Another group reported on a similar initiative to facilitate generation of care plans using EHRs.[166] Care plan creation took a mean 12 minutes (range 10–15 minutes). However, a study in which EHR-based treatment summaries were abstracted and cross-checked revealed that 30% contained ≥1 omissions, and 10% contained ≥1 errors, indicating that autopopulation systems will require manual double-checking to ensure accuracy.[167] Thus, providing a survivorship care plan is time-consuming and resource-intensive and could have unforeseen harms.[154,168]

Because definitive evidence that survivorship care plans improve outcomes is lacking, the NCCN Survivorship Panel currently recommends planning for ongoing survivorship care, but does not mandate the use of survivorship care plans. The planning should include:

- Information on treatment received including all surgeries, radiation therapy, and systemic therapies
- Information regarding follow-up care**,** surveillance, and screening recommendations
- Information on post-treatment needs, including information regarding acute, late and long-term treatment-related effects, and health risks when possible (See NCCN Guidelines for Treatment of Cancer by Site)
- Delineation regarding roles of oncologists, PCPs, and subspecialty care physicians in long-term care and timing of transfer of care if appropriate
- Healthy behavior recommendations
- Periodic assessment of ongoing needs and identification of appropriate resources

Data from ongoing trials will help inform future recommendations.

Surveillance for Cancer Recurrence

Screening for cancer recurrence is an important aspect of survivorship care. In general, this surveillance is performed by the oncology team. When surveillance is overseen by the primary care team, the oncologist should provide evidence-based recommendations based on currently available guidelines. Specific recommendations for surveillance testing vary between cancer site and stage and individualized patient risk and are not addressed in these guidelines. Please see individual NCCN Guidelines for Treatment of Cancer by Site (available online at www.NCCN.org) for disease-specific surveillance recommendations. Additional lab work, imaging studies, or other studies to evaluate for recurrence should be based on clinical presentation and judgment. The use of radiologic imaging studies (ie, CT) should be based on evidence that early detection of recurrence will improve cancer-related outcomes, because evidence suggests that excess radiation exposure associated with CT imaging may be associated with an increased risk of developing a radiation-associated cancer.[169,170]

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Assessment for Effects of Cancer and Its Treatment

All survivors should be assessed at least annually for symptoms related to cancer and prior cancer treatment, with appropriate follow-up care as clinically indicated. This assessment can be done by the oncologist or PCP. Shared, coordinated care between the oncology, primary care, and subspecialty care providers is encouraged. Depending on the cancer type and stage of disease, transition of care to primary care may be done when deemed clinically appropriate, with referral back to oncologic care as needed. The panel does not assume that all survivorship issues will be addressed at every visit.

Some tools that screen for long-term and late physical and psychosocial effects of cancer and its treatment in survivors have been validated.[171-176] In addition, the NCCN Survivorship Panel created a sample screening instrument that is guideline-specific and can be self-administered or administered by an interviewer. This assessment tool was developed specifically for use in combination with the NCCN Guidelines for Survivorship to help providers deliver necessary and comprehensive survivorship care. Although this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment via validated tools and/or clinical evaluation.

In addition to screening by history and physical examination, care providers should assess the following at regular intervals:

1. Current disease status
2. Functional/performance status
3. Medication use (including over-the-counter medications and supplements)
4. Comorbidities
5. Prior cancer treatment history and modalities used
6. Family history
7. Psychosocial factors
8. Weight and health behaviors that can modify cancer and comorbidity risk (including cigarette/tobacco, alcohol use)
9. Disease-specific recommendations for surveillance/follow-up (see NCCN Guidelines for Treatment of Cancer by Site, at www.NCCN.org)

This information can also inform about the patient's risk for specific late or long-term effects, including risks for subsequent primary cancers and comorbidities. For example, patients who received pelvic irradiation or surgery are at risk for sexual dysfunction; patients with a history of brain metastasis or cranial irradiation have an elevated risk for cognitive dysfunction. In general, those who underwent more intensive therapy are at higher risk for multiple late and/or long-term effects. Survivors undergoing certain treatments, such as mantle field radiation or certain systemic therapies, may be at increased risk for subsequent malignancies. Those survivors who continue to smoke are at increased risk for smoking-related comorbidities and subsequent primary cancers.

Reassessment

Survivors should be followed and reassessed at regular intervals, depending on the nature and severity of late and long-term effects being treated. At each time point, assessment of disease status and ongoing effects of cancer and its treatment should be addressed. In addition, survivors should be periodically rescreened for the development of new late and long-term effects of cancer and its treatment. The outcomes of any interventions for ongoing effects of cancer and its treatment should be evaluated regularly based on best practices and available resources. Outcome assessment may include survivor satisfaction with the effectiveness of the intervention in reducing symptom burden, adequate pain control, receipt of recommended immunizations and preventive care,

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and improved adherence to guideline recommendations for health behaviors.

Survivorship Research

The IOM survivorship report cites a paucity of longitudinal cohort studies linking specific cancer types or treatments with specific late effects, making it difficult to predict risk for individual patients.[28] Research is needed to increase understanding of the prevalence of, mechanisms of, and risks factors for late and long-term effects of cancer and its treatment. In addition, research is needed to better define interventions that relieve symptoms, restore function, and improve the quality of life of survivors.[177] Finally, research can help better define optimal follow-up and surveillance schedules for cancer survivors after treatment.[178,179]

An ASCO survey report highlighted several key gaps in current survivorship research.[180] For instance, more research pertaining to survivors >65 years of age, to survivors of cancers other than breast, and to long-term survivors (>5 years) is needed. In addition, research focused on patterns and quality of survivorship care is lacking. A study of NIH survivorship grants in fiscal year 2016 showed a need for research including more diverse cancer types, older and longer-term survivors, and more ethnoculturally diverse populations of survivors.[181]

In June 2012, the ACS, CDC, LIVESTRONG Foundation, and NCI held a joint meeting and created an action plan to facilitate the translation of survivorship research into survivorship care.[182] The plan is driven by collaboration between researchers, survivors, clinicians, and public health professionals; the use of technology, such as EHRs; analysis of information from the viewpoints of multiple stakeholders; and the integration and synthesis of knowledge using systematic reviews and meta-analyses.

Recommendations for Preventive Health

Analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS) indicates that a large proportion of cancer survivors have significant comorbidities, smoke, are obese, and/or do not engage in physical activity.[183] Analysis of data from other studies, including the National Health Interview Survey, showed similar results.[184-187] Separate surveys by the ACS and the CDC found that 9.3% and 17% of survivors smoke, respectively.[186,188] In addition, many survivors forego recommended cancer screenings (ie, colorectal and cervical screening) and follow-up surveillance[189-191] or demand more intense surveillance than evidence supports.[84]

Healthy Lifestyles

Healthy lifestyle habits, such as engaging in routine physical activity, maintaining a healthy diet and weight, and avoiding cigarette/tobacco use, have been associated with improved health outcomes and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.[192-199] In fact, the maintenance of a healthy lifestyle is associated with a decrease in premature death in cancer survivors.[200] Therefore, survivors should be encouraged to achieve and maintain a healthy lifestyle, including attention to weight management, physical activity, metabolic health, and dietary habits. Setting incremental goals for diet, physical activity, and weight management should be advised. Survivors should be counseled to limit alcohol intake and avoid or stop using cigarette/tobacco products, with emphasis on tobacco cessation if the survivor is a current smoker or user of smokeless tobacco (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[201] Clinicians should also advise survivors to practice sun safety habits as appropriate, such as using a broad-spectrum sunscreen, avoiding peak sun hours, and using physical barriers. Survivors should also be encouraged to get an adequate amount of sleep. Finally, survivors should be encouraged to see a PCP regularly and adhere to age-

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appropriate and treatment-associated health screenings, preventive measures (eg, immunizations), and cancer screening recommendations.

The panel made specific recommendations regarding physical activity, weight management, nutrition, and supplement use, which are discussed herein. Although achieving all of these healthy lifestyle goals may be difficult for many survivors, even small reductions in weight among overweight or obese survivors or small increases in physical activity among sedentary individuals are thought to yield meaningful improvements in cancer-specific outcomes and overall health.[202] Clinicians should assess individual and community-level barriers to meeting the healthy lifestyle recommendations and support patients in developing strategies to overcome challenges.

Physical Activity

During cancer treatment, many survivors become deconditioned and can develop impaired cardiovascular fitness because of the direct and secondary effects of therapy.[203] Randomized trials have shown that exercise training is safe, tolerable, and effective for most survivors. Structured aerobic and resistance training programs after treatment can improve cardiovascular fitness and strength and can have positive effects on balance, body composition, fatigue, emotional well-being, and quality of life.[204-216] The effectiveness of exercise is especially well studied in women with early-stage breast cancer. Survivors of breast cancer who exercise have improved cardiovascular fitness and therefore an increased capacity to perform daily life functions, resulting in a better quality of life.[214,215,217-219] Furthermore, a study of adult survivors of childhood Hodgkin lymphoma found that vigorous exercise was associated with a reduction in the risk of major cardiovascular events after a median follow-up of 11.9 years.[220] In fact, the finding was dose-dependent, and survivors who reported ≥9 metabolic equivalent (MET) h/wk experienced a 51% reduction in risk compared with those reporting <9 MET h/wk (P = .002). A similar study in patients with breast cancer found a similar reduction in the risk of cardiovascular events with ≥9 MET h/wk.[221]

In addition, observational studies have consistently found that physical activity is linked to decreased cancer incidence and recurrence and increased survival for certain tumor types.[209,222-239] For example, one meta-analysis of 6 studies including more than 12,000 survivors of breast cancer found that post-diagnosis physical activity reduced all-cause mortality by 41% (P < .00001) and disease recurrence by 24% (P = .00001).[226] Data from other meta-analyses primarily consisting of observational studies of survivors of colorectal, ovarian, non-small cell lung, brain, prostate, and breast cancers show that physical activity is associated with decreased all-cause mortality and/or cancer-specific mortality.[224,227,236,240] In fact, analyses of data from 986 survivors of breast cancer from the National Runners' and Walkers' Health Studies found that mortality decreased with increased rates of energy expenditure.[237] Evidence in other disease sites is less robust, but also suggests survival benefits associated with exercise in survivors after treatment.[240]

Data also support the idea that inactivity/sedentary behavior is a risk factor for cancer incidence and mortality and impacts mood and quality of life in survivors, independent of the level of an individual's recreational or occupational physical activity.[192,241-247] For example, in a cohort of more than 2000 survivors of nonmetastatic colorectal cancer, those who spent more leisure time sitting had a higher mortality than those who spent more time in recreational activity.[192]

Evaluation and Assessment for Physical Activity

Survivors should be asked about readiness for participation in and their current level of physical activity at regular intervals. The Godin Leisure-Time Exercise Questionnaire is one tool that can be used to assess a survivor's exercise behavior, with a modified version also able to assess daily time in moderate-to-vigorous activity.[248,249]

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For survivors who are not meeting the guideline recommendations (see later discussion), barriers to physical activity should be discussed and addressed, if possible. Common barriers include not having enough time to exercise, not having access to an acceptable exercise environment, uncertainty about safety of exercise post-treatment, lack of knowledge regarding appropriate activities, and physical limitations.[250] Alleviation of pain, fatigue, distress, or nutritional deficits can facilitate the initiation of an exercise program.

Risk Assessment for Exercise-Induced Adverse Events

Exercise is considered safe for most survivors.[214,215,251] However, a significant portion of survivors may have comorbid conditions or risk factors that make them unable to safely exercise without trained supervision.[252] Therefore, a risk assessment is required for all survivors before prescribing a specific exercise program.[214,253] The type of cancer, treatment modalities received, and the number and severity of comorbidities determine risk levels.[251] Thus, disease and treatment history, late and long-term effects, and comorbidities should be assessed. A standardized pre-participation screening questionnaire, such as the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+),[254] can also be considered to identify patients for whom unsupervised physical activity is likely safe versus those for whom it may pose undue risk.

Survivors with peripheral neuropathy, poor bone health, arthritis, or musculoskeletal issues are considered to be at moderate risk for exercise-induced adverse events. Stability, balance, and gait should be assessed in survivors with peripheral neuropathy and possibly in survivors with poor bone health before they engage in exercise, and exercise choice should be made based on the results (ie, stationary bike or water aerobics for survivors with poor balance). In addition, balance training can be recommended for patients at risk for falls. Moderate-risk survivors can often follow the general recommendations for physical activity; however, medical clearance and/or referrals to trained personnel such as a physical or occupational therapist, certified exercise professional, or rehabilitation specialist can also be considered. Specialized training in working with survivors is available for both physical therapists and exercise professionals through the American College of Sports Medicine (ACSM; http://www.acsm.org/get-certified) and the American Physical Therapy Association (APTA) Oncology section (http://oncologypt.org/). Survivors should be encouraged to use an ACSM- or APTA-certified trainer when available.

Lymphedema is not a contraindication for physical activity, and no special precautions are required for cardiovascular/aerobic exercise or strength training of unaffected limbs (see *Survivor Lymphedema Education,* below).[255-260] Progressive resistance training under supervision is recommended as part of treatment for survivors with lymphedema (see *Treatment of Lymphedema,* above).

Survivors at high risk for exercise-associated adverse events include those with a history of lung surgery or major abdominal surgery, an ostomy, cardiopulmonary comorbidities (eg, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF], coronary artery disease [CAD], cardiomyopathy), ataxia, severe nutritional deficiencies, severe fatigue, or worsening/changing physical condition (eg, lymphedema exacerbation). These survivors should receive medical evaluation and clearance prior to initiation of an exercise program and referral to trained personnel for a supervised exercise program.[251] In general, exercise should be individualized to the participant based on current exercise level and medical factors and should be increased in terms of intensity, duration, and frequency as tolerated.

Physical Activity Recommendations for Survivors

Both the ACS and the ACSM have made physical activity recommendations for cancer survivors.[212,261] In addition, the panel also

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considered the physical activity guidelines for Americans published by the Department of Health and Human Services (HHS) and those on diet and physical activity for the prevention of cancer by the ACS.[262,263] The panel supports the recommendations by these groups and has adapted them as follows:

1. Physical activity and exercise recommendations should be tailored to individual survivors' abilities and preferences.
2. Survivors who are able should be encouraged to engage in daily physical activity, including exercise, routine activities, and recreational activities.
3. All survivors should be encouraged to limit sedentary behavior (eg, sitting for long periods) and return to daily activities as soon as possible.
4. Physical activity for cancer survivors:
    - Overall volume of weekly activity should be at least 150 to 300 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity, or an equivalent combination spread out over the course of the week;
    - Individuals should engage in 2 to 3 sessions per week of strength training (see *Resistance Training*, below) that include major muscle groups; and
    - Major muscle groups should be stretched at least 2 days per week on days that other exercises are performed.

The panel acknowledges that most survivors do not meet these exercise recommendations, and a significant portion reports that they perform no leisure-time activity.[183,264] However, the evidence suggests that even light-intensity physical activity can improve physical functioning in survivors.[265] For survivors who are inactive, clinicians should not advise the immediate initiation of a high-intensity, high-frequency program.[266,267] Instead, the panel suggests that clinicians provide sufficient information to encourage survivors to avoid a sedentary lifestyle.[253] Survivors and providers should work together to address barriers to physical activity and develop incremental short- and long-term physical activity goals. These goals may include incremental increases in time spent in physical activity or in intensity of activity over time. The panel suggested a possible initial physical activity prescription (starting inactive survivors with 1 to 3 light-/moderate-intensity sessions of 20 minutes or more per week), with progression based on tolerance.[266] For survivors tolerating the minimum guideline recommendations, clinicians should consider encouraging incremental increases in time spent in physical activity or in intensity of activity. Walking and using a stationary bike are safe for virtually all survivors.

Resistance Training

The health benefits of resistance training include improvement in muscle strength and endurance, improvements in functional status, and maintenance/improvement in bone density. Core and strength training is important to maintain balance and minimize fall risk. Studies in survivors have shown improvements in lean body mass, muscular function, and upper body strength, and a slowing of physical function deterioration.[268-273] A recent systematic review of 15 studies of resistance training interventions during and/or after cancer treatment concluded that meaningful improvements in physiologic and quality-of-life outcomes can be achieved.[270] A similar review of 11 randomized controlled trials came to similar conclusions.[273] One recent study that included 2863 cancer survivors found resistance exercise to be associated with a 33% lower risk of all-cause mortality (95% CI, 0.45–0.99), independent of aerobic exercise.[274]

All major muscle groups (chest, shoulders, arms, back, core, and legs) should be incorporated into a resistance training program. For survivors who do not currently engage in resistance training, referral to trained personnel or an exercise specialist is recommended if available. Clinicians

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should recommend 2 to 3 sets of each exercise at a weight that allows the performance of 10 to 15 repetitions; however, individualizing recommendations for resistance and strength training is important. Survivors can consider increasing the weight when 3 sets of 10 to 15 repetitions become easy.

Interventions to Increase Physical Activity

Dozens of studies have looked at the efficacy of a variety of behavioral and exercise interventions for increasing exercise behavior in cancer survivors.[211,214,275-277] However, data comparing different interventions are limited, and there is currently no "best" physical activity program for cancer survivors.[278-281] Several studies have examined the physical activity and counseling preferences of survivors, with the goal of informing possible strategies to best encourage increased activity in this population.[282-284]

The panel suggests several strategies to help increase physical activity. These strategies include a simple recommendation from a physician, physical therapist, and/or certified exercise physiologist.[285-287] In addition, participation in supervised exercise programs or classes or enlisting the support of an exercise group or buddy may be helpful for survivors.[288-291] In addition, setting short- and long-term goals and considering the use of a pedometer or wearable activity tracker to monitor these goals (eg, achieving 10,000 steps per day) can be helpful.[292-301] Print materials, telephone counseling, motivational interviewing, and theory-based behavioral approaches (discussed in *Health Behavioral Change*, below) are other strategies that may be effective for increasing physical activity in the survivor population.[289,296,302-307] Combination approaches (eg, oncologist recommendation plus exercise DVDs, pedometers, exercise diaries, exercise education sessions) may also increase exercise participation in survivors.[308]

Nutrition and Weight Management

Weight gain after cancer diagnosis and treatment is common, and the prevalence of obesity in the survivor population is greater than in the general population and has increased at a faster rate.[309-311] The vast majority of studies on weight and weight gain in survivors have been performed in survivors of breast cancer, but some studies have also been done in survivors of other cancers. Weight gain or being overweight or obese can exacerbate a survivor's risk for functional decline, comorbidity, and cancer recurrence or death, and can reduce quality of life.[309,312-320] For example, a systematic review and meta-analysis of studies in survivors of breast cancer found a correlation between higher body mass index (BMI) and higher risk of total and breast cancer-specific mortality.[314] Additionally, a meta-analysis demonstrated that this risk for increased breast cancer mortality is predominantly confined to the pre- and perimenopausal, hormone receptor-positive population.[321] A retrospective study of survivors of stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that survivors with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[193,197] In addition, some evidence suggests that weight loss or gain increases mortality risk in survivors, suggesting that weight maintenance is optimal.[322]

ASCO published a position statement on obesity and cancer.[323] The ASCO panel established an initiative to reduce the impact of obesity on cancer through education, tools, and resources for clinicians by promoting research (eg, in health behavioral change) and advocating for policies that can help patients with cancer manage their weight.

Nutrition and Weight Management Assessment

The BMI of survivors should be evaluated at regular intervals. A BMI of 18.5 to 24.9 kg/m^2 is considered ideal. It is important to inform patients of their weight status, particularly if they are underweight (BMI <18.5), overweight (BMI = 25–29.9), or obese (BMI ≥30), and discuss the

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importance of interventions to attain a normal body weight and avoid weight gain in adulthood. The panel notes, however, that BMI should be considered in context of body composition. For more muscular survivors, waist circumference may be a better measure of overall disease risk. A waist circumference of >35 inches for women and >40 inches for men increases risk for diabetes, hypertension, and CVD.[324]

Current dietary and physical activity habits and potential barriers to physical activity or a healthful diet of those in high-risk groups should be ascertained either by the oncologist or other appropriate allied health personnel (eg, nurses, dietitians). In addition, effects of cancer treatment and other medical issues, including psychosocial distress and fear of recurrence, should be assessed and addressed as necessary.

Weight Management for Survivors

Providers should discuss strategies to prevent weight gain for normal and overweight/obese survivors. Clinicians should reinforce the importance of maintaining a normal body weight throughout life and encourage all cancer survivors to achieve and maintain a normal BMI and strive for metabolic health. In conjunction with primary care, survivors should be assessed for metabolic health, body composition, and BMI. Regardless of BMI, all survivors should be advised about the panel's nutrition, weight management, and physical activity recommendations (see pages SNWM-1, SNWM-2, and SPA-1 in the algorithm, above). Contributing treatment effects and risk factors should be managed as clinically indicated. In addition, a workup for disease recurrence should be considered in the setting of involuntary weight loss or gain of >5% within 3 months or if cachexia is present.

For additional resources, see the ASCO Tool Kit on Obesity and Cancer (https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/obesity-cancer) and the LIVESTRONG MyPlate Calorie Tracker (http://www.livestrong.com/myplate/).

Recommendations for Normal Weight Survivors

In addition to discussing nutrition, weight management, and physical activity, clinicians should reinforce the importance of maintaining a normal weight throughout life in survivors with a BMI in the normal range. In particular, the importance of avoiding high-calorie, low-nutrient foods (eg, regular soft drinks, sugary desserts, fried foods) and focusing on lower-calorie, high-nutrient foods (eg, vegetables [especially those lower in starch], broth-based soups, fresh fruit for desserts, and beverages such as water, unsweetened tea, and black coffee) is especially important.

Recommendations for Overweight/Obese Survivors

Survivors with a BMI in the overweight or obese range should be engaged in discussions about nutrition, weight management, and physical activity, as outlined in these guidelines. In addition, clinicians should specifically discuss portion control; substituting high-calorie foods with low-calorie, healthful, nutrient-dense foods; and tracking diet, calories, and physical activity. Clinicians should also refer overweight/obese survivors to a PCP or appropriate hospital-based or community resources. Furthermore, contributing psychosocial factors should be assessed and addressed. Referrals can also be made to a registered dietitian, especially those who are Certified Specialists in Oncology Nutrition (CSO) or members of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics. Diet, exercise, and behavioral modification are the cornerstones of weight management; however, in cases of morbid obesity, pharmacologic agents or bariatric surgery can be considered with appropriate referral to primary care and other providers. Of note, the safety and efficacy of weight loss drugs or bariatric surgery in cancer survivors are currently unknown.

Randomized trials have shown that intensive behavioral weight loss interventions can lead to weight loss in overweight/obese cancer survivors.[325-330] For example, the ENERGY trial used a group-based

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behavioral intervention with telephone counseling and newsletters and achieved a 6.0% weight loss compared with a 1.5% weight loss in the control group at 12 months.[330] In general, however, these trials see some weight regained in survivors at the end of the intervention; maintenance of weight loss remains a challenge in this population.[325]

Recommendations for Underweight Survivors

Survivors with a BMI in the underweight range should be engaged in discussions about nutrition (see below), and contributing psychosocial factors should be assessed and addressed. In addition, advising underweight survivors to increase their frequency of eating and to avoid fluid intake with meals may help with weight gain. Furthermore, smoking status, dental health, swallowing and taste/smell disorders, and gastrointestinal motility should be assessed and addressed as appropriate. Foods that are both high in calories and nutrient-dense (eg, avocados, nuts) should be encouraged. Consideration can also be given to referral to a registered dietitian for individualized counseling.

Nutrition in Survivors

Systematic reviews and meta-analyses of observational studies have shown that healthy dietary patterns are associated with a decreased risk of primary cancer development and improved subsequent outcomes.[331-334] A population study in England with >65,000 participants found that consumption of ≥7 servings daily of fruit and vegetables reduced cancer incidence by 25% (HR, 0.75; 95% CI, 0.59–0.96).[335] A prospective cohort study that included >40,000 participants also found that a healthy diet is associated with a lower risk for cancer (12%; 95% CI, 8%–16%; $P <$ .0001).[336] In addition, results of randomized trials support the link between a healthful diet and reduced incidence of cancer. For instance, results of a randomized controlled trial, in which 4282 women were randomly assigned to a Mediterranean diet with olive oil, a Mediterranean diet with mixed nuts, or a control low-fat diet, suggest that the olive oil/Mediterranean diet reduced the risk of invasive breast cancer (HR, 0.32; 95% CI, 0.13–0.79).[337] In the Women's Health Initiative (WHI) Dietary Modification trial, nearly 49,000 postmenopausal women with a history of breast cancer and with a dietary fat intake of ≥32% of energy were randomized 3:2 to a usual diet group or a dietary intervention group.[338] After an average follow-up of 8.1 years, 655 (0.42%) women in the intervention group and 1072 women (0.45%) in the comparison group developed invasive breast cancer (HR, 0.91; 95% CI, 0.83–1.01). Furthermore, after a median cumulative follow-up of 19.6 years in the WHI Dietary Modification trial, a significant reduction in deaths after breast cancer that was seen after earlier follow-up persisted (HR, 0.85; 95% CI, 0.74–0.96; $P = .01$) and a significant reduction in deaths as a result of breast cancer emerged (HR, 0.79; 95% CI, 0.64–0.97; $P = .02$).[339]

Data also suggest that healthy dietary patterns (as characterized by plant-based diets that have ample amounts of fruits, vegetables, and whole grains, with limited quantities of red and processed meats and refined grains and sugars) are associated with a decrease in cancer recurrence and improved outcomes in survivors.[212,340-342] In survivors of stage III colon cancer, a diet consisting of more fruits, vegetables, whole grains, poultry, and fish, and less red meat, refined grains, and concentrated sweets was found to be associated with an improved outcome in terms of cancer recurrence and death, as well as overall survival.[343] Higher dietary glycemic load (associated with high intakes of refined starches and sugars) was associated with an increased risk of recurrence and mortality in this same population.[344] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intakes of red and processed meat had a higher risk of colorectal cancer-specific mortality than those with low intakes (RR, 1.79; 95% CI, 1.11–2.89).[345] For survivors of non-colorectal cancers, the evidence linking a healthy diet

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with better outcomes is less robust. A study of 1901 survivors of early-stage breast cancer found that a diet higher in fruits, vegetables, whole grains, and poultry and lower in red and processed meats and refined grains resulted in a decreased risk of overall death and death from non-breast cancer causes, but was not associated with risk of breast cancer recurrence or death from breast cancer.[346]

Unfortunately, cancer survivors often do not follow recommendations for a healthy diet and, in some studies, show worse patterns than non-cancer controls.[347,348] For example, a national survey of 1533 adult cancer survivors and 3075 matched controls found that cancer survivors had worse dietary patterns.[348] Other studies show that survivors may make improvements to their diet quality post-diagnosis.[349-351]

Recommendations for Nutrition in Survivors

All survivors should be encouraged to make informed choices about food to ensure variety and an adequate nutrient intake. Recommendations for food sources in a healthy diet are included in the guidelines. In general, a healthy diet is rich in plant sources, such as vegetables, fruits, whole grains, legumes, olive or canola oil, avocados, seeds, and nuts. Fish and poultry are recommended, whereas red meats should be limited and processed meats avoided. Other processed foods and foods and beverages with high amounts of added sugars and/or fats should also be limited. Other nutrition recommendations for survivors include eating a diet that is at least 50% plant-based, with the majority of food being vegetables, fruit, and whole grains, and tracking calorie intake. Self-monitoring of caloric intake has been shown to be an effective strategy for weight management.[352,353]

In addition, survivors should be advised to avoid alcohol, or if partaking, limit alcohol intake to one drink per day for a woman and two drinks per day for a man.[212] This is especially important for survivors of liver, esophageal, kidney, and head and neck cancers, who should refrain from alcohol due to an increased risk of mortality with alcohol consumption.[341,354,355] Survivors of breast cancer do not need to be advised to refrain completely from alcohol consumption, because it has no proven impact on outcomes, but should adhere to general population recommendations.[341,356,357]

Currently, no consensus regarding the role of soy foods in cancer control exists. Several large studies have found no adverse effects on breast cancer recurrence or total mortality related to the intake of soy food.[358-362] In fact, trends towards decreased recurrence and mortality were observed. The panel therefore considers moderate consumption of soy foods (≤3 servings a day) to be prudent.

For patients desiring further recommendations for dietary guidelines, a referral to a dietitian or nutritionist should be considered. The USDA approximate food plate volumes (www.choosemyplate.gov) are:

- Vegetables and fruits should comprise half the volume of food on the plate (30% vegetables; 20% fruit)
- Whole grains should comprise 30% of the plate
- Protein should comprise 20% of the plate

Sources of dietary components:

- Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and fatty fish
- Carbohydrates: vegetables, fruits, whole grains, and legumes
- Protein: poultry, fish, legumes, low-fat dairy foods, and nuts

The use of healthy recipes, such as those found in resources such as the ACS's "Find Healthy Recipes" website, http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/index, should be encouraged.

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Supplement Use in Survivors

Numerous systematic reviews and meta-analyses and a few randomized controlled trials have assessed the role of various vitamins or other dietary supplements for the purposes of primary cancer prevention, cancer control, or preventing cancer recurrence.[363-377] No clear evidence supports an effect of dietary supplements for cancer prevention, control, or recurrence, although a few exceptions may warrant further studies.[378,379] In fact, a prospective cohort study of 2118 postmenopausal cancer survivors found that post-diagnosis dietary supplement use was associated with a trend towards higher mortality among those with a poor diet.[380]

Although the FDA regulates dietary supplement products under the Dietary Supplement Health and Education Act of 1994 (DSHEA),[381] analyses of dietary supplements from multiple manufacturers have found that many products do not contain the purported active ingredient and can contain unlisted ingredients such as cheap fillers (eg, rice, house plants) or banned pharmaceutical ingredients.[382,383] Furthermore, dietary supplements may remain available to consumers even following FDA class I drug recalls.[382]

Despite the lack of data supporting supplement use and the lack of assurance regarding supplement quality, as many as 70% to 85% of survivors take some vitamin or mineral dietary supplements, often without disclosing this information to their physicians.[380,384-386] Thus, the panel recommends that providers ask survivors about supplement use at regular intervals.

The panel notes that supplement use is not recommended for most survivors, except in instances of documented deficiencies (eg, survivors of gastric cancer), inadequate diet, or comorbid indications (eg, osteoporosis,[387] ophthalmologic disorders,[388] cirrhosis[389,390]). Survivors should be advised that taking vitamin supplements does not replace the need for adhering to a healthy diet. If deemed necessary (eg, for survivors taking multiple and/or or unfamiliar supplements), referral to a registered dietitian, especially a CSO, should be considered for guidance in supplement use.

Health Behavioral Change

Lifestyle behaviors are one area survivors can control if they are encouraged to change and are aware of resources to help them. Ambivalence about changing behavior is common in the general population, but among cancer survivors levels of motivation are often heightened, especially close to the time of diagnosis.[205,285,391]

Data suggest that recommendations from the oncologist can carry significant weight for patients with cancer, yet many providers do not discuss healthy lifestyle changes with survivors.[285-287,392] Print materials and telephone counseling are other strategies that may be effective for improving healthy behavior in the survivor population, and several trials show support for these strategies.[289,296,304-307,326,393] In fact, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer.[305,394] Moreover, results of the recently completed Reach Out to Enhance Wellness (RENEW) trial showed that an intervention of telephone counseling and mailed materials in 641 older, obese, and overweight survivors of breast, prostate, and colorectal cancers not only resulted in improved diet quality, weight loss, and physical activity but also had a long-lasting effect that was sustained a year after the intervention was complete.[289] The Exercise and Nutrition Routine Improving Cancer Health (ENRICH) intervention, which includes 6 theory-based 2-hour sessions, has also shown a positive effect on physical activity, diet, weight, and BMI.[395]

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Another strategy, motivational interviewing, may be an effective technique for increasing physical activity and other healthy behaviors in cancer survivors.[302,303] Motivational interviewing focuses on exploring the survivor's thoughts, wants, and feelings and is directed at moving ambivalence so survivors choose to change their behavior.[396] Other behavioral strategies may also be useful, such as improving self-efficacy (ie, the belief that one can perform the actions of new activity and maintain this practice by addressing barriers and planning for behavior change) and self-monitoring.[397,398] Clinicians can consider referral to a provider trained in the techniques of motivational interviewing.

Immunizations and Prevention of Infections

Cancer survivors are at elevated risk for infection because of immune suppression associated with previous cancer treatments, such as chemotherapy, radiation, corticosteroids, certain surgeries, and stem cell transplantation. In fact, antibody titers to vaccine-preventable diseases decrease after anti-cancer treatment.[399,400] In addition, survivors are at increased risk of complications from vaccine-preventable diseases, such as those caused by HPV and influenza viruses.[400,401]

Many infections in survivors can be prevented by the use of vaccines. However, data from the BRFSS found that 42% of survivors did not receive an influenza vaccination in 2009, and 52% reported never receiving a pneumococcal vaccination.[183] Analysis of the SEER-Medicare database showed that survivors of breast cancer, aged ≥65 years, were less likely to receive an influenza vaccination than matched non-cancer controls.[141] A separate analysis of the SEER-Medicare database by another group found similar results.[402]

Vaccines represent a unique challenge in cancer and transplant survivors, because they may or may not trigger the desired protective immune responses due to possible residual immune deficits.[403-405] In addition, certain vaccines, such as those that are live attenuated (eg, zoster [ZVL, MMRV, or VAR]; MMR), are contraindicated in actively immunosuppressed survivors because of an increased risk of developing the disease and/or prolonged shedding of the live organism given in the vaccine.

Risk Assessment and Screening for Immunizations and Prevention of Infections

Survivors are at elevated risk for infections if their cancer treatment included chemotherapy, monoclonal antibodies (eg, rituximab, alemtuzumab), radiation, corticosteroids, splenectomy, CAR T-cell therapy, and/or HCT (which includes peripheral blood stem cell transplantation, bone marrow transplantation, and cord blood transplantation). Risk is also elevated if the survivor has prior or current exposure to endemic infections or epidemics, or has a history of blood transfusion.

Interventions for Prevention of Infections

Infection in survivors can be prevented by education, antimicrobial prophylaxis, and the judicious use of vaccines. For information regarding antimicrobial prophylaxis, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available online at www.NCCN.org).

Education

Survivors should be educated about safe pet care, the avoidance of zoonosis, travel precautions, gardening precautions, proper hand hygiene, and avoidance of respiratory droplets during a respiratory virus pandemic.[406-413] Contact with pets did not increase the risk of fever, bacteremia, pneumonia, and gastroenteritis in children with acute myeloid leukemia (AML),[414] and the panel believes that contact with pets is generally safe for most survivors. However, survivors should wash hands with soap and running water after handling animal feces. If possible,

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survivors at high risk for immune suppression should avoid direct contact with animal feces and other bodily secretions. Survivors with elevated risk of infection and those who are immunocompromised are at higher risk for zoonoses and should use extra caution and avoid contact with exotic animals (ie, snakes, turtles). Travel precautions include education on the need for pre-travel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections.[415] Travelers may find useful information at https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/immunocompromised-travelers or by consulting a travel clinic. Gardening precautions include wearing gloves to avoid cuts and punctures that could be delayed in healing or become infected with fungus or staphylococcus/streptococcus that may be present on thorns, and wearing a protective mask to avoid inhalation of spores.

Immunizations

Vaccination, or "active immunization," involves administration of all or part of a microorganism or a modified product of a microorganism (eg, a toxoid, a purified antigen, an antigen produced by genetic engineering) to produce an immunologic response that mimics that of natural infection but usually presents little or no risk to the recipient. The use of vaccines that do not contain live organisms should be considered and encouraged in all cancer and transplant survivors who have completed immune-suppressive therapy (ie, chemotherapy or antibody-based therapy) at least 3 months prior to the planned vaccination. Patients receiving anti-estrogen or other hormone-modulating therapy do not have to delay vaccination for the completion of therapy. In general, the usual doses and schedules are recommended, as outlined by the Advisory Committee on Immunization Practices (ACIP).[416] The Infectious Diseases Society of America (IDSA) has outlined guidance for vaccination in immunocompromised patients, including those with cancer and those post-HCT.[417] The NCCN Survivorship Panel outlined immunization guidelines specific to survivors of hematologic malignancies and solid tumors, with separate guidelines for survivors who have received cellular therapies (ie, CAR T-cell therapy, HCT). In survivors who received anti–B-cell antibody therapy, vaccination should be delayed for at least 6 months after chemotherapy or the last dose of such therapy to allow for reconstitution of the B-cell population. More details are available in the guidelines.

Before vaccination, immune system viability and history of allergic reactions to vaccines should be assessed. Baseline white blood cell (WBC) counts should be in the normal range or within reasonable limits before starting vaccinations, unless they are elevated because of disease status. The survivor should not be on immunosuppressive drugs or chemotherapy, and ongoing infection should not be present.

The following vaccines should be considered and encouraged for all survivors, and administered according to the usual doses and schedules: influenza vaccine (only inactivated or recombinant); tetanus, diphtheria, pertussis; recombinant zoster vaccine (RZV) in all survivors ≥50 years; and HPV in previously unvaccinated survivors through age 45 years.[416] These vaccines do not contain live organisms; instead, they contain inactivated organisms, purified antigens, bacterial components, or genetically engineered recombinant antigens. Whereas the effectiveness of these vaccinations might be suboptimal because of lingering immune suppression,[405] their administration is likely worthwhile to achieve some protection in the absence of known harm.

Pneumococcal vaccine (PPSV-23/PCV-13) is recommended for all adults aged ≥65 years and those at any age with immunocompromising conditions.[418,419] Pneumococcal vaccination is also recommended for survivors of lung cancer and those who had lung resection. Data from a population-based matched cohort study in Taiwan found that administration of PPSV-23 to ≥5-year survivors of cancer reduced hospitalization for pneumonia.[420] Other vaccines, as listed in the

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guidelines, should be considered in consultation with an infectious disease or travel medicine specialist if unique circumstances in the survivor's lifestyle, upcoming travel, functional or anatomic asplenia, or local epidemic/risks merit their use.

Live Viral Vaccines

Vaccines that contain live attenuated organisms (eg, live-attenuated influenza vaccine; MMR; ZVL; VAR; yellow fever vaccine) are contraindicated in actively immunocompromised survivors because of a proven or theoretical increased risk of disease and prolonged shedding of the live organism present in the vaccine. They should not be offered to actively immunocompromised survivors, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist.

Live viral vaccines can be administered, however, to immunocompetent survivors 3 or more months after chemotherapy or 6 or more months after anti–B-cell antibody therapy, although consultation with an infectious disease specialist or clinician familiar with vaccination in patients with cancer is strongly recommended. Live viral vaccines should not be administered to survivors who had cellular therapies (ie, CAR T-cell therapy, HCT) with active graft-versus-host disease (GVHD) or ongoing immunosuppression. They should only be administered to HCT survivors without active GVHD or ongoing immunosuppression following consultation with an infectious diseases specialist. For all survivors, when other vaccine options exist, they are preferred over live-attenuated vaccines (eg, RZV).

Healthy immunocompetent individuals who live in a household with immunocompromised survivors can receive the following live vaccines with caution: MMR, varicella zoster (VAR, MMRV, or ZVL), yellow fever, rotavirus, and oral typhoid vaccines.[417] Immunocompromised survivors should avoid contact with persons who develop skin lesions after receipt of varicella zoster vaccination until the lesions clear. In addition, immunocompromised survivors should avoid handling diapers of children who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.

Influenza Vaccines

Annual influenza vaccination is recommended for all cancer and transplant survivors.[421] Live attenuated influenza vaccines should be avoided in some survivors (see *Live Viral Vaccines*, above).[422,423] Therefore, preferred vaccines include inactivated influenza vaccines (ie, trivalent [IIV3] standard-dose, trivalent [IIV3] high-dose, and quadrivalent [IIV4] standard-dose) or recombinant influenza vaccine (ie, trivalent [RIV3] or quadrivalent [RIV4]).[416,422,423] Some evidence suggests that the high-dose IIV3 vaccine may provide better protection than standard-dose IIV3 in individuals 65 years or older.[424] No studies have addressed the superiority of any influenza vaccine in the cancer survivor population specifically. Administration of the influenza vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions, as currently recommended for all individuals.[425]

Zoster (Shingles) Vaccine

A new recombinant zoster vaccine (RZV) has become available in the United States. The recombinant vaccine is the preferred zoster vaccine for cancer survivors, and is recommended for survivors aged ≥50 years.[426] Studies have shown it to be safe and effective in survivor populations.[427,428] In survivors who have previously received the live-attenuated zoster vaccine, immunization with RZV should be considered. The recombinant vaccine should not be given sooner than 2 months after administration of the live attenuated vaccine.

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If RZV is unavailable or access to it is an issue, live zoster vaccine can be given as a single dose to survivors aged ≥60 years without active or ongoing immunodeficiency, no history of cellular immunodeficiency or HCT, and who have not received chemotherapy or radiation within the past 3 months, or it can be given at least 4 weeks before initiation of chemotherapy or immunosuppressive drugs.[417,429] Live zoster vaccine can also be considered for survivors aged 50 to 59 years with a history of varicella zoster virus (VZV) infection or VZV seropositivity with no previous doses of VAR vaccine if the recombinant vaccine is unavailable. Live zoster vaccine should be avoided in immunocompromised survivors, but VAR can be considered in transplant survivors without active GVHD or enhanced immunosuppression 24 or more months after transplantation.

Recommendations for Specific Effects of Cancer and Its Treatment

Randomized controlled trials have provided evidence for the effectiveness of interventions for cancer survivors to lessen symptoms such as depression, fatigue, pain, sleep disorders, and sexual dysfunction.[179] The NCCN Survivorship Panel used such evidence as the basis for the recommendations in these guidelines. When evidence in survivorship populations was lacking, extrapolation from other populations was used as deemed appropriate. The panel also evaluated existing guidelines from other organizations as appropriate when making recommendations. Otherwise, expert opinion and panel consensus was used to form recommendations. These recommendations and their evidence base are discussed below. The panel also notes that referral to other health care disciplines/providers or community resources may be used to address several indications or identified issues with one intervention (eg, rehabilitation for fatigue, depression, and pain).

Cardiovascular Disease Risk Assessment

CVD and cancer are the two leading causes of death in the United States, together accounting for approximately 44% of deaths in 2017.[430] CVD is also a leading cause of death in cancer survivors; for survivors of most cancer types, it is the most common cause of non-cancer death.[431] In fact, survivors of most cancers have a markedly increased risk of developing CVD compared with non-cancer populations.[432-435] One reason for this increased CVD risk in cancer survivors is that cytotoxic, hormonal, and targeted systemic cancer therapies (eg, HER2-directed therapy, VEGF signaling pathway inhibitors, cisplatin, anthracyclines with or without taxanes, androgen deprivation therapy [ADT]) and radiation therapy are associated with cardiovascular toxicities and can result in diverse cardiovascular issues, including cardiomyopathy, hypertension, hyperlipidemia, cardiac arrhythmia, myocardial infarction, and cerebrovascular accidents.[436-444] In addition, shared risk factors for both cancer and CVD likely contribute to the development of CVD and structural heart disease or heart failure in cancer survivors. These risk factors include well-established and well-studied risk factors such as tobacco use, obesity, and poor health behaviors, as well as recently discovered ones. For example, somatic mutations in blood cells cause clonal hematopoiesis of indeterminate potential (CHIP) and increase the risk of hematologic malignancies; CHIP is also emerging to be an important causal risk factor for CVD.[445] Other well-defined CVD risk factors (eg, hypertension, hyperlipidemia, diabetes) are more common in cancer than non-cancer populations.[446,447] Most CVDs (eg, atherosclerosis) develop over time as a result of these and other risk factors. Thus, the risk of CVD-related death varies with years from cancer diagnosis, with most survivors being at greatest risk 5 or more years after diagnosis and completion of curative therapy.[448]

Control of CVD and shared CVD/cancer risk factors can decrease the risk of subsequent cardiovascular events.[448,449] Data show that attention to and

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counseling about CVD/cancer risk factors may improve cancer- and cardiovascular-related outcomes. [450] However, data also show that fewer than half of cancer survivors discuss diet, exercise, or smoking or other lifestyle changes with their physician.[287,446]

Tools exist to help quantify atherosclerotic CVD risk (eg, ASCVD risk score[451]), but these tools do not take into account cancer treatment history (eg, anthracycline or tyrosine kinase inhibitor [TKI] exposure) and thus may not accurately capture true CVD risk in a given survivor.

The panel recommends that physicians provide CVD risk assessment and counseling on CVD risk factor management to all cancer survivors throughout the survivorship continuum. The assessment should include: 1) pre-existing and emerging CVD including CAD, CHF, peripheral vascular disease, and arrhythmias including atrial fibrillation; 2) CVD risk factors including hypertension, dyslipidemia, obesity, cigarette/tobacco use, and diabetes mellitus; 3) cancer treatment history including systemic therapy regimen and radiation field, including cumulative doses received of applicable cardiotoxic therapies; and 4) diet and exercise habits and cigarette/tobacco use. The counseling should include discussions of any increased risk of CVD the survivor may have based on prior cancer treatment, comorbidity, or CVD risk factors and on the ABCDE's of CVD Prevention. Interventions for modifiable risk factors should be recommended as appropriate. Cooperation and shared care with primary care providers, and with cardiovascular specialists as needed, is key to optimizing cardiac and vascular outcomes in cancer survivors. Referral to cardio-oncology or a cardiology specialist should be considered for cancer survivors deemed to be at high risk for the development of CVD.

The *ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors* table in the Guidelines above was adapted from a paradigm developed to address CVD risk factors in survivors of breast and prostate cancer.[452,453] The table includes items such as aspirin use for secondary prevention (with clinician-survivor discussion required for primary prevention with careful weighing of benefits and risks), blood pressure monitoring/management, cholesterol assessment/management, healthy lifestyle recommendations including diet/weight management and exercise, and an echocardiogram (ECHO) and/or electrocardiogram (ECG) based on individual risk.

Anthracycline-Induced Cardiac Toxicity

Many cancer treatments, including chemotherapeutics, targeted agents, hormonal therapies, and radiation, are associated with cardiovascular toxicities.[436-442] Cardiovascular sequelae can include arrhythmias, pericardial disease, hypertension, thrombosis, cardiomyopathy/heart failure, and vascular and metabolic issues. Survivors of some cancer types have a markedly increased risk of developing CVD compared with non-cancer populations.[432-434] As a result, a new field, called “Cardio-Oncology,” focused on the cardiovascular health of patients with cancer and survivors has become established.[448,454]

Anthracyclines (eg, doxorubicin, epirubicin, daunorubicin) are used to treat many cancer types, including lymphoma, sarcoma, and breast cancer, and are among the best-studied and most common causes of cancer treatment-induced cardiac injury.[455-457] The mechanism by which anthracyclines cause cardiomyopathy is not fully understood, but likely involves the formation of reactive oxygen species (ROS), oxidative injury, and the subsequent induction of apoptosis in cardiac cells.[458] A role for topoisomerase-IIβ in cardiomyocytes in the production of ROS in response to anthracyclines has been suggested.[459]

Studies suggest that the incidence of clinical CHF after anthracycline-based therapy for adult-onset cancer is <5%.[460-463] For instance, in the NSABP B-31 trial of patients with breast cancer, the rates of symptomatic heart failure after 7 years were 4% in patients treated with anthracycline-

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based chemotherapy and trastuzumab and 1.3% in those treated with anthracycline-based chemotherapy alone.[462] However, a significantly higher percentage of patients have evidence of subclinical heart failure with reports of asymptomatic left ventricular ejection fraction (LVEF) decline being 9% to 50% in various studies.[460,464-466]

The panel has focused specifically on anthracycline-induced cardiac toxicity in these guidelines. Other systemic therapies (eg, HER2-targeted agents, angiogenesis inhibitors, immunotherapies) may cause cardiomyopathy or other myopathies like myocarditis,[437,467,468] and the panel acknowledges that some of the concepts presented in these recommendations may apply to these other cardiomyopathies. However, it is important to note that fewer data are available on the cardiomyopathies associated with non-anthracycline systemic therapies and that these cardiomyopathies may differ in nature from those induced by anthracyclines.[437] More research is needed to understand the specific mechanisms of cardiomyopathies associated with newer agents. In addition, the panel emphasizes that the approach to cardiomyopathy may be different than the approach to other cardiac diseases such as CAD, which could occur, for example, as a result of radiation therapy.[469]

Panel Considerations Regarding Anthracycline-Induced Cardiac Toxicity

Anthracycline-induced heart failure may take years or decades to manifest. Previous dogma has suggested that anthracycline-induced heart failure portends poor prognosis and is not responsive to therapy. However, emerging data in heart failure due to other types of cardiac injury suggest that signs of cardiac dysfunction can be seen early, prior to the development of symptoms.[470] Additionally, data from these other types of cardiac injury suggest that early intervention with cardioprotective medications results in better long-term cardiac function.[471,472] It is possible that if anthracycline-induced cardiac dysfunction is detected early, it may also be responsive to cardioprotective medications.[437,470-473] In fact, data from a prospective study that followed 2625 patients who received anthracycline-containing therapy through the survivorship phase suggest that early initiation of heart failure therapy may allow for at least partial recovery of LVEF in this population.[464] In this study, survivors were started on treatment when LVEF decreased by >10 absolute points and was <50%. A full recovery was observed in 11% of treated survivors (LVEF increased to the baseline value), and 71% had partial recovery (LVEF increased by >5 absolute points and reached >50%). In addition, a growing body of preclinical, observational, and pilot research suggests that lifestyle changes, such as weight control,[474-476] dietary modification (either through correcting dietary deficiencies or increasing intake of various nutrients),[477] and exercise,[220,221,478-480] may also be helpful at these early stages, prior to the onset of heart failure symptoms, although more research is necessary.[481,482]

These emerging issues in anthracycline-induced cardiomyopathy are consistent with the changes in the cardiology community's approach to heart failure at large. Clinical heart failure has established risk factors, and the earliest signs of heart failure begin with the accumulation of these risk factors over time, ultimately resulting in structural cardiac abnormalities and later symptomatic heart failure. As a result, more than a decade ago, this evolutionary and progressive nature of heart failure was recognized by cardiologists and incorporated into the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Evaluation and Management of Heart Failure.[483] In 2001, the AHA/ACC guidelines proposed a new classification for heart failure.[483] Traditional classifications only recognized heart failure when patients presented with clinical signs and symptoms. The 2001 classification scheme, in contrast, introduced stages of heart failure beginning before the patient is symptomatic, and emphasized the importance of prevention in heart failure management.

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The panel believes that this revised AHA/ACC classification is particularly relevant to cardio-oncology populations. Therefore, in formulating the present recommendations for screening, evaluation, and treatment of cardiac dysfunction in survivors who received anthracyclines during their cancer treatment, the panel took into consideration the updated AHA/ACC classification and guidelines for management of heart failure. For these NCCN Guidelines for Survivorship, the panel emphasized early recognition of cardiac toxicity with the goal of preventing the development of clinical, symptomatic heart failure by addressing other known risk factors for heart failure. In particular, appropriate use of cardioprotective medications, such as neurohormonal antagonists (ie, angiotensin-converting enzyme [ACE] inhibitors, beta-blockers), can be considered with the goal of preventing cardiac remodeling over time in some patients. In this respect, the panel emphasizes a thorough clinical screen for heart failure for all survivors with exposure to anthracyclines after completion of therapy, with the additional consideration of an echocardiographic screen in high-risk survivors, as discussed in more detail below. The panel also believes that early involvement of a cardio-oncologist or cardiologist in the care of the cancer survivor is important. Therefore, there should be a low threshold for referral to a cardio-oncologist or cardiologist. In addition, symptoms of heart failure may mimic other conditions such as pulmonary issues and/or cardiac ischemia; therefore, a global approach may be necessary when assessing survivors with decreased cardiorespiratory fitness.[484]

Classification of the Stages of Heart Failure

The revised AHA/ACC classification identifies patients who do not have symptoms associated with heart failure but are either at risk for heart failure (Stage A) or have structural abnormalities of the heart (Stage B).[483] This revised classification has both diagnostic and therapeutic utility, because evidence suggests that treatments prescribed in the absence of structural heart abnormalities or symptoms can reduce the morbidity and mortality of heart failure in the general population.[437,464,470-473] Left untreated, however, the accumulation of cardiac risk factors leads to injury or stress on the myocardium and generates a cascade of signaling events in the heart. The subsequent change in the geometry and structure of the left ventricle, often referred to as cardiac remodeling (Stage B), may manifest as cardiac hypertrophy or chamber dilatation. In other cases, the result may be decreased cardiac contractility, which can result in decreased LVEF (also Stage B). Cardiac remodeling generally precedes the development of symptoms (by months or even years), continues after symptoms become evident, and contributes substantially to symptom progression and mortality despite treatment. Individuals are considered to have Stage C heart failure when clinical signs and symptoms accompany structural changes to the heart. Stage D is the most advanced stage, with patients showing advanced structural heart disease and significant heart failure symptoms at rest that are refractory to medical therapy; these patients require specialized interventions.

The panel also considered the New York Heart Association's (NYHA) functional classification of heart failure.[485] In this system, which is based on limitations to physical activity and the effect of physical activity on heart failure symptoms, NYHA Class I is similar to AHA/ACC Stage B, while NYHA Class II and III would be considered AHA/ACC Stage C and NYHA Class IV is similar to AHA/ACC Stage D.

Assessment for Anthracycline-Induced Cardiac Toxicity

The panel recognizes a lack of high-quality data to inform the benefits of screening for heart failure among patients treated with anthracyclines. However, the panel believes that all survivors who have completed anthracycline therapy should undergo a clinical evaluation to assess for signs and symptoms of heart failure. The lack of data is illustrated in a 2007 clinical evidence review by ASCO, which concluded that no studies had systematically addressed the benefits of screening adult cancer

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survivors with a history of anthracyclines for cardiotoxicity.[486] The review also found no direct evidence showing the effectiveness of cardiac treatment on outcomes of asymptomatic survivors.[486] A 2008 multidisciplinary task force from the Children's Oncology Group came to largely similar conclusions regarding screening for cardiotoxicity in survivors of pediatric cancers.[487] Some reasons for the lack of data on screening survivors for cardiotoxicity have been discussed,[488] and, unfortunately, high-quality data have not been forthcoming since ASCO's 2007 review.

In the absence of data, the Children's Oncology Group relied on the collective clinical experience of its panel members and recommended echocardiograms or comparable imaging to evaluate cardiac anatomy and function for survivors of pediatric cancer at the conclusion of treatment and then every 1 to 5 years for life depending on age at treatment, anthracycline dose, and chest irradiation (http://www.survivorshipguidelines.org). An international collaborative supports lifelong echocardiographic surveillance at least every 5 years in survivors of childhood cancer treated with anthracyclines.[489] Although the frequency of cardiac assessment using echocardiograms or multigated acquisition (MUGA) scans in this population has been a matter of debate, there is general support for at least one assessment in children who have completed anthracycline therapy.[490,491]

A 2014 joint expert consensus statement from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommends yearly cardiovascular assessment of adult survivors after the completion of potentially cardiotoxic therapy to look for early signs and symptoms of CVD, with cardiac imaging used at the discretion of the clinician.[492] The groups recommend echocardiogram as the preferred imaging modality, when imaging is performed. The report also acknowledged the limited data available to inform their recommendations.

In 2017, ASCO released a clinical practice guideline for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers.[493] The ASCO panel gave a moderate-strength recommendation (as based on evidence and the balance between harms and benefits) that echocardiogram can be performed for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction at 6 to 12 months after treatment, including survivors with a history of anthracycline therapy. Insufficient evidence prevented the ASCO panel from making a recommendation regarding the frequency and duration of additional surveillance of survivors who are asymptomatic and who showed no signs of cardiac dysfunction on initial assessment.

The NCCN Survivorship Panel defined its screening recommendations based largely on consensus and on the idea that early recognition and treatment of cardiotoxicity can allow for earlier interventions that may improve prognosis (discussed below).

Assessment for Symptoms of Heart Failure

According to the 2013 AHA/ACC guidelines, the cardinal manifestations of clinical heart failure (Stage C) include dyspnea and fatigue (which may lead to limited exercise tolerance) or fluid retention (which may lead to pulmonary and peripheral edema).[494] These symptoms can lead to decreased functional capacity and affect quality of life. Heart failure symptoms associated with fluid retention may also include orthopnea or paroxysmal nocturnal dyspnea. Therefore, the panel recommends a history and physical to look for these symptoms to help identify survivors who might already be symptomatic. These survivors should undergo evaluation with an echocardiogram. If no evidence of structural heart disease is seen, then a workup for other causes of the symptoms is warranted with referral to other specialties (eg, pulmonology or cardiology) as needed. Symptomatic survivors with evidence of structural heart disease require immediate referral to a cardio-oncologist or cardiologist.

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Assessment of Comorbidities and Cardiovascular Risk Factors

The panel recommends assessment of comorbidities and other traditional risk factors for heart disease (see *Cardiovascular Disease Risk Assessment*, above). Furthermore, the oncologic history of the survivor should be reviewed. Chest radiation can increase the risk of ischemic cardiac disease, which can contribute to heart failure.[436,442,448,495] The addition of other cardiotoxic therapies (eg, HER2-targeted agents) to anthracyclines can further increase the risk of heart failure over that seen with the use of anthracyclines alone.[496] Older survivors, those with a higher cumulative anthracycline dose (cumulative doxorubicin dose of 250 mg/m^2 or equivalent[497]), those with underlying CVD or risk factors, and those who had a low-normal (50%–54%) baseline ejection fraction are also at increased risk for the development of heart failure. Recent data also showed that being overweight or obese and visceral and intramuscular adiposity are risk factors for cardiotoxicity from anthracyclines in breast cancer survivors.[498,499] In addition, the risk of cardiac events and death in survivors of breast cancer has been shown to increase as the number of cardiovascular risk factors increases.[500]

Imaging

When developing these imaging guidelines for screening for cardiac toxicity in survivors with a history of anthracycline exposure, the panel considered several questions: 1) Is the prevalence of structural heart disease high enough to warrant screening of anthracycline-treated survivors?; 2) Is an abnormal echocardiogram post-anthracycline therapy associated with an increased risk for the future development of symptomatic heart failure?; and 3) Does the recognition of cardiac abnormalities and treatment of cardiac risk factors post-anthracycline therapy affect outcomes?

As for the prevalence of structural heart disease in patients treated with anthracyclines, a study of 2625 patients with cancer (mostly breast cancer or non-Hodgkin lymphoma) assessed LVEF before, every 3 months during anthracycline chemotherapy and during the following year, every 6 months for the next 4 years, and annual after that.[464] Cardiotoxicity, defined as LVEF <50% and decreased by >10 absolute points, was observed in 9% of the study population. In the large randomized controlled NSABP B-31 trial, cardiac function was assessed by cardiac imaging in patients after initial anthracycline-based therapy as a requirement for further treatment with trastuzumab.[501] Over 7% of patients experienced cardiac symptoms and/or a decrease in LVEF of >15% after receiving anthracyclines, thus excluding them from being considered for trastuzumab. It is important to note that this was a clinical trial patient population without significant cardiac risk factors or history of cardiac disease. In a non-clinical trial population of patients with cancer, many may already have cardiac risk factors or actual cardiomyopathy prior to treatment, thus elevating the risk of developing heart failure. Together, these results indicate that a significant proportion of survivors with early-onset Stage B or greater heart failure can be identified with appropriate imaging after therapy. However, it is not clear that these declines in LVEF after anthracycline therapy were associated with an increased risk of developing subsequent heart failure.

Regarding the second question, little is known regarding the natural history of heart failure in survivors with Stage B heart failure post-anthracycline therapy, and the long-term prognosis of survivors with cardiac structural abnormalities following anthracycline exposure is not known. However, regarding the final question, limited evidence suggests that further remodeling of the heart may be able to be mitigated by initiation of cardioprotective medications. A number of observational and retrospective studies have suggested that early intervention with cardioprotective medication may decrease the rate of cardiac remodeling and progression to heart failure. A randomized controlled trial of 135 survivors of pediatric cancer with ≥1 cardiac abnormality found that the angiotensin-converting enzyme (ACE) inhibitor enalapril reduced left

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ventricular end-systolic wall stress compared to placebo (P = .03).[473] The authors concluded that any theoretical benefit of reduced left ventricular end-systolic wall stress must be weighed against the side effects of treatment; dizziness or hypotension was observed in 22% of the treatment group versus 3% of those receiving placebo (P = .0003), and fatigue was observed in 10% versus 0% (P = .013) of participants. More recently, a review of 247 patients with cancer and declines in LVEF at the Stanford cardiology clinic found that mean LVEF increased after treatment (most often with ACE inhibitors and beta-blockers) and rose to ≥50% in 77% of patients.[472] In addition, a study of 201 adult patients with cancer, who were treated with anthracyclines and had an LVEF of ≤45%, found that earlier initiation of enalapril (and sometimes the beta-blocker carvedilol) was associated with a higher likelihood of LVEF recovery.[470] In addition, in the larger study by this group (2625 patients), heart failure therapy was initiated in all patients with LVEF <50% that had decreased by >10 absolute points, and 82% of patients experienced a full or partial recovery.[464] In the non-cancer setting, a randomized controlled trial of >4200 participants found that treatment of patients with asymptomatic left ventricular dysfunction (ejection fraction ≤35%) with enalapril reduced the incidence of heart failure compared with placebo (20.7% vs. 30.2%; P < .001).[471]

Considering these data, the panel believes that survivors with a high cumulative anthracycline dose (ie, cumulative doxorubicin dose ≥250 mg/m^2 or equivalent) or a low cumulative anthracycline dose and 1 or more heart failure risk factors (ie, hypertension, dyslipidemia, diabetes mellitus, family history of cardiomyopathy, age >65 years, low-normal baseline LVEF [50%–54%], history of other cardiovascular comorbidities [atrial fibrillation, known CAD, baseline evidence of structural heart disease], smoking, obesity) can be considered for assessment for structural heart disease with appropriate cardiac imaging within 12 months of the last anthracycline dose. In one study with a median follow-up of 5.2 years, 98% of cases of cardiotoxicity were observed within the first year after treatment.[464] The prevalence of late-onset cardiotoxicity has not been well studied beyond 5 years, but the panel acknowledges that longer-term cardiovascular surveillance may be needed for survivors of certain cancer types (see the NCCN Guidelines for Treatment of Cancer by Site, at www.NCCN.org, for specific monitoring recommendations).

The panel recommends two-dimensional echocardiogram, coupled with Doppler flow studies, as the cardiac imaging modality of choice when imaging is performed. This technique is widely available and inexpensive, gives no radiation exposure, and is the most useful diagnostic test in the evaluation of patients with possible heart failure.[502,503] It can recognize early stages of heart failure by revealing abnormalities of the pericardium, myocardium, and heart valves.[494] While radionuclide ventriculography (also called radionuclide angiography or MUGA scan) can provide accurate measurements of left ventricular size and function and assessment of ventricular enlargement, it cannot assess valvular abnormalities or cardiac hypertrophy and exposes patients to radiation. Other imaging modalities for the assessment of heart failure have been reviewed elsewhere.[502,504]

In agreement with these guidelines, ASCO's guidelines that address monitoring of cardiac toxicity after treatment in survivors of adult-onset cancer indicate that echocardiogram can be considered for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction, including survivors with a history of anthracycline therapy.[493]

Biomarkers

The panel recognizes the growing body of literature suggesting the possible utility of cardiac biomarkers (specifically troponin) as a non-invasive marker of cardiotoxicity. The panel believes that more prospective, multi-institutional studies are needed, but that biomarker use can be considered in select patients at high risk for heart failure. The

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optimal timing of troponin assessment in relation to completion of chemotherapy is currently unclear, the cut-off point for a positive test is undefined, and the optimal assay platform remains to be determined. In addition, the sensitivity and specificity of troponin I levels for predicting cardiotoxicity are fairly low, reported at 48% (95% CI, 0.27–0.69) and 73% (95% CI, 0.59–0.84), respectively.[505] A systematic review of the role of post-treatment cardiac troponins as predictive markers of anthracycline-induced left ventricular dysfunction revealed few studies and inconsistent data.[506] The utility of other potential cardiac biomarkers has been reviewed elsewhere.[504]

Treatment of Anthracycline-Induced Cardiac Toxicity

Progression of heart failure is accelerated with accumulation of risk factors. Injury or stress on the myocardium (such as during and after treatment with anthracyclines) can lead to activation of endogenous neurohormonal systems, which play a critical role in cardiac remodeling and therefore progression to Stage B heart failure.

The panel recommends that heart failure risk factors, including hypertension, obesity, metabolic syndrome, and diabetes, be addressed in all survivors who have completed anthracycline therapy. In addition, survivors with a history of anthracycline therapy should be advised to engage in regular physical activity, eat a healthy diet, and avoid behaviors that may increase the risk of heart failure or CVD (eg, cigarette/tobacco or illicit drug use). Physical activity has been shown to improve control of hypertension and to slow cardiac remodeling in breast cancer survivors with heart failure.[507] Involvement of the survivor's primary care provider in managing risk factors is encouraged.

The panel recommends that a low threshold be established for referral to a cardio-oncologist or cardiologist for all patients previously treated with an anthracycline. Additional recommendations for each stage of heart failure are discussed below.

Treatment of Stage A Heart Failure

Stage A heart failure recognizes several well-established risk factors, each of which contribute to early stages of heart failure. These include hypertension, CAD, diabetes mellitus, a family history of heart failure, or a history of cardiotoxins such as anthracyclines. Therefore, all survivors with exposure to anthracyclines have, by definition, at least one risk factor that predisposes them to cardiac disease and should be treated as appropriate. Other anti-cancer systemic therapies are potentially cardiotoxic and may increase the risk of cardiac disease.[439] Involvement of the survivor's PCP in the management of survivors with cardiac risk factors is encouraged. Management can include addressing underlying risk factors, recommending physical activity and healthy dietary habits, and referral to a cardiologist.

Treatment of Stages B, C, and D Heart Failure

The panel recommends referral to a cardiologist for all survivors with Stages B, C, or D heart failure. The sooner treatment is initiated, the more likely it is to be successful.[470]

Anxiety, Depression, Trauma, and Distress

Cancer survivors are at elevated risk for anxiety, depression, and other forms of psychosocial distress and mental health concerns. A large nationwide matched cohort study in Sweden found that mental health disorders can persist in survivors for as long as 10 years post-diagnosis.[508] Unfortunately, the majority of community-based physicians report insufficient psycho-oncology services and difficulty in the referral process, such that psycho-oncology needs often do not receive the attention they need.[509]

Many cancer survivors do not have psychiatric clinical diagnoses but still have symptoms that can have a negative impact on quality of life and require further evaluation and intervention. Such survivors have what the

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NCCN Guidelines for Distress Management (available at www.NCCN.org) define as distress: "a multifactorial unpleasant experience of a psychological (ie, cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with one's ability to cope effectively with cancer, its physical symptoms, and its treatment." Distress, often related to fear of recurrence, is common in survivors and can negatively impact quality of life.[19,69,510-512] Survivors with untreated, uncontrolled emotional distress are less likely to adhere to recommended surveillance and are less likely to engage in health-promoting activities, such as exercise and smoking cessation.[120] Sometimes these individuals develop thoughts of ending their lives; the incidence of completed suicide among patients with cancer and survivors in the United States is about twice that of the general population.[513-518]

Risk factors for psychosocial distress in cancer survivors include persistent problems with physical health; enduring physical signs of cancer/negative body image; a tendency towards self-criticism; non-white race; low educational, financial, or social support; financial concerns; being unmarried; and having survived multiple primary cancers.[519]

Fear of recurrence, with persisting worry and distress sometimes reaching levels of clinical anxiety, is common, occurring in up to 80% of cancer survivors.[519] This fear can increase at times of routine cancer surveillance testing or with physical symptoms that may or may not be related to the cancer diagnosis.[19,69,510-512,520] Anxiety and/or depression can also occur in survivors secondary to physical compromise, social isolation, or work and financial problems that result from cancer treatment.[66,69,73,512,521] These challenges are accentuated by the usual decreased medical and interpersonal support following completion of treatment and transition to the surveillance phase of care.[179]

Anxiety and/or depression affect up to 29% of survivors.[66,69,74-76,522,523] Studies also show that 17% to 38% of survivors have PTSD symptoms while 5% to 12% meet full criteria, and symptoms do not resolve with time for many survivors.[519] A meta-analysis determined the log odds ratio for a PTSD diagnosis in cancer survivors compared with non-cancer controls to be 1.66 (95% CI, 1.09–2.53).[524] In one longitudinal study, 12% of survivors reported that their PTSD symptoms resolved over 5 years, whereas 37% reported that their symptoms persisted or worsened during that time.[75] Another study found that 22% of survivors had PTSD symptoms at 6 months, and 6% had such symptoms at 4 years.[525] PTSD symptoms in survivors can fluctuate over time, because of other events or trauma occurring in the survivor's life.

The panel's recommendations for the management of anxiety, depression, and distress in survivors adhere to the following general structure: screen regularly, refer those with needs beyond the clinician's scope of expertise, and ensure the safety of the survivor. Referral to mental health services may include a psychiatrist, psychologist, advanced practice clinicians, and/or social worker, or management with oncology or primary care support and online, telephone-based, or community support resources. Therapists with psycho-oncology training are preferred if available; therefore, distance-based methods may be needed for those without resources in their communities.

For additional information regarding anxiety, depression, and distress in patients with cancer, please see the NCCN Guidelines for Distress Management (available at www.NCCN.org). The NCCN Guidelines for Survivorship complement the NCCN Guidelines for Distress Management. These guidelines may be modified to accommodate the individual circumstances of cancer survivors.

Screening for Anxiety, Depression, and Distress

Psychosocial problems are pervasive in survivors and many distressed survivors may not appear distressed. Therefore, all survivors should be screened for anxiety, depression, and distress, especially at times of

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disease transition, surveillance, significant loss, major life events, and social isolation. Survivors who present with multiple or repeated somatic complaints should also be screened as part of their overall workup.

The panel lists questions that can be asked of survivors to determine if they have been feeling nervous/anxious or sad/depressed and whether these moods are impacting quality of life. The panel does not recommend use of the NCCN Distress Thermometer (DT) as an initial screening tool in survivors, because studies generally find that it lacks sufficient sensitivity and specificity in this population.[526-533] For example, a study of 120 survivors of adult-onset cancer found that the DT had a sensitivity of 47.6% and 51.7%, using cutoff values of 5 and 4, respectively.[531] The panel therefore recommends supplemental screening when the DT is used as an initial screening tool. Survivors with an elevated level of distress by the DT should still be asked the initial screening questions provided in these guidelines. These more specific questions allow the clinician to determine what particular psychological symptoms are affecting the survivor and may provide more sensitivity and specificity than the DT in identifying distressed survivors who need treatment or additional resources.

Diagnosis of Anxiety, Depression, and Distress

Oncologists and PCPs generally do not feel comfortable diagnosing major psychiatric disorders, nor should they be doing so. Therefore, these guidelines do not specify the full diagnostic criteria for depression, anxiety, PTSD, etc. Instead, the guidelines list the essential criteria for screening psychiatric diagnoses that are most common in survivors and some key symptoms from the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5[534]). The panel's intent is to provide information to facilitate initial steps in providing care and decisions about referrals rather than to provide guidelines for psychiatric diagnosis and extended treatment.

Safety Evaluation

Cancer survivors with anxiety, depression, PTSD, or another psychiatric disorder that is impacting quality of life should undergo a safety evaluation to assess whether they are a danger to themselves or others.[535] Risk factors to assess include previous attempts at suicide or self-injury, a family history or other exposure to suicide, not having a spouse or live-in partner, social isolation, and other factors that suggest difficulty with severe stress. These include perceiving oneself as a burden, recent loss of an important person, a relationship breakdown, chronic illness or recent change in health status, alcohol or other substance abuse, loss of rational thinking, feeling hopelessness or loss of control, financial instability, and access to firearms/weapons or potentially lethal medications (eg, opioids, benzodiazepines [BZDs], antidepressants). Males and those in their late teens or age >55 years are also at elevated safety risk. Medical risk factors should also be assessed, including the presence of a sleep disorder, which has been shown to be associated with an increased risk of suicide.[536]

Protective factors also should be considered to balance against risk factors.[535] Survivors who are married, have child-rearing responsibilities, and/or are employed are less likely to pose a danger to themselves or others. In addition, survivors with strong interpersonal bonds to family or community, who identify reasons for living, or with cultural, spiritual, and religious beliefs about the meaning and value of life are at lower risk. The panel lists additional protective factors in the algorithm above.

Survivors with suicidal or homicidal thoughts or a plan and/or with multiple other risk factors are at an elevated risk of danger to themselves or others. In addition, the inability of the survivor to care for his- or herself may also indicate an elevated safety risk. Survivors judged to be at elevated risk require an emergency intervention that includes arranging to have weapons secured, maintaining direct observation of the individual, and

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possibly calling 911, along with following other state mental health emergency plans or referring the person to emergency psychiatric evaluation procedures onsite.

Survivors with intermittent suicidal ideation or thoughts that they might be better off dead, but no plan to harm themselves nor thoughts of endangering others, are at lower safety risk, as are those with fewer risk factors. A safety plan should be developed with these survivors and their families and should include immediate referral for mental health evaluation based on urgency, regular follow-up and monitoring until psychiatric care is in place, and having the survivor agree to contact a health care provider, call 911, or go to an emergency room if suicidal thoughts increase or change. Underlying conditions and risk factors that contribute to suicidal thoughts should be addressed whenever possible.

Management of Anxiety, Depression, and Distress

Survivors with suspected major psychiatric diagnoses, including mania or psychosis, those with an extensive psychiatric history, and those with a moderate to high safety risk should be referred for psychiatric evaluation and treatment. Survivors with substance abuse issues should be referred to a substance abuse specialist. Survivors with moderate- to severe-intensity major depression, generalized anxiety, panic, or PTSD also should be referred for evaluation and treatment by a mental health professional; however, pharmacologic and/or nonpharmacologic treatments, as described below, can also be considered for these survivors.

All treatable contributing factors (eg, pain, sleep disturbance, fatigue, metabolic/endocrine problems, other medical comorbidities) should be addressed. Reassurance can be offered that symptoms of worry, stress, anxiety, and depression are common problems among cancer survivors and that these symptoms can be treated. In addition, support and education should be provided to the survivor and family regarding normal recovery phases after treatment, common stresses, distress, and fears, and strategies for managing uncertainty and distress. Finally, resources need to be provided for social support networks and specific social, emotional, spiritual, intimacy, and practical needs. Additional treatment options are described below.

Nonpharmacologic Treatments

Treatment recommendations for managing depression, anxiety, and distress include a strong recommendation for regular physical activity, which has been shown in clinical trials and meta-analyses to have significant effects in reducing symptoms of anxiety and depression among survivors.[537-539] In fact, evidence suggests that exercise and antidepressants (discussed below) may be equally effective in the treatment of depression.[540]

Psychotherapy, and in particular cognitive behavioral therapy (CBT) and problem-solving therapy, have been shown to be effective at treating depression, anxiety, and PTSD in the general population.[541-546] Therapy, including CBT, has also been shown to be effective at reducing anxiety, depression, and distress in the survivorship population.[179,547-555] One study found that a psychoeducation program that included three telephone-based psychotherapy sessions reduced the severity of fear of recurrence in melanoma survivors.[556] Another study randomly assigned 222 participants to either an attention control or to five face-to-face sessions of a program called ConquerFear, which included attention training, metacognitions, acceptance/mindfulness, screening behavior, and values-based goal setting.[557] Those in the ConquerFear group experienced clinically and statistically greater improvements in total scores immediately post-therapy and 3 and 6 months later on the Fear of Cancer Recurrence Inventory than those in the control group. Greater improvements were also seen immediately post-therapy in symptoms including total cancer-specific distress and general anxiety.

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Other alternative treatments (eg, yoga, tai chi, mindfulness) may also be helpful to survivors suffering from distress, although data showing their effectiveness are limited.[558-562] Mindfulness is possibly the best-studied alternative treatment for psychological problems in cancer survivors.[563-567] For example, a randomized controlled trial of 322 survivors of breast cancer found that a 6-week mindfulness-based stress reduction (MBSR) program reduced anxiety and fear of recurrence and also improved fatigue.[567] In non-cancer settings, weight loss interventions have improved depression in obese individuals,[568] although evidence in cancer or survivor populations is lacking.

Pharmacologic Treatments

Cancer survivors use medication for anxiety and depression at a rate about twice that of the general population.[569] A population-based study in Canada found that 44% of cancer survivors were using an anxiolytic, and 22% were using an antidepressant.[570] Antidepressants and antianxiety drugs have been shown to be beneficial for the treatment of depression and anxiety in patients with cancer.[571-578] Evidence of these effects is lacking in cancer survivors, although these drugs have been studied in this population for their effects on vasomotor symptoms (see *Hormone-Related Symptoms*). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can therefore be used in survivors with moderate- to severe-intensity major depression, generalized anxiety, panic, or PTSD. SNRIs should be considered for concomitant pain or concomitant hot flashes (also see *Hormone-Related Symptoms*). Psychotropics with cytochrome P450 interactions (ie, fluoxetine, paroxetine, sertraline, bupropion, fluvoxamine, nefazodone, duloxetine, clomipramine) should be used with caution in survivors taking tamoxifen. Pure SSRIs, and in particular paroxetine, block conversion of tamoxifen to active metabolites through CYP2D6 and should be used with caution for women on tamoxifen (see *Hormone-Related Symptoms* for a discussion of psychotropics and cytochrome P450 interactions).[579-581]

Survivors should be counseled that it may take up to 2 to 6 weeks at a therapeutic dose for SSRIs and SNRIs to take effect, and that a trial of several different drugs may be needed to find the best option for an individual. BZDs (ie, clonazepam, lorazepam) can be used for acute anxiety relief or while waiting for antidepressants to take effect. The BZD dose should be adjusted once SSRIs or SNRIs are fully effective and symptoms are partially or completely abated. Survivors should also be counseled that symptoms of withdrawal may occur should any of the above-mentioned medications be abruptly discontinued. Referral to a mental health professional should be considered if the response to first-line treatment is inadequate.

Cognitive Dysfunction

Cognitive impairment is a common complaint among cancer survivors and may be a consequence of the tumors themselves or of the direct effects of cancer-related treatment (eg, chemotherapy, radiation therapy). This symptom may be especially prominent in survivors of primary central nervous system (CNS) cancers or those with brain metastases, but survivors who never had brain involvement may also report difficulties in cognition.[582] For some survivors, symptoms persist long-term.[583] When severe, the presence of cognitive dysfunction can impact quality of life and function. Cognitive dysfunction is most commonly connected with chemotherapy (sometimes referred to as “chemobrain”), but evidence suggests that therapies other than chemotherapy, such as endocrine therapy, radiation, and surgery may be associated with cognitive impairments.[584-594] A national cross-sectional study found that a history of cancer is independently associated with a 40% increase in the likelihood of self-reported memory problems.[595]

Cancer-related cognitive changes have primarily been studied in patients with CNS cancer, breast cancer, and lymphoma and in those who have undergone hematopoietic stem cell transplant (HSCT), with a reported

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incidence ranging widely from 19% to 78%.[583,596-610] In the 2010 LIVESTRONG survey of 3108 post-treatment survivors of a variety of cancer types, approximately 46% of respondents perceived cognitive deficits.[611] In a prospective, longitudinal study of 581 patients with breast cancer treated at several U.S. community oncology clinics and 364 controls, patients reported significantly greater cognitive difficulties than controls before chemotherapy, post-chemotherapy, and after an additional 6 months, with 45% of patients reporting a decline in cognitive function over time compared with 10% of controls.[612]

Growing evidence supports the patient experience of cognitive dysfunction associated with cancer diagnoses and treatments, with deficits commonly occurring in the domains of executive function, learning and memory, attention, and processing speed.[583,609,613-615] In one meta-analysis of 17 studies, women previously treated with chemotherapy for breast cancer (n = 807) had lower functional abilities than those not treated with chemotherapy (n = 291).[600] These deficits were limited to verbal (eg, word-finding) and visuospatial (eg, copying complex images) abilities. However, when compared with their pre-chemotherapy baseline, no differences were noted among patients complaining of cognitive dysfunction. In another study, cognitive function was compared among 196 long-term survivors of breast cancer treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) who were, on average, 21 years out from diagnosis, and 1509 control patients with no history of cancer.[616] The chemotherapy group did significantly worse on several neuropsychological tests (eg, immediate and delayed verbal memory, executive functioning, psychomotor speed). Another study compared 101 patients who underwent an HSCT with 82 patients treated with a non-myeloablative therapy; both groups showed mild cognitive impairments at baseline.[617] Although no significant differences in cognitive dysfunction were identified at 2-year follow-up, patients who underwent HSCT had poorer performances in several areas, including executive and psychomotor functions and attention. More recent prospective, longitudinal studies have seen declines in neurocognitive or neuropsychological test results in survivors of head and neck cancer (eg, in intellectual capacity, concentration/short-term attention, verbal memory, executive function) and survivors with a history of hematopoietic cell transplantation (HCT) (eg, in fine motor dexterity, verbal speed, processing speed, auditory memory, executive function).[618,619]

The correlation between patient reports of cognitive decline and results of neuropsychological testing has not been consistently demonstrated, possibly because of various definitions of cognitive dysfunction and differences in the statistical analyses across studies.[609] Other reasons for the weak correlation between perceived and objective cognitive decline have been proposed, including the fact that perceived cognitive decline is influenced by patient expectations whereas expectations do not affect objective assessments and that objective assessments assess cognitive performance under optimal rather than real-life conditions.[620] However, some studies have shown a strong correlation. For example, a study of 189 breast cancer survivors found that memory and executive function complaints, present in approximately 20% of the cohort, showed a statistically significant association with results of domain-specific neuropsychological tests.[621] A study that included 291 participants with stage I–III colorectal cancer before or after surgery and healthy controls found that 45% of patients with cancer had cognitive impairment versus 15% of the control group (odds ratio [OR], 4.51; $P < .001$), with the largest effects seen in complex processing speed, attention/working memory, and verbal learning efficiency.[589] Results of this study suggest that the cancer diagnosis itself and/or the surgical intervention contribute to cognitive dysfunction, because these patients had not received chemotherapy at the time of neurocognitive testing.

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The underlying mechanisms that might increase the risk for cancer-related cognitive changes are not known. Studies have reported elevated levels of cytokines or DNA damage as some of the possible mechanisms.[622] Structural studies have supported the hypothesis that neurotoxicity resulting in damage to white matter of the brain may play an important role in cognitive deficits after chemotherapy treatment,[583,586,599,623,624] and functional MRI studies show that changes in brain activity accompany cognitive complaints or cognitive deficits in survivors.[624-626] In addition, insomnia, fatigue, and depression, common in cancer survivors, may negatively influence cognitive function, although several studies have found that cognitive dysfunction does not correlate with mood.[616,627,628] Psychosomatic effects can also contribute, as evidenced by a study of patients to be treated with chemotherapy that found that those who were informed of the possible cognitive side effects were more likely to report cognitive dysfunction and perform worse on neuropsychological testing than uninformed patients.[629] A better understanding of the mechanisms that cause cancer-related cognitive impairment is essential for the development of treatments to improve cognitive function and quality of life in patients with cancer and survivors.[582,630,631]

In October 2006, the International Cognition and Cancer Task Force (ICCTF) was formed, comprising a multidisciplinary group of health professionals and health advocates. The mission of ICCTF is to advance understanding of the impact of cancer and cancer-related treatment on cognitive and behavioral functioning in patients with CNS and non-CNS cancers.[632] The group published recommendations regarding neuropsychological testing, defining cognitive impairment/changes, neuroimaging, and future study design.[631,633]

These NCCN Guidelines address cognitive function of survivors with non-CNS malignancies who did not have CNS-directed therapies.

Assessment and Evaluation for Cognitive Dysfunction

Patients who report cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, including depression, pain, fatigue, and sleep disturbance. Some medications can also contribute to cognitive impairment. Therefore, current medications, including over-the-counter medications and supplements, should be reviewed.

For those who present with concomitant focal neurologic deficits and those whose symptoms evolve to include these findings, imaging is indicated to rule out structural abnormalities (ie, brain or CNS disease). In addition, imaging in the absence of focal findings may be appropriate for patients deemed to be at high risk for recurrence or metastatic disease involving the CNS.

Unfortunately, no effective brief screening tool for cancer-associated cognitive dysfunction in the asymptomatic cancer survivor currently exists. The Mini-Mental State Examination (MMSE[634]) and similar screening tools lack adequate sensitivity to detect the subtle decline in cognitive performance seen in most cancer survivors. Instead, the panel listed several questions that can help clarify the nature of the impairment, including inquiries about the ability to pay attention, find words, remember things, think clearly, and perform functions. The time of onset of symptoms and the trajectory over time should also be assessed.

Management of Cognitive Dysfunction

Survivors benefit from validation of their symptom experience and should be reassured that, in most survivors, cognitive dysfunction does not worsen over time. In fact, data from breast cancer survivors suggest that symptoms may improve over time.[585] The panel recommends the use of nonpharmacologic interventions whenever possible, with pharmacologic interventions as a last line of therapy in survivors for whom other interventions have been insufficient, as discussed in the following

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sections. Additional recommendations for cognitive dysfunction in older adults can be found in the cognitive function section of the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org).

Nonpharmacologic Interventions for Cognitive Dysfunction

Prospective data to inform the use or potential benefits of non-pharmacologic interventions for cancer survivors who complain of cognitive dysfunction are limited. Practical suggestions include instruction in self-management and coping strategies (eg, using planners, reminder notes, and/or smart phone technology; keeping items in the same place), which the panel believes can be very helpful to patients. Discontinuation or limitation of use of medications known to cause or contribute to cognitive impairment should be attempted. Management of depression/emotional distress, pain, sleep disturbances, and fatigue should be provided. In fact, a study showed that CBT for fatigue was effective at reducing self-reported cognitive disability and concentration problems in 98 severely fatigued cancer survivors randomized to CBT compared with those randomized to a wait list.[635] However, no difference in neuropsychological test performance was observed.

CBT for cognitive dysfunction may also help some survivors. In one small study, CBT was evaluated in 40 breast cancer survivors using a waitlist control trial design.[636] Although overall quality of life improved with the intervention, statistically significant improvement was noted only with verbal memory, not with self-reports of daily cognitive complaints. Another study of CBT delivered by video conference in 47 survivors of breast cancer found that CBT led to improvements in self-reported cognitive impairment and in neuropsychological processing speed compared with supportive therapy.[637]

Routine physical activity should be encouraged. Substantial evidence shows that physical activity enhances cognitive function in elderly people in general, although only few studies specific to cancer survivors have been reported.[638-642] A small randomized controlled trial of an exercise intervention versus control in breast cancer survivors evaluated objective and self-reported cognition.[642] The exercise intervention significantly improved processing speed among those who had been diagnosed within the past 2 years, but no other significant differences were observed.

Cognitive training (ie, brain games) can also be considered. Cognitive training has demonstrated benefits in self-reported and objectively assessed cognitive function, including memory, executive function, and verbal function.[639,643] One study randomized 157 breast cancer survivors to web-based cognitive training with telephone support or to wait-list control.[644] Verbal learning and results on a working memory test showed statistically significant improvement in the cognitive training group, but no improvements were seen for an objective measure of working memory and a measure of perceived cognitive functioning. Another study used a 5-session, small-group intervention of psychoeducation and cognitive exercises in 48 breast cancer survivors.[645] Compared to survivors randomized to a wait-list control group, survivors in the intervention arm experienced improvements in self-reported cognitive complaints and memory functioning on neurocognitive testing. A larger study of 242 survivors with self-reported, persistent cognitive symptoms after chemotherapy for non-CNS cancers found that survivors randomized to a web-based cognitive training program had statistically significant improvements in perceived cognitive impairment immediately and 6 months after the intervention.[646] Improvements in anxiety, depression, fatigue, and stress were also seen after the intervention, which used adaptive exercises that targeted cognitive domains, such as visual precision, working memory, and visual processing speed.

Relaxation, stress management, meditation, and yoga can also be considered. A small pilot randomized controlled trial of 71 fatigued survivors showed that MBSR improved some domains of cognitive

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function.[647] A larger study also found improvements in cognitive symptoms after a mindfulness-based approach.[565] Two studies have assessed the effects of yoga on cognition in survivors.[648,649] Both reported improvements in patient-reported cognitive dysfunction.

Neuropsychological evaluation can be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation. Cognitive rehabilitation, including occupational therapy, speech therapy, and treatment by a neuropsychologist, may also be useful. Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for individuals who note the impact of specific functional limitations, such as word finding, comprehension, and task completion, on work performance, quality of life, or role expectations.[650] Psychotherapy is another option.

Pharmacologic Interventions for Cognitive Dysfunction

If nonpharmacologic interventions have been insufficient, consideration of a trial of medications such as methylphenidate, modafinil, or donepezil is reasonable in select survivors or certain clinical scenarios, although data informing the efficacy of these agents are lacking. Trials assessing the effects of the psychostimulant methylphenidate have reported mixed results.[651] For example, a randomized, placebo-controlled, double-blind trial found that d-methylphenidate had no effect on neuropsychological test scores.[652] In contrast, a randomized, double-blind, crossover trial of child survivors of acute lymphoblastic leukemia (ALL) or brain tumors showed that methylphenidate was more effective than placebo at improving attention, cognitive flexibility, and processing speed.[653]

Results of studies on modafinil, another psychostimulant, are more consistent. A randomized controlled trial assessing the efficacy of modafinil for fatigue and cognitive function in breast cancer survivors found significantly greater improvement in memory and attention among patients receiving modafinil than in the placebo group.[654] Similarly, a double-blind, randomized, crossover trial also in breast cancer survivors found that participants receiving modafinil performed significantly better on cognitive tests of attention and psychomotor speed.[655] Benefits with treatment were also noted among patients with primary brain tumors.[656]

Donepezil is an acetylcholinesterase inhibitor used to treat patients with Alzheimer's disease. It has been studied for its effects on cognitive impairments after the treatment of brain tumors, with modest improvements seen in attention/concentration, memory, and motor speed and dexterity.[657,658] Donepezil was also studied in a randomized trial of 62 breast cancer survivors who had received adjuvant chemotherapy.[659] Although there were no differences in subjective cognitive function, the donepezil group showed improved memory on objective tests. Further work is needed before concrete recommendations for pharmacologic therapy in survivor populations can be made.

Fatigue

Note: The Discussion text regarding fatigue in survivors has been adapted from the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org).

NCCN defines cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[660] Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.[661-663] According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[664,665] Cancer survivors report that fatigue continues to be a

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disruptive symptom after treatment ends,[666-674] with studies showing that 17% to 29% of cancer survivors experience persistent fatigue for years after the completion of active therapy.[675-677] In fact, a study of 6011 long-term cancer survivors found that 39% to 51% (depending on tumor type) were classified as fatigued after completion of the Fatigue Assessment Scale compared with 21% of a representative normal population.[678]

Persistent cancer-related fatigue affects quality of life, because individuals become too tired to fully participate in the roles and activities that make life meaningful.[668,679] In fact, severe fatigue in survivors of Hodgkin lymphoma is associated with a decreased likelihood of employment.[680] Disability-related issues are also relevant for cancer survivors, because obtaining or retaining disability benefits from insurers is often difficult for patients with cancer-related fatigue. Identification and management of fatigue remain an unmet need for many cancer survivors.

The specific mechanisms involved in the pathophysiology of cancer-related fatigue are unknown. Proposed mechanisms include pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation.[681-686] Several studies have focused on the cause of fatigue, especially in cancer survivors with no evidence of active disease, and have suggested that persistent immune system activation and chronic inflammatory processes may be involved.[666,687-689] Evidence supporting these mechanisms is limited.

Screening for Fatigue

All survivors should be screened for fatigue to ensure that those with moderate to severe fatigue are identified and treated promptly and effectively. Because fatigue is a subjective experience, clinicians must rely on patients' descriptions of their fatigue level. The panel recommends the use of a severity scale, with survivors being asked, "How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?" Alternatively, screening can be performed with patients asked to rate their fatigue as none, mild, moderate, or severe. Scores of 0 to 3 or none to mild fatigue require no further assessment or interventions; these patients should be rescreened at regular intervals. Patients with scores of 4 or greater or indicating moderate or severe fatigue should be evaluated further. Studies in patients with cancer have revealed a marked decrease in physical functioning at a reported fatigue level of 7 or higher on the 0 to 10 scale.[690,691]

Evaluation for Moderate to Severe Fatigue

When fatigue is rated as moderate to severe, with a score of 4 to 10, a more focused history and physical examination should be conducted. A thorough history is warranted, because the recommended workup for fatigue differs according to the timing of fatigue onset in relation to the completion of active therapy and the presence of predisposing factors and other symptoms. Fatigue has a variable natural history, with some patients complaining of only mild levels of fatigue even during active therapy and others experiencing severe fatigue for years after treatment completion.

In general, mild to moderate levels of fatigue that persist for 6 to 12 months after the completion of therapy do not warrant an extensive workup, unless other symptoms are present. Conversely, when moderate to severe fatigue begins after or worsens during this period, or when other symptoms are present, such as pain, pulmonary complaints, or unintentional weight loss, a more extensive workup is warranted to screen for the presence of metastatic disease or other comorbidities. Referral to a pulmonologist should be made for pulmonary complaints.

Regardless of fatigue onset, it is always relevant to screen for common contributing factors such as emotional distress, sleep disturbance, pain, and the use of prescriptions or over-the-counter medications or supplements. Possible medical causes of fatigue, including cardiac disease, gastrointestinal or hepatic dysfunction, and hypothyroidism,

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should also be assessed. Disease and treatment considerations also affect recommendations for screening, such as the inclusion of echocardiograms for patients who received cardiotoxic treatments and thyroid screening for patients who received radiation to the neck or thorax or agents such as immunotherapies or small molecule TKIs.

Management of Fatigue

Several interventions and strategies have been shown to help alleviate fatigue and reduce distress caused by this symptom in patients with cancer and survivors; recommended strategies and interventions are described herein. For additional information about fatigue in survivors and patients with cancer, please see the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org). These guidelines may be modified to fit the individual survivor's circumstances.

Treatment of Contributing Factors

Management of fatigue in survivors first includes the treatment of contributing factors such as pain, distress, anemia, and sleep disturbances (more information on the treatment of pain, anxiety/depression, and sleep disorders in survivors can be found throughout these guidelines). In a randomized controlled trial of 152 fatigued patients with advanced cancer, treatment of accompanying physical symptoms, including pain, nausea, vomiting, and shortness of breath, resulted in a significantly higher impact on general fatigue, activity, and motivation than usual care.[692]

Patient and Family Education and Counseling

Education and counseling can be beneficial in helping patients cope with fatigue. Understanding typical patterns of fatigue during and after treatment can help patients set reasonable expectations regarding improvements in energy after the completion of cancer therapy and can help allay concerns that persistent fatigue after the completion of therapy is evidence of disease recurrence. Counseling can help patients develop strategies for self-monitoring of fatigue and techniques such as energy conservation that may be helpful in the immediate post-treatment period.[693]

Physical Activity

Activity enhancement is a category 1 recommendation for the management of fatigue in survivors. Improving strength, energy, and fitness through regular exercise, even a moderate-intensity walking program, has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase tolerance for physical activity. Therefore, survivors with moderate to severe fatigue should be encouraged to maintain adequate levels of physical activity (category 1). Robust data support the efficacy of increased physical activity for reducing fatigue in patients with cancer and survivors.[204,210,215,217,219,560,694-700] Multiple meta-analyses of randomized controlled trials have found that cancer survivors who participate in exercise interventions, either during or after treatment for cancer, experience significant improvements in fatigue compared with patients randomized to the control group.[204,700-703] A randomized phase 3 trial that included 410 cancer survivors showed that a 4-week yoga therapy program led to improvements in fatigue and sleep quality and reductions in daytime dysfunction.[704]

Survivors at a higher risk of injury should be referred to a physical therapist or exercise specialist (also see *Healthy Lifestyles*, above).

Psychosocial and Other Interventions

Psychosocial interventions, such as CBT, MBSR, psycho-educational therapy, and supportive expressive therapy, including support groups, counseling, and journal writing (all category 1 recommendations), have also been shown to reduce fatigue in cancer survivors, although data are not entirely consistent.[567,705-710] Several meta-analyses have evaluated the role of psychosocial interventions in reducing fatigue.[700,705,709,711] For

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example, Kangas et al[709] reported a weighted pooled mean effect of −0.31 for psychosocial interventions on fatigue in an analysis of 3620 patients with cancer from 41 studies. Jacobsen et al[711] analyzed 30 randomized controlled trials and found a significant effect size (dw) for psychological interventions (dw, 0.10; 95% CI, 0.02–0.18) but not for activity-based programs (dw, 0.05; 95% CI, −0.08–0.19). A meta-analysis by Duijts et al[705] reported that, like exercise programs, behavioral techniques, including CBT, relaxation techniques, counseling, social support, hypnosis, and biofeedback, are beneficial in improving fatigue among patients with breast cancer during and after treatment (standardized mean difference [SMD], −0.16).

Several published studies support the conclusion that CBT interventions designed to optimize sleep quality (CBT for insomnia; CBT-I) in patients with cancer may also improve fatigue.[712-716] Two randomized clinical trials of patients who reported chronic insomnia in the survivorship phase demonstrated improvements in both sleep and fatigue after 4 to 5 weekly behavioral therapy sessions.[706,707,717] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[712,715] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[716,718] The American Academy of Sleep Medicine (AASM) has recommended three specific therapies for the initial approach to chronic insomnia in healthy individuals: relaxation therapy, CBT-I, and stimulus control therapy.[719]

Acupuncture and acupressure have been studied for the treatment of fatigue in patients with cancer and survivors.[720-727] A pilot study in 30 breast cancer survivors found that acupuncture resulted in a significant reduction in fatigue after 2 weeks.[725] In addition, a phase 3 randomized, single-blind clinical trial in 424 breast cancer survivors found that self-administered relaxing acupressure reduced persistent fatigue and improved sleep quality and quality of life.[727] Although results of studies are mixed and many compared acupuncture to usual care rather than sham acupuncture or another active comparator, the panel believes acupuncture is an acceptable option that may improve symptoms for survivors with moderate to severe fatigue.

Pharmacologic Interventions

Psychostimulants, such as methylphenidate, are also used to treat fatigue, although data regarding their use to treat fatigue in cancer survivors are very limited. A 54% response rate to methylphenidate was reported in a phase II trial of 37 breast cancer survivors.[728] A randomized trial in 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the dexmethylphenidate arm.[729] A recent meta-analysis of five randomized controlled trials of patients with cancer found limited evidence for the efficacy of 4 or more weeks of methylphenidate treatment for cancer-related fatigue (mean difference, −3.70; 95% CI, −7.03 to −0.37; P = .03).[730] However, another meta-analysis identified seven trials of methylphenidate and concluded that it was superior to placebo for the treatment of cancer-related fatigue.[731] A Cochrane review found that methylphenidate was likely effective for cancer-related fatigue and warrants further study.[732] However, a second comprehensive meta-analysis did not support this finding, nor did it support the use of pharmacologic interventions for the treatment of cancer-related fatigue.[700]

Other drugs, including modafinil, have also been studied for post-treatment fatigue.[733,734] In particular, a large phase III trial of 631 patients receiving chemotherapy suggested that modafinil is beneficial in patients with severe fatigue.[734] However, a placebo-controlled, double-blind, randomized controlled trial in 208 patients with non-small cell lung cancer (NSCLC) showed no effect of modafinil on cancer-related fatigue.[735] In addition, a meta-analysis identified three studies evaluating modafinil for fatigue in patients with cancer and found that the drug was not better than

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placebo.[731] Recommendations for modafinil have therefore been removed from both the NCCN Guidelines for Cancer-Related Fatigue and the NCCN Guidelines for Survivorship. Both guidelines continue to recommend that methylphenidate may be considered after ruling out other causes of fatigue and failure of other interventions, although they acknowledge the limited data supporting the use of this agent in this setting, especially in cancer survivors.

Small pilot studies and one recent randomized controlled trial have evaluated the impact of supplements, including ginseng and vitamin D, for cancer-related fatigue.[736] The evidence to date is inconsistent, and the panel currently does not recommend the use of supplements for the treatment of fatigue.

Lymphedema

Lymphedema is a common side effect of cancer treatment, occurring on the same side of the body as the cancer treatment, resulting from damage to the lymphatic system. It occurs when lymph fluid accumulates in the interstitial tissue, causing swelling of the limb or other areas such as the neck, trunk, or genitals. Lymphedema is most often diagnosed within 18 months of treatment; however, it can develop any time in the life of the survivor.

More than 20% of cancer survivors reported lymphedema as a physical concern in a survey of almost 14 million survivors in the United States in a 2010 LIVESTRONG study.[23] The incidence of lymphedema varies by disease site. In one study, 41% of almost 1000 breast cancer survivors developed lymphedema by 10-year follow-up.[737] In a study of survivors of gynecologic cancers, the incidence of lymphedema in one or both legs 2 years after surgery was 37%.[738] In one study of 431 survivors of melanoma who had been treated with complete lymph node dissection and/or wide local excision and axillary or inguinal sentinel lymph node surgery, the reported incidence of lymphedema was 25%.[739]

Lymphedema may cause or exacerbate psychological distress.[740,741] In a study that included 692 breast cancer survivors with lymphedema, almost half reported moderate to extreme distress related to their lymphedema.[742] Lymphedema can also affect social roles, employment, medical expenses, physical function, and quality of life and can cause disability.[743-746] Unfortunately, only 55% of cancer survivors with self-reported lymphedema in the LIVESTRONG study said that they received care for lymphedema.[23]

Risk Factors for Lymphedema

Survivors whose cancer treatment included surgery and/or radiation to the axillary, supraclavicular, cervical, or inguinal lymph node system are at risk for the development of lymphedema.[747-750] Sentinel lymph node biopsy also appears to increase the risk of lymphedema, although it poses less risk than complete dissection or radiation to the nodal group, and data are not completely consistent.[748,751-755] Other treatment-related factors that have been associated with an increased risk of lymphedema are receipt of chemotherapy or radiation and the extent of lymph node dissection.[737,738,747-750,753,755-757] Overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2), localized infection, and higher initial stage of disease also raise the risk of lymphedema development.[737,738,747,748,750,755,757-759]

Assessment and Workup for Lymphedema

Survivors with a history of radiation or surgery to the lymph nodes should be asked about swelling or feelings of heaviness, fatigue, or fullness at each visit. Early detection and diagnosis are key for optimal lymphedema management, because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment (see *Definition and Stages of Lymphedema* in the algorithm). Swelling on the same side as the cancer treatment is a universal symptom of lymphedema. Additional initial

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symptoms may include pain or discomfort and/or sensations of heaviness, fatigue, fullness, and/or tightness in the skin. Symptoms including decreased range of motion or strength and thickening of the skin may occur in later stages. If symptoms are present, survivors should be asked about the frequency and severity of swelling, pain and/or discomfort, any issues with strength or range of motion and mobility (ie, bending, stretching, flexibility), and whether symptoms interfere with daily activities.

If lymphedema symptoms are present, a recurrence of cancer should be ruled out. The survivor should then be referred to a certified lymphedema therapist, if available, for additional assessments. These assessments can include subjective signs and symptoms of lymphedema and limb volume measurements. Ideally, pretreatment limb measurement of both sides should be performed as a baseline prior to initiation of any therapy for those with treatment-related or individual risk factors. If not, the contralateral limb can be used for comparison in the post-treatment setting. Clinical examination by a lymphedema therapist may include range of motion, muscle performance, circulation, sensation, hemodynamic monitoring, and functional mobility.

Survivors with lymphedema should also be assessed for distress (see *Anxiety, Depression, Trauma, and Distress*, above).

Treatment of Lymphedema

High-level evidence supporting treatments for lymphedema are lacking, and most studies have been performed in breast cancer survivors.[31,760-762] Most of the recommendations made by the panel are thus based on lower-level evidence, clinical experience, and expert consensus.

The oncology team should provide education regarding self-care management, including infection prevention measures, risk-reduction strategies, and maintenance of skin integrity on the affected side (see *Survivor Lymphedema Education*, below). Distress should be treated if present (see *Anxiety, Depression, Trauma, and Distress*, above). Referral should be made to a certified lymphedema therapist, if available, for prescription and fitting of compression garments, performance of manual lymphatic drainage, and direction of supervised progressive strength training. If a certified lymphedema therapist is not available, referral to an appropriate alternative provider for treatment should be considered.

Compression garments have been shown to reduce limb volume, and are often used with other modalities such as manual lymphatic drainage.[762-764] Manual lymphatic drainage is performed by a specific massage technique designed to encourage lymph fluid to drain from the affected area. Systematic reviews and meta-analyses have assessed the efficacy of manual lymphatic drainage in breast cancer survivors with lymphedema and found that it can provide additional benefit when added to standard therapy.[765,766] In particular, compression bandaging alone leads to limb volume reductions of 30% to 39%, and manual lymphatic drainage appears to increase that reduction by an additional 7%.

Progressive strength training and physical activity are not associated with exacerbation or development of lymphedema, and may improve lymphedema symptoms.[214,255-259,767-770] The WISER Survivor trial randomized 351 overweight breast cancer survivors with lymphedema to a control group that received hospital-based care, a home-based exercise intervention group, a home-based weight loss intervention group, or a combined home-based exercise/weight loss group.[771] Although the groups that included a weight-loss intervention experienced about a 7% to 8% weight loss, no group experienced improvements in breast cancer-related lymphedema outcomes. This result suggests that home-based interventions may not be effective for treatment of lymphedema in cancer survivors.

Progressive strength under supervision is recommended for survivors with lymphedema. However, caution is advised in this population,[260] and

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survivors with or at risk for lymphedema should consider discussing physical activity plans with a lymphedema specialist before starting a program that involves strength training. Survivors with lymphedema should work with trained exercise professionals with knowledge of cancer-related physical activity principles and initiate strength training exercise involving the affected body part only if lymphedema is stable (eg, no need for lymphedema therapy within the past 3 months, no recent limb infections requiring antibiotics, no change in limb circumference >10%, no change in the ability to perform activities of daily living). Survivors should undergo baseline and periodic evaluation for development or exacerbation of lymphedema and should stop exercise and see a lymphedema specialist if exacerbation of lymphedema occurs. Weights should be slowly progressed as tolerated, and lymphedema should be evaluated periodically. Compression garments may be required during training sessions.

The National Lymphedema Network has published a position statement with additional guidance for exercise in individuals with lymphedema.[768]

Survivor Lymphedema Education

Early detection and diagnosis is key for optimal lymphedema management because earlier stages are reversible. Therefore, survivors should be educated about the signs and symptoms of lymphedema and the importance of rapid reporting to the treatment team. Survivors should be told to inform their medical provider if subtle swelling or any other symptoms (eg, fullness, tightness, heaviness, pain) on the treated side are noted.

Survivors at risk for lymphedema and those with lymphedema are at a higher risk of localized infection in the affected area. These infections can require hospitalization for IV antibiotics. Therefore, survivors with or at risk for lymphedema should be educated to inform their medical provider immediately of signs of infection in the affected area. Risk of infections can be reduced by safe pet care and gardening techniques (See *Immunizations and Prevention of Infections*, above). Survivors should also be educated on how to maintain skin integrity with meticulous skin care of the affected area that includes avoidance of cuts, burns, skin irritants and allergens, insect bites, and pet scratches.[772,773] The use of moisturizing soaps and over-the-counter, fragrance-free emollients may also be helpful.[773]

Observational studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[747,749,758,759,774-777] For instance, in one study of 632 women with breast cancer prospectively screened for lymphedema with 3041 arm volume measurements, no association was found between the development of lymphedema and blood draws, injections, or air travel.[759] In the absence of high-level data, however, the panel recommends that medical procedures such as venipuncture and blood pressure measurements be done on the non–at-risk arm/limb if possible.[778] If necessary, procedures may be done using the at-risk arm/limb. More research is needed to determine the effect of these procedures on the risk of lymphedema.

Survivors should be informed that lymphedema is not a contraindication for physical activity and that no special precautions are required for cardiovascular/aerobic exercise or strength training of unaffected limbs.[255-260] In addition, continued full use of the involved extremity and range-of-motion exercises should be encouraged to maintain strength and range of motion even in the presence of lymphedema. Progressive strength training under supervision is recommended for patients with lymphedema, as discussed above (see *Treatment of Lymphedema*). Exercise and physical therapy may also help prevent lymphedema symptoms. In the randomized controlled Lymphedema Education and Prevention study (CALGB 70305),

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women randomized to the education plus exercise arm self-reported greater range of motion at 12 months after lymph node dissection (a pre-specified secondary outcome) compared with women in the education only arm (left, 91% vs. 84%; *P* = .16; right, 90% vs. 83%; *P* = .02).[779] Finally, survivors can be informed that water exercise under supervision may be an option to consider in the absence of any skin integrity and/or incision issues.[780] In a controlled clinical intervention study, 88 patients with lymphedema secondary to cancer participated in either a water-based or land-based exercise program.[780] A higher proportion of those who performed water exercises experienced a reduction in their secondary arm limb volume (*P* = .029) and self-reported frequency of swelling (*P* = .031).

Surveillance of Survivors with Lymphedema

Survivors with lymphedema should have follow-up with the treatment team as clinically indicated. Clinicians should check range of motion, inquire about the fit and age of compression garments, replace compression garments if needed, and inquire about the performance of prescribed exercises and self-care management. Assessment for distress should also be performed as part of routine surveillance.

Hormone-Related Symptoms

Hormonal symptoms in cancer survivors have been most extensively studied in female survivors after treatment of breast cancer. Hot flashes are reported to occur in about 46% to 73% of breast cancer survivors.[781-784] In one study of breast cancer survivors diagnosed at age 40 years or younger, 46% of women reported hot flashes, 51% reported vaginal dryness, and 39% reported dyspareunia.[784] Similarly, about 50% to 80% of men on ADT experience hot flashes, which can persist after treatment.[785-790] The incidence of gynecomastia in men on ADT varies with the method of ADT used and can be as high as 80% in men on estrogen therapy.[787,791]

The NCCN Guidelines for Survivorship define menopause as no menses for one year in the absence of prior chemotherapy or tamoxifen use or no menses after surgical removal of all ovarian tissue. Healthy women reach menopause at a mean age of 51 years, with 95% of women reaching menopause between 45 and 55 years of age.[792] Many cancer survivors experience menopausal symptoms without meeting the definition of menopause, including female survivors on tamoxifen or aromatase inhibitors or with a history of oophorectomy or chemotherapy and male survivors who received or are receiving androgen ablative therapies (ie, ADT). These symptoms can include hot flashes/night sweats, vaginal dryness, urinary complaints, sexual dysfunction, sleep disturbance, mood disturbance, depression, cognitive dysfunction, arthralgias/myalgias, and fatigue. Hormonal symptoms can occur in both men and women. Males may experience many of the same symptoms as women, as well as gynecomastia, decreased testicle size, and thinning of body hair. Hormonal symptoms can have a profound impact on quality of life.[783,793]

Premenopausal cancer survivors who have received chemotherapy may experience transient or permanent menopause, dependent on the age of the patient and the type of chemotherapy.[794-796] If appropriate and desired, referral for fertility preservation should be considered before chemotherapy, because studies report that 33% to 73% of premenopausal women treated for breast cancer become peri- or postmenopausal after treatment.[783] Younger survivors with irregular menses may have primary ovarian insufficiency and may develop menopausal symptoms.[797] These women may or may not be fertile, and should be counseled about the possibility of pregnancy despite amenorrhea if they are sexually active and do not meet the definition of menopause. In non-cancer populations, primary ovarian insufficiency or early menopause may be associated with specific menopause-related health risks. However, there are limited data in cancer survivors.

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Assessment and Evaluation for Hormonal Symptoms

Survivors with hormonal symptoms disruptive to quality of life should be assessed and treated for medical causes of hormonal symptoms such as thyroid disease and diabetes. Lab evaluation includes estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, as clinically indicated. For peri- or pre-menopausal female survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including FSH, anti-Müllerian hormone (AMH), and inhibin may provide additional information on ovarian status in female cancer survivors with prior chemotherapy or pelvic radiation exposure or those on tamoxifen, but alone are not reliable to ensure menopausal status.[798,799] In male survivors, morning total testosterone and free testosterone may also be checked if hypogonadism is suspected.[800] For women with complaints of vaginal dryness, a pelvic evaluation should be done to assess for vaginal atrophy and can be accomplished by referral to an appropriate specialist.

Management of Hormonal Symptoms in Female Survivors

Management of sexual dysfunction, lack of sexual desire, sleep disturbance, mood disturbance, depression, cognitive dysfunction, fatigue, and arthralgias/myalgias is described in other sections of these guidelines. Management of hot flashes, vaginal dryness, and urogenital complaints associated with menopause are described herein. The panel prefers the use of non-hormonal options as first-line therapy for female survivors with hormonal symptoms disruptive to quality of life, but hormonal therapies can also be used after consideration of the risks and benefits to an individual survivor.

Non-Hormonal Pharmacologic Treatment of Hot Flashes

For the management of hot flashes, non-hormonal pharmacologic options include antidepressants, anti-convulsants, neuropathic pain relievers, and certain anti-hypertensives.[801-804] When antidepressants are used, a lower dose than typically given for depression is often effective to treat hot flashes.

SSRIs and SNRIs have been shown to improve vasomotor symptoms in the general population, although the degree of symptom reduction may be smaller than with hormonal treatments.[805-807] A randomized clinical trial in healthy postmenopausal women showed that low-dose paroxetine reduces the frequency and severity of hot flashes.[807] Small studies have shown that SSRIs and SNRIs also reduce the severity and frequency of hot flashes in female cancer and survivor populations.[808-817] One of these studies was a randomized, double-blind, placebo-controlled study in 80 survivors of gynecologic cancers.[809] Results showed that 7.5 mg daily of paroxetine reduced the frequency and severity of vasomotor symptoms and the number of resultant nighttime awakenings. However, pure SSRIs, and in particular paroxetine, should be used with caution in women on tamoxifen, because these drugs block the conversion of tamoxifen to active metabolites through inhibition of cytochrome P450 2D6 (CYP2D6).[580,818] However, an analysis of a large database that included almost 17,000 breast cancer survivors found no evidence of an increase in cancer recurrence in women on concurrent tamoxifen and antidepressants, including SSRIs such as paroxetine.[579] In contrast, a study of 2430 breast cancer survivors found an increased risk of cancer death in those taking tamoxifen and an SSRI.[819] The panel recommends alternative therapy if available for survivors on tamoxifen, although no definitive conclusion regarding the impact of the interaction between pure SSRIs and tamoxifen can be drawn. Doses of antidepressants required for improvements in vasomotor symptoms are typically much lower than those needed for depression, and the response is typically faster. Side effects include dry mouth, decreased appetite, fatigue, nausea, constipation, and possible sexual dysfunction. Upon discontinuation, SNRIs and SSRIs should be gradually tapered to minimize withdrawal symptoms. Venlafaxine has been the most well studied, and the panel lists

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venlafaxine as the preferred antidepressant for the treatment of vasomotor symptoms.

The anticonvulsants gabapentin and pregabalin have also been shown to improve hormone-related vasomotor symptoms in the general population and in female cancer survivors.[820-825] For example, one trial of 420 survivors of breast cancer experiencing ≥2 hot flashes/day found that 900 mg/day gabapentin decreased the hot flash severity score by 46% at 8 weeks compared with a 15% reduction in the placebo group.[824] The panel lists gabapentin as the preferred anticonvulsant for the treatment of vasomotor symptoms. As with antidepressants, the doses of anticonvulsants used in this setting are lower than in other settings. Side effects of anticonvulsants include somnolence, so they may be particularly useful when given at bedtime in patients with hot flashes disturbing sleep.

Small studies provide evidence that the alpha agonist antihypertensive clonidine can reduce hot flashes in some healthy postmenopausal women.[826,827] Randomized controlled trials in breast cancer survivors also show that clonidine can reduce hot flash frequency and severity in postmenopausal women taking tamoxifen.[828,829] Side effects include sleep difficulties, dry mouth, fatigue, dizziness, and nausea.

Several studies have compared non-hormonal pharmacologic treatments. For example, venlafaxine has been compared with clonidine in breast cancer survivors.[830-832] Results of these studies have varied, but it appears that venlafaxine may have a faster effect but is less well tolerated than clonidine. A randomized, crossover study compared venlafaxine with gabapentin in breast cancer survivors.[825] Whereas both treatments resulted in similar reductions in hot flash severity, 68% of participants indicated a preference for venlafaxine compared with 32% who preferred gabapentin.

Non-Pharmacologic Treatment of Hot Flashes

Non-pharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss if overweight or obese, hypnosis, and CBT may help survivors manage hot flashes.[309,801,803,804,833-837] Phytoestrogens, botanicals, and dietary supplements are often used for treatment of vasomotor symptoms; however, data are limited on the effectiveness and safety of these particular treatments in the general menopausal population and in survivors.[802,838-845] Vitamin E has been thought to have marginal improvement in vasomotor symptoms in both general menopause and in patients with breast cancer, but data are limited and have shown mixed results.[846] Limited data show a possible benefit of black cohosh for vasomotor symptoms in the general population.[847-849] However, randomized data in breast cancer survivors show no benefit.[850] Furthermore, there is concern about potential liver toxicity with long-term use of black cohosh. The panel consensus is that the efficacy and safety data for these treatments are too limited to make a recommendation for use.

Acupuncture is used as a treatment for hot flashes in the general population, although evidence supporting its benefit is limited in the non-cancer setting.[851,852] Several studies in women with cancer or female survivors have shown acupuncture to be a safe and effective option for managing vasomotor symptoms.[853-856] In fact, three of these studies compared acupuncture with either venlafaxine or gabapentin and found acupuncture to be equivalent to or better than drug treatment.[853,855,856]

Yoga may also help survivors manage hot flashes. A randomized trial in 355 healthy peri- and postmenopausal women found that yoga improved quality of life associated with menopause, including an improvement in the vasomotor symptom domain.[857] Another randomized controlled trial showed that yoga improved sleep but did not affect the frequency of symptomatic burden of vasomotor symptoms.[858]

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Evidence that exercise/physical activity helps manage hot flashes in postmenopausal women is inconclusive.[801,857,859-865] In fact, a randomized controlled trial of 261 peri-menopausal and postmenopausal women found no difference in the frequency of hot flashes between those randomized to an exercise intervention and the control group.[860] A similar trial involving 248 women also found that physical activity did not improve vasomotor symptoms.[863] Studies in the survivorship and cancer populations are limited and also do not support a role for the use of physical activity specifically to improve hot flash symptoms.[866] Despite the lack of data suggesting a benefit for vasomotor symptoms, the panel believes that physical activity should be recommended in menopausal cancer survivors given the many beneficial effects on overall health.

Other lifestyle modifications may also help minimize vasomotor symptoms. In the WHI Dietary Modification trial of 17,473 postmenopausal women who were not taking menopausal hormone therapy (MHT), those who lost ≥10% of their body weight were more likely to eliminate hot flash symptoms than those who maintained their body weight.[835] Data in breast cancer survivors also suggest that weight loss may help alleviate hot flashes in this population.[309,837] A longitudinal study in 761 women showed that those who quit smoking saw improvements in the frequency and severity of hot flashes compared to women who continued to smoke.[867] Although studies of this sort have not been done in survivor populations, data suggest that survivors who are current smokers are more likely to experience hot flashes.[868] Individual vasomotor responses to alcohol vary.[869] If alcohol triggers hot flashes in an individual survivor, limiting intake should be recommended.

Evidence suggests that CBT may reduce vasomotor symptoms in the general population.[870,871] CBT has also been studied for the management of vasomotor symptoms in cancer and survivor populations. In one trial, patients with breast cancer were randomized to receive CBT, CBT plus an exercise intervention, or to a control group.[866] Results suggested that CBT lessened the perceived burden of hot flashes. Another study randomized 96 women with hormonal symptoms after breast cancer treatment to a group CBT intervention or a usual care group.[872] The hot flashes and night sweats problem rating was significantly reduced in the CBT arm. Another trial randomized 254 breast cancer survivors to three groups: therapist-guided CBT, self-managed internet-based CBT (iCBT), or wait-list control.[873] Both of the CBT groups reported a significant decrease in the perceived impact of hot flashes compared to the control group. Improvements were also seen in sleep quality and the overall levels of menopausal symptoms.

Hormonal Treatment of Hot Flashes

MHT is the most effective treatment for the management of vasomotor symptoms in postmenopausal women.[792,874-879] However, the use of long-term MHT is controversial because, for many women, the health risks associated with MHT are thought to outweigh the potential benefits. In the past, MHT was typically given to postmenopausal women not only to treat vasomotor symptoms, but with the thought that MHT was effective at preventing heart disease. The best data looking at health benefits and risks came from the large WHI study that showed that estrogen alone in older postmenopausal women with prior hysterectomy was associated with an increased risk of stroke and decreased risk of hip fracture, and had no effect on coronary heart disease or breast cancer incidence.[880] In the WHI, estrogen plus progestin in older postmenopausal women with a uterus was associated with a decreased risk of colorectal cancer and hip fracture, and an increased risk of stroke, pulmonary embolism, and invasive breast cancer.[881] The women in these trials also had a higher rate of death from lung cancer during the intervention and were diagnosed with more advanced stages of colorectal cancer during the intervention and follow-up than women who received placebo.[882-884] MHT was also associated with an increase in breast cancer incidence and the cancers

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were more likely to be lymph node positive.[885,886] However, the absolute numbers of trial participants diagnosed with breast cancer were small, and the absolute risk was low. After longer follow-up, all-cause, cardiovascular, and cancer-specific mortality were not affected by MHT.[887] A systematic review of randomized double-blind studies of MHT versus placebo found no evidence that MHT affects the incidence of colorectal cancer, but found that MHT increases the risk of breast cancer and death from lung cancer in postmenopausal women taking estrogen and progestins combined.[888]

Data from retrospective studies and an incomplete randomized controlled trial suggest that MHT is safe to use in survivors of early-stage endometrial cancer.[889-893] In survivors of breast cancer, the data are inconclusive, because the only two randomized controlled trials of MHT in breast cancer survivors had conflicting results. The HABITS trial found an increased risk of breast cancer recurrence with the use of MHT; the cumulative incidence at 5 years was 22.2% in the MHT arm and 8.0% in the control arm.[894] In the Stockholm trial, no difference was seen in breast cancer recurrence after 10.8 years of follow-up.[895]

Overall, based on these data, the panel believes that MHT can be used in appropriate female cancer survivors. Alternatives to MHT should typically be tried first and patients should be referred to an appropriate specialist for dosing and management of MHT. MHT is contraindicated in survivors with a history of hormonally mediated cancers, although as noted above MHT is likely safe in survivors of early-stage endometrial cancer. Other contraindications for survivors mirror those for the general population, and include a history of abnormal vaginal bleeding, active or recent history of a thromboembolic event, pregnancy, and active liver disease. In addition, MHT should be used with caution in survivors with coronary heart disease or hypertension, in current smokers, and in those with increased genetic cancer risk. In general, the lowest dose possible to control symptoms should be used, and treatment should be individualized based on risks.

Hormonal treatments for the relief of hot flashes in women include combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus). There are different local and systemic formulations of hormones including oral, transdermal, vaginal ring, and an intrauterine device. Estrogen transdermal formulations may be preferred over other formulations due to lower rates of venous thromboembolism (VTE) and stroke.[896] Micronized progestin may be preferred over medroxyprogesterone acetate (MPA) due to lower rates of VTE and breast cancer risk. Other hormonal options for treating hot flashes include novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen, creating a tissue-selective estrogen complex (TSEC). One of these TSECs contains a conjugated estrogen and the SERM bazedoxifene,[897] and is FDA-approved for treating menopausal symptoms in healthy postmenopausal women. Custom compounded bioidentical hormones are not recommended, because data supporting claims that they are safer and more effective than standard hormones are lacking and they may be harmful.[898,899] Furthermore, these compounds are contraindicated in survivors of hormonally mediated cancers, and should only be used with caution in those with increased genetic cancer risk. Young cancer survivors experiencing menopause at an early age can consider oral contraceptives or MHT for symptom relief and potential cardiac and bone benefits as long as not contraindicated.

Treatment of Vaginal Dryness

Vaginal dryness can be treated with over-the-counter vaginal moisturizers, gels, oils, and topicals for comfort (category 2B).[900,901] Lubricants can be used for sexual activity.[902,903] In one study of breast cancer survivors, the control group used a non-hormonal moisturizer and saw a transient improvement in vaginal symptoms.[900] Survivors should be cautioned that some lubricants may be irritating to the area of application.

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Local hormonal treatments can also be used (category 2B), although some data suggest that they may not be more effective than vaginal gels or moisturizers.[881,904-910] Furthermore, some controversy exists regarding their safety in survivors of hormone-dependent cancers.[911] However, evidence suggests that local estrogen does not increase the risk of breast cancer recurrence.[912] Vaginal estrogen preparations include rings, suppositories, and creams and have been shown to be effective for managing symptoms of vaginal dryness in menopausal women.[910,913] Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories, and they are therefore preferred for survivors with hormonally sensitive tumors if estrogen-based treatment is warranted.[911,914] Other topical hormones (ie, testosterone, DHEA) can also be considered, but data regarding their safety or effectiveness are limited. One randomized controlled trial of 464 survivors of breast or gynecologic cancer showed that vaginal DHEA led to significant improvements in sexual desire, arousal, pain, and overall sexual function, although a plain moisturizer also improved symptoms.[905] In this trial, clinically important systemic estrogenic activity was not evident, and the treatment was safe and well tolerated. Overall, the decision to use local hormones should be individualized with a discussion of the possible risks and benefits. Referral to an appropriate specialist for management can also be considered. DHEA should be used with caution in survivors with a history of estrogen-dependent cancers.

The use of a fractional microablative CO_2 laser has been studied for the treatment of vaginal dryness and other genitourinary symptoms in postmenopausal women. Significant improvements in symptoms were observed in as many as 84% of women, although sample sizes are small.[915-917] Limited data also suggest that the laser treatment is effective in breast cancer survivors.[918-921] Studies suggest that adverse events are infrequent and include pelvic pain, vaginal infections, genital herpes reactivation, and postmenopausal bleeding.[915,918,920] However, the FDA issued a safety communication in July 2018 warning that energy-based devices such as lasers used for vaginal procedures including the treatment of menopausal symptoms may be associated with serious adverse events.[922] The FDA has not cleared or approved for marketing any energy-based devices for the treatment of menopausal symptoms and notes that the safety and effectiveness of these devices for these types of treatments have not been established. The panel believes that larger trials are needed before this technique can be recommended.

Treatment of Urogenital Complaints

Women sometimes present with urogenital complaints associated with menopause, such as urogenital atrophy and urinary incontinence. The panel recommends treatment with local vaginal estrogen and referral to an appropriate specialist.[913,923] See *Treatment of Vaginal Dryness*, above, for a discussion on the safety of vaginal estrogen.

Management of ADT-Related Symptoms in Male Survivors

Survivors of prostate cancer may be on ADT (see the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org), and may experience many symptoms, including hot flashes, gynecomastia, and anemia.

Vasomotor Symptoms

For vasomotor symptoms disruptive to quality of life in men, alternative ADT options, such as intermittent ADT, can be tried if deemed appropriate by the oncologist (see the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org).

Androgens (eg, testosterone) are used for the relief of hot flashes in men who have hypogonadism from chemotherapy or radiation for other malignancies. Hormonal options for the relief of hot flashes in survivors on ADT include MPA, estrogen, and cyproterone acetate.[924-927] Men with vasomotor symptoms should be offered medication for symptomatic

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improvements. Options include venlafaxine, MPA, cyproterone acetate, and gabapentin.[928]

The non-hormonal options include the SSRIs venlafaxine and the anti-convulsant gabapentin. Gabapentin has been shown to be safe and moderately effective at controlling hot flashes in men with prostate cancer in two randomized controlled trials.[929-931] Case reports and small pilot studies have shown that venlafaxine may improve hot flash symptoms in men with prostate cancer undergoing ADT.[932] The panel lists venlafaxine as the preferred antidepressant and gabapentin as the preferred anticonvulsant for hormone-related symptoms.

As in female cancer survivors, men with ADT-related symptoms can try non-pharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss if overweight or obese, hypnosis, and CBT.[928] Small studies in prostate cancer survivors with a history of ADT have also found that acupuncture is effective at controlling hot flashes in this population.[933,934] A study of 68 patients with prostate cancer on ADT also found that CBT reduced the perceived burden of hot flashes compared with usual care.[935]

As in women with vasomotor symptoms, phytoestrogens, botanicals, and dietary supplements are often used in males. However, data are limited on the effectiveness and safety of these nonpharmacologic treatments in survivors on ADT.[936] Furthermore, there are concerns that supplemental vitamin E may increase the risk for prostate cancer.[937,938] The panel consensus is that the efficacy and safety data for these treatments are too limited to make a recommendation for use.

Hypogonadism

Clinicians should consider measuring free and total testosterone, LH, and prolactin in men with anemia, bone density loss, diabetes, exposure to chemotherapy or testicle radiation, HIV/AIDS, chronic narcotic use, infertility, pituitary dysfunction, and chronic corticosteroid use.[939] Clinicians should check testosterone levels, even if the patient has a history of cancer not typically associated with hormonal changes. Diagnosis of hypogonadism requires two total testosterone measurements taken on separate, early-morning blood draws. Testosterone therapy should be discussed when testosterone levels are low (<300 ng/dL) or low normal and the patient is symptomatic.[928] When to initiate or resume treatment for low testosterone in survivors of prostate cancer who have no evidence of recurrent disease and are not on ADT is controversial and should be coordinated with the patient's primary cancer physician (ie, surgeon, oncologist, radiation oncologist). Men still receiving ADT should not receive androgens (eg, testosterone).

Androgens are contraindicated in men diagnosed with prostate cancer on active surveillance or observation, in patients actively being treated for prostate cancer, and in men with advanced prostate malignancy on ADT. The 2018 AUA Guidelines Committee found insufficient evidence to quantify the risk-benefit ratio of testosterone therapy in men with prior history of prostate cancer.[939] After curative-intent therapies for prostate cancer, patients should discuss with their surgeon or radiation oncologist when to resume testosterone (if they had a history of hypogonadism prior to treatment of prostate cancer) or when to initiate testosterone therapy for hypogonadism.

Gynecomastia

Gynecomastia and breast pain can be treated in men on ADT by prophylactic radiation (must be delivered prior to development of breast tissue), tamoxifen, or reduction mammoplasty.[791,940,941]

Anemia

Anemia in men on ADT is generally responsive to erythropoietin (EPO) or blood transfusion. These men can be treated as per the NCCN Guidelines

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for Cancer- and Chemotherapy-Induced Anemia (available at www.NCCN.org).

Pain

More than one-third of post-treatment cancer survivors experience chronic pain, which often leads to psychological distress; decreased activity, motivation, and personal interactions; and an overall poor quality of life.[942-946] Pain in survivors is often ineffectively managed. Barriers to optimal pain management in cancer survivors include health care providers' lack of training, fear of side effects and addiction, and reimbursement issues.[947]

Pain has two predominant mechanisms: nociceptive and neuropathic.[948,949] Injury to somatic and visceral structures and the resulting activation of nociceptors present in skin, viscera, muscles, and connective tissues cause nociceptive pain. Somatic nociceptive pain is often described as sharp, throbbing, or pressure-like, and often occurs after surgical procedures. Visceral nociceptive pain is often diffuse and described as aching or cramping. Neuropathic pain is caused by injury to the peripheral nervous system or CNS and might be described as numbness or as burning, sharp, tingling, prickling, electrical, or shooting pain. Neuropathic pain often occurs as a side effect of chemotherapy or radiation therapy or is caused by surgical injury to the nerves.

The incidence of chronic pain after surgical treatment varies with the type of procedure and is as high as 60% in patients treated with breast surgery and 50% in those treated with lung surgery.[942] Arthralgias, characterized by joint pain and stiffness, occur in roughly half of women taking aromatase inhibitors as adjuvant therapy for breast cancer.[950] Pelvic pain often occurs after pelvic radiation, resulting from fractures, fistulae, proctitis, cystitis, dyspareunia, or enteritis.[942]

These NCCN Guidelines for Survivorship make recommendations for the management of seven categories of cancer pain syndromes: neuropathic pain, chronic pain syndromes (ie, pain syndromes after amputation, neck dissection, mastectomy, thoracotomy), myalgias/arthralgias, skeletal pain, myofascial pain, gastrointestinal/urinary/pelvic pain, and postradiation pain. Recommendations for the prevention and management of chemotherapy-induced peripheral neuropathy (CIPN) in survivors can be found in ASCO's clinical practice guideline.[951] ASCO also has a clinical practice guideline for the management of chronic pain in survivors of adult cancers.[952]

Screening for and Assessment of Pain

All cancer survivors should be screened for pain at regular intervals. If pain is present, the intensity should be quantified by the survivor. Because pain is inherently subjective, self-report of pain is the current standard of care for assessment. Intensity of pain should be quantified using a 0 to 10 numeric rating scale, a categorical scale, or a pictorial scale (eg, Wong-Baker FACES Pain Rating Scale).[953-956] In addition, the survivor should be asked to describe the characteristics of the pain (eg, aching, burning). Severe uncontrolled pain is a medical emergency and should be addressed promptly. In addition, an oncologic emergency should also be ruled out in these cases.

A comprehensive evaluation, as outlined in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org), is essential to ensure proper pain management. The survivor's goals for comfort and function and the cause and pathophysiology of the pain should be identified to determine the optimal therapeutic strategy. If the pain is new and acute, the possibility of pain due to cancer recurrence should be considered. If the pain is chronic, a specific cancer pain syndrome should be identified if possible. Referral to a PCP can be made for non-cancer or non-cancer-treatment–related workup and pain management (ie, rheumatoid arthritis).

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Management of Pain

The goals of pain management are to increase comfort, maximize function, and improve quality of life. A multidisciplinary approach, which may include a combination of pharmacologic treatments, psychosocial and behavioral interventions, physical therapy and physical activity, occupational therapy, local therapies, and interventional procedures, is recommended.[943,957,958] These approaches are discussed in more detail below. For survivors with refractory pain and/or those who might benefit from further pain interventions, referral to a specialist (ie, pain management services, interventional specialist, physical therapy, physical medicine, palliative care, rehabilitation, interventional pain, urology, gynecology, orthopedic surgery, gastroenterology, other appropriate consultants) can also be considered. Finally, psychological support for survivors with chronic pain is necessary, and referral to psychosocial services should be considered for survivors in distress.

The panel acknowledges the legalization of medical marijuana for various conditions in multiple states. However, there are presently not enough data to make any guideline recommendations regarding use in cancer survivors.

For more information about the management of cancer-related pain, please see the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). These guidelines include information on opioid use and controlled substance agreements for patients at risk for medication misuse or diversion; adjuvant analgesics; and psychosocial support and behavioral interventions that may be modified to fit the individual survivor's circumstances.

Pharmacologic Interventions

Pharmacologic measures are the foundation of treatment of many of the common pain syndromes in survivors. Pharmacologic recommendations in these guidelines vary depending on the pain syndrome and include opioids, adjuvant analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants.[943,959-961] Topical medications are discussed in *Local Therapies*, below.

Opioids: Opioids may be recommended for the treatment of neuropathic pain, skeletal pain, and chronic pain syndromes in survivors.[962] An opioid analgesic with a dual mechanism of action as both a mu-opioid agonist and a noradrenaline reuptake inhibitor is also a recommended option for the treatment of neuropathic pain in survivors based on the available data. Tapentadol is a dual-action mu-opioid agonist/noradrenaline reuptake inhibitors.[963]Two separate randomized controlled trials in patients with painful diabetic peripheral neuropathy (n = 588 and n = 358) showed that tapentadol improved pain intensity compared with placebo.[964,965] Two other randomized trials in patients with chronic malignant tumor-related pain (n = 325 and n = 236) also showed improvements in pain intensity with tapentadol compared with placebo.[966,967] No studies in cancer survivors or in chemotherapy-induced neuropathy were identified by the panel. Data on the long-term use of opioids in survivors are lacking.[958,960,968] In fact, data on the long-term safety and effectiveness of opioids in the non-cancer setting are scarce as well.[969]

Opioid prescribing rates among cancer survivors are substantially higher compared to controls, even long after attaining cancer survivorship.[970,971] In a retrospective, population-wide cohort study, cancer survivors in Ontario, Canada, diagnosed ≥5 years prior were found to have an adjusted relative rate of opioid prescriptions of 1.22 (95% CI, 1.11–1.34).[970] The 3-year mean cumulative number of filled opioid prescriptions was 7.7 in survivors compared with 6.3 in matched controls ($P < .0001$). Furthermore, a study of national insurance claims data showed that approximately 10% of opioid-naïve patients prescribed opioids for curative-intent cancer surgery continued to fill their prescriptions for 90 to

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180 days after surgery, suggesting that aberrant opioid use or diversion of pain medication may be an issue in the survivor population.[972]

The NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org) recommend screening for risk factors of aberrant opioid use or diversion of pain medication, using a detailed patient evaluation and/or tools such as the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) or Opioid Risk Tool (ORT) before prescribing.[973-977] Patients and caregivers should be educated on the potential risks and benefits of opioid therapy, including the potential for diversion or misuse of opioids and safe storage and disposal of opioid medications. Various strategies may be employed to support patients determined to be at high risk for opioid misuse; behavioral/cognitive-behavioral interventions, education on naloxone, pain medication diaries/pill counts, and urine drug testing represent just a few of these strategies. Furthermore, the FDA has established Risk Evaluation and Mitigation Strategy (REMS) programs for opioid products to reduce addiction, misuse, abuse, overdose, and death through provider, patient, and family/caregiver education.[978-980] In addition, if opioids are deemed necessary for any survivor (regardless of aberrant use risk level), the NCCN Survivorship Panel recommends using the lowest dose possible for the shortest period of time possible and reevaluating the effectiveness and necessity of opioids on a regular basis. Pain treatment agreements can also be considered.[981]

In March 2016, the CDC released guidelines for prescribing opioids for chronic pain.[982] In May 2016, ASCO released a policy statement, describing principles to help balance concerns for the abuse and misuse of opioids with concerns for appropriate access of opioids for pain management in patients with cancer and survivors.[983] The NCCN Survivorship Panel shares these concerns and supports ASCO's statement. Overall, the panel believes that the concerns for the abuse and misuse of opioids must be balanced with concerns for appropriate access of opioids for pain management in patients with cancer and survivors.[983-985]

Adjuvant Analgesics: Adjuvant analgesics include antidepressants (eg, SNRIs, tricyclic antidepressants) and anticonvulsants (eg, gabapentin, pregabalin).[962] These are recommended for the treatment of survivors with neuropathic pain, post-radiation pain, chronic pain syndromes, myalgias, and arthralgias. The term adjuvant refers to the fact that they are often co-administered with an opioid to enhance analgesia or reduce the opioid requirement, but they may also be used as the sole pain treatment. A systematic review found that antidepressants, anticonvulsants, other adjuvant analgesics, and opioids were all effective at reducing neuropathic pain in patients with cancer.[960] Another review found that antidepressants and anticonvulsants may provide additional neuropathic pain relief when added to opioids in patients with cancer.[986]

Tricyclic antidepressants have been shown to relieve neuropathic pain in the non-cancer setting.[987,988] In addition, the SNRI duloxetine was shown to effectively reduce pain in a multi-institutional, randomized, double-blind, placebo-controlled, crossover trial of 231 patients with painful CIPN.[989] The ASCO clinical practice guidelines for the prevention and management of CIPN in survivors of adult cancers recommend duloxetine in this setting.[951] Duloxetine can also improve aromatase inhibitor-associated arthralgia. A randomized, double-blind, placebo-controlled, phase III trial, which included 299 postmenopausal survivors of early-stage breast cancer with joint pain, showed that duloxetine improved average joint pain score, worst pain, joint stiffness, pain interference, and functioning at 12 weeks.[990] SNRIs are therefore listed as a category 1 recommendation for survivors with aromatase inhibitor-induced arthralgia.

The most commonly used anticonvulsant drugs for the treatment of cancer-related pain are gabapentin and pregabalin. They are recommended in these guidelines for the treatment of myalgias and

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arthralgias.[991] Both drugs have also demonstrated efficacy in diabetic and postherpetic neuropathy,[992-994] but have not been well-studied in the cancer or survivorship settings.[951] One randomized, placebo-controlled, crossover trial in 115 survivors found that gabapentin did not effectively treat CIPN.[995] However, because high-level evidence is limited to this one trial, the panel concurs with ASCO's CIPN panel and believes that extrapolation from other neuropathic pain conditions is reasonable and that gabapentin can be offered to select survivors with CIPN after informing them about the inconclusiveness of the evidence and of potential harms, benefits, and costs.[951] A randomized, double-blind trial of pregabalin compared with placebo in 128 patients with neuropathic pain following radiation therapy for head and neck cancer found that pregabalin reduced pain scores to a greater extent than placebo.[996] A ≥30% pain relief was achieved by 59% versus 33% of participants (P = .006), and a ≥50% pain relief was achieved by 30% versus 8% (P = .003).

Corticosteroids are not recommended for the management of pain in cancer survivors. A randomized, placebo-controlled, double-blind trial of adult patients with advanced cancer receiving opioids found that methylprednisolone did not provide additional analgesia over that provided by the opioids.[997]

Nonsteroidal Anti-Inflammatory Drugs: NSAIDs, including COX-2 inhibitors, and acetaminophen are recommended for the treatment of myofascial, skeletal, and post-radiation pain, and for myalgias and arthralgias. NSAIDs are non-opioid analgesics that block the biosynthesis of prostaglandins, which are inflammatory mediators that can initiate, cause, intensify, or maintain pain. A systematic review found that data supporting the use of NSAIDs for control of pain in patients with advanced cancer are limited and weak, but suggest some efficacy at reducing pain and opioid dose requirement.[998]

A discussion of contraindications and safety precautions that should be considered before prescribing NSAIDs is provided in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org).

Muscle Relaxants: Muscle relaxants (eg, diazepam, lorazepam, metaxalone) reduce muscle spasms and are recommended for the treatment of skeletal pain, myalgias, and arthralgias. Evidence for their efficacy in providing pain relief in the non-cancer setting is limited.[999,1000] No data could be found in the setting of cancer-related pain.

Psychosocial Support and Behavioral Interventions

Cognitive interventions are aimed at enhancing a sense of control over the pain or its underlying cause. Breathing exercises, relaxation, imagery or hypnosis, and other behavioral therapies can be very useful.[944,1001-1006] A randomized controlled trial of 129 breast cancer survivors with pain found that an 8-week mindfulness-based cognitive therapy program reduced pain intensity and nonprescription pain medication use compared with a waitlist control group.[1007] Quality of life was also improved in the intervention arm, but distress was not reduced.

Psychosocial support and education should also be provided.[1008] Some studies in patients with cancer suggest that psychosocial and behavioral interventions such as skills training, education, relaxation training, supportive–expressive therapy, and CBT may be effective at reducing pain.[1003,1009] Hypnosis can also be considered for treatment of neuropathic pain. Overall, data support the benefit of hypnosis for controlling pain in cancer and other settings, but are lacking in the survivorship population.[1010]

Mirror therapy, if available, can be considered for the treatment of chronic "phantom limb" pain after amputation. In mirror therapy the survivor views a reflected image of his or her intact limb in a mirror while trying to move the amputated limb. In a small randomized trial, mirror therapy reduced

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pain in 6 of 6 patients and in 8 of 9 patients who switched to mirror therapy from the control conditions (covered mirror or mental visualization).[1011] One case report suggests that this therapy can be effective in survivors.[1012]

In general, studies regarding psychosocial support and behavioral interventions for reducing pain in survivors are limited. A systematic review and meta-analysis assessed the efficacy of psychosocial interventions for treating pain in patients with breast cancer and survivors.[1013] Although results suggest an effect, more studies are clearly needed in the survivorship population.

Physical Therapy and Physical Activity

Physical therapy and general physical activity may also be effective for the treatment of pain in survivors, with the main goal of increasing mobility.[210,944,957,1014] Several randomized controlled trials have reported a reduction of neck and shoulder pain associated with exercise or therapy programs.[1015-1019] In one study, 52 survivors of head and neck cancer were randomized to a progressive resistance exercise training (PRET) program or standard therapeutic exercise for 12 weeks.[1017] Pain scores decreased more dramatically in the PRET group (P = .001). In another study of 66 survivors of breast cancer, those randomized to an 8-week water exercise program experienced a greater reduction of neck and shoulder pain than those randomized to usual care.[1015] A more recent randomized trial showed that breast cancer survivors with aromatase-inhibitor–induced arthralgia randomized to an exercise arm (150 min/wk of aerobic exercise plus supervised strength training twice per week) experienced greater improvements in worst joint pain scores, pain severity, and pain interference than those in the usual care arm (all P < .001).[1018] Physical activity is thus listed as a category 1 recommendation for survivors with aromatase inhibitor-induced arthralgia.

In addition, group exercise in the community with trainers specifically trained to work with cancer survivors has been shown to reduce pain and other symptoms.[291] Yoga may also be helpful for pain management in cancer survivors. In a randomized controlled trial of 167 breast cancer survivors on aromatase inhibitors or tamoxifen, yoga reduced musculoskeletal pain symptoms.[1020]

Local Therapies

Local therapies, including heat, cold packs, massage, and medicated creams, ointments, and patches, are recommended for the treatment of myalgias, arthralgias, and neuropathic pain.[944] Specifically, topical ointments (ketamine) and patches (ie, lidocaine, capsaicin) are recommended for myofascial pain. Compounded creams containing agents such as lidocaine, capsaicin, baclofen, ketamine, and amitriptyline are recommended for treatment of neuropathic pain. Use of transcutaneous electrical nerve stimulation (TENS) can be used for neuropathic pain and for chronic post-mastectomy and post-thoracotomy pain.

Data are limited on the effectiveness of ketamine and amitriptyline,[1021-1026] but the evidence for the effectiveness of lidocaine and capsaicin is stronger.[1021,1023-1025] In a randomized trial of 208 participants with CIPN, the group that received a compounded topical gel containing baclofen, amitriptyline, and ketamine showed a trend towards improvements in the sensory and motor subscales of the EORTC QLQ-CIPN20 compared with the placebo group.[1027] The greatest improvements were seen in tingling, cramping, shooting/burning pain in the hands, and difficulty holding a pen. Lidocaine has been shown to reduce the severity of postherpetic neuropathy and cancer-related pain.[1028,1029] In a randomized trial of 35 patients with non–cancer-related postherpetic, postoperative, or diabetes-related neuropathic pain, pain intensity was reduced with topical lidocaine but not with topical amitriptyline when compared with placebo.[1024] A larger

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trial with a similar population of 92 patients found no effect of topical amitriptyline, ketamine, or a combination of the two.[1030] Another study found that a higher dose of amitriptyline had some efficacy in reducing peripheral neuropathy, but also showed systemic effects.[1031] More recently, results of a multicenter, phase III, randomized, double-blind, placebo-controlled trial of 462 survivors with CIPN found that ketamine/amitriptyline cream had no effect.[1032] Similarly, a randomized trial that included 133 patients with non-cancer neuropathic pain found that compounded cream containing ketamine, gabapentin, clonidine, and lidocaine was no more effective than placebo at reducing the average pain score 1 month after treatment.[1033]

TENS is a noninvasive procedure in which electrodes are placed on or around the painful area.[944] A systematic review demonstrated that data supporting the efficacy of TENS for reducing cancer-related pain are inconclusive.[1034] The goal of invasive interventions, such as an intercostal nerve block, is to interrupt nerve conduction by either destroying nerves or interfering with their function.[944] The data on these interventions are also limited.[944]

Acupuncture

Acupuncture is recommended as a possible option for the treatment of myofascial or neuropathic pain in survivors. Evidence supporting the efficacy of this technique for reducing cancer-related pain is evolving.[1035-1037] A small randomized controlled trial compared electro-acupuncture (EA) to white light cystoscopy (WLC) and sham acupuncture in 67 postmenopausal women with breast cancer and aromatase inhibitor-associated arthralgia.[1038] Pain severity was improved in both the EA and sham acupuncture arms compared with the control arm (mean reduction in pain severity in the EA vs. WLC groups at week 8, -2.2 vs. -0.2; P = .0004). Another trial randomized 226 postmenopausal women with early-stage breast cancer and AI-induced joint pain 2:1:1 to acupuncture, sham acupuncture, or waitlist.[1039] The acupuncture group experienced a small but statistically significant reduction in joint pain at 6 weeks. Acupuncture is thus listed as a category 1 recommendation for survivors with aromatase inhibitor-induced arthralgia. Neuropathic pain was also reduced with acupuncture in a small randomized trial of 40 breast cancer survivors with CIPN.[1040]

Management of Refractory Pain

For refractory pain, referral to pain management services, an interventional specialist, physical therapy, physical medicine and rehabilitation, and/or palliative care should be considered. Intercostal nerve blocks, neurotomy with radiofrequency ablation, and dorsal column stimulation are some of the options that can be considered.

Sexual Dysfunction

Cancer treatment, especially hormonal therapy and surgical and/or radiation therapy directed towards the pelvis, can often impair sexual function. In addition, depression and anxiety, which are common in survivors, can contribute to sexual problems. Thus, sexual dysfunction is common in survivors and can cause increased distress and have a significant negative impact on quality of life.[1041-1046] Nonetheless, sexual function is often not discussed with survivors.[1047-1051] Reasons for this include a lack of training of health care professionals, discomfort of providers and/or survivors with the topic, survivors' perception of discomfort from the provider, and insufficient time during visits for discussion.[1041] However, effective strategies for treating both female and male sexual dysfunction exist, making these discussions a critical part of survivorship care.

Panel recommendations for the management of sexual dysfunction in survivors are described herein. Cancer Care Ontario has developed recommendations for the management of sexual problems in patients with

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cancer that ASCO has endorsed.[928,1052] Most of their recommendations are consistent with those put forth by the NCCN Survivorship Panel.

NCCN is aware that many regenerative, restorative, or rejuvenation therapies are being marketed to patients with sexual dysfunction. Survivors should be aware that the FDA has not approved injections of autologous platelet-rich plasma or stem cells for treatment of male sexual dysfunction. The FDA has not cleared energy-based devices (ie, vaginal rejuvenation by lasers or erectile dysfunction [ED] by shock waves, also discussed in *Treatment of Vaginal Dryness,* above and *Interventions for Male Sexual Dysfunction,* below) for treatment of menopausal changes, ED, or incontinence. Cancer survivors with sexual dysfunction should be referred to specialists for discussions of non–FDA-approved therapeutics and special consideration should be given to their primary diagnosis of cancer prior to enrollment in clinical trials for sexual dysfunction or incontinence.

Female Sexual Dysfunction

Female sexual problems relate to issues with sexual desire, arousal, orgasm, and pain.[1053-1055] Sexual dysfunction after cancer treatment is common in female survivors.[30,1045,1056-1061] A survey of 221 survivors of vaginal and cervical cancer found that the prevalence of sexual problems was significantly higher among survivors than among age- and race-matched controls from the National Health and Social Life Survey (mean number of problems 2.6 vs. 1.1; $P < .001$).[1060] A survey of survivors of ovarian germ cell tumors and age- and race- and education-matched controls found that survivors reported a significant decrease in sexual pleasure.[1062]

Female sexual dysfunction varies with cancer site and treatment modalities.[1057,1058] For example, survivors of cervical cancer who were treated with radiotherapy had worse sexual functioning scores (for arousal, lubrication, orgasm, pain, and satisfaction) than those treated with surgery, whose sexual functioning was similar to that of age- and race-matched non-cancer controls.[1057] A systematic review of sexual functioning in cervical cancer survivors found similar results, except that no differences in orgasm/satisfaction were observed.[1063] Chemotherapy seems to be linked to female sexual dysfunction in breast cancer survivors,[1058] possibly related to the prevalence of chemotherapy-induced menopause in this population.[1054] Furthermore, body image changes related to breast cancer surgery and reconstruction can affect women's sexual health and well-being.[1064] In addition, survivors with a history of HSCT may have multiple types of sexual dysfunction even 5 to 10 years after diagnosis.[1065-1067] Some of the sexual dysfunction associated with HSCT is related to GVHD, which can result in vaginal fibrosis, stenosis, mucosal changes, vaginal irritation, bleeding, and increased sensitivity of genital tissues.[1066,1068] In addition, high-dose corticosteroids used for chronic GVHD can increase emotional lability and depression, affecting feelings of attractiveness, sexual activity, and quality of sexual life.

Male Sexual Dysfunction

The NIH Consensus Conference on Impotence defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[1069] In fact, impotence and ED are not synonymous. Impotence can involve problems of sexual desire, orgasm, or ejaculation, which are not necessarily linked with achieving or maintaining an erection.[1070]

ED associated with a cancer diagnosis and cancer therapy may have a psychologic component, but is most often physiologic and iatrogenic. In the case of surgery, ED may be immediately evident; in the case of radiation treatments, presentations can be delayed. ED occurs frequently in the general population and increases with age.[1071] In one community-based study, 33% of men aged ≥75 years reported moderate or worse ED.[1072] ED is also very common in male cancer survivors. Anticancer

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treatment modalities used in a variety of cancers have the potential to damage blood vessels, leading to a reduction in blood circulation to the penis and/or damage to the autonomic nervous system. Thus, higher rates of ED are seen in cancer survivors than in the general population. The prevalence of ED in male survivors of colorectal cancer has been reported to range from 45% to 75%,[1042,1073,1074] and it has been reported in up to 90% of survivors of prostate cancer.[1075-1079]

Male cancer survivors exposed to radiation or chemotherapy often experience hypogonadism—usually primary hypogonadism. Hypogonadism in men refers to a decrease in the production of sperm and/or testosterone. Primary hypogonadism is the result of testicular failure. In these men testosterone levels and sperm counts are below normal, and serum LH and FSH are above normal. Secondary hypogonadism is a disease of the pituitary or hypothalamus. In men with secondary hypogonadism, serum testosterone levels and sperm counts are subnormal, and the serum LH and FSH levels are normal or reduced. Adult-onset hypogonadism is characterized by a deficiency of testosterone and a failure of the body to produce an adequate compensatory response. In these men, low testosterone levels are associated with normal or low levels of gonadotropins, suggesting physiologic failure of both the testicles and hypothalamic-pituitary system.[1080]

Evaluation and Assessment for Sexual Function

All adult cancer survivors, regardless of gender identity and sexual orientation, should be asked about their sexual function at regular intervals, by inquiring about any concerns or distress regarding sexual function, sexual activity, sexual relationships, or sex life. Cancer survivors who report distress should be evaluated further. Inquiries into treatment-related infertility should be made if indicated, with referrals as appropriate. ASCO's recently updated clinical practice guidelines on fertility preservation for patients with cancer have more information on the topic.[1081] It is important for providers to be aware that fertility issues should be addressed in the survivorship phase, whether or not they were addressed prior to treatment.[1082-1084] A discussion regarding the need for contraception may also be helpful in some cases, because the incidence of unplanned pregnancies is approximately three times higher in cancer survivors than in the general population.[1085]

Survivors for whom screening does not indicate an issue with sexual function should be rescreened at subsequent visits. For survivors with sexual function concerns who do not wish to discuss them at the current visit, referral can be made to a sexual health specialist if the survivor is interested. These survivors should also be re-evaluated and engaged in discussions about the potential impact of treatment on sexual function at future visits.

For survivors who want to discuss their sexual function further, screening tools can be considered. Several screening tools are available for both men and women. For women, options include the Brief Sexual Symptom Checklist for Women, the Arizona Sexual Experience Scale (ASEX), the Female Sexual Function Index (FSFI), and a breast cancer-specific adaptation of the FSFI (FSFI-BC).[1086-1089] For men, the Sexual Health Inventory for Men (SHIM), the Sexual Quality of Life Questionnaire-Men, and the PROMIS Brief Function Profile-Male are examples.[1071,1090,1091] The FSFI has been validated in patients with cancer and cancer survivors.[1092,1093] The FSFI and ASEX were also identified in a systematic review as tools that have acceptable psychometric properties in patients with breast cancer.[1094] The other tools have not been validated in cancer or survivor populations.

Survivors with concerns about their sexual function should undergo a more thorough evaluation, including screening for possible psychosocial problems or mental health issues (ie, anxiety, depression, relationship issues, body image concerns, drug or alcohol use) that can contribute to

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sexual dysfunction. It is also important to identify prescription and over-the-counter medications (especially hormone therapy, narcotics, beta-blockers, and SSRIs) that could be a contributing factor. Traditional risk factors for sexual dysfunction, such as CVD, diabetes, obesity, smoking, and alcohol abuse, should also be assessed, as should the patient's oncologic and treatment history. In addition, the impact of cancer and cancer treatment on sexual function should be explored further. Finally, for men, total morning testosterone should be measured if indicated by concerns regarding hypogonadism.[800]

Interventions for Female Sexual Dysfunction

Female sexual dysfunction is often multifactorial in nature. Therefore, treatment of sexual dysfunction often requires a multidimensional treatment plan that addresses the underlying issues, which can be physiologic (eg, menopause, illness), disease-induced, medication-induced, psychologic (eg, anxiety, depression), and interpersonal. Informed patient and physician decision-making is the standard for guiding treatment decisions for treatment of female sexual dysfunction. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, gynecologic care, sexual health specialist) should be made if appropriate and available.

Overall, the evidence base for interventions to treat female sexual dysfunction in survivors is weak and high-quality studies are needed.[1095,1096] Based on evidence from other populations, evidence from survivors when available, recommendations from the American College of Obstetricians and Gynecologists (ACOG),[1053] and consensus among NCCN Survivorship Panel Members, the panel made recommendations for treatment of female sexual dysfunction in survivors. The panel recommends that treatment be guided by the specific type of problem. Treatments depend on the type of sexual dysfunction and may include both over-the-counter and prescription options, as well as pelvic physical therapy and integrative therapies. When prescription medications are being considered, the risks and benefits should be discussed, or the survivor should be referred to an appropriate health care provider (eg, sexual health specialist) for prescription and/or treatment. The evidence base for each recommendation is described herein.

Integrative therapies, including yoga and meditation, may be helpful for female survivors with sexual dysfunction.[857,1097] In addition, CBT has been shown to be effective at improving sexual functioning in breast cancer survivors.[1098]

Vaginal moisturizers, vaginal gels, oils, and topical vitamin D or E can help alleviate symptoms such as vaginal dryness and sexual pain,[901,1099] although data on these over-the-counter products are limited in the general population (also see *Treatment of Vaginal Dryness*, under *Hormone-Related Symptoms* above). Topical anesthetics may help with vaginal pain as shown in a study in 46 breast cancer survivors that found that application of lidocaine to the vulvar vestibule before vaginal penetration improved dyspareunia.[1100]

Pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual pain, arousal, lubrication, orgasm, and satisfaction. A small study of 34 survivors of gynecologic cancers found that pelvic floor training significantly improved sexual function.[1101]

Vaginal dilators are an option for survivors with pain during sexual activity. In addition, vaginal dilators are used for survivors with vaginal stenosis from pelvic radiation. However, evidence for the effectiveness of dilators is limited.[1102]

Several topical prescription medications can also be considered for female survivors with sexual dysfunction (also see *Treatment of Vaginal Dryness*, under *Hormone-Related Symptoms* above). For example, vaginal

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estrogen (pills, rings, or creams) has been shown to be effective in treating vaginal dryness, itching, discomfort, and painful intercourse in postmenopausal women.[881,906-910] A study in 76 postmenopausal breast cancer survivors on aromatase inhibitor therapy found that intravaginal testosterone cream or an estradiol-releasing vaginal ring were safe and improved vaginal atrophy and sexual function.[1103] The panel notes that focal application of creams applied to external vulvar regions are absorbed to a lesser degree than creams placed inside the vagina.

Vaginal androgens (ie, DHEA; also known as prasterone) can be considered for vaginal dryness or pain with sexual activity (also see *Treatment of Vaginal Dryness*, under *Hormone-Related Symptoms* above). Vaginal DHEA received FDA approval in 2016. Several studies have shown it to be effective at reducing dyspareunia in postmenopausal women.[1104-1108] However, a systematic review and meta-analysis published in 2015 concluded that it is uncertain whether vaginal DHEA improves vasomotor symptoms and vaginal dryness.[1109] A randomized controlled trial of 464 survivors of breast or gynecologic cancer showed that vaginal DHEA led to significant improvements in sexual desire, arousal, pain, and overall sexual function, although a plain moisturizer also improved symptoms.[905] In this trial, clinically important systemic estrogenic activity was not evident, and the treatment was safe and well tolerated. Overall, safety data for the use of androgen-based therapy in survivors of hormonally mediated cancers are limited. The FDA label for vaginal DHEA warns that exogenous estrogens are contraindicated in women with a history of breast cancer.[1110] The panel cautions that DHEA should be used with caution in survivors with a history of estrogen-dependent cancers.

In 2013, the FDA approved the SERM ospemifene for treating moderate to severe dyspareunia in postmenopausal women without known or suspected breast cancer and without a history of breast cancer.[1111] Ospemifene has been studied in several large trials of women with postmenopausal vulvar and vaginal atrophy and was found to effectively treat vaginal dryness and dyspareunia.[1112-1114] Data in the survivor population are very limited. One prospective study, in which 52 survivors of stage I–IIa cervical cancer with vulvovaginal atrophy were treated with ospemifene, found improvements in vaginal health and function, sexual activity, body image, sexual enjoyment, global health status, and emotional and social functioning.[1115] The panel recommends consideration of ospemifene for dyspareunia in survivors of cancers that are not hormonally sensitive.

In August 2015, the FDA approved flibanserin to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women.[1116] Meta-analyses have shown that flibanserin resulted in approximately 1 additional satisfying sexual event every 2 months in premenopausal women.[1117,1118] This drug has not been studied in patients with cancer or survivors, but it is a reasonable option to discuss with premenopausal survivors with low or lack of desire, libido, or intimacy.

In June 2019, the FDA approved bremelanotide for the treatment of premenopausal women with acquired, generalized HSDD as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to 1) a coexisting medical or psychiatric condition; 2) problems with the relationship; or 3) the effects of a medication or drug substance.[1119] The safety and efficacy of bremelanotide in premenopausal women with HSDD was evaluated in two phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trials (RECONNECT; BMT-301, and BMT-302).[1120] Bremelanotide administered subcutaneously as needed was generally well tolerated, with nausea, flushing, and headache (mild-to-moderate in most participants) reported more frequently than in patients taking placebo. Women in the bremelanotide group experienced a statistically significant increase in sexual desire (BMT-301: 0.30, $P < .001$; BMT-302: 0.42, $P < .001$) and a statistically significant reduction in

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distress related to low sexual desire (BMT-301: -0.37, *P* < .001; BMT-302: -0.29, *P* = .005) compared with placebo. Bremelanotide has not been studied in cancer survivors, but the panel believes it may be an appropriate option for some survivors with HSDD.

Other options for female survivors with low or lack of desire, libido, or intimacy include bupropion and buspirone.[1121] These drugs have been studied in a few trials involving non-cancer populations.[1122-1124] Despite limited safety and efficacy data, these drugs may be considered as options for HSDD.

Currently, the panel does not recommend the use of oral phosphodiesterase type 5 inhibitors (PDE5i) for female sexual dysfunction because of the lack of data regarding their effectiveness in women. Although thought to increase pelvic blood flow to the clitoris and vagina,[1125,1126] PDE5i showed contradictory results in randomized clinical trials of various non-cancer populations of women being treated for sexual arousal disorder.[1127-1132] More research is needed before a recommendation can be made regarding the use of sildenafil for the treatment of female sexual dysfunction.

Interventions for Male Sexual Dysfunction

Using a consensus-based approach, the NCCN Survivorship Panel concluded that: 1) informed patient and physician decision-making is the standard for guiding treatment decisions for treatment of male sexual dysfunction; and 2) a psychological overlay frequently exists in patients with sexual dysfunction and may be even more pronounced in the face of cancer survivorship. Thus, treatment of male sexual dysfunction may require a multidimensional treatment plan that addresses the underlying issues. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, urology, sexual health specialist) should be made if appropriate and available. Treatment of sexual dysfunction in male survivors should be guided by the specific type of problem.

Treatment for male sexual dysfunction should include modification of risk factors, such as smoking cessation, weight loss, increasing physical activity, and avoiding excess alcohol consumption. Several trials have shown that such lifestyle modifications can improve sexual function in men.[1133-1136] In fact, one study found that PDE5i treatment with an aerobic activity program was more effective than PDE5i treatment alone in 60 men with ED.[1137] Evidence for these effects in patients with cancer and survivors is lacking.

In addition, treatment of psychosocial problems, with referral to sex and couples therapy as appropriate, can often alleviate symptoms of male sexual dysfunction.[1138-1142] Small studies in survivors of prostate cancer suggest that these approaches can be helpful in the survivorship population as well.[1143,1144] Therapy is often offered in conjunction with medical therapy.

PDE5i treatment has been shown to improve the symptoms of ED and be well tolerated.[1145,1146] The 2017 ASCO Practice on Interventions to Address Sexual Problems in People with Cancer recommends PDE5i medications be used to help men with ED.[928] Many studies have also shown the efficacy and tolerability of PDE5i for treating ED in patients with cancer and survivors.[1147,1148] Importantly, PDE5i are contraindicated in patients taking oral nitrates, because together they can lead to a dangerous decrease in blood pressure.[1149,1150] The timing and dose of on-demand PDE5i should be started conservatively, and it should be titrated to the maximum dose as needed.[1070] Survivors on PDE5is should be monitored periodically for efficacy, side effects, and any significant change in health status. In addition to on-demand PDE5i treatment, studies have shown that daily, low-dose treatment with these drugs can be effective.[1151-1154]

If total morning testosterone is <300 ng/dL, then hypogonadism is diagnosed and testosterone therapy may relieve symptoms of ED,

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problems with ejaculation, or problems with orgasm.[1155] A randomized controlled trial in 470 men older than 65 years of age with testosterone levels <275 ng/dL found that testosterone gel led to improvements in sexual function, desire, and activity.[1156,1157] Other studies have shown that the addition of testosterone to PDE5i therapy in men with low serum testosterone levels helps improve ED.[1158-1163] Testosterone therapy should not be used if contraindicated by the primary oncologic diagnosis (eg, prostate cancer on active surveillance, prostate cancer on ADT).

Other treatments may help with ED and with ejaculation and orgasm issues. Although evidence in the general population is lacking,[1164] studies in prostate cancer survivors suggest that pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual function in this population.[1165,1166] Vibratory therapy may reduce problems with premature ejaculation.[1167] Cancer therapies can result in a variety of ejaculatory dysfunctions (premature, absent, delayed, or climacturia), and these are best addressed with urology specialist consultation.[1168-1171]

Survivorship caregivers should be aware that “restorative or regenerative” therapies for ED are being widely advertised in the United States, but, as of the publication of these NCCN Guidelines, none of these treatments has been approved or cleared by the FDA for the treatment of ED. Survivors should be made aware that regenerative therapies for ED are being administered in cash-only practices. The Sexual Medicine Society of North America position statement on regenerative therapies for ED concludes: “given the current lack of regulatory agency approval for any restorative (regenerative) therapies for the treatment of ED and until such time as approval is granted, SMSNA believes that the use of shock waves or stem cells or platelet rich plasma is experimental and should be conducted under research protocols in compliance with Institutional Review Board approval. Patients considering such therapies should be fully informed and consented regarding the potential benefits and risks. Finally, the SMSNA advocates that patients involved in these clinical trials should not incur more than basic research costs for their participation.”[1172]

Sleep Disorders

Sleep disturbances include insomnia (trouble falling or staying asleep resulting in daytime dysfunction), excessive sleepiness (which can result from insufficient sleep opportunity, insomnia, or other sleep disorders), and sleep-related movement or breathing disorders.[1173] Sleep disturbances are common, affecting 30% to 50% of patients with cancer and survivors, often in combination with pain, fatigue, anxiety, and/or depression.[1173-1184] In fact, sleep disorders have been shown to be a risk factor for suicide.[536] Improvements in sleep quality lead to improvements in fatigue, mood, and overall quality of life.[717] Most clinicians, however, do not know how best to evaluate and treat sleep disorders.[1173]

Sleep disorders are common in patients with cancer as a result of multiple factors, including disease- or treatment-related biologic changes in sleep and wake regulation, the stress of diagnosis and treatment, and side effects of therapy (eg, pain, fatigue).[1185] In addition, evidence suggests that changes in inflammatory processes from cancer and its treatment play a role in sleep disorders. These sleep disturbances can be perpetuated in the survivorship phase by chronic side effects, anxiety, depression, medications, and maladaptive behaviors such as shifting sleep times, excessive time in bed because of fatigue, and unplanned naps.[1185]

Additional information about sleep disorders in patients with cancer can be found in the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org). These guidelines may be modified to fit the individual survivor’s circumstances.

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Screening for and Assessment of Sleep Disorders

Survivors should be screened for possible sleep disorders at regular intervals, especially when they experience a change in clinical status or treatment. The panel lists screening questions that can help determine whether concerns about sleep disorders or disturbances warrant further assessment. Other tools to screen for sleep problems have also been validated and may be used for individual intensive screening to assess sleep quality.[1186-1189] It is important to note that survivors may have more than 1 sleep disorder simultaneously.

The panel recommends that sleep/wake timing and/or sleep logs or diaries be reviewed. Many survivors may be using wearable devices to track sleep. However, studies have shown that these devices do not accurately measure sleep when compared to results of polysomnography.[1190-1195] Results from wearable devices may be useful for tracking sleep patterns, but should not be used for diagnosis or clinical decision-making.

If concerns regarding sleep quality are significant, the panel recommends that treatable or modifiable contributing factors be assessed and managed. Comorbidities that can contribute to sleep problems include alcohol and substance abuse, obesity, cardiac dysfunction, endocrine dysfunction, respiratory disorders, anemia, neurologic disorders (including CIPN), pain, fatigue, and emotional distress. Screening for common sleep disorders such as obstructive sleep apnea (OSA), restless legs syndrome (RLS, also known as Willis-Ekbom disease), and circadian rhythm sleep wake disorders (such as shift work) can help identify specific therapies for these conditions that may be helpful. In addition, some medications, both prescription and over-the-counter, can contribute to sleep issues. For instance, pain medication, antiemetics, antihistamines, antidepressants, and antipsychotics can all contribute to sleep disturbance, as can the persistent use of sleep aids.

Diagnosis of Sleep Disorders

The panel divided sleep disorders into two general categories: 1) insomnia; and 2) sleep disturbance and/or excessive sleepiness. Insomnia is diagnosed when patients have difficulty falling asleep, staying asleep, or waking up too early at least 3 times per week for at least 4 weeks. These categories were based on the most common types of symptoms that patients with sleep disturbances are likely to report.

Diagnosing patients with excessive sleepiness can be challenging, because it can be caused by a variety of factors. When excessive sleepiness is associated with observed apneas or snoring, the STOP questionnaire can be used as a screening tool to determine the risk of OSA.[1196] Other screening tools for OSA risk have also been validated.[1197,1198] Sleep studies can confirm the diagnosis of OSA; alternatively, referral can be made to a sleep specialist or PCP for further evaluation. Narcolepsy should be considered when excessive sleepiness is accompanied by cataplexy. Parasomnias (eg, sleep walking, sleep paralysis, periodic limb movement disorder) and circadian rhythm disorders (eg, shift work sleep disorder, advanced or delayed sleep phase disorders) should also be considered; survivors with these types of sleep disturbances may also present with symptoms of insomnia.

Excessive sleepiness can also be associated with uncomfortable sensations or an urge to move the legs (and sometimes the arms or other body parts). These symptoms are usually worse at night and with inactivity, may be improved or relieved with movement such as walking or stretching, and indicate RLS. In these individuals, a history and physical exam should be performed, with evaluation for iron deficiency if RLS is diagnosed.[1199,1200] Alternatively, referral can be made to a sleep specialist or PCP for further evaluation.

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Evaluation for Insomnia

If insomnia is diagnosed, details should be obtained regarding the course of insomnia, including the duration of symptoms. Insomnia is considered to be chronic if symptoms have been ongoing for ≥3 months. It should also be determined whether or not the insomnia symptoms are causing distress, impacting daytime functioning, or affecting the survivor's quality of life.

Management of Sleep Disorders

In all cases, comorbidities that may be contributing to the sleep disorder should be addressed. Survivors should also be advised that sleepiness can increase the risk of accidents, including while operating a motor vehicle. In addition, several types of interventions are recommended, as described below.[1173,1201,1202] Referral to a sleep specialist can be considered in most cases, especially for OSA, RLS, parasomnias, circadian rhythm disorders, narcolepsy, and chronic or refractory insomnia. Referral to a PCP can also be considered, except in cases of circadian rhythm disorder, prolonged wakefulness or awakenings, prolonged nocturnal sleep (ie, >9 hours for adults), cataplexy, frequent short naps, vivid dreams, disrupted sleep, or sleep paralysis, in which cases a sleep specialist is recommended.

Sleep Hygiene Education

Educating survivors about general sleep hygiene is recommended, especially for the treatment of circadian rhythm disorders, insomnia, and excessive sleepiness associated with insufficient sleep time.[1203-1205] Key points are listed in the guidelines and include regular morning or afternoon physical activity; daytime exposure to bright light; keeping the sleep environment dark, quiet, and comfortable; and avoiding heavy meals, moderate to strenuous physical activity, alcohol, and nicotine near bedtime. However, sleep hygiene alone is insufficient for the effective management of sleep disorders.

Physical Activity

Physical activity can improve sleep in middle-aged and older individuals in non-cancer settings.[1206-1208] Physical activity may also improve sleep in patients with cancer and survivors.[210,1209-1214] One randomized controlled trial compared a standardized yoga intervention plus standard care with standard care alone in 410 survivors (75% breast cancer; 96% women) with moderate to severe sleep disruption.[1211] Participants in the yoga arm experienced greater improvements in global and subjective sleep quality, daytime functioning, and sleep efficiency (all $P \leq .05$). In addition, the use of sleep medication declined in the intervention arm ($P \leq .05$). However, a 2013 systematic review concluded that the evidence that yoga programs aimed at cancer survivors improve insomnia or sleep quality is very limited.[1215] Another randomized controlled trial assessed the effects of a 3-month physical activity behavior change intervention on 222 breast cancer survivors.[1216] Participants in the intervention arm experienced significant improvement in self-reported global sleep quality at 3 and 6 months. However, actigraphy results showed no differences between the intervention and usual care arms. Overall, data supporting improvement in sleep with physical activity are limited in the survivorship population.

Psychosocial Interventions

Cognitive behavior treatments such as CBT-I, iCBT, relaxation therapy, stimulus control, and sleep restriction are recommended to treat sleep disturbances in survivors.[1217-1219] These approaches are preferred over pharmacologic interventions as first-line therapy.

Several randomized controlled trials have shown that CBT improves sleep in the survivor population.[706-708,716,1220-1222] For example, a randomized controlled trial in 150 survivors (58% breast cancer; 23% prostate cancer; 16% bowel cancer; 69% women) found that a series of 5 weekly group CBT sessions was associated with a reduction in mean wakefulness of almost 1 hour per night, whereas usual care (in which physicians could

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treat insomnia as they would in normal clinical practice) had no effect on wakefulness.[706] Another trial randomized 96 survivors (68% breast cancer; 87% female) to a 7-week intervention of CBT, armodafinil, CBT plus armodafinil, or placebo.[1222] CBT resulted in significant improvements in insomnia symptoms and sleep quality at 0 and 3 months after the intervention, but armodafinil had no effect. A recent meta-analysis identified 8 studies, including 752 cancer survivors, and found large effect sizes for self-reported insomnia severity (d = .77) following CBT.[1223] Further, a meta-analysis of randomized controlled trials in cancer survivors found strong evidence that CBT-I can produce large and durable effects on insomnia severity.[1223] In fact, the American College of Physicians recommends that CBT be the initial treatment for all adults with chronic insomnia disorder.[1217]

A small randomized controlled trial of 57 survivors (54% breast cancer; 75% women) found that mind–body interventions (mindfulness meditation or mind-body bridging) decreased sleep disturbance more than sleep hygiene education did.[1224] A preliminary report of a subset of participants in a larger randomized controlled trial of breast cancer survivors showed that MBSR improved objective sleep parameters, including sleep efficiency and percent of sleep time.[1225]

A randomized, partially blinded, noninferiority trial compared CBT with MBSR in 111 patients with cancer.[1226] Both groups experienced improvements in sleep diary-measured sleep onset latency, wake after sleep onset, total sleep time, stress, and mood disturbance. MBSR was inferior to CBT for improving insomnia severity immediately following the intervention, but was noninferior at 5 months. These results have not been replicated in survivors, and the relative efficacy of these strategies is not established in this population. Another randomized study compared Tai Chi Chih, a mindful movement meditation, with CBT-I in 90 breast cancer survivors and found it to be non-inferior for improving insomnia symptoms at 3, 6, and 15 months after the intervention.[1227]

Pharmacologic Interventions

Many pharmacologic treatments for sleep disturbances are available, including hypnotics for insomnia (eg, zolpidem, ramelteon).[1228,1229] Many of the FDA-approved hypnotics are BZD receptor agonists and can be associated with dependence, abuse, and withdrawal. The panel therefore recommends that survivors taking these medications be assessed every 1 to 3 months to determine if they are still needed. In addition, survivors should be informed that hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating).

In addition, antidepressants, antihistamines, atypical antipsychotics, other BZD receptor agonists, and nutritional/herbal supplements (eg, melatonin) are often used off-label for the treatment of insomnia, even though limited to no efficacy or effectiveness data are available for this use. The panel noted that these medications are associated with significant risks and should be used with caution. One small, open-label study found that the antidepressant mirtazapine increased the total amount of nighttime sleep in patients with cancer.[1230] A recent randomized, double-blind, placebo-controlled study of 95 postmenopausal breast cancer survivors found that melatonin subjectively improved sleep quality after 4 months of treatment (mean change in Pittsburgh Sleep Quality Index [PSQI] score, -0.1 for placebo and -1.9 for melatonin; $P < .001$).[845] Overall, however, data on pharmacologic interventions aimed at improving sleep in patients with cancer and survivors are lacking.[1183]

Treatment of Obstructive Sleep Apnea

Weight loss should be recommended to survivors with OSA, because studies have shown weight loss to be associated with reduced hypoxia and excessive sleepiness in patients with OSA.[1231] Small randomized

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studies have also shown that physical activity can improve OSA symptoms independent of weight loss.[1232,1233] In addition, survivors with OSA should be referred to a sleep specialist or PCP. The most common medical treatment for OSA is continuous positive airway pressure (CPAP).[1234]

Treatment of Restless Legs Syndrome

For RLS associated with iron deficiency, iron replacement can improve symptoms. In addition, preferred first-line treatments for RLS are dopamine agonists, gabapentin, and enacarbil.[1235-1243] Two separate recent meta-analyses found dopamine agonists and calcium channel alpha-2-delta ligands (eg, gabapentin) to be helpful for reducing RLS symptoms and improving sleep in the non-cancer setting.[1243,1244]

Additional treatment options include opioids, clonazepam, and sleep hygiene education. Referral to a sleep specialist or PCP is also an appropriate option for survivors with RLS. In addition, certain mind-body interventions and dietary supplementation may benefit some patients with RLS, although data are limited.[1245] The American Academy of Neurology also has clinical practice guidelines for the treatment of adults with RLS.[1246]

Summary

With improved diagnostic and treatment modalities, the population of cancer survivors is rapidly growing. Many survivors will experience late and/or long-term effects of cancer and its treatment that can include physical and/or psychosocial problems. These issues need to be addressed in a regular and systematic manner. Unfortunately, many of these effects are not addressed until discharge from the oncologist, and interventions may be left to health care providers who may not have much experience treating the concerns of cancer survivors. The NCCN Survivorship Panel hopes that these guidelines can help both oncologic and primary health care professionals lessen the burden left on survivors by their cancer experience so they can transition back to a rewarding life.

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