National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Survivorship

Version 2.2024 — December 9, 2024

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Survivorship

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NCCN Survivorship Panel Members
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Summary of the Guidelines Updates

General Survivorship Principles
- Definition of Survivorship (SURV-1)
- Standards for Survivorship Care (SURV-2)
- General Principles of the Survivorship Guidelines (SURV-3)
- Screening for Subsequent New Primary Cancers (SURV-4)
- Principles of Screening for Treatment-Related Subsequent Primary Cancers (SURV-4A)
- Principles of Cancer Risk Assessment and Counseling (SURV-5)
- Assessment by Health Care Provider at Regular Intervals (SURV-6)
- Survivorship Assessment (SURV-A)
- Survivorship Resources for Health Care Professionals and Survivors (SURV-B)

Preventive Health
- Healthy Lifestyles (HL-1)
  - Physical Activity (SPA-1)
  - Nutrition and Weight Management (SNWM-1)
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- Immunizations and Infections (SIMIN-1)

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- 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)
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- Hormone-Related Symptoms (SHRS-1)
- Sexual Health (SSH-1)
- Fertility (SF-1)
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- Employment and Return to Work (SWORK-1)

Abbreviations (ABBR-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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

NCCN Categories of Evidence and Consensus.

Updates in Version 2.2024 of the NCCN Guidelines for Survivorship from Version 1.2024 include:

MS-1
- The Discussion has been updated to reflect the changes in the algorithm.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

General Survivorship Principles

SURV-4
- 1st bullet revised: "...longer be involved in the survivor's care *and may also occur at younger ages than in the general population*."
- 2nd bullet revised: "... (eg, smoking, environmental exposures, health behaviors, human papillomavirus [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~~."
- 3rd bullet revised: Treatment-related subsequent primary cancers vary with the type and intensity of ~~anti~~cancer treatment..."
- Bullet removed: Healthy lifestyle and behavioral counseling are important to reduce risk factors that may contribute to subsequent cancers (HL-1).

SURV-4A 1 of 5
- General:
  - New bullet added at the top: These treatment related screening and early detection recommendations are distinct from and should not replace surveillance for recurrence of the index cancer.
  - The "Treatment-Related Subsequent Primary Cancers by Treatment Exposure" tables (formerly SURV-C) were moved up in the algorithm to follow the section on "Screening for Subsequent New Primary Cancers" (SURV-4). Previously the table followed the "Survivorship Resources For Health Care Professionals And Survivors" pages (SURV-B).
    - ◊ New statement added to the table title: This table does not cover all populations, and additional cancer screenings may be warranted depending on clinical circumstances.
    - ◊ Radiation Therapy, Including Total Body Irradiation (TBI); Head and neck; Mucosal head and neck cancer
      - – Screening and Early Detection Recommendations revised: Annual head and neck exam *(including direct or indirect laryngoscopy as clinically indicated)*, and/or otolaryngology referral.
      - – Comments: Bullet added, For smoking-related cancer, evaluate indications for lung cancer screening

SURV-4A 3 of 5
- Radiation Therapy, Including Total Body Irradiation (TBI); Abdomen/Flank/Pelvic; Colorectal cancer; Comments revised:
  - New bullet added: Repeat colorectal cancer screening every 3 years after multi-target stool DNA test or every 5 years after colonoscopy. Consultation with primary care, gastroenterologist, or oncologist should be considered as clinically indicated.
  - New bullet added: Also see NCCN Guidelines for Colorectal Cancer Screening
  - Bullet removed: Repeat colorectal cancer screening based on findings, in consultation with primary care, gastroenterologist, or oncologist.
- Footnote c is new: Children's Oncology Group Long-Term Follow Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers – Version 6.0 (October 2023).

SURV-4A 4 of 5
- Transplant Conditioning Therapy (RT or chemotherapy); Hematopoietic Cell Transplantation; Screening and Early Detection Recommendations: New arrow sub-bullet added, Consider increased frequency/intensity of cancer screenings (eg, cervical) for immunocompromised individuals.
- Systemic Therapy; PARP Inhibitors Lutetium-octreotide; Screening and Early Detection Recommendations: New bullet added, Consider referral to hematology for work up for persistent cytopenias or leukopenias.
- Footnote d is new: Specific populations such as hematopoietic cell transplantation (HCT) survivors may have additional considerations for cancer screening.

Continued
UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

General Survivorship Principles (continued)

SURV-6

- Care providers are also encouraged to assess the following at regular intervals; Point #9 revised: Fertility concerns for adults of ~~childbearing potential~~ *reproductive age*

SURV-A 2 of 2

- Survivorship Assessment; Healthy Lifestyle; Provider Key section revised: If NO to question 23 or 24, or YES to question 25, OR if question 23a is less than 3 times per week, OR if body mass index (BMI) *is* not ~~in the healthy range~~ *between 18.5–24.9 kg/m²*, refer to HL-1

SURV-B 1 of 5 through SURV-B 5 of 5 Survivorship Resources For Health Care Professionals And Survivors

- General Online Information
  - Revised: National Cancer Institute: ~~Cancer Survivorship Research~~ *Office of Cancer Survivorship (OCS)*
    - ◊ Springboard Beyond Cancer removed from the informational bullet
    - ◊ Website updated: https://cancercontrol.cancer.gov/ocs
    - ◊ Websites removed:
      - – http://survivorship.cancer.gov
      - – https://survivorship.cancer.gov/springboard
- Integrative Therapies
  - Added: Society for Integrative Oncology: https://integrativeonc.org/
- Information About LGBTQ Individuals with Cancer
  - Added: National LGBT Cancer Project: https://www.lgbtcancer.org/
- Nutrition and Weight Management
  - Added: World Cancer Research Fund: Diet, Activity and Cancer Guidelines: https://www.wcrf.org/diet-activity-and-cancer/
  - Removed: LIVESTRONG MyPlate Calorie Counter: http://www.livestrong.com/myplate
- Cardiovascular Health
  - Removed: CardioOnc.org (database of cancer drugs and cardiac toxicities) (http://cardioonc.org/providers)
- Sleep Disorders
  - Added: The Society of Behavioral Sleep Medicine: https://www.behavioralsleep.org/
  - Added: U.S. Department of Veterans Affairs: CBT-i Coach: https://mobile.va.gov/app/cbt-i-coach

PREVENTIVE HEALTH

Healthy Lifestyles

HL-1

- 3rd bullet;
  - 4th arrow sub-bullet revised: Maintain a healthy diet high in vegetables, fruits, *beans/legumes,* and whole grains.
  - 7th arrow sub-bullet; New diamond sub-bullet added: Avoid secondary exposure to cigarette smoke.
  - 9th arrow and diamond sub-bullets revised
    - ◊ Strive for ~~at least 7–9 hours of~~ *sufficient* sleep on a regular basis (SSD-1). *Recommended total sleep duration*:
      - – ~~Younger adults require more sleep~~. *Adults: 7–9 hours*
      - – ~~Teenagers may require 9 or more hours of sleep~~. *Adolescents: 8–10 hours*
      - – *Older adults: 7–8 hours*

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Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

PREVENTIVE HEALTH

Healthy Lifestyles

HL-1A

- Footnote a revised: ~~Highly (sometimes referred to as "ultra") processed foods are made mostly or entirely from substances derived from foods and additives, with little or no intact food (eg, soft drinks, sweet or savory packaged snacks, reconstituted meat products [eg, sausage, chicken nuggets], prepared frozen dishes). Monteiro CA, et al. Public Health Nutr 2018;21:5-17.~~ *Highly (sometimes referred to as "ultra") processed foods are industrial formulations typically with 5 or more and usually many ingredients (eg, soft drinks, sweet or savory packaged snacks, reconstituted meat products [eg, sausage, chicken nuggets], prepared frozen dishes). Besides salt, sugar, oils, and fats, ingredients of ultra-processed foods include food substances not commonly used in culinary preparations, such as hydrolyzed protein, modified starches, and hydrogenated or interesterified oils, and additives whose purpose is to imitate sensorial qualities of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product. (Martínez Steele E, et al. BMJ Open 2016;6:e009892)*.
- Reference is new: Paruthi S, et al. J Clin Sleep Med 2016;12:785-786.

Physical Activity

SPA-1

- 5th bullet revised: Avoid prolonged sedentary behavior (eg, sitting for long periods, *prolonged screen-based activities*)
- Footnote a: 2nd and 3rd bullet references updated

SPA-2

- Physical Activity Assessment; Assessment of comorbidities and treatment effects as appropriate
  - 12th bullet revised: Thrombocytopenia*/pancytopenia* and/or coagulopathies
  - New bullet added: Presence of limb prosthesis

SPA-3

- Risk Assessment For Physical Activity-Induced Adverse Events; 1st column; 2nd pathway; New bullet added: Presence of limb prosthesis.

SPA-A

- 6th bullet revised: ~~For survivors with peripheral neuropathy, resistance weight machines and/or training with resistance bands are recommended over free weights.~~ *If there is a concern that peripheral neuropathy may increase the risk of dropping free weights, survivors could consider utilizing weight machines and/or training with resistance bands*.

SPA-B

- Examples of Physical Activity: The activities for all three levels of exercise were alphabetized.

SPA-C

- Considerations for Specific Populations;
  - Survivors with established lymphedema; New arrow sub-bullet added: Survivors at risk for upper extremity lymphedema should be encouraged to perform arm/shoulder exercises (SLYMPH-1).
  - New bulleted section added for Presence of limb prosthesis or limb amputation
  - Survivors with peripheral neuropathy
    - ◊ 2nd arrow sub-bullet revised: "Consider alternative aerobic exercise (stationary biking, water aerobics, *yoga*)..."
    - ◊ 1st diamond sub-bullet revised: "Consider use of water shoes*/protective footwear* with aerobic exercise..."
    - ◊ New diamond sub-bullet added: Assistance with walking should be provided if alternative aerobic activities are not possible
  - Survivors with bone loss or bone metastases; New bullet added: Consider checking vitamin D levels and use of supplemental vitamin D if appropriate

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

PREVENTIVE HEALTH

Nutrition and Weight Management

SNWM-1

- 1st bullet revised: "...as well as red and processed meats, alcohol, *dietary supplements,* and processed foods..."
- 3rd bullet; All survivors should be encouraged to; Arrow sub-bullets revised:
  - ....fruit, *beans/legumes*, and whole grains
  - ~~Eat~~ *Limit consumption of* processed meats such as ham, hot dogs, deli cuts, bacon, and sausage ~~sparingly if at all~~.
  - Limit consumption of ~~"fast foods" and other~~ processed foods that are high in fat...
  - ~~Track~~ *Monitor* calorie intake.
- 4th bullet; 1st arrow sub-bullet revised: Consider referral to a registered dietitian ~~or nutritionist~~
- 5th Bullet; Arrow sub-bullets revised
  - Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and ~~fatty~~ *cold water* fish
  - Protein: poultry, fish, legumes, low-fat dairy foods, *eggs,* and nuts
- Footnote "f" is new: Examples of "cold water fish" include mackerel, salmon, herring, and others

SNWM-2

- 1st bullet revised: All survivors should be encouraged to achieve and maintain a ~~normal~~ BMI *between 18.5 and 24.9 kg/m^2* and strive..."
- Arrow sub-bullets revised
  - *Intentional* weight gain should be a priority for survivors who have underweight. (SNWM-4)
  - *Intentional* weight loss should be a priority for survivors who have overweight/obesity.
    - ◊ Diamond sub-bullet revised: Weight gain after cancer diagnosis and treatment is common and ~~can~~ *may* exacerbate risk for functional decline, comorbidity, and possibly cancer recurrence or death, and ~~can~~ *may* reduce quality of life.
  - Weight maintenance should be a priority for survivors who have *a* ~~normal weight~~ *BMI between 18.5 and 24.9 kg/m^2*.
- 4th bullet revised: Providers should discuss strategies *and goal setting* for weight management...
  - ◊ Diamond sub-bullet revised: ~~Track~~ *Monitor* weight, diet, calories...
- Footnote h revised: Many hospitals ~~employ~~ *use* CSOs and those in private practice...

SNWM-3

- Footnote j revised: "...~~Normal~~ *Healthy* weight (BMI, 18.5–24.9 kg/m^2)..."
- Footnote l revised: For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/2014-Obesity-Cancer-Guide-Oncology-Providers.pdf ~~and the "LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate~~." (Also for SNWM-4A)

SNWM-4

- Weight gain
  - 2nd bullet revised: Discuss increasing frequency of feeding *and portion size*
  - 5th bullet revised": "Consider referral to *registered* dietitian for individualized counseling
  - New bullets added
    - ◊ Optimize nutritional density and caloric quality of food
    - ◊ Consider appetite stimulants
    - ◊ Monitor weight regularly
- Weight maintenance
  - 1st bullet revised: Reinforce maintenance of ~~normal~~ *healthy* body weight throughout lifetime
  - Bullet added: Promote regular physical activity (SPA-1)

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Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

PREVENTIVE HEALTH

Nutrition and Weight Management

SNWM-4

- Weight loss
  - New bullet added: Promote regular physical activity (SPA-1)
  - 9th bullet revised: Refer to *registered* dietitian or weight management programs for individualized help as needed
  - Last bullet revised: Consider evaluation for bariatric surgery or pharmacologic therapy as appropriate ~~(if BMI ≥30 kg/m²)~~

General Principles of Supplement Use

SSUP-1

- 1st bullet revised: Supplement use is not recommended for most survivors, except in instances of documented deficiencies, inadequate diet, *previous gastrointestinal surgery that may cause deficiencies (eg, Roux-en-Y gastric bypass)*, or comorbid indications...
- 5th bullet revised: Refer survivors using supplements not prescribed by a medical provider to a registered ~~nutritionist/~~dietitian...

Immunizations and Infections

SIMIN-1

- General: Link to the NCCN COVID-19 Resources (https://www.nccn.org/covid-19) was removed from the algorithm.
- Footnote b revised: Also see: ~~Freedman MS, Ault K, Bernstein H. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2021. MMWR Morb Mortal Wkly Rep 2021;70:193-196~~ *Murthy N, Wodi AP, McNally VV, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:11-15*. (Also for SIMIN-C)

SIMIN-2

- Footnote h revised: "...Travelers may find useful information at ~~https://wwwnc.cdc.gov/travel/yellowbook/2020/travelers-with-additional-considerations/immunocompromised-travelers~~ *https://wwwnc.cdc.gov/travel/yellowbook/2024/additional-considerations/immunocompromised-travelers*..."

SIMIN-3

- Recommended for all cancer survivors; Treatment: Tetanus, diphtheria, pertussis ~~(Tdap) vaccine~~ *vaccination*

SIMIN-3A

- Footnotes revised
  - Footnote q: Recommendations regarding COVID-19 vaccines are continually changing (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html). For guidance about ~~COVID-19 vaccine usage in patients with cancer~~ *the management of concurrent COVID-19 and cancer, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections*. ~~please see NCCN: Cancer and COVID-19 Vaccination https://www.nccn.org/covid-19~~.
  - Footnote s: Recommended in high-risk patients or those with functional or anatomic asplenia. ~~Committee on Infectious Diseases. Pediatrics 2016;138:e20161890~~ *Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep 2020;69:1-41*.

Continued
UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

PREVENTIVE HEALTH

Immunizations and Infections

SIMIN-B **General Principles Of Vaccines In Cancer Survivors**

SIMIN-B 1 of 6

- Meningococcal conjugate vaccine, quadrivalent (MCV4); Population revised: ~~Splenectomized/functional asplenia survivors~~ *Survivors with surgical or functional asplenia*

SIMIN-B 2 of 6

- Vaccination in Survivors Who Had Cellular Therapy (ie, HCT, CAR T-cell therapy)
  - Measles, mumps, rubella (MMR) vaccine; Recommended Dose/Timing bullet revised: A 2-dose series of MMR vaccine should be administered 24 months after HCT and 8–11 months after the last dose of *intravenous immunoglobulin* ~~immune globulin~~ ~~intravenous~~ (IVIG)
  - COVID-19 vaccine; Recommended Dose/Timing bullet revised: Recommendations regarding COVID-19 vaccines are continually changing (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html.) ~~For guidance about COVID-19 vaccine usage in patients with cancer, please see NCCN: Cancer and COVID-19 Vaccination: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v5-0.pdf?sfvrsn=b483da2b_78.~~ *For guidance on the management of concurrent COVID-19 and cancer, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections*. (Also for SIMIN-B 4 of 6)

SIMIN-B 3 of 6

- Vaccination in All Other Survivors
  - Pneumococcal vaccine; Population; New bullet added: Survivors with surgical or functional asplenia
  - Vaccine: *Haemophilus influenzae type b (Hib) vaccine* recommendations added to the table

SIMIN-B 4 of 6

- Vaccination in All Other Survivors
  - Meningococcal conjugate vaccine quadrivalent (MCV4); Population revised: Splenectomized/functional asplenia survivors changed to *Survivors with surgical or functional asplenia*

SIMIN-B 5 of 6

- References updated as follows:
  - Refrence 3 ~~Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71;109-117~~ *Kobayashi M, Pilishvili T, Farrar JL, et al. Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023. MMWR Recomm Rep 2023;72*:1-39.
  - Reference 4 ~~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~~ *Anderson TC, Masters NB, Guo A, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:80-84*.
  - Reference 5 ~~Freedman MS, Ault K, Bernstein H. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2021. MMWR Morb Mortal Wkly Rep 2021;70:193-196.~~ *Murthy N, Wodi AP, McNally VV, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2024. MMWR Morb Mortal Wkly Rep 2024;11;73:11-15*. (Also for SIMIN-C)
  - Refrence 6 is new: Briere EC, Rubin L, Moro PL, et al. Prevention and Control of Haemophilus influenzae Type b Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014;(RR01):1-14.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

PREVENTIVE HEALTH

Immunizations and Infections

SIMIN-B 6 of 6

- Footnote g revised: 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 *if an egg-based vaccine is used*. ~~Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2021-2022 influenza season. MMWR Recomm Rep 2021;70:1-28~~ *Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72:1-25.* (Also for SIMIN-C)

SIMIN-C

- Principles of Influenza Vaccine(s)
  - 2nd bullet link updated: ~~https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8407757~~ https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html
  - Preferred Vaccines list revised as follows
    - ◊ Inactivated influenza vaccine (IIV)
      - – ~~Trivalent (IIV3), standard dose~~
      - – ~~Trivalent (IIV3), high dose~~
      - – Quadrivalent (IIV4), standard dose
      - – Quadrivalent ~~(IIV4)~~, high-dose (*HD-IIV4;* preferred ~~in~~ *option for* survivors ≥65 y)
      - – *Quadrivalent adjuvanted inactivated influenza vaccine (aIIV4; preferred option for survivors ≥65 y)*
    - ◊ Recombinant influenza vaccine (RIV)[a]
      - – ~~Trivalent (RIV3)~~
      - – Quadrivalent (RIV4*; preferred option for survivors ≥65 y*)

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Cardiovascular Disease Risk Assessment

SCVD-1

- 4th bullet revised: Cancer treatments (immunotherapy, cytotoxic, *HCT,* and targeted systemic therapies, RT) can result...
- 7th bullet revised: Tools exist to help quantify atherosclerotic CVD (ASCVD) risk (eg, ASCVD risk score) *and thus determine appropriate risk reduction strategies*.
- Bullet removed: Consider referral to cardio-oncology or a cardiology specialist for high-risk survivors.

Anthracycline-Induced Cardiac Toxicity

SCARDIO-2

- Initial Clinical Assessment For Patients Who Have Received Previous Anthracycline Therapy; 3rd bullet; 2nd arrow sub-bullet revised: Other systemic therapy *(eg, anti-HER2 treatment)* and/or chest RT.
- Footnote d revised: "...shortness of breath when ~~sleeping~~ *laying flat (ie, orthopnea)*, waking up at night due to shortness of breath...

Continued
UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Anthracycline-Induced Cardiac Toxicity

SCARDIO-3

- Treatment
  - Stage A; 3rd bullet revised: Consider referral ~~to cardiologist~~ for management
  - Stage B, Stage C, Stage D pathways; Bullet revised: Referral to ~~cardiologist~~ *cardiovascular specialist (ie, cardiologist, cardio-oncologist)* for management
- Footnote n revised: Consider referral to a cardiologist, ~~especially~~ *cardio-oncologist, survivorship specialist, or PCP for serial surveillance based on cardiotoxicity risk of cancer treatment regimen or* if additional anthracycline therapy or other cardiotoxic treatment is needed.

Anxiety, Depression, Trauma, and Distress

SANXDE-7

- Social/External Factors; New arrow sub-bullet added: Discrimination or marginalization because of race, ethnicity, sexual orientation, sexual identity, or disability status

Cognitive Function

SCF-1

- General Principles; 3rd bullet revised: "...cancer-associated cognitive dysfunction has been identified*, and screening tools*~~. Existing diagnostic tools~~ do not strongly correlate with patient reports of cognitive dysfunction.

SCF-3

- General Strategies for Management of Cancer-Associated Cognitive Dysfunction: New bullet added, Involve social support system to help with completion of tasks and activities

SCF-4

- Second-line Interventions; 1st bullet revised: "...and care for survivors who continue to have ~~memory~~ *cognitive* problems after rehabilitation

Fatigue

SFAT-1

- Considerations For Fatigue In Cancer Survivors
  - 1st bullet; 1st arrow sub-bullet revised: "Receipt of chemotherapy, radiation, endocrine, *immunotherapy,* targeted, and/or cellular therapies..."
  - New arrow sub-bullet added: Assessment and communication regarding fatigue and anticipated recovery after treatment should be done periodically.

Lymphedema

SLYMPH-1

- Footnotes revised
  - Footnote a: National Cancer Institute Lymphedema (PDQ)~~® Health Professional~~ *Patient* Version: ~~https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq~~ *https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema*. (Also for SLYMPH-2A)
  - Footnote b: ~~International Society of Lymphology. Executive Committee. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology 2016;49:170-184.~~ *Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology 2020;53:3-19. https://pubmed.ncbi.nlm.nih.gov/32521126/*

Continued

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Lymphedema

SLYMPH-3

- Screening; 1st bullet; 3rd arrow sub-bullet revised: Swelling*, tightness, or uncomfortable sensation* that interferes with daily activities
- Workup If Lymphedema Is Suspected; 1st bullet revised: Rule out recurrence of cancer*, infection, or deep vein thrombosis (DVT) of an extremity*

SLYMPH-A

- Survivor Lymphedema Education; 1st bullet; 3rd arrow sub-bullet revised: "...maintenance of skin integrity on the affected side*, manual drainage, and range of motion exercise*."
- Footnote b revised: 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~~ https://lymphnet.org/position-papers.
- Footnote c is new: Limb elevation can be used as an option for early-stage lymphedema for short-term improvement, but data are limited.

Pain

SPAIN-1

- 6th bullet; New arrow sub-bullet added: Hypnosis, meditation, acupuncture, cognitive restructuring, and behavioral activation can be considered to control pain and maximize function.
- The arrow sub-bullet "Physical modalities (heat, cold, massage, acupuncture, physical therapy, or occupational therapy) are useful and should be considered for some pain syndromes." was previously the 7th bullet.
- Footnote is new: Thompson T, Terhune DB, Oram C, et al. The effectiveness of hypnosis for pain relief: A systematic review and meta-analysis of 85 controlled experimental trials. Neurosci Biobehav Rev 2019;99:298-310.

SPAIN-2

- 4th Bullet: Link regarding pain patient agreements removed, https://nida.nih.gov/sites/default/files/SamplePatientAgreementForms.pdf

SPAIN-9

- GI/urinary/pelvic pain; Treatment; For GI pain (abdominal pain/cramping): *Bowel regimen* added as an option

Hormone-Related Symptoms

SHRS-1

- Principles of Menopause Symptom Management In Female Survivors; Treatment Options for Vasomotor Symptoms; Hormonal therapies; New arrow sub-bullet added: Survivors often use herbal supplements for vasomotor symptom management. However, some supplements may interfere with hormonal cancer treatments, and routine use of supplements is not recommended (SSUP-1). Providers should encourage survivors to discuss such therapies prior to use. (Also for SHRS-2A)

SHRS-A 1 of 2

- Non-Hormonal Pharmacologic Treatments And Dosing For Vasomotor Symptoms; New drug class entry and recommendations added for Selective neurokinin-3 (NK3) receptor antagonist

SHRS-B

- Principles Of Menopausal Hormone Therapy (MHT) Use In Female Survivors; 2nd bullet, New sub-bullets added
  - The tissue-selective estrogen complex (TSEC) conjugated estrogens/bazedoxifene is FDA-approved for treating menopausal symptoms in healthy post-menopausal survivors.
    - These drugs are contraindicated in survivors of hormonally dependent cancers.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Sexual Health

SSH-3

- Male with concerns/issues regarding sexual health; Problems with ejaculation (premature, absent, delayed, or climacturia); Treatment Options; 4th bullet revised: "For climacturia: Empty bladder prior to sex, pelvic physical therapy, or ~~trial of imipramine~~ *use of condoms to catch urine*"

SSH-3A

- Footnote m revised: "...prostate cancer under therapy with androgen deprivation). *Exogenous testosterone therapy should not be prescribed to those who are currently trying to conceive. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility*."

Sleep Disorders

SSD-1

- 3rd column; H&P; Arrow sub-bullet; Comorbidities; Revised: Iron and ferritin levels *and when indicated transferrin saturation %*
- 4th column; Bottom pathway; Sleep disturbance and/or excessive sleepiness:
  - New bullet added: Sleep disordered breathing (includes obstructive sleep apnea [most common] and central sleep apnea)
  - Bullet removed: Obstructive sleep apnea

SSD-1A

- Footnote c revised: ~~Consider~~ *Medication review: Re-evaluate the need for* persistent use of sleep aids, pain medications, antiemetics, stimulants..."
- Footnote e revised: "Note that *sleep disordered breathing (eg*, obstructive sleep apnea*),* RLS, circadian rhythm sleep wake disorders, and parasomnias..."

SSD-2

- 3rd column; Top pathway; Evaluate for and address comorbid causes; New bullet added: Other sleep disorders

SSD-3

- Associated with observed apneas, snoring pathway; Diagnosis revised for Sleep Study: Obstructive sleep apnea changed to Sleep disordered breathing
- Associated with uncomfortable sensation; Treatment; Management options revised under "Initial preferred therapy"
  - Gabapentin enacarbil added
  - Enacarbil removed
- Footnote o revised: The following tools may be used to help identify individuals at high risk for *obstructive* sleep apneas...
- Footnote r revised: Sleep studies can be ~~done~~ *performed* as *an in*-laboratory polysomnography or as home sleep study. However, survivors with ~~known~~ *certain medical disorders (ie,* cardiac, ~~disease or~~ *respiratory*, neurologic ~~disease~~*)*, ~~who have used~~ *or currently on* opiates for cancer-related pain, may not be good candidates for ~~some~~ home sleep ~~tests~~ *studies*.
- Footnote t revised: The most common medical treatment for ~~obstructive sleep apnea~~ *sleep disordered breathing* is continuous positive airway pressure (CPAP).

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Survivorship from Version 1.2023 include:

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Sleep Disorders

SSD-A

- Other Sleep Interventions revised
  - 1st bullet: If survivor is not able to fall asleep within ~~45 minutes~~ *what feels like 20 minutes (survivor should not check the clock)* or...
  - Arrow sub-bullets:
    - ◊ Get up, go to a different location, but stay in a darkened room and do non-stimulating activity like ~~watching a relaxing TV show or~~ reading..."
    - ◊ "...reduce worrying (ie, write a "to do" list or set aside "worry time" *[eg, 10–15 mins] earlier in the day, not close to bedtime)*"

SSD-B

- Footnote b is new: There are paid and/or free guided, semi-guided, and unguided CBT-I digital resources available. See Survivorship Resources for Health Care Professionals and Survivors (SURV-B).

SSD-C

- Footnote d revised: "...and nutritional/herbal supplements ~~(eg, melatonin)~~. They do not have an FDA-approved indication..."

SSD-D

- Section title revised: ~~Iron Deficiency And~~ Restless Legs Syndrome
- New arrow sub-bullet added: Consider referral to specialist for refractory symptoms (See NCCN Guidelines for Palliative Care)
- New bullet added: Consider modification of lifestyle factors and medications that can exacerbate RLS symptoms
- Footnote c is new: Alcohol, nicotine, caffeine, centrally active antihistamines, SSRI, SNRI, and dopaminergic medications are associated with worsening of RLS symptoms.

ABBR-1 and ABBR-2

- The abbreviations pages were updated to reflect changes in the algorithm.

General Survivorship Principles

DEFINITION OF SURVIVORSHIP

- **An individual is considered a cancer survivor from diagnosis, through the balance of life.[a] This includes survivors living with cancer and those free of cancer. The panel recognizes that not all individuals with a history of cancer identify with the term "survivor." These guidelines are meant to be inclusive and use the term "survivor" to describe anyone with a history of cancer.**
- **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 physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing. It is appropriate to counsel on these impacts early in the treatment trajectory and at regular intervals thereafter.**
- **These guidelines are applicable to survivors across the continuum of care, including those on prolonged therapy, those with chronic cancers (eg, metastatic disease), and long-term survivors.**
- **The panel recognizes the growing population of individuals who are living with metastatic disease and that many aspects of these guidelines pertain to this population of survivors. This group is included in the definition of survivorship, and these guidelines are meant to be applied when helpful to meet the individuals' needs.**
- **The panel recommends reviewing the NCCN Guidelines for Survivorship in conjunction with the cancer-specific guidelines for individuals with metastatic disease. As more evidence is established for this population, more specific survivorship guidelines for individuals living with metastatic cancers may be developed.**

[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/definitions.

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.

STANDARDS FOR SURVIVORSHIP CARE[b]

Care of the cancer survivor should include:

1. **Surveillance for cancer spread or recurrence, and screening for subsequent primary cancers (SURV-4)[c]**
2. **Monitoring long-term effects of cancer, including psychosocial, physical, and immunologic effects**
3. **Prevention and detection of late effects of cancer and therapy**
4. **Evaluation and management of cancer-related syndromes, with appropriate referrals for targeted intervention**
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 (RT), and systemic therapies**
   - ◊ **Information regarding follow-up care, surveillance, and screening recommendations**
   - ◊ **Information on post-treatment needs, including information on acute, late, and long-term treatment-related side effects and health risks when possible (NCCN Guidelines for Treatment of Cancer by Site)**
   - ◊ **Delineation of roles of all health care providers (including oncologists, primary care physicians [PCPs], and subspecialists) in long-term survivorship care with coordinated timing of care and transfer of care as appropriate**
   - ◊ **Promotion of adherence to healthy behavior recommendations (HL-1)**
   - ◊ **Periodic assessment of ongoing needs and identification of appropriate resources**

[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.

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GENERAL PRINCIPLES OF THE SURVIVORSHIP GUIDELINES

- **Cancer survivors include those who are initiating treatment, in ongoing treatment, have completed cancer treatment, or are in clinical remission. (Also see the NCCN Guidelines for Supportive Care Table of Contents)**
- **These guidelines provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment. They can be used to optimize health and wellness for all survivors; however, they were created to assist 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.**
- **The panel recognizes that many of the post-treatment issues covered in these Guidelines are best addressed before cancer treatment begins so that many problems can be prevented or minimized.**
- **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, with the appropriate disease-specific guideline, provide a framework for the coordination of care between the survivor's health care providers to ensure 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).**
- **The panel recommends stakeholders ensure the implementation of guideline-concordant survivorship care within their unique health systems.[1] Specifically, institutions are encouraged to determine how to systematically deliver the six key components of survivorship care (SURV-1).[1-3] There are several models of care that frame the implementation of survivorship care according to provider type(s), clinic type(s), patient risk, and other factors.[4-7] Engaging these models of care will facilitate implementation planning.[7] Panel members recommend institutions provide the resources necessary to plan, deliver, and evaluate their survivorship care program(s).[1-2]**
- **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.**

[1] Jazieh AR, McClure JS, Carlson RW. Implementation Framework for NCCN Guidelines. J Natl Compr Canc Netw 2017;15:1180-1185.
[2] Commission on Cancer. American College of Surgeons Optimal Resources for Cancer Care: 2020 Standards. https://www.facs.org/media/whmfnppx/2020_coc_standards.pdf
[3] The Advisory Board Company: Oncology Round Table. The Survivorship Challenge. https://www.advisory.com/-/media/project/advisoryboard/advisory/topics/oncology/survivorship-challenge/Survivorship-Challenge.pdf
[4] Sussman J, Souter LH, Grunfeld E, et al. Models of Care for Cancer Survivorship 2017; Cancer Care Ontario Evidenced-Based Series 26-1;Version 2: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/246
[5] Halpern MT, Viswanathan M, Evans TS, et al. Models of cancer survivorship care: Overview and summary of current evidence. J Oncol Pract 2015;11:e19-27.
[6] Jefford M, Howell D, Li Q, et al. Improved models of care for cancer survivors. Lancet 2022;399:1551-1560.
[7] ASCO Determining the Best Model for You: https://old-prod.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/survivorship-compendium/needs-assessment

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.

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 and may also occur at younger ages than in the general population.**
- **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, human papillomavirus [HPV]), and mutagenic effects of cancer treatment.**
- **Treatment-related subsequent primary cancers vary with the type and intensity of cancer treatment and are associated in particular with RT and specific chemotherapeutic agents. For recommendations for screening considerations, see Principles of Screening for Treatment-Related Subsequent Primary Cancers (SURV-4A).**
- **Screening for subsequent primary cancers should be a shared responsibility between primary and oncology care physicians. For survivors living with metastatic disease, recommendations for screening should be tailored to the survivor's individualized risk and disease status. (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-5.**

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.

PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

- **As part of screening and early detection for subsequent primary cancers, history and physical exam (H&P) are recommended at least annually.**
- **Also see the NCCN Guidelines for Adolescent and Young Adult (AYA) 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.**
- **These treatment related screening and early detection recommendations are distinct from and should not replace surveillance for recurrence of the index cancer.**

Treatment-Related Subsequent Primary Cancers by Treatment Exposure
(This table does not cover all populations, and additional cancer screenings may be warranted depending on clinical circumstances.)

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 if clinically indicated due to signs or symptoms of disease	
	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 (including direct or indirect laryngoscopy as clinically indicated), and/or otolaryngology referral	• Counsel on avoidance of tobacco and heavy alcohol use • Based on age, consider HPV vaccination counseling as appropriate. (SIMIN-1) • For smoking-related cancer, evaluate indications for lung cancer screening
	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 if clinically indicated due to signs or symptoms of disease	
	Soft tissues sarcomas	Imaging if clinically indicated due to signs or symptoms of disease	

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.

Continued

PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

Treatment-Related Subsequent Primary Cancers by Treatment Exposure
(This table does not cover all populations, and additional cancer screenings may be warranted depending on clinical circumstances.)

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			
Mantle/Chest	Breast cancer (assigned female at birth)[a]	Breast MRI and mammogram annually, starting at age 30 or 8 years after radiation, whichever occurs last, for exposure ≥10 Gy and <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 if clinically indicated due to signs or symptoms of disease	
	Lung cancer	Consider imaging if clinically indicated due to signs or symptoms of disease	• Smoking substantially increases risk. For survivors who smoke or have a history of smoking: ▸ 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
	Thyroid and parathyroid cancer	Imaging and/or testing if clinically indicated due to signs or symptoms of disease	

[a] Screening should be individualized based on risk factors and individual anatomy.

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Continued

PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

Treatment-Related Subsequent Primary Cancers by Treatment Exposure
(This table does not cover all populations, and additional cancer screenings may be warranted depending on clinical circumstances.)

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[b]	• Repeat colorectal cancer screening every 3 years after multi-target stool DNA test or every 5 years after colonoscopy. Consultation with primary care, gastroenterologist, or oncologist should be considered as clinically indicated.[c] • Also see NCCN Guidelines for Colorectal Cancer Screening
	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 if clinically indicated due to signs or symptoms of disease	
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 if clinically indicated due to signs or symptoms of disease	

[b] 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.
[c] Children's Oncology Group Long-Term Follow Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers – Version 6.0 (October 2023).

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PRINCIPLES OF SCREENING FOR TREATMENT-RELATED SUBSEQUENT PRIMARY CANCERS

Treatment-Related Subsequent Primary Cancers by Treatment Exposure
(This table does not cover all populations, and additional cancer screenings may be warranted.)

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 Cell Transplantation[d]	• May increase the risk for a variety of hematologic or solid tumor cancers, including skin cancer, myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), liver cancer, cervical cancer, or oral cancer • May increase the risk for lymphoproliferative disorders	• CBC if clinically indicated due to signs or symptoms of disease • Adhere to age-appropriate cancer screening recommendations ▸ Consider increased frequency/ intensity of cancer screenings (eg, cervical) for immunocompromised individuals • 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 if clinically indicated due to signs or symptoms of disease	
Alkylating Agents	Bladder cancer	Urine cytology if clinically indicated due to signs or symptoms of disease	When given in combination with pelvic radiation, risk is increased
Tamoxifen	Endometrial cancer	Assess vaginal pain or bleeding annually; If abnormal uterine bleeding, referral to gynecology for consideration of transvaginal ultrasound and biopsy[e]	Very little risk in premenopausal survivors; risk is primarily in postmenopausal survivors with a uterus.
PARP Inhibitors Lutetium-octreotide	MDS; AML	• CBC if clinically indicated due to signs or symptoms of disease • Consider referral to hematology for work up for persistent cytopenias or leukopenias	MDS and AML are rare; usually after long-term treatment[3,4]

[d] Specific populations such as hematopoietic cell transplantation (HCT) survivors may have additional considerations for cancer screening.
[e] If there is abnormal uterine bleeding in survivors in peri- and premenopausal age ranges, consider first checking estradiol levels, then do additional interventions if reasonable.

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REFERENCES

[1] Gunduz M, Ozen M, Sahin U, et al. Subsequent malignancies after allogeneic hematopoietic stem cell transplantation. Clin Transplant 2017;31.
[2] Rambhia PH, Conic RZ, Atanaskova-Mesinkovska N, et al. Role of graft-versus-host disease in the development of secondary skin cancers in hematopoietic stem cell transplant recipients: A meta-analysis. J Am Acad Dermatol 2018;79:378-380.e3.
[3] LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol 2019;20:e15-e28.
[4] Strosberg JR, Caplin ME, Kunz PL, et al; NETTER-1 investigators. 177Lu-Dotatate plus long-acting octreotide versus high dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:1752-1763. Erratum in: Lancet Oncol 2022;23:e59.

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **Periodic updating of family cancer history (when known) is recommended to reassess hereditary risk. 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.**
- **Many cancer survivors, particularly those diagnosed at younger ages, as well as those diagnosed with rare cancers, multiple primary cancers, or cancers associated with high-risk cancer syndromes, and those with one or more relatives with the same or related cancers are 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. (See General Testing Criteria [CRIT-1] from the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)**
  - **Criteria for formal genetic risk assessment and/or testing, and for care 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**
      - **Principles of Cancer Risk Assessment and Counseling (EVAL-A)**
      - **Pedigree: First-, Second, and Third-Degree Relatives of Proband (EVAL-B)**
    - **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 for genetic risk assessment for patients who do not meet the criteria but who request it.**
- **Consider referral to genetic counseling services for risk assessment and/or testing if the survivor did not have a comprehensive evaluation at time of 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.**
- **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. **Weight and health behaviors that can modify cancer and comorbidity risk (including tobacco/alcohol use)**
  9. **Fertility concerns for adults of reproductive age**
  10. **See the NCCN Guidelines for Treatment of Cancer by Site for disease-specific recommendations for surveillance/follow-up**

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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, anger, fear of recurrence, or distress about effects of cancer treatment 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
Pain	13. Have you had any pain in the past week? Yes/No 14. How would you rate your pain on a scale of 0 (none) to 10 (extreme) over the past week? 0–10
Hormone-Related Symptoms	15. Have you been bothered by hot flashes/night sweats? Yes/No 16. Have you been bothered by other hormone-related symptoms (ex, vaginal dryness, erectile dysfunction, urinary incontinence)? Yes/No
Sexual Health	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
Fertility	19. Do you have concerns about fertility or family planning? Yes/No
Sleep Disorder	20. Are you having problems falling asleep, staying asleep, or waking up too early? Yes/No 21. 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 22. Have you been told that you snore frequently or that you stop breathing during sleep? Yes/No
Healthy Lifestyle	23. Do you engage in regular physical activity or exercise, such as brisk walking, jogging, weight/resistance training, bicycling, swimming, etc.? Yes/No ▸ 23a. If you answered "Yes," how often? 24. Excluding white potatoes, do you eat at least 2½ cups of fruits and/or vegetables each day? Yes/No 25. Do you have concerns about your weight? Yes/No 26. Do you take vitamins or other supplements? Yes/No
Immunizations and Infections	27. Have you received your flu vaccine this flu season? Yes/No 28. Are you up to date on your vaccines? Yes/No/Don't know
Employment/ Return to Work	29. 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
Pain	Questions 13–14	If YES to question 13 and a rating of >4 to question 14, refer to SPAIN-1
Hormone-Related Symptoms	Questions 15–16	If YES to any question, refer to SHRS-1
Sexual Health	Questions 17–18	If YES to any question, refer to SSH-1
Fertility	Question 19	If YES, refer to SF-1
Sleep Disorder	Questions 20–22	If YES to any question, refer to SSD-1
Healthy Lifestyle	Questions 23–26	If NO to question 23 or 24, or YES to question 25, OR if question 23a is less than 3 times per week, OR if body mass index (BMI) is not between 18.5–24.9 kg/m^2, refer to HL-1 If YES to question 26, refer to SSUP-1
Immunizations and Infections	Questions 27–28	If NO to question 27, or NO or DON'T KNOW to question 28, refer to SIMIN-1
Employment and Return to Work	Question 29	If YES to question 29, refer to SWORK-1

[a] The tool can be used to guide providers to topics within the guidelines that require more in-depth assessment based on survivor response. While this instrument has not yet been piloted or validated, validated questions have been included when possible.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND SURVIVORS[a]

General Online Information	
National Coalition for Cancer Survivorship (NCCS)	http://www.canceradvocacy.org
American Association for Cancer Research (AACR)	http://www.aacr.org
(ACS) • Survivorship information • Cancer Survivors Network • National Cancer Survivorship Resource Center • Physical side effects information, including sexual health	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, and 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/news-initiatives/current-initiatives/cancer-care-initiatives/survivorship-compendium
Cancer Care: Free, professional support services for anyone affected by cancer	www.cancercare.org
Be The Match	https://bethematch.org
Centers for Disease Control and Prevention (CDC): Survivorship information	https://www.cdc.gov/cancer/survivors/index.htm
Leukemia & Lymphoma Society (LLS): Survivorship information	https://www.lls.org/managing-your-cancer
LIVESTRONG	http://www.livestrong.org
National Cancer Institute: Office of Cancer Survivorship (OCS) • Facing Forward series, designed to educate cancer survivors, family members, and health care providers about the challenges associated with life after cancer treatment	https://cancercontrol.cancer.gov/ocs http://cancercontrol.cancer.gov/ocs/resources/ffseries.html
National Comprehensive Cancer Network (NCCN) NCCN Guidelines for Patients: Survivorship	https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients
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
General Help Lines	
American Cancer Society	1.800.227.2345 http://www.cancer.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

[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 SURVIVORS[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	
National Institutes of Health Office of Dietary Supplements	https://ods.od.nih.gov/factsheets/list-all
National Center for Complementary and Integrative Resources for Health Care Providers	https://nccih.nih.gov/health/providers
Society for Integrative Oncology	https://integrativeonc.org/
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
NCCN Employer Tool Kit	https://www.nccn.org/business-policy/business/employer-resources/employer-toolkit
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
Triage Cancer	https://triagecancer.org

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Continued

SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND SURVIVORS[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 https://cancer-network.org/welcoming-spaces
National LGBT Cancer Project	https://www.lgbtcancer.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	
ACS • Nutrition and Physical Activity Guidelines for Cancer Survivors, Patient Page • "Physical Activity and the Cancer Patient" guide	https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21721 http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingactive/physical-activity-and-the-cancer-patient
American College of Sports Medicine (ACSM): • ACSM ProFinder: Search for Certified Professionals • ACSM Guidelines for Exercise and Cancer	https://www.acsm.org/get-stay-certified/find-a-pro https://www.acsm.org/blog-detail/acsm-certified-blog/2019/11/25/acsm-guidelines-exercise-cancer-download
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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Continued

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

Nutrition and Weight Management	
ASCO Obesity and Cancer: A Guide for Oncology Providers	https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/2014-Obesity-Cancer-Guide-Oncology-Providers.pdf
ASCO/Cancer.Net Managing Your Weight After a Cancer Diagnosis: A Guide for Patients and Families	https://www.cancer.net/sites/cancer.net/files/weight_after_cancer_diagnosis.pdf
Cancer Nutrition Consortium: Nutritional Guidance & Support	https://www.cancernutrition.org
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 and 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
World Cancer Research Fund: Diet, Activity and Cancer Guidelines	https://www.wcrf.org/diet-activity-and-cancer/
Cardiovascular Health	
American Heart Association/American Stroke Association Tools	https://millionhearts.hhs.gov/tools-protocols/tools.html
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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Continued

SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND SURVIVORS[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
The Society of Behavioral Sleep Medicine	https://www.behavioralsleep.org/
U.S. Department of Veterans Affairs: CBT-i Coach	https://mobile.va.gov/app/cbt-i-coach
Smoking Cessation	
ACS: Smoking cessation support	http://www.cancer.org/healthy/stayawayfromtobacco/index
ASCO: Tobacco Cessation and Control Resources	https://old-prod.asco.org/news-initiatives/current-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	
988 Suicide and Crisis Lifeline	https://988lifeline.org Call or text 988
American Psychosocial Oncology Society (APOS) Helpline	1.866.276.7443 http://apos-society.org
Cancer Support Community–Cancer Support Helpline	1.888.793.9355 https://www.cancersupportcommunity.org/cancer-support-helpline
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 During Cancer Care	https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients
Anxiety and Depression Association of America • Mobile app • Pocket SAFE-T Card	https://adaa.org https://adaa.org/find-help/support/mental-health-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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Preventive Health

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.
- Cancer prehabilitation[1,2] is appropriate for many newly diagnosed survivors prior to initiating treatment with surgery or chemotherapy. Referrals to physical therapy or exercise oncology specialists should be considered.
- For optimal health, all survivors should be encouraged to set incremental as well as ultimate goals for diet, physical activity, and weight management. At a minimum all survivors should be encouraged to:
  - Achieve and maintain a healthy body weight throughout life (SNWM-2).
  - Avoid inactivity.
  - Engage in physical activity (eg, exercise, take the stairs, park in the back of parking lot) daily (SPA-1).
  - Maintain a healthy diet high in vegetables, fruits, beans/legumes, and whole grains.
  - Limit intake of red and cured meats and highly processed foods,[a,b] particularly those high in fats and sugars (SNWM-1).
  - Drink alcohol sparingly if at all (SNWM-1).
  - Discontinue use of cigarettes, other tobacco products (including hookah), and e-cigarettes (NCCN Guidelines for Smoking Cessation).
    - Avoid secondary exposure to cigarette smoke.
  - 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).
    - Do not use tanning beds.
    - Avoid sunburns.
    - Seek shade and wear protective clothing (ie, hats and long-sleeved garments) if outside for prolonged periods of time or during peak direct sun hours.
  - Strive for sufficient sleep on a regular basis (SSD-1).[3] Recommended total sleep duration:
    - Adults: 7–9 hours[4,5]
    - Adolescents: 8–10 hours[4,5]
    - Older adults: 7–8 hours[4,5]
  - Follow up with PCP regularly.
    - Adhere to age-appropriate and treatment-associated health screening, preventive measures (SIMIN-1), and cancer screening recommendations (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).
- A multidisciplinary approach (including but not limited to clinicians, physical therapists, dieticians, social workers, and patient navigators) should be utilized to:
  - Assess individual and community-level barriers to meeting the healthy lifestyle recommendations.
  - Support patients in developing strategies to overcome challenges throughout the continuum of survivorship care (from diagnosis to long-term survivorship).
  - Consider specialty referrals to supportive programs offered by medical centers or the community (ie, Livestrong at the YMCA).

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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.

Footnotes on (HL-1A)
References on (HL-1A)

FOOTNOTES AND REFERENCES FOR GENERAL PRINCIPLES OF HEALTHY LIFESTYLES

Footnotes

[a] Highly (sometimes referred to as "ultra") processed foods are industrial formulations typically with 5 or more and usually many ingredients (eg, soft drinks, sweet or savory packaged snacks, reconstituted meat products [eg, sausage, chicken nuggets], prepared frozen dishes). Besides salt, sugar, oils, and fats, ingredients of ultra-processed foods include food substances not commonly used in culinary preparations, such as hydrolyzed protein, modified starches, and hydrogenated or interesterified oils, and additives whose purpose is to imitate sensorial qualities of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product. (Martínez Steele E, et al. BMJ Open 2016;6:e009892).

[b] Consumption of highly-processed foods is associated with an increased risk of cancer. Fiolet T, et al. BMJ 2018;360:k322.

References

[1] Michael CM, et al. Cancer Med 2021;10:4195-4205.
[2] Mina DS, et al. Front Oncol 2021;10:598425.
[3] Watson NF, et al. J Clin Sleep Med 2015; 38:843-844.
[4] Hirshkowitz M, et al. Sleep Health 2015;1:40-43.
[5] Paruthi S, et al. J Clin Sleep Med 2016;12:785-786.

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GENERAL PRINCIPLES OF PHYSICAL ACTIVITY

- **Physical activity and exercise recommendations should be tailored to individual survivor's abilities and preferences.**
- **When it is deemed unsafe or impractical for a survivor to participate in a home exercise program due to specific impairments or need for supervision, referral to skilled therapy (eg, physical and/or occupational therapy) should be made.**
- **Physical activity for cancer survivors[a,b]:**
  - **Survivors should strive for at least 150 minutes of weekly activity with an ultimate goal of 300 minutes or more of moderate-intensity[c] activity or 75 minutes of vigorous-intensity[c] activity or equivalent combination spread out over the course of the week.**
  - **Engage in two to three sessions per week of strength/resistance training that include major muscle groups (SPA-A).**
  - **Stretch major muscle groups prior to aerobic/endurance exercises and at least 2 days per week on days that exercises on those muscle groups are not performed.**
  - **Core exercises and balance training are recommended especially for older survivors and those at risk for falls.**
- **Engage in general physical activity daily (eg, take the stairs, park 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, prolonged screen-based activities).**
  - **Schedule movement/activity breaks regularly.**
  - **Stand or move while talking on the phone, using the computer, or watching television.**

[a] Additional resources for physical activity in cancer survivors:

- Rock CL, Thomson CA, Sullivan KR, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. CA Cancer J Clin 2022;73:230-262.
- Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 2020;70:245-271
- Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. JAMA 2018;320:2020-2028.
- 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.
- Patel AV, Friedenreich CM, Moore SC, et al. American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. Med Sci Sports Exerc 2019;51:2391-2402.

[b] All exercise should be preceded by a light-intensity aerobic warm-up and stretching.

[c] 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/body mass index (BMI)
- Blood pressure
- Functional status
- Assess baseline level of activity prior to diagnosis and current level of activity[d]
- Barriers to physical activity as assessed by survivor
  - Environmental (eg, home, gym access, outdoor space, physical safety)
  - Financial
  - Physical limitations
  - Time/competing demands
  - Motivation level
  - Social support
  - Stress
- Review of systems
- Disease status

Assessment of modifiable barriers to physical activity:
- Pain
- Fatigue
- Emotional distress
- Nutritional deficits/imbalance
- Medications/side effects

→

Assessment of comorbidities and treatment effects as appropriate:
- Cardiovascular disease (CVD) (including cardiomyopathy)
- Pulmonary disease
- Arthritis/musculoskeletal issues
- History of major musculoskeletal surgery
- 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)
- Thrombocytopenia/pancytopenia and/or coagulopathies
- Steroid myopathy
- Presence of limb prosthesis

→

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

[d] Ask survivor about duration, intensity, and frequency of activity. For example, see Godin G, Shepard RJ. Godin Leisure-Time Exercise Questionnaire. Med Sci Sports Exerc 1997;29:S36-S38. (https://journals.lww.com/acsm-msse/Fulltext/1997/06001/Godin_Leisure_Time_Exercise_Questionnaire.9.aspx)

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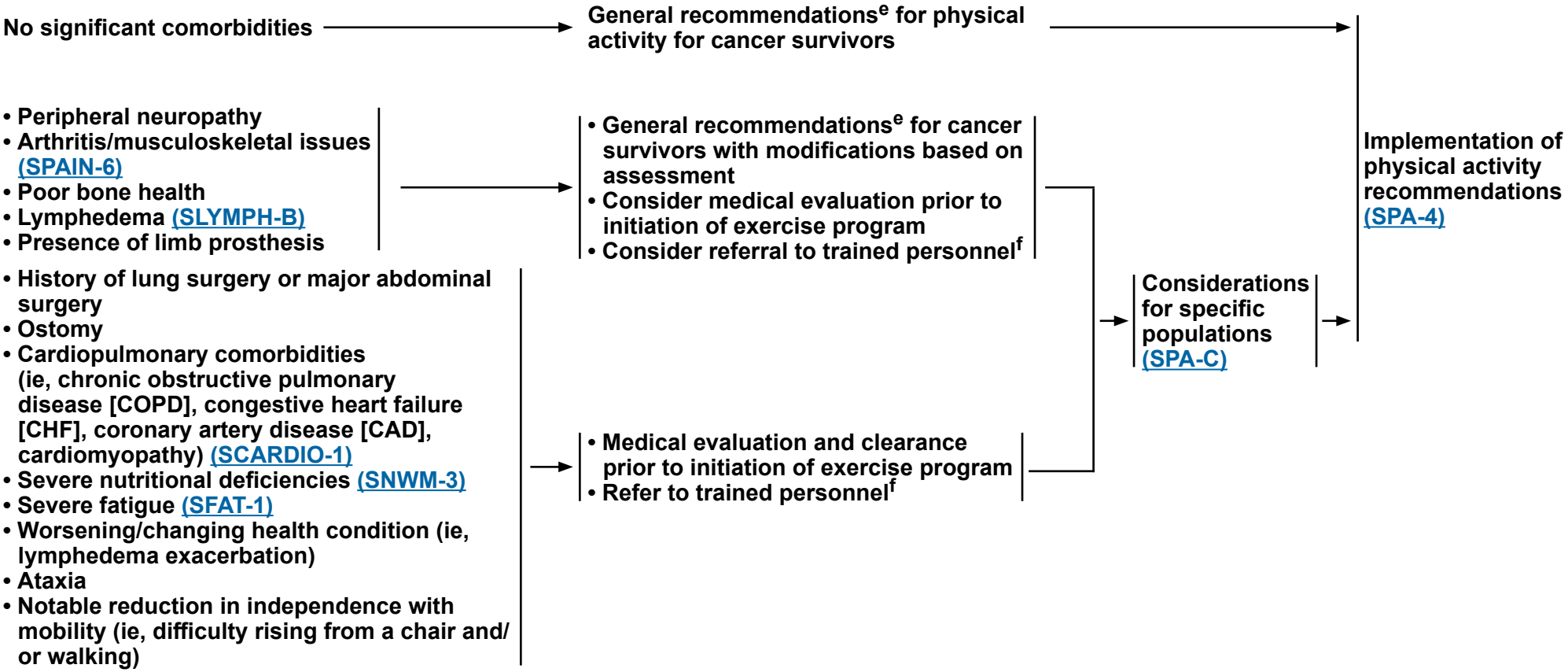
RISK ASSESSMENT FOR PHYSICAL ACTIVITY-INDUCED ADVERSE EVENTS



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

[f] 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: ACSM [http://www.acsm.org/get-stay-certified] and American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org].

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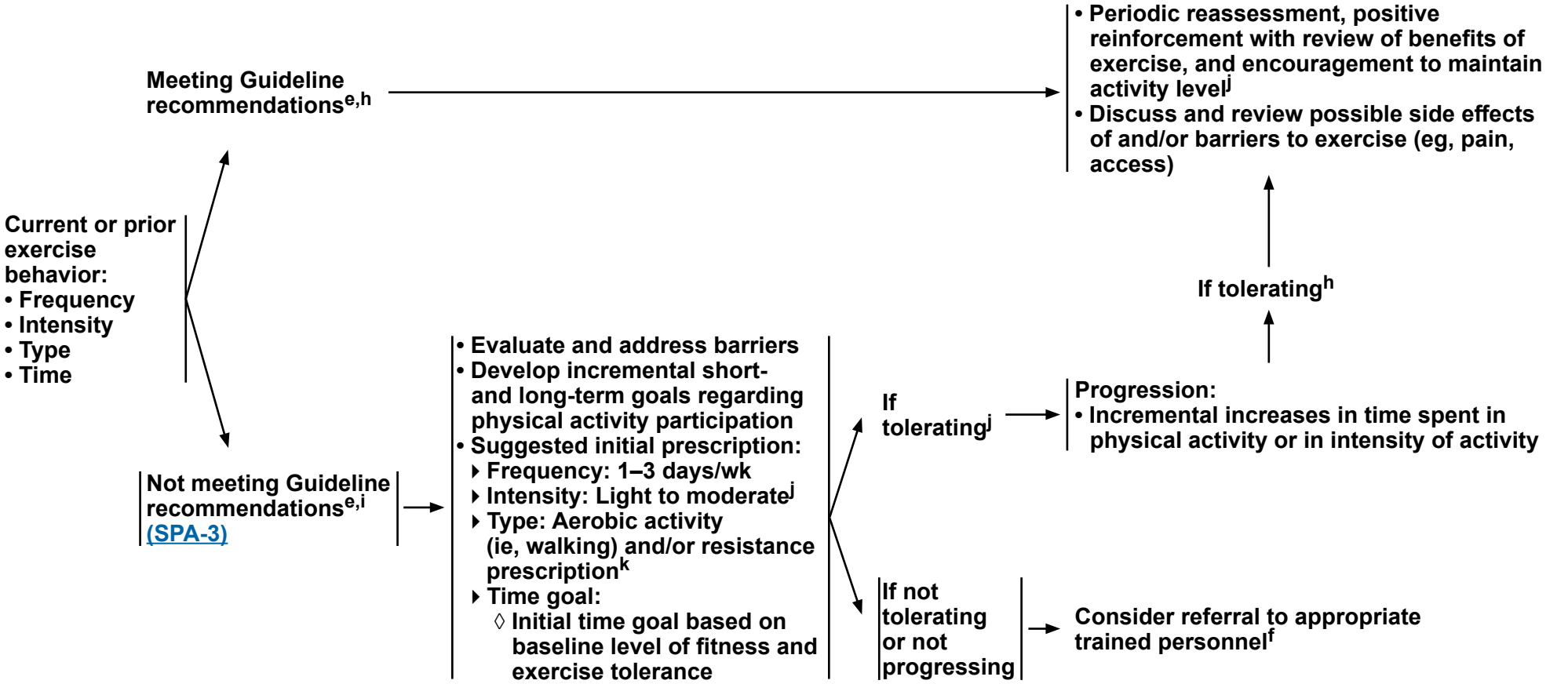
IMPLEMENTATION OF RECOMMENDATIONS[g]



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

[f] 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 (ACSM [http://www.acsm.org/get-stay-certified] and APTA Oncology section [http://oncologypt.org]).

[g] 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.

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

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

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

[k] 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 are 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.**
- **If there is a concern that peripheral neuropathy may increase the risk of dropping free weights, survivors could consider utilizing weight machines and/or training with resistance bands.**
- **For survivors at risk for or with lymphedema, see SLYMPH-B.**

[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 (ACSM [http://www.acsm.org/get-stay-certified] and APTA Oncology section [http://oncologypt.org]).

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

[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.

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Continued

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, and self-efficacy, utilizing behavior change techniques (eg, action planning, feedback and monitoring, habit formation and tracking)
• Cancer survivor-specific materials and resources (SURV-B 3 of 5)
• Set SMART (specific, measurable, achievable, realistic, timebound) short- and long-term goals[1]
• Consider use of pedometer or wearable fitness tracker to monitor activity goals (eg, obtain at least 7000–10,000 steps per day[2])
• Encourage social support (exercise buddy, group)

Footnotes
[c] Consider referral to trained personnel.

References
[1] Rethorn ZD, Covington K, Cook CE, Bezner JR. J Orthop Sports Phys Ther 2022;52:236-242.
[2] Paluch AE, Bajpai S, Bassett DR, et al. The Lancet Public Health 2022;7:e219-e228.

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CONSIDERATIONS FOR SPECIFIC POPULATIONS[a]

- **Survivors with established lymphedema:**
  - **For workup and treatment of established lymphedema (SLYMPH-3)**
  - **For considerations regarding physical activity in survivors with established lymphedema (SLYMPH-B)**
  - **Survivors at risk for upper extremity lymphedema should be encouraged to perform arm/shoulder exercises (SLYMPH-1)**

- **Survivors with ostomy:[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.**

- **Presence of limb prosthesis or limb amputation:**
  - **Referral to trained personnel (eg, physical therapist) to develop a physical activity recommendation program to support the survivor**
  - **Ensure proper fit of limb prosthesis and understanding of proper use**
  - **Encourage assistive device use as necessary**

- **Survivors with peripheral neuropathy:**
  - **Stability, balance, and gait should be assessed before engaging in exercise; consider balance training under the care of a trained professional**
  - **Consider alternative aerobic exercise (stationary biking, water aerobics, yoga) rather than walking if neuropathy affects stability**
    - ◊ **Consider use of water shoes/protective footwear with aerobic exercise to minimize risk of skin breakdown**
    - ◊ **Assistance with walking should be provided if alternative aerobic activities are not possible**
  - **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**

- **Survivors with bone loss or bone metastases:**
  - **Avoid exercises that place high load on fragile skeletal sites**
  - **Minimize fall risk**
  - **Refer for medical evaluation if bone pain develops**
  - **Consider weight-bearing exercises to improve bone density[2]**
  - **Consider checking vitamin D levels and use of supplemental vitamin D if appropriate**

- **Older adults:**
  - **Assess baseline fitness and functional status**
  - **Recommend core exercises and balance training**
  - **See NCCN Guidelines for Older Adult Oncology**

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:ACSM [http://www.acsm.org/get-stay-certified] or 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.

[2] Zhang S, Huang X, Zhao X, et al. Effect of exercise on bone mineral density among patients with osteoporosis and osteopenia: A systematic review and network meta-analysis. J Clin Nurs 2021;31:2100-2111.

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GENERAL PRINCIPLES OF NUTRITION

- Assess dietary pattern for daily intake of fruits, vegetables, and whole grains, as well as red and processed meats, alcohol, dietary supplements, and processed foods or beverages with added fats and/or sugars.
- Assess timing of meals and snacking habits, portion size, frequency of eating out, and use of added fats and/or sugars to foods or beverages.
- All survivors should be encouraged to:
  - Follow a predominantly nutrient-rich plant-based diet, including vegetables, fruit, beans/legumes, and whole grains.[a,b,1]
  - Make informed choices about food to ensure variety and adequate nutrient intake.
  - Limit consumption of red meat such as beef, pork, or lamb to no more than 18 ounces (cooked) per week.
  - Limit consumption of processed meats such as ham, hot dogs, deli cuts, bacon, and sausage.[c]
  - Limit consumption of processed foods that are high in fat, starches, or sugars such as chips, cookies, candy bars, desserts, processed baked goods, sugary cereals, and fried foods.
  - Limit refined sugars to <6 tsp (25 g) for a 2000-calorie daily diet and <9 tsp (38 g) for a 3000-calorie daily diet. One medium cookie has about 2 tsp of sugar; a 12-oz can of a soft drink has about 10 tsp.
  - Monitor calorie intake.
    - ◊ Self-monitoring of food and beverage intake has been shown to be an effective strategy for weight management.
    - ◊ Prolonged periods of fasting may impair adequate caloric and nutrient intake.
  - Drink alcohol sparingly if at all.[2,d] Lower levels of alcohol consumption are associated with a lower risk of cancer.
- For patients desiring further recommendations for dietary guidelines:
  - Consider referral to a registered dietitian.
  - The USDA approximate food plate volumes (https://www.myplate.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 cold water fish[e,f]
  - Carbohydrates: fruits, vegetables, whole grains, and legumes
  - Protein: poultry, fish, legumes, low-fat dairy foods, eggs, and nuts
- While the risks and benefits of soy foods for cancer survivors have been debated for many years, most studies to date show that moderate consumption of soy foods (up to 3 servings per day) are beneficial in promoting overall health and survival, with the strongest evidence existing for the prevention of lung cancer and reduction of breast cancer recurrence.[g,3]

References on (SNWM-1A)
Footnotes on (SNWM-1A)

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GENERAL PRINCIPLES OF NUTRITION
FOOTNOTES AND REFERENCES

Footnotes

[a] Recommendation for healthy food portion sizes can be found on the AICR New American Plate website (https://www.aicr.org/cancer-prevention/food-facts/aicrs-new-american-plate) as well as the USDA "My Plate" website (https://www.myplate.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] Consumption of processed meats is associated with an increased risk of colorectal and gastric cancers (Bouvard V, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015;16:1599-1600).

[d] There are some cancers for which survivors should abstain from alcohol. These include liver, esophageal, breast, colon, and head and neck cancers. For some survivors, there may be an increased risk of certain cancers; however, data are limited, especially on risk of recurrence. Recommend drinking alcohol sparingly, if at all (Goding Sauer A, et al. Cancer Epidemiol 2021;71:101893).

[e] These types of fats should be prioritized over saturated fats and used in moderation in the context of weight loss strategies.

[f] Examples of "cold water fish" include mackerel, salmon, herring, and others.

[g] AICR. Soy: Intake Does Not Increase Risk for Breast Cancer Survivors (https://www.aicr.org/cancer-prevention/food-facts/soy).

References

[1] AICR: https://www.aicr.org/cancer-prevention/how-to-prevent-cancer.

[2] Rock CL, Thomson CA, Sullivan KR, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. CA Cancer J Clin 2022;72:230-262.

[3] Yang WS, Va P, Wong MY, et al. Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies. Am J Clin Nutr 2011;94:1575-1583.

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GENERAL PRINCIPLES OF WEIGHT MANAGEMENT

- **All survivors should be encouraged to achieve and maintain a BMI between 18.5 and 24.9 kg/m^2 and strive for metabolic health.**
  - **Intentional weight gain should be a priority for survivors who have underweight. (SNWM-4)**
  - **Intentional weight loss should be a priority for survivors who have overweight/obesity.**
    - ◊ **Weight gain after cancer diagnosis and treatment is common and may exacerbate risk for functional decline, comorbidity, and possibly cancer recurrence or death, and may reduce quality of life.**
  - **Weight maintenance should be a priority for survivors who have a BMI between 18.5 and 24.9 kg/m^2.**
- **In conjunction with primary care, survivors should be assessed for metabolic health and body composition independently of BMI.**
- **Weight management includes a three-pronged approach: caloric management, physical activity, and behavior modification.**
- **Providers should discuss strategies and goal setting for weight management and optimal metabolic health, including how to achieve low overall body fat and higher amounts of muscle mass.**
  - ◊ **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).**
  - ◊ **Monitor 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.[h]**
- **There is no current evidence to support the use of weight loss supplements in cancer survivors.**

[h] Many hospitals use 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[i]

- Evaluate weight status based on BMI criteria[j]
- Evaluate involuntary weight change[k]

→

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[l]
  - 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
  - Gastrointestinal (GI) dysmotility
  - Swallowing issues/ dysphagia
  - Dysgeusia/change in taste
  - Oropharyngeal anatomic changes
  - Bowel dysfunction
  - Digestive enzyme insufficiency
  - GI tract reconstruction/anastomoses
- Comorbidities:
  - CVD
  - 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" (SNWM-1)
- Discuss "General Principles of Weight Management" (SNWM-2)
- Discuss "General Principles of Physical Activity" (SPA-1)

→

Additional Nutrition and Weight Management Interventions (SNWM-4)

[i] Coordination with PCPs and other involved providers is recommended.
[j] The following BMI calculator from the CDC 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 (lb) x 703 / height in inches squared. The weight categories are as follows: Underweight (BMI, <18.5 kg/m2), Healthy weight (BMI, 18.5–24.9 kg/m^2), Overweight (BMI, 25–29.9 kg/m2), Obese (BMI, ≥30 kg/m2).
[k] Consider workup for disease recurrence in the setting of cachexia or significant involuntary weight loss/gain >5% within 3 months.
[l] For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/2014-Obesity-Cancer-Guide-Oncology-Providers.pdf.

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NCCN Guidelines Version 2.2024
Survivorship: Nutrition and Weight Management

NCCN Guidelines Index
Table of Contents
Discussion

GOAL	ADDITIONAL NUTRITION AND WEIGHT MANAGEMENT INTERVENTIONS[i,l]
Weight gain[m] →	• 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 (NCCN Guidelines for Smoking Cessation) ‣ Contributing psychosocial factors (SANXDE-1) ‣ Barriers to access of healthy food such as living too far from grocery store, lack of transportation, or lack of resources to prepare food • Discuss increasing frequency of feeding and portion size • Discuss avoiding fluid intake with meals • Encourage foods that are both high in calories and nutrient-dense (eg, avocados, nuts) • Consider referral to registered dietitian for individualized counseling • Optimize nutritional density and caloric quality of food • Consider appetite stimulants • Monitor weight regularly
Weight maintenance →	• Reinforce maintenance of healthy body weight throughout lifetime • Monitor weight regularly[n] • Limit foods that are high in calories, particular those that provide relatively few nutrients such as sugar-sweetened beverages and foods with high amounts of fats and sugars • Practice portion control through plate and serving size awareness • Promote regular physical activity (SPA-1)
Weight loss[l] →	• Manage contributing treatment effects and risk factors as clinically indicated ‣ Contributing psychosocial factors, including depression (SANXDE-1) ‣ Barriers to access of healthy food such as living too far from grocery store, lack of transportation, or lack of resources to prepare food • Monitor weight regularly[n] • Recommend weight loss of no more than 2 lb per week and no more than 1 lb per week in survivors >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 fats 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 • Promote regular physical activity (SPA-1) • Refer to community resources or PCP • Refer to registered dietitian or weight management programs for individualized help as needed[o] • Consider evaluation for bariatric surgery or pharmacologic therapy[p] as appropriate

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Footnotes on SNWM-4A

FOOTNOTES FOR SNWM-4

[i] Coordination with PCPs and other involved providers is recommended.
[l] For additional resources see the ASCO Toolkit on Obesity and Cancer: https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/2014-Obesity-Cancer-Guide-Oncology-Providers.pdf.
[m] Modification of diet and dietary components should be done on an individual basis.
[n] Daily monitoring has been shown to be associated with improved weight loss (Steinberg, et al. J Acad Nur Diet 2015;115:511-518 and Zheng Y, et al. Int J Obes (Lond) 2016;40:1392-1396).
[o] Strongly consider for survivors with negligible weight loss from diet and exercise interventions.
[p] The safety and efficacy of these drugs in cancer survivors is unknown. Lifestyle modifications are preferred over pharmacologic therapy.

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.

NCCN Guidelines Version 2.2024
Survivorship: Supplement Use

NCCN Guidelines Index
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Discussion

GENERAL PRINCIPLES OF SUPPLEMENT USE

- **Supplement use is not recommended for most survivors, except in instances of documented deficiencies, inadequate diet, previous gastrointestinal surgery that may cause deficiencies (eg, Roux-en-Y gastric bypass), or comorbid indications (eg, osteoporosis, ophthalmologic 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 supplements not prescribed by a medical provider to a registered dietitian, preferably one with oncology credentials, or other cancer care team members such as integrative medicine or clinical pharmacist.**
- **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 the NCCN Guidelines for Gastric Cancer).**

[a] Referral to registered dietitians, especially those who are 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 [HepB]) 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, measles, mumps, rubella [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 [RZV]).**
- **Ideally, clinicians should have administered all indicated vaccines to patients before initiation of cancer treatment (if possible, at least 2 weeks before cancer treatment).[d]**
  - **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 (IIV) can be administered during cancer treatment.**
  - **Live viral vaccines[e] 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.**
  - **COVID-19 vaccine is recommended as appropriate. See https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html**
- **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: Murthy N, Wodi AP, McNally VV, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:11-15.
[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] Cancer treatment includes chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, and splenectomy.
[e] Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors or In Close Contacts of Immunocompromised Survivors (SIMIN-A).

Note: All recommendations are category 2A unless otherwise indicated.
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RISK ASSESSMENT AND SCREENING

Risk factors for infections:
- **Underlying disease and/or comorbidities**
- **Splenectomy**
- **Ongoing or recent exposures (ie, <3 months)**
  - **Cytotoxic chemotherapy**
  - **Monoclonal antibodies (eg, rituximab, alemtuzumab)**
  - **Radiation**
  - **Corticosteroids**
- **Prior cellular therapies**
  - **HCT[f]**
  - **Chimeric antigen receptor (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[e,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)

→ **SIMIN-3**

[e] 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, 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/2024/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 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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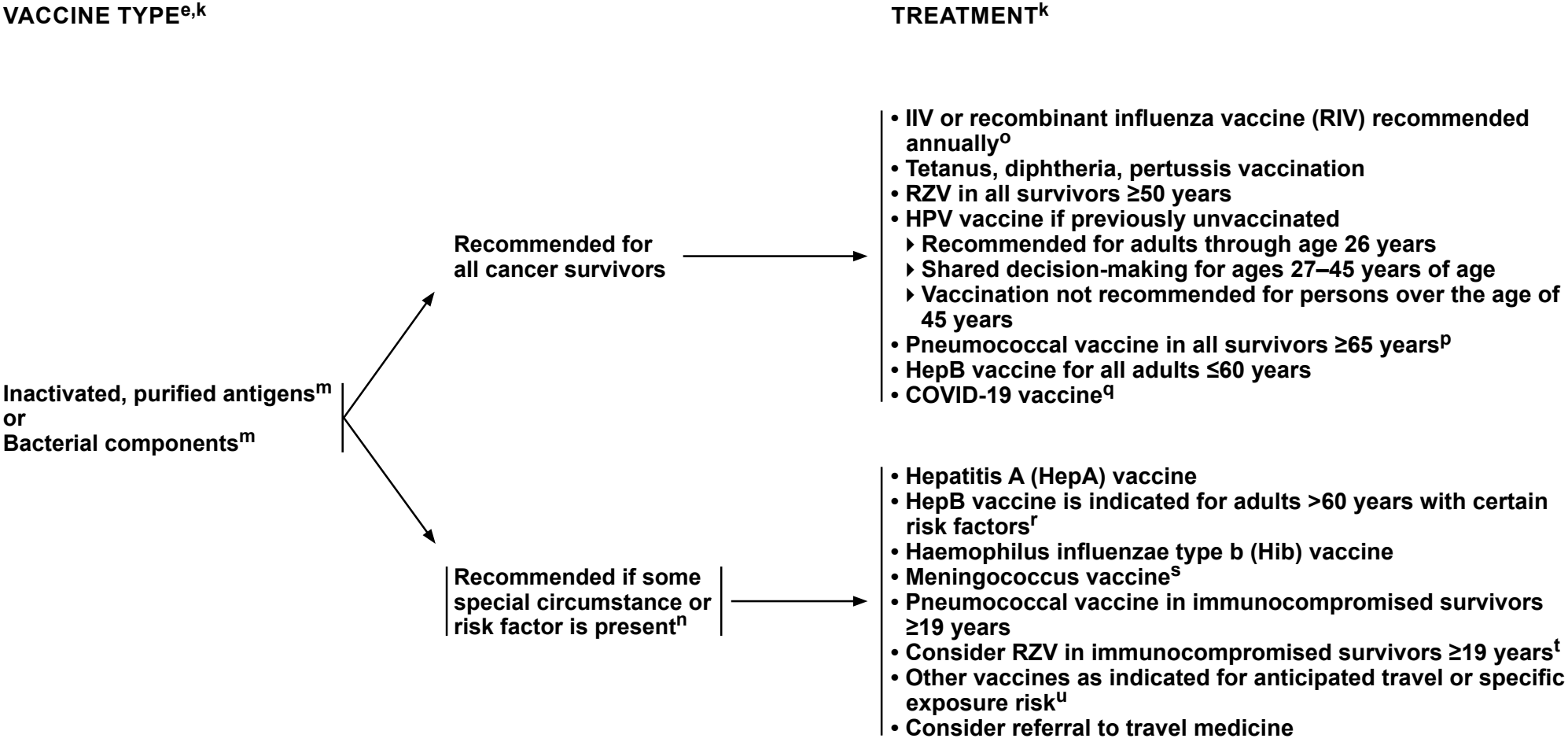
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



Footnotes on SIMIN-3A

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FOOTNOTES FOR SIMIN-3

[e] 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 cytotoxic chemotherapy or RT and 6 months after HCT (a dose of IIV 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 a survivor'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 cellular therapy can be found on SIMIN-B.
[o] Principles of Influenza Vaccine(s) (SIMIN-C).
[p] General Principles of Vaccines in Cancer Survivors (SIMIN-B).
[q] Recommendations regarding COVID-19 vaccines are continually changing (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html). For guidance about the management of concurrent COVID-19 and cancer, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[r] For a list of risk factors for hepatitis B, see the CDC's Hepatitis B Vaccination of Adults: https://www.cdc.gov/hepatitis/hbv/vaccadults.htm.
[s] Recommended in high-risk patients or those with functional or anatomic asplenia. Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep 2020;69:1-41.
[t] Anderson TC, et al. MMWR Morb Mortal Wkly Rep 2022;71:80-84.
[u] For travel-related vaccine recommendations, see the CDC website at https://wwwnc.cdc.gov/travel.

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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)** • **Oral typhoid** • **Yellow fever** • **Rotavirus[b]** • **Nasal influenza vaccine** • **Varicella vaccine (single or combined with MMR)**

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] 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 Survivors Who Had Cellular Therapy (ie, HCT,[a] CAR T-cell therapy)[1]

- **For infection concerns and recommended prophylaxis for immune-targeted agents, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**
- **Live viral vaccines should not be administered to HCT survivors 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 disease specialist.**
- **There is a lack of comprehensive data regarding the use of vaccines after CAR T-cell therapy. Due to the significant immune suppression post CAR T-cell therapy, recommendations for vaccination should be individualized to the survivor based on the type of CAR T-cell therapy the survivor received.**
- **The following vaccines can be administered to survivors who had cellular therapy:**

Vaccine	Population	Recommended Dose/Timing
Influenza vaccine[2] (Principles of Influenza Vaccine(s) [SIMIN-C])	All cellular therapy survivors	1 dose annually, 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[3,b]	• Adult cellular therapy survivors ≥65 years • Adult cellular therapy survivors who are immunocompromised	• PCV20 or PCV15 is recommended: ▸ 1 dose of 20- or 15-valent pneumococcal conjugate vaccine (PCV20 or PCV15) if never vaccinated against pneumococcus ▸ When PCV15 is used, it should be followed by a dose of PPSV23 at least 1 year later • Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose • Adults with previous PCV13 who have not completed their recommended pneumococcal vaccine series with PPSV23 can receive one dose of PCV20 if PPSV23 is not available.
Haemophilus influenzae type b (Hib) vaccine	All cellular therapy survivors	3 doses of Hib vaccine should be administered 6–12 months after HCT
Meningococcal conjugate vaccine, quadrivalent (MCV4)	Survivors with surgical or functional asplenia	2-dose series at least 8 weeks apart and revaccinate every 5 years if risk remains
	• Consider in cellular therapy survivors in outbreak situations or in endemic areas	1 dose and revaccinate every 5 years if risk remains
Tetanus, diphtheria, pertussis vaccine (DTaP/Td or Tdap/DT/Td)	All cellular therapy survivors	• 3 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 3-dose regimen should be followed by Td boosters every 10 years • Alternatively, 1 dose of Tdap and 2 doses of DT or 1 dose of Tdap and 2 doses of Td can be given
Hepatitis A (HepA) vaccine	All cellular therapy survivors	• 2 doses of single-antigen HepA vaccine or • 3-dose series of combination HepA and HepB vaccine

Footnotes on (SIMIN-B 5 of 6) References on (SIMIN-B 5 of 6)

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Continued

GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Survivors Who Had Cellular Therapy (ie, HCT,[a] CAR T-cell therapy)[1] (continued)

Vaccine	Population	Recommended Dose/Timing
Hepatitis B (HepB) vaccine	All cellular therapy survivors	• 2 doses of HepB vaccine, recombinant (adjuvanted) given at least 4 weeks apart or 3 doses of HepB vaccine administered 6–12 months after HCT • 3 doses of a different HepB vaccine (at 0, 1, and 6 months) 40 mcg/mL • If a post-vaccination anti-hepatitis B surface antigen (anti-HBsAg) concentration of ≥10 mIU/mL is not obtained, a second series of HepB vaccine is recommended • First dose of HepB vaccine (after which anti-HBsAg is tested) using high dose (40 µg) should be administered
Inactivated polio vaccine (IPV)	All cellular therapy survivors	3 doses of IPV vaccine should be administered 6–12 months after HCT
HPV vaccine	• Recommended for adults ≤26 years • Shared decision-making for ages 27–45 years of age • Vaccination not recommended for persons >45 years	3 doses of HPV vaccine 6–12 months after HCT (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html)
Measles, mumps, rubella (MMR) vaccine	Measles-seronegative adolescent and adult cellular therapy survivors with neither chronic GVHD nor ongoing immunosuppression	• MMR vaccine should be avoided within 4 weeks before HCT • A 2-dose series of MMR vaccine should be administered 24 months after HCT and 8–11 months after the last dose of intravenous immunoglobulin (IVIG)
Recombinant zoster vaccine (RZV)[4]	• Survivors aged ≥50 years • Consider in cellular therapy survivors ≥19 years[c]	• A 2-dose series of RZV should be administered 24 months after HCT and 8–11 months after the last dose of IVIG • In survivors who have previously received the live attenuated zoster vaccine, immunization with RZV should be considered. The recombinant vaccine should not be given less than 2 months after receiving the live attenuated vaccine
COVID-19 vaccine	All cellular therapy survivors	• Recommendations regarding COVID-19 vaccines are continually changing (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html.) • For guidance on the management of concurrent COVID-19 and cancer, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Footnotes on (SIMIN-B 5 of 6)

References on (SIMIN-B 5 of 6)

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Continued

GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in All Other Survivors[5]

- **The following vaccines can be administered to survivors of hematologic or solid tumor malignancies who did not receive cellular therapy (except those receiving anti–B-cell antibodies):[d]**

Vaccine	Population	Recommended Dose/Timing
Influenza vaccine (Principles of Influenza Vaccine(s) [SIMIN-C])	All survivors	Annually
Pneumococcal vaccine[3,b]	• Adult survivors ≥65 years • Adult survivors who are immunocompromised • Survivors with surgical or functional asplenia	• PCV20 or PCV15 is recommended: ▸ 1 dose of 20- or 15-valent pneumococcal conjugate vaccine (PCV20 or PCV15) if never vaccinated against pneumococcus ▸ When PCV15 is used, it should be followed by a dose of PPSV23 at least 1 year later • Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose • Adults with previous PCV13 who have not completed their recommended pneumococcal vaccine series with PPSV23 can receive one dose of PCV20 if PPSV23 is not available.
Haemophilus influenzae type b (Hib) vaccine[6]	• Survivors with surgical or functional asplenia • Survivors living with HIV infection	3 doses of Hib vaccine should be administered
Tetanus, diphtheria, pertussis vaccine (Td/Tdap)	• Adult survivors <65 years of age who have not received Tdap previously • Adult survivors <65 years of age for whom vaccine status is unknown	• Substitute 1-time dose of Tdap for Td booster • Boost with Td or Tdap booster every 10 years
	• All other survivors	• Td or Tdap booster every 10 years

References on (SIMIN-B 5 of 6)

Footnotes on (SIMIN-B 5 of 6)

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Continued

GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in All Other Survivors[5]

• The following vaccines can be administered to survivors of hematologic or solid tumor malignancies who did not receive cellular therapy (except those receiving anti–B-cell antibodies)[d]:

Vaccine	Population	Recommended Dose/Timing
HPV vaccine	• Recommended for adults ≤26 years • Shared decision-making for ages 27–45 years of age • Vaccination not recommended for persons >45 years	For dosing and schedules see https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html
Recombinant zoster vaccine (RZV)[4]	Survivors aged ≥50 years[c]	A 2-dose series of RZV is recommended
Meningococcal conjugate vaccine quadrivalent (MCV4)	Survivors with surgical or functional asplenia	2-dose series at least 8 weeks apart and revaccinate every 5 years if risk remains
Hepatitis B (HepB) vaccine	Adult survivors ≤60 years	• 2 doses of HepB vaccine, recombinant (adjuvanted) given at least 4 weeks apart or • 3 doses of a different HepB vaccine (at 0, 1, and 6 months) 40 mcg/mL
COVID-19 vaccine	All survivors	• Recommendations regarding COVID-19 vaccines are continually changing (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html.) • For guidance on the management of concurrent COVID-19 and cancer, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Footnotes on (SIMIN-B 5 of 6)

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FOOTNOTES FOR GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS
(SIMIN-B 1 OF 6 TO SIMIN-B 4 OF 6)

Footnotes

[a] HCT includes peripheral blood stem cell transplantation, bone marrow transplantation, and cord blood transplantation.
[b] There are data on immune response to PCV-13 post HCT, but not yet for PCV15 or PCV20. Kobayashi M, Farrar JL, Gierke R, et al. MMWR Morb Mortal Wkly Rep 2022;71;109-117.
[c] Consider RZV in immunocompromised survivors ≥19 years (Anderson TC, et al. MMWR Morb Mortal Wkly Rep 2022;71:80-84).
[d] 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] 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.
[2] Walti CS, Loes AN, Shuey K, et al. Humoral immunogenicity of the seasonal influenza vaccine before and after CAR-T-cell therapy: a prospective observational study. J Immunother Cancer 2021;9:e003428.
[3] Kobayashi M, Pilishvili T, Farrar JL, et al. Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023. MMWR Recomm Rep 2023;72:1-39.
[4] Anderson TC, Masters NB, Guo A, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:80-84.
[5] Murthy N, Wodi AP, McNally VV, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2024. MMWR Morb Mortal Wkly Rep 2024;11;73:11-15.
[6] Briere EC, Rubin L, Moro PL, et al. Prevention and Control of Haemophilus influenzae Type b Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014;(RR01):1-14.

Continued

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccines Considered Safe for Cancer and Transplant Survivors and Close Contacts[e]	
Inactivated or purified antigens or bacterial components[f]	**Recombinant viral antigens**

• Influenza: inactivated influenza virus vaccine[g]
  ▸ Trivalent (IIV3), standard dose
  ▸ Trivalent (IIV3), high dose
  ▸ Quadrivalent (IIV4), standard dose
• Pneumococcus:
  ▸ Pneumococcal conjugate vaccine (PCV)
  ▸ Pneumococcal polysaccharide vaccine (PPSV)
• Meningococcus[6]:
  ▸ Quadrivalent meningococcal conjugate vaccine (MCV4: serotypes A, C, W, Y)
  ▸ Meningococcal vaccine (serotype B)
• Tetanus, diphtheria, pertussis (Td/Tdap)
• Hepatitis A (HepA)
• Haemophilus influenzae type b (Hib)
	• Hepatitis B (HepB)
	• Human papillomavirus (HPV)
	• Recombinant trivalent influenza vaccine (RIV3)[e]
	• Recombinant zoster vaccine (RZV)

Footnotes

[e] 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).

[f] For patients traveling to endemic countries, vaccines such as typhoid bacterial capsular polysaccharide, IPV, Japanese encephalitis, and rabies virus are recommended by the CDC (www.cdc.gov).

[g] 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 if an egg-based vaccine is used. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72:1-25.

References

[6] Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep 2020;69:1-41.

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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.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html**
- **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 (IIV)**
  - **Quadrivalent (IIV4), standard dose**
  - **Quadrivalent, high-dose (HD-IIV4; preferred option for survivors ≥65 y)**
  - **Quadrivalent adjuvanted inactivated influenza vaccine (aIIV4; preferred option for survivors ≥65 y)**
- **Recombinant influenza vaccine (RIV)[a]**
  - **Quadrivalent (RIV4; preferred option for survivors ≥65 y)**

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

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 if an egg-based vaccine is used. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72:1-25.

References

[1] Murthy N, Wodi AP, McNally VV, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2024. MMWR Morb Mortal Wkly Rep 2024;11;73:11-15.

[2] Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72:1–25.

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Late Effects/Long-Term Psychosocial and Physical Problems

PRINCIPLES OF CARDIOVASCULAR DISEASE RISK ASSESSMENT

- **CVD remains a leading cause of death in cancer survivors. CVD-related comorbidity and mortality may detrimentally affect patients with cancer and survivors with short- and long-term sequelae. Counseling regarding cardiovascular risk factors and lifestyle modifications are paramount in cancer survivors and patients with favorable prognoses. 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.**
- **Referral to a cardiologist or cardio-oncologist in patients at elevated CVD risk should be considered at any stage of the cancer journey.[e]**
- **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 (immunotherapy,[a] cytotoxic, HCT, and targeted systemic therapies,[b] RT) can result in diverse cardiovascular issues, including cardiomyopathy, hypertension, hyperlipidemia, cardiac arrhythmia, myocardial infarction, carotid stenosis after head and neck and mantle radiation, and cerebrovascular accidents.**
  - **Survivors treated with anthracyclines are at increased risk for heart failure (SCARDIO-1).**
  - **Androgen or estrogen deprivation therapy may elevate cardiovascular risk.[c]**
- **Most CVDs (such as atherosclerosis) develop over time as a result of well-defined risk factors such as hypertension, hyperlipidemia, use of tobacco products, 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, CAD, CHF, peripheral vascular disease, arrhythmias including atrial fibrillation) and CVD risk factors (eg, hypertension, dyslipidemia, obesity, cigarette/tobacco use, diabetes mellitus), with intervention for modifiable risk factors as necessary**
  - **Cancer treatment history (eg, regimen/dose,[b] radiation field, dose/volume)**
  - **Diet and exercise habits**
- **Tools exist to help quantify atherosclerotic CVD (ASCVD) risk (eg, ASCVD risk score[d]) and thus determine appropriate risk reduction strategies.**
- **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.**

[a] Drobni ZD, Alvi RM, Taron J, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. Circulation 2020;142:2299-2311.
[b] HER2-directed therapy, VEGF signaling pathway inhibitors, cisplatin, anthracyclines, and androgen or estrogen deprivation therapy are possible CVD risk factors.
[c] Okwuosa TM, Morgans A, Rhee JW, et al. Impact of hormonal therapies for treatment of hormone-dependent cancers (breast and prostate) on the cardiovascular system: Effects and modifications: A scientific statement from the American Heart Association. Circ Genom Precis Med 2021;14:14:e000082.
[d] The ASCVD Risk Estimator Plus from the American College of Cardiology is available at http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate.
[e] Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893-911.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF CARDIOVASCULAR DISEASE RISK ASSESSMENT[e]

Table 1: ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors[f]	
A	• Awareness of risks and presentation of heart disease • Assessment of CVD 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)[g]
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 (NCCN Guidelines for Smoking Cessation)
D	• Diet and weight management (SNWM-1) • Dose (cumulative) of anthracyclines and/or radiation to heart • Diabetes mellitus prevention/treatment
E	• Exercise (SPA-1)[h] • Echocardiogram (ECHO) and/or electrocardiogram (ECG) based on individual risk

[e] Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893-911.
[f] Adapted with permission from Montazeri K, Unitt C, Foody JM, et al. ABCDE Steps to Prevent Heart Disease in Breast Cancer Survivors. Circulation 2014;130:e157-e159.
[g] U.S. Preventive Services Task Force; Davidson KW, Barry MJ, Mangione CM, et al. Aspirin use to prevent cardiovascular disease: U.S. Preventive Services Task Force Recommendation Statement. JAMA 2022;327:1577-1584.
[h] Gilchrist SC, Barac A, Ades PA, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: A scientific statement from the American Heart Association. Circulation 2019;139:e997-e1012.

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PRINCIPLES OF ANTHRACYCLINE-INDUCED CARDIAC TOXICITY[a]

- **Cancer treatments can result in diverse cardiovascular issues (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/cardiomyopathy 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/cardiomyopathy 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 develop cardiomyopathy[b] (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 heart failure risk factors, including hypertension, dyslipidemia, and diabetes be 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.[c]**
- **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.**

[a] Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893-911.
[b] 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.
[c] High cumulative anthracycline dose is defined as cumulative doxorubicin dose at or higher than or equal to 250 mg/m^2 or equivalent.

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INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- H&P
  - Assess for signs and symptoms of heart failure[d,e]
  - 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 (eg, anti-HER2 treatment) and/or chest RT
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - High cumulative anthracycline dose[f]
  - Low-normal left ventricular ejection fraction (LVEF) (50%–54%) at baseline
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known CAD, baseline evidence of structural heart disease)
  - Smoking
  - Obesity
  - Physical inactivity

→

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

→

No evidence of structural heart disease, but symptomatic[d] →
- 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 → **Stage A (SCARDIO-3)**

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

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

[d] Signs and symptoms of heart failure include: shortness of breath or chest pain after physical activity or exercise, shortness of breath when laying flat (ie, orthopnea), waking up at night due to shortness of breath, and swelling in the legs.
[e] Patients with symptoms of heart failure should undergo an ECHO.
[f] High cumulative anthracycline dose is defined as cumulative doxorubicin dose ≥250 mg/m^2 or equivalent.
[g] Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[h] Referral to cardiologist/cardio-oncologist if there are echocardiographic abnormalities and/or any cardiovascular symptoms or concerns.
[i] 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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NCCN Guidelines Version 2.2024
Survivorship: Anthracycline-Induced Cardiac Toxicity

NCCN Guidelines Index
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Discussion

STAGES OF CARDIOMYOPATHY (HEART FAILURE)[j]	TREATMENT	SURVEILLANCE
Stage A **(No structural disorder of the heart, but at risk of developing heart failure)[j,k,l]** **• Patients may have any of the following:** **▸ History of potentially cardiotoxic chemotherapy[m] (including anthracyclines)** **▸ History of chest irradiation (especially mantle and left-sided)** **▸ Hypertension, CAD, diabetes mellitus** **▸ History of alcohol use disorder, personal history of rheumatic fever, family history of cardiomyopathy**	**• Address underlying risk factors (hypertension, lipids, cigarette/tobacco use, obesity, metabolic syndrome, diabetes)[g]** **• Recommend regular physical activity and healthy diet habits (HL-1)** **• Consider referral for management[n]**	**Reassess based on symptoms**
Stage B **(Structural heart disease but no signs or symptoms of heart failure)[j]** **• Patients may have any of the following:** **▸ LV hypertrophy** **▸ LV dilatation or hypocontractility** **▸ Asymptomatic valvular heart disease** **▸ Previous myocardial infarction**	**• Measures under Stage A as appropriate** **• Referral to cardiovascular specialist (ie, cardiologist, cardio-oncologist) for management**	
Stage C **Signs and symptoms of heart failure with underlying structural heart disease[j]**	**Referral to cardiovascular specialist (ie, cardiologist, cardio-oncologist) for management**	
Stage D **Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and requiring specialized interventions[j]**		

[g] Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[j] Yancy CW, et al. Circulation 2013;128:e240-e327.
[k] Consider use of biomarkers in select patients at high risk for heart failure (Stage A) (Discussion).
[l] Any patient who has received potentially cardiotoxic chemotherapy and/or chest radiation (and specifically anthracycline-based chemotherapy) should be considered Stage A cardiomyopathy.
[m] For a list of potentially cardiotoxic chemotherapy agents, see Moslehi JJ. N Engl J Med 2016;375:1457-1467.
[n] Consider referral to a cardiologist, cardio-oncologist, survivorship specialist, or PCP for serial surveillance based on cardiotoxicity risk of cancer treatment regimen or 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 (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.**
    - ◊ **Survivors may not appear to be distressed and should be encouraged to inform their health care provider when they are feeling increased distress, worry, anxiety, or depression. See NCCN Distress Thermometer Screening Tool (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 (DIS-A), or PROMIS measures.**
  - **Clinical assessments should include and evaluate psychosocial aspects of a survivor's background, including trauma (SANXDE-7).**
  - **Caregivers and all family members of the survivor, including younger children, are vulnerable to the same psychosocial stresses and symptoms as survivors, though often at different times or for different reasons. If needs are observed, they can be offered resources and referred for evaluation.**
- **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 (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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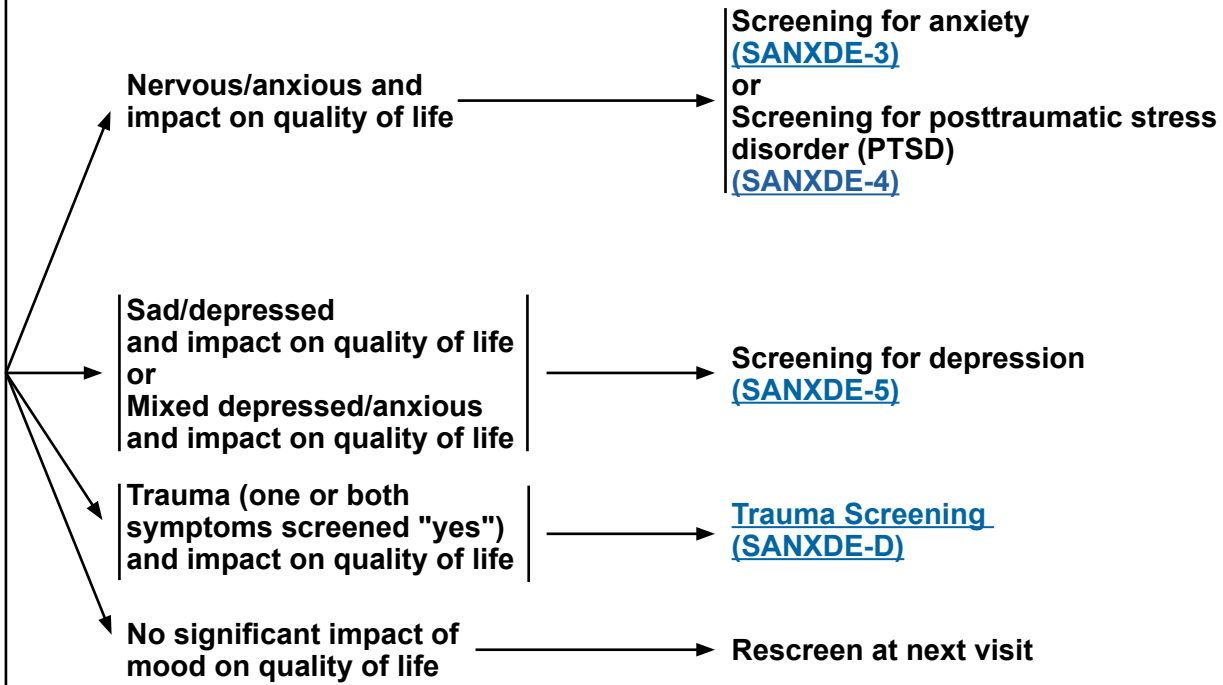
SCREENING: ANXIETY, DEPRESSION, AND TRAUMA

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 2 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, your treatment, or other effects of treatment when you did not want to?**
    - ◊ **tried hard not to think about events or effects 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]

DIAGNOSIS

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**

≥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 → **Screening (SANXDE-6)**

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**

→ **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] Safety Evaluation for Anxiety and Depression (SANXDE-A).
[h] Psychiatrist, psychologist, advanced practice clinician, and/or social worker.

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SCREENING: POSTTRAUMATIC 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 (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

- **Posttraumatic stress symptoms impacting quality of life**
- **Consider adjustment disorder/distress (SANXDE-6)**

→ **Safety evaluation[g]** →

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

[g] 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 posttraumatic stress symptoms.

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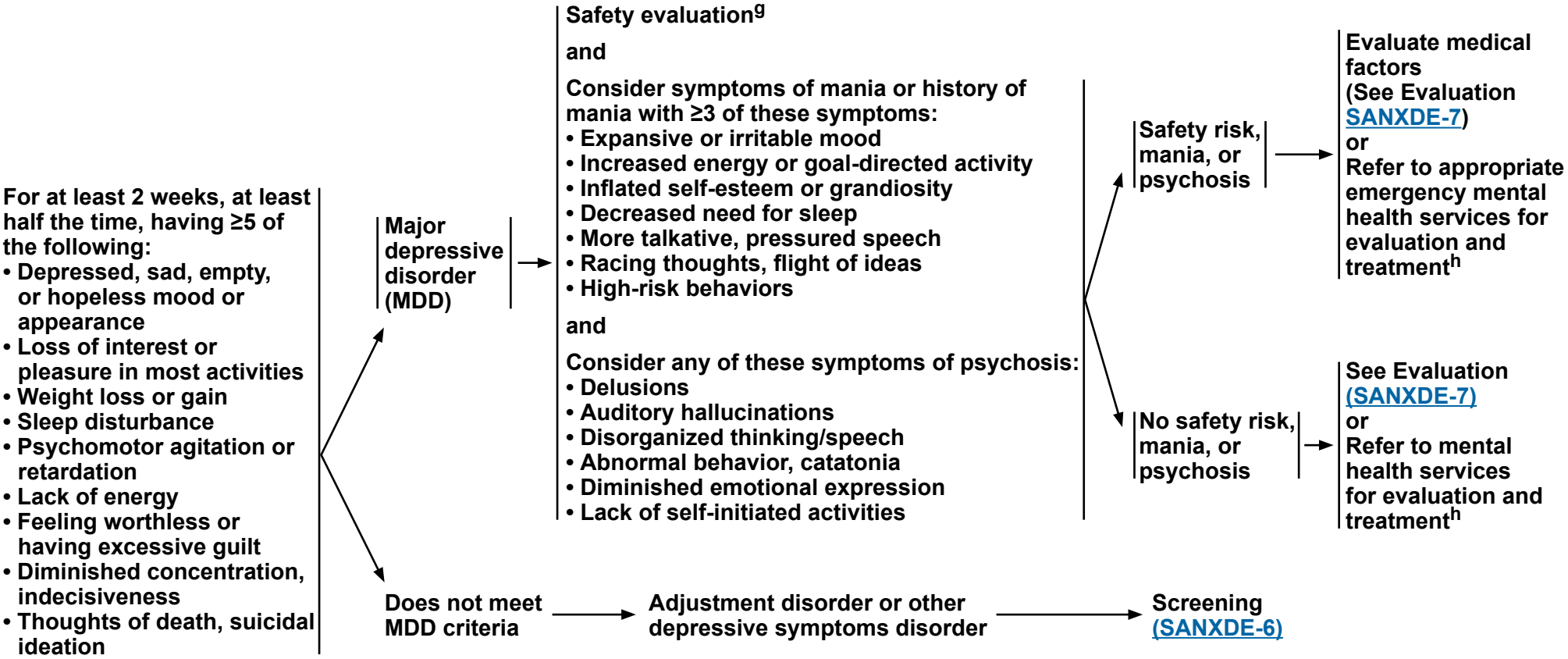
SCREENING: DEPRESSION[i,l,m] DIAGNOSIS



[g] 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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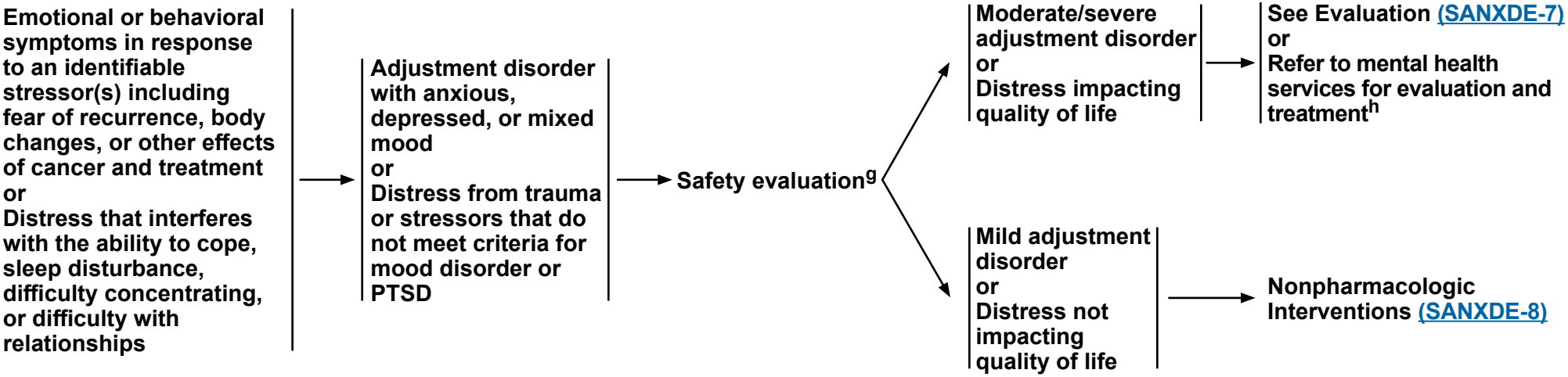
SCREENING: ADJUSTMENT DISORDER/DISTRESS[i,n]

DIAGNOSIS



[g] 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 coexisting medical conditions
  - Substance use disorder
  - History of prior mental health problems including depression, anxiety, phobias, panic, psychoses, or suicide attempt
  - History of childhood or adult trauma prior to or after cancer diagnosis
  - Fatigue level (SFAT-1)
  - Functional status
  - Current coping strategies
  - Sexual health (SSH-1)
  - Infertility
  - Other medical factors including cognitive function (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: ECG, ECHO, stress test (SCARDIO-1)
  - Pulmonary function tests
  - Sleep evaluation (SSD-1)

→

Psychiatric/Emotional Factors

- Identify content of distress including recurrence, health problems, body and sexuality changes, financial burden, or other concerns
- Symptom review based on the Survivorship Anxiety Depression, Trauma, and Distress 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
  - Discrimination or marginalization because of race, ethnicity, sexual orientation, sexual identity, or disability status.
  - Other stresses

→

Management and Treatment (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 recurrence, 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) (SURV-B).
  - Develop a plan for regular physical activity and healthy nutrition (HL-1).

- For adjustment disorder or distress without safety risk, mania, or psychosis:
  (See DIS-10 and DIS-17 in 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 psychosocial 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 use disorder[p]:
  - Safety evaluation (SANXDE-A)
  - See DIS-21 in 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 (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: (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
- Inquire about use of OTC medications
- Consider drug-drug interactions
- 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
- Reinforce treatment adherence
- 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
- Choose once daily dosing, if possible, to improve adherence

[q] Principles of Pharmacologic Interventions (SANXDE-C).
[r] Psychiatrist, psychologist, or 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 (SSD-1)**
    - ◊ **Poor physical and emotional function, including disability**
    - ◊ **Access to potentially lethal medications (ie, 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**
  - **Seeks help**
  - **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 (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 or call, text, or chat 988 Suicide & Crisis Lifeline; or call 911; or go to the nearest emergency room if suicidal thoughts increase or change
- Provide contact information for local crisis hotlines or counselors. (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 off-site and threat is to others or patient is agitated or threatening:
  - Call 911
    and/or
  - Identify a caregiver who is with patient to take to emergency room; call 911; or call, text, or chat 988 Suicide & Crisis Lifeline
    and/or
  - Follow state mental health emergency plan
- If on-site and patient becomes agitated or threatening:
  - Involve other staff/security, keep door open, call 911, and maintain direct observation of patient
  - Assess environmental risks for harm to self or others, such as sharp objects as well as items that could be used for hanging
  - Refer to emergency psychiatric evaluation procedures on-site
  - Identify and follow any state reporting or other requirements

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NCCN Guidelines Version 2.2024
Survivorship: Anxiety, Depression, Trauma, and Distress

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SAFETY EVALUATION	ACUTE (URGENT/EMERGENT) INTERVENTIONS
DANGER FOR ABUSE OR NEGLECT OF VULNERABLE PERSON (CHILD, OLDER ADULT, 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, HCT, 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) (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 (SFAT-1)
  - Consider less-sedating antidepressants such as bupropion
  - Consider bright white light therapy[1]
  - Evidence for psychostimulant effects for depression and fatigue are limited and mixed (SFAT-5)
- Insomnia
  - See Sleep Disorders (SSD-1)

Caveats (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 ECG 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] (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 is unsuccessful 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…

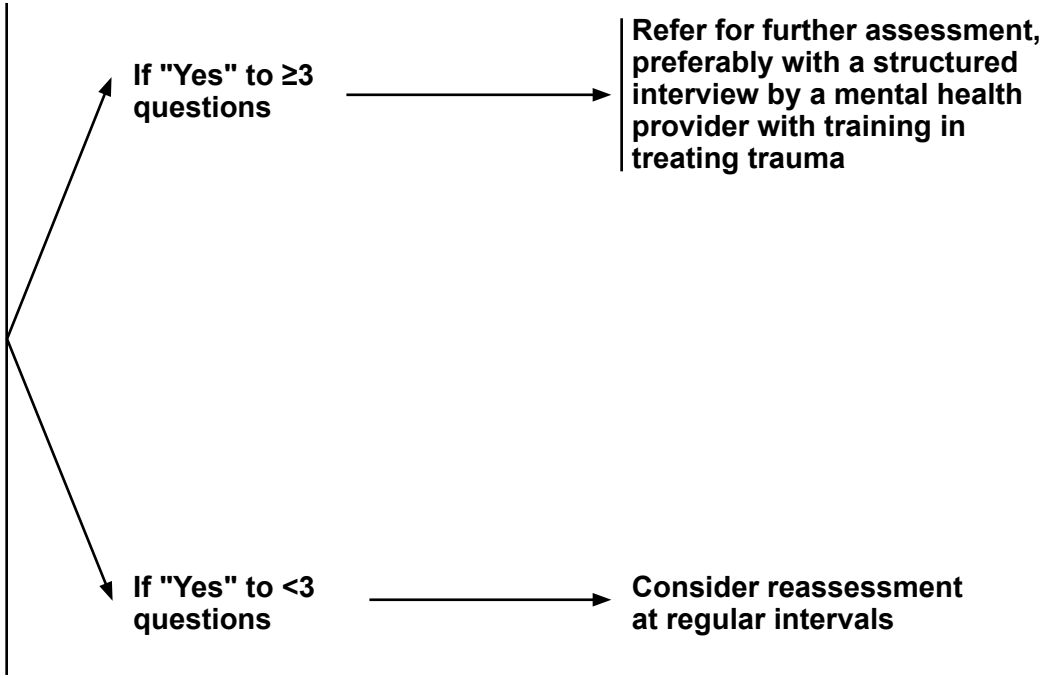
1. Had nightmares or thoughts about your cancer or treatment when you did not want to?
YES NO

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)[c]	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	30–60	30–120	0	0	1	0	0	2	0–1	1	CYP2D6 **moderate**	May improve neuropathic pain
Venlafaxine[g]	37.5 BID	37.5 BID – 125 TID	0	1	1	0	1	2	0	3	CYP2D6 mild	Safe with tamoxifen; may improve hot flashes; short half-life so withdrawal can occur more readily with short-acting preparation
Venlafaxine XR[g]	75	37.5–350	0	1	1	0	1	2	0–1	3	CYP2D6 mild	
Atypical agents												
Bupropion	100 BID	200–450 total per day, max 150/dose	0	0	2	0	1	1	0	0	CYP2D6 **strong**	Caution with sorafenib, tamoxifen; can be helpful for energizing; contraindicated if seizure history or bulimia; used for smoking cessation
Bupropion SR 12 hr	150	150–200 BID	0	0	1	0	1	1	0	0	CYP2D6 **strong**	
Bupropion XL 24 hr	150	150–450	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

† BID twice daily; TID, three times daily; 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 GI discomfort upon initiation or dose increase.

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Footnotes on (SANXDE-E 2 of 2)

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 older adults, those with renal or hepatic compromise, drug-sensitive survivors, or those with low BMI 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, and screening 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.**
- **Cognitive concerns should be systematically assessed using self report.**
- **Providers need to be aware that self-report of cognitive concerns, or the lack thereof, is not a surrogate for measurement of the presence or absence of impairment in cognitive function.**
- **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, delirium).**
- **These guidelines address cognitive function of survivors with non-CNS malignancies who did not have CNS-directed therapies.**

[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 (SPAIN-1)
  - Fatigue (SFAT-1)
  - Sleep disturbance (SSD-1)
- Comorbidities
- Use of alcohol and other agents that alter cognition
- New-onset vitamin deficiencies and endocrinopathies (eg, thyroid-stimulating hormone (TSH), B_1, B_{12}, D)

SPECIALIZED EVALUATION

Neuroimaging →

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 (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)
- Involve social support system to help with completion of tasks and activities
- For older adults also see the cognitive function section in 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 (SSD-1)
  - Fatigue (SFAT-1)
  - Contributing symptoms such as pain (SPAIN-1)
  - Medical comorbidities

→ **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/testing and recommendations[c]**
- **Cognitive rehabilitation**
  - **Occupational therapy[d]**
  - **Speech therapy**
  - **Neuropsychologist**
- **Psychotherapy**
- **Recommend routine physical activity (HL-1)**

SECOND-LINE INTERVENTIONS

- **Consider referral to a clinician with expertise in memory or cognitive concerns for further evaluation and care for survivors who continue to have cognitive problems after rehabilitation**
- **Consider trial use of medications (methylphenidate, modafinil, or donepezil)[e]**

[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, immunotherapy, 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 their 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.**
  - **Assessment and communication regarding fatigue and anticipated recovery after treatment should be done periodically.**
- **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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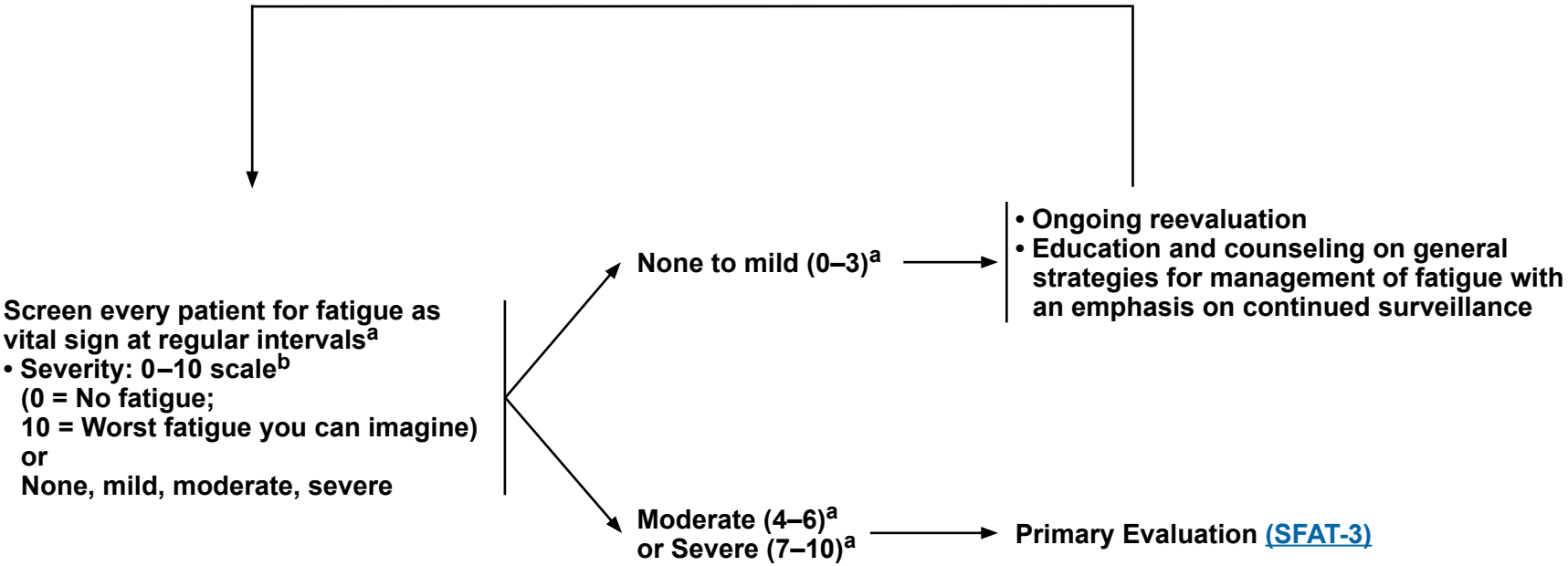
SCREENING



[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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Survivorship: Fatigue

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

EVALUATION

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 use disorder
    - ◊ Organ dysfunction[c]
    - ◊ Infection
    - ◊ Anemia
    - ◊ Arthritis
  - Prescribed or OTC medications (eg, sleep aids, pain medications, antiemetics)
  - Emotional distress- screen for anxiety and depression (SANXDE-1)
  - Sleep disturbance (eg, insomnia, sleep apnea, vasomotor symptoms, restless legs syndrome [RLS]) (SSD-1)
  - Pain (SPAIN-1)
  - Nutritional issues
    - ◊ Weight/caloric intake changes (SNWM-1)
  - Deconditioning/loss of muscle mass
  - Physical inactivity or sedentary behavior

→

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 (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]

→ **Treatment of Contributing Factors (SFAT-4)**

[c] Cardiac, endocrine (eg, hypothyroidism, hypogonadism, adrenal insufficiency), GI, 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 (SPAIN-1)**
  - **Emotional distress (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 (SSD-1)**
  - **Nutritional deficit/imbalance**
  - **Comorbidities**

→ **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) (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 ACSM
  - 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 (CBT-I) (category 1) (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 if other interventions are unsuccessful

[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 1250–10,000 lux is most frequently self-administered in the early morning for 30–40 minutes. Timing needs to be adjusted for those who sleep during the day. Xiao P, et al. J Pain Symptom Manage 2022;63:e188-e202.
[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. Fungal infection and papilloma may occur. Pitting can be absent due to progressive deposition of fat and fibrosis, which is the hallmark of later stage lymphedema.**

[a] National Cancer Institute Lymphedema (PDQ)–Patient Version https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema
[b] Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology 2020;53:3-19. https://pubmed.ncbi.nlm.nih.gov/32521126/

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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. Approximately 3 in 4 cases of lymphedema are diagnosed within 3 years 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. It can impact any area of the body (eg, arms, legs, face, trunk, groin).
- 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 function and thickening of the skin may occur in later stages.[a]
- Survivors who had surgery, radiation, or chemoradiation to the axillary, supraclavicular, cervical, or pelvic 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.
- BMI ≥30 kg/m^2, localized infection, increased number of nodes removed, and higher initial extent of disease raise the risk of lymphedema development.
- If possible, 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 and early referral are key for optimal lymphedema management because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment. Therefore, survivors at risk for lymphedema should be regularly screened for lymphedema by symptom assessment, clinical exam, and, if available, bioimpedance spectroscopy. Patients should be educated about early symptoms and signs of lymphedema including fullness, tightness, heaviness, and pain.
- Lymphedema may cause or exacerbate psychological distress (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, the panel recommends medical procedures such as venipuncture and blood pressure measurements be done on the non–at-risk limb; however, if necessary, procedures may be done using the at-risk limb.[h] More research is needed to determine the effect of these procedures on the risk of lymphedema.

Footnotes on SLYMPH-2A

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FOOTNOTES FOR SLYMPH-2

[a] National Cancer Institute Lymphedema (PDQ)–Patient Version https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema
[c] 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.
[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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Survivorship: Lymphedema

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SURVIVOR AT RISK FOR LYMPHEDEMA

Survivor at risk for lymphedema

SCREENING

- Inquire at regular intervals about:
  - Swelling or feeling of heaviness, fatigue, or fullness
  - Frequency and severity of swelling
  - Swelling, tightness, or uncomfortable sensation that interferes with daily activities
  - Pain/discomfort
  - Range of motion and mobility (ie, bending, stretching, flexibility)
  - Strength
- Perform clinical examination, which may include, but is not limited to:
  - Range of motion
  - Muscle performance
  - Circulation
  - Sensation
  - Hemodynamic functioning
  - Functional mobility
  - If available, obtain objective measurements to identify early signs of lymphedema; tools may include bioimpedance spectroscopy

WORKUP IF LYMPHEDEMA IS SUSPECTED

- Rule out recurrence of cancer, infection, or deep vein thrombosis (DVT) of an extremity
- Refer to a certified lymphedema therapist (if available)[i] for assessments such as:
  - Subjective symptoms/signs
  - Limb volume measurement[j]
  - Clinical examination, which may include, but is not limited to range of motion, muscle performance, circulation, sensation, hemodynamic monitoring, and functional mobility
- Lymphoscintigraphy, if clinically indicated
- Assess distress (SANXDE-1)

TREATMENT[k]

- Survivor lymphedema education, including self-care management, skin care, and self-bandage (SLYMPH-A)
- Refer to certified lymphedema therapist (if available)[i] for consideration of the following:
  - Compression[l]
    - ◊ Fit for compression garments
    - ◊ Review use of garments
    - ◊ Pneumatic compression for ongoing home management
  - Progressive resistance training under supervision[m,n]
  - Manual lymphatic drainage[i,o]
- Refer to qualified therapist for range-of-motion exercises[p]
- For select patients, consider referral to a lymphedema surgeon, in consultation with a certified lymphedema therapist and/or physiatrist specializing in lymphedema

→ Surveillance (SLYMPH-4) or If no response, but persistent symptoms, consider reviewing adherence to treatment plan and/or self care management

Footnotes on (SLYMPH-3A)

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FOOTNOTES FOR LYMPHEDEMA TREATMENT (SLYMPH-3)

[i] Certified lymphedema therapists can be located using the following resource: https://www.clt-lana.org/therapists. NCCN recommends attention to evidence-based practice and specialized training for lymphedema management.

[j] If baseline measurement is not available, measure unaffected contralateral limb as a reference.

[k] Lymphedema Management: The Comprehensive Guide for Practitioners. Joachim Ernst Zuther, Steve Norton (Autoren) Buch | Hardcover 592 Seiten; 2017 | 4th New edition; Thieme Medical Publishers Inc (Verlag); 978-1-62623-433-8 (ISBN); Chapter 5.

[l] Compression garments should be prescribed. Optimally, they should be fitted and measured by a certified lymphedema therapist.

[m] 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.

[n] Aerobic exercise or other forms of physical activity as tolerated. See Principles of Physical Activity for Survivors with or At Risk for Lymphedema (SLYMPH-B).

[o] If a certified lymphedema therapist is not available, consider referral to appropriate provider for treatment.

[p] 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: ACSM [http://www.acsm.org/get-stay-certified] and APTA Oncology section [http://oncologypt.org].

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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 (SLYMPH-A)
- Continue treatment as clinically indicated (SLYMPH-3)
- Assess for distress (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, manual drainage, and range of motion exercise[c]**
  - **Consideration of compression garments, manual lymphatic drainage, and pneumatic compression for ongoing home management**
- **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] (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 (SLYMPH-B).**
    - ◊ **Water exercise under supervision may be an option to consider after assessing any skin integrity and/or incision issues, although evidence that water exercise helps decrease lymphedema symptoms is limited.[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 (SIMIN-2).
[b] For a complete list of lymphedema risk reduction practices, see the Position Statement from the National Lymphedema Network: https://lymphnet.org/position-papers.
[c] Limb elevation can be used as an option for early-stage lymphedema for short-term improvement, but data are limited.

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.
[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, Dunberger G, et al. 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 in consultation with a certified lymphedema therapist and/or physiatrist specializing in lymphedema management. Avoid exercise in the setting of an acute injury or infection of the affected area.**
- **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 (ACSM [http://www.acsm.org/get-stay-certified] or APTA Oncology section [http://oncologypt.org]).

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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 pain syndrome should be identified if possible.**
- **Conduct a discussion with the patient and caregivers regarding realistic treatment goals, including improvement in function, side effects of pain regimen and, if on opioids, safe opioid use, as well as pain relief.**
- **Non-cancer pain in cancer survivors should be treated congruent with pain diagnosis, with opioids remaining the last resort. In addition to non-cancer–related pain, differential diagnosis should include cancer recurrence or progressive disease. Consider referring to primary care service for management of non-cancer pain.**
- **Use a multimodality approach to pain management if those resources are available.**
- **Non-opioid adjuvant analgesics 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.**
  - **Hypnosis,[a] meditation, acupuncture, cognitive restructuring, and behavioral activation can be considered to control pain and maximize function.**
- **Opioid treatment is sometimes necessary, and the lowest appropriate dose should be used for the shortest amount of time possible.**
- **Psychological support of the survivor with chronic pain is necessary, and referral to psychosocial services should be considered for survivors in distress (SANXDE-1).**
- **Consider referral to a specialist for survivors who might benefit from further pain interventions. This could include referral to interventional pain, physical medicine and rehabilitation, palliative care, pain specialist, urology, gynecology, orthopedic surgery, gastroenterology, or other appropriate consultants.**
  - **If these resources are available, consider referral as early as possible during the course of treatment planning.**
- **Opioids and pregnancy:**
  - **Ensure appropriate opioid prescribing and screening for opioid use disorder (OUD) for survivors of childbearing potential.**
  - **If a survivor on chronic opioids is pregnant or wants to become pregnant, do not stop opioids abruptly but coordinate further pain management with the obstetrician. If the survivor has OUD and takes buprenorphine for addiction and/or pain, provide access to addiction services without stopping buprenorphine. OUD can cause preterm birth, stillbirth, and neonatal abstinence syndrome.**
- **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.**

[a] Thompson T, Terhune DB, Oram C, et al. The effectiveness of hypnosis for pain relief: A systematic review and meta-analysis of 85 controlled experimental trials. Neurosci Biobehav Rev 2019;99:298-310.

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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, risks including risk of psychological and/or physical dependence and addiction, safe storage, and disposal.**
- **Consider prescribing naloxone and educate the patient and the caregivers on its use. Instruct caregivers to call 911 Emergency Service if naloxone is administered.**
- **Functional outcomes are important measures for patients on opioid therapy. The expected outcome (ie, improvement in function and/or pain) and terms of monitoring for outcomes, adherence, and safety should be clearly discussed with survivors and caregivers, agreed upon, and documented upon initiation and continuation of chronic therapy. Consider establishing pain treatment agreements/contracts in consultation with state and/or institutional requirements. Pain treatment agreements can be a useful tool in the overall strategy to manage opioid use and long-term pain in survivors[b].**
- **Re-evaluate the effectiveness, safety, and necessity of opioids at regular intervals.**
  - **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 (see PAIN-G 3 of 13 in the NCCN Guidelines for Adult Cancer Pain).**
- **Address medical-related issues due to chronic or high-dose opioids.**
  - **Endocrine/hypopituitary abnormalities**
    - ◊ **Testosterone deficiency**
  - **Manage opioid adverse effects (ie, constipation, nausea, pruritus, delirium, motor and cognitive impairment, respiratory depression, sedation) (see PAIN-H in the NCCN Guidelines for Adult Cancer Pain).**
- **Monitor for aberrant drug-taking behaviors[c] and for signs of substance use disorder (see PAIN-G 6 of 13 in the NCCN Guidelines for Adult Cancer Pain).**
  - **If there is evidence of aberrant opioid use, verbalize concerns to the survivor and refer as early as possible to pain specialist, 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.**
- **If opioids are indicated, advocacy to ensure access to the appropriate opioid regimen may be needed to address possible insurance, pharmacy, and other barriers as well as survivors' and caregivers' concerns about addiction.**

[b] Chou R, et al. J Pain 2009;10:113-130.
[c] Aberrant behaviors may include family member using drugs prescribed to the survivor.

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Survivorship: Pain

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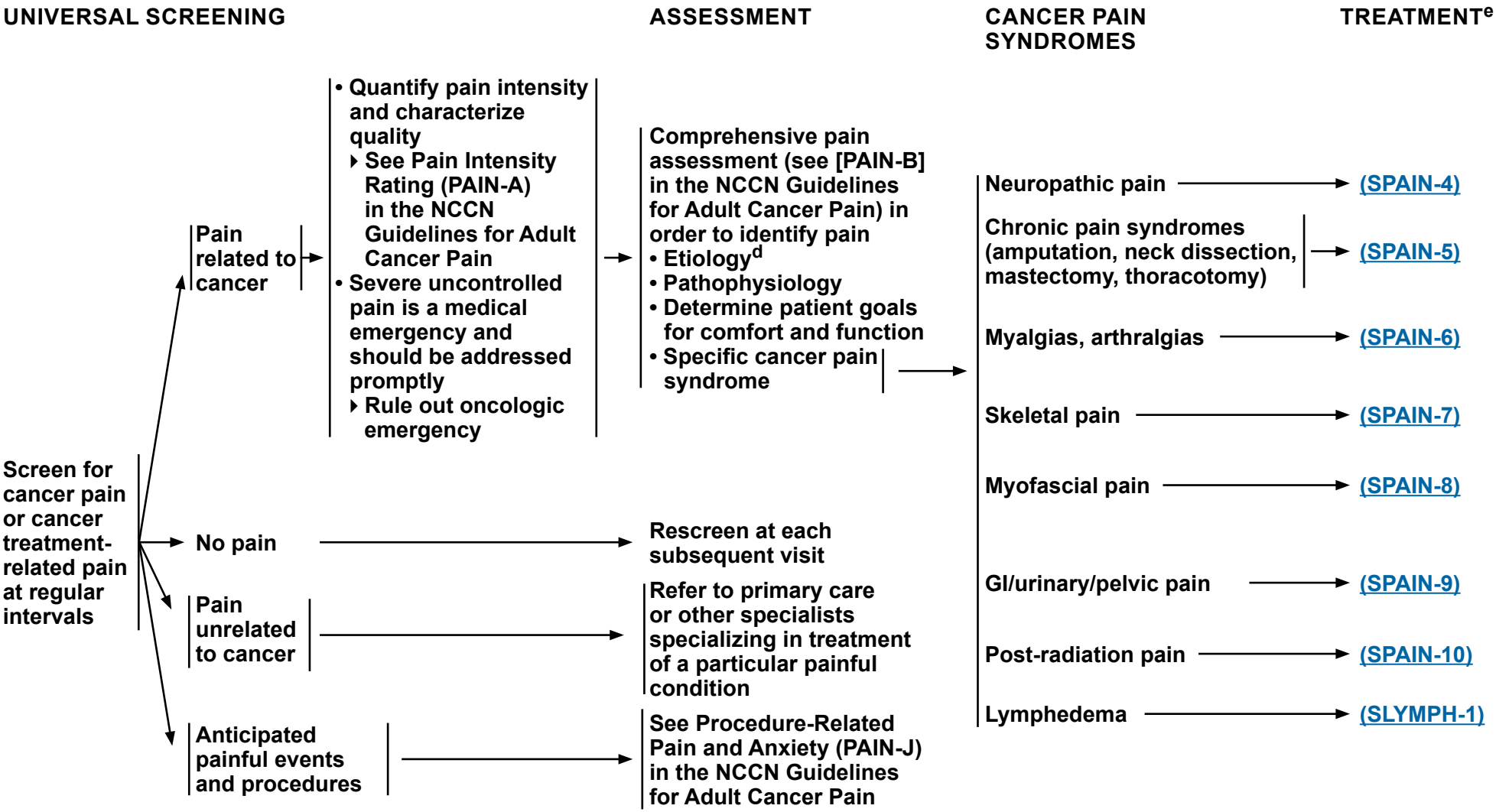

[d] Referral to PCP for non-cancer treatment-related workup and pain management (ie, rheumatoid arthritis) and consider the possibility of pain due to cancer recurrence.
[e] General Principles of Pain Management (SPAIN-1).

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CANCER PAIN SYNDROME	TREATMENT
Neuropathic pain[f] • Paresthesias (tingling or prickling) • Shooting, "electrical" • Numbness • Allodynia (pain with non-painful stimulus)	• General measures: ▸ Pharmacologic ◊ Non-opioid/Adjuvant analgesics (See [PAIN-E] in the NCCN Guidelines for Adult Cancer Pain) – Antidepressants: SNRIs (including duloxetine[g], TCAs, anticonvulsants ◊ Topicals – Patches (ie, lidoderm, capsaicin) – Creams/gels: Diclofenac topical gel – Compounded creams (eg, combinations of lidocaine, baclofen, ketamine, and amitriptyline) ▸ Non-pharmacologic ◊ CBT and psychosocial support (See [PAIN-C] in the NCCN Guidelines for Adult Cancer Pain) ◊ Physical modalities – Heat – Ice – Acupuncture – Transcutaneous electrical nerve stimulation (TENS) unit • For moderate or severe pain, opioids and dual-action opioid agonist/noradrenaline reuptake inhibitor[h,i] See (PAIN-3, PAIN-4, and PAIN-5) in the NCCN Guidelines for Adult Cancer Pain • Consider referral to pain management services, interventional specialist,[j] physical therapy, physical medicine and rehabilitation, integrative services, and/or palliative care as appropriate

[f] Also see NCCN Guidelines for Adult Cancer Pain and Loprinzi CL, et al. J Clin Oncol 2020;38:3325-3348.
[g] Duloxetine has the most evidence for treating neuropathic pain.
[h] Principles of Opioid Use in Long-Term Survivors (SPAIN-2).
[i] Initiating opioids in cancer survivors should be carefully considered if other interventions are unsuccessful.
[j] Scrambler therapy can be considered. Loprinzi C, et al. Support Care Cancer 2020;28:1183-1197.

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.

CANCER PAIN SYNDROME

Chronic pain syndrome (amputation, neck dissection, mastectomy, thoracotomy)

TREATMENT

- **General measures:**
  - **Non-opioids/Adjuvant analgesics**
    See (PAIN-E) in the NCCN Guidelines for Adult Cancer Pain
  - **Psychosocial support and behavioral interventions**
    See (PAIN-C) in the NCCN Guidelines for Adult Cancer Pain
- **For moderate to severe pain:**
  - **Opioids[h,i]**
    See (PAIN-3, PAIN-4, and PAIN-5) in the NCCN Guidelines for Adult Cancer Pain
- **Consider referral to pain management services, interventional specialist, orthopedic services, physical therapy, physical medicine and rehabilitation, integrative services, and/or palliative care as appropriate**

Specific chronic pain syndromes[k]

ADDITIONAL INTERVENTIONS

- **For post-amputation syndrome:**
  - **Physical therapy for desensitization**
    - **◊ Consider mirror therapy**
  - **Cognitive therapy**
  - **Upper extremities:**
    - **◊ Consider stellate ganglion block**
  - **Lower extremities:**
    - **◊ Consider lumbar sympathetic block**
  - **Neuromas:**
    - **◊ Consider phenol/alcohol block**
- **For post-radical neck dissection syndrome:**
  - **Physical therapy for stretching, range of motion**
  - **Myofascial release**
  - **Soft tissue massage**
  - **Trigger point injections**
  - **Possible botulinum toxin injection**
- **For post-mastectomy or post-thoracotomy syndrome:**
  - **Physical therapy or structured exercise**
  - **Intercostal nerve block**
  - **TENS unit**
  - **Possible botulinum toxin injection**

[h] Principles of Opioid Use in Long-Term Survivors (SPAIN-2).
[i] Initiating opioids in cancer survivors should be carefully considered if other interventions are unsuccessful.
[k] 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[l] ▸ Massage ▸ Acupuncture (category 1 for AI-induced arthralgia) ▸ Yoga • Pharmacologic[m] ▸ 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

[l] 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.
[m] Consider switching to an alternative AI or tamoxifen for AI-induced arthralgia.

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.

CANCER PAIN SYNDROME

Skeletal pain[n] →

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[h,i]**
    - ◊ **Bracing (ie, thoracolumbar sacral orthosis [TLSO], Jewett brace)**
    - ◊ **Limited bed rest**
    - ◊ **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[h]**
  - **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[h]**

[h] Principles of Opioid Use in Long-Term Survivors (SPAIN-2).
[i] Initiating opioids in cancer survivors should be carefully considered if other interventions are unsuccessful.
[n] For skeletal metastases and/or bone pain, see (PAIN-D) in 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[l] ▸ 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

[l] 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
GI/urinary/pelvic pain →	• For GI pain (abdominal pain/cramping): ▸ Adequate hydration ▸ Consider referral to gastroenterologist ▸ Bowel regimen • For chronic pelvic pain[o]: ▸ 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: (SSH-2) ▸ Consider referral to gynecologist or sexual health specialist • For refractory GI/urinary/pelvic pain: ▸ Consider referral to pain management services, interventional specialist, physical therapy, physical medicine and rehabilitation, and/or palliative care

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

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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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PRINCIPLES OF MENOPAUSE SYMPTOM MANAGEMENT IN FEMALE SURVIVORS[a]

Menopause

- Many survivors may experience symptoms whether or not they have ovarian function.
- In 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 premenopausal 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 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 should be counseled on the need for contraception to prevent unintended pregnancy if they do not meet the definition of menopause and if their sexual activity could result in pregnancy.
  - 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

Treatment Options for Vasomotor Symptoms (SHRS-4)

- Non-hormonal options
  - Prescription alternatives (SHRS-A)
  - OTC options
  - Integrative therapies
  - Lifestyle modifications (HL-1)
- Hormonal therapies (relatively contraindicated in survivors of hormonally mediated cancers; use with caution in those with increased genetic cancer risk) (SHRS-B)
  - Combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors without a uterus)
  - Survivors often use herbal supplements for vasomotor symptom management. However, some supplements may interfere with hormonal cancer treatments, and routine use of supplements is not recommended (SSUP-1). Providers should encourage survivors to discuss such therapies prior to use.

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF MANAGEMENT OF HORMONAL SYMPTOMS IN MALE SURVIVORS[a]

- **Survivors who have received RT, 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.**
- **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 those who had pre-existing hypogonadism is controversial and should be coordinated with the patient's PCP (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.**
- **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**
  - **CVD[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**

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.
[b] ADT may increase cardiovascular morbidity and mortality, notably in the first 6 months of therapy and in individuals 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 individuals 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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PRINCIPLES OF MANAGEMENT OF HORMONAL SYMPTOMS IN MALE SURVIVORS[a]

Treatment Options for Vasomotor Symptoms (SHRS-6)

- **Non-hormonal options**
  - **Prescription alternatives (SHRS-A)**
  - **OTC options**
  - **Integrative therapies**
  - **Lifestyle modifications (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 individuals with carcinoma of the breast or known or suspected prostate cancer**
  - **Medroxyprogesterone acetate (a progestin)**
  - **Cyproterone acetate (an antiandrogen)**
  - **Estrogen (eg, diethylstilbestrol)**
  - **Survivors often use herbal supplements for vasomotor symptom management. However, some supplements may interfere with hormonal cancer treatments, and routine use of supplements is not recommended (SSUP-1). Providers should encourage survivors to discuss such therapies prior to use.**

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

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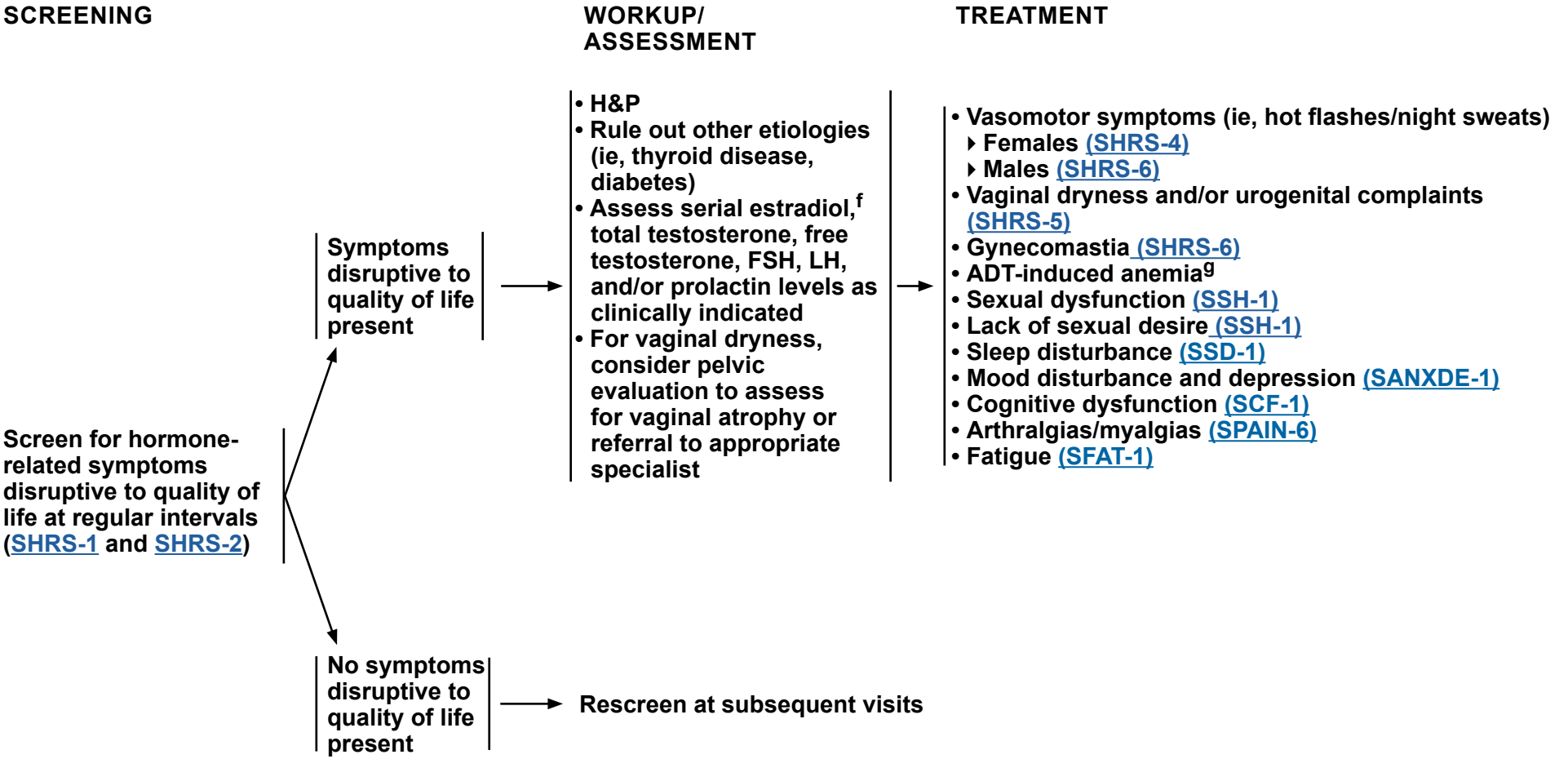

[f] For peri- or premenopausal survivors who have become amenorrheic and later develop bleeding, serial estradiol levels can be useful to determine return of ovarian function. Other markers including FSH, AMH, and inhibin may provide additional information on ovarian status in cancer survivors with prior 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[a]	**• 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 survivor has obesity or overweight (SNWM-1)** **‣ Acupuncture** **‣ Exercise/physical activity (SPA-1)** **‣ Lifestyle modifications[m] (HL-1)** **‣ Integrative therapies including CBT, yoga, and hypnosis** **• If no response after 2 or 3 lines of therapy, consider referral to specialists as appropriate**

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

[h] Principles of Menopausal Hormone Therapy (MHT) Use In Survivors (Females) (SHRS-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] Non-Hormonal Pharmacologic Treatments and Dosing (SHRS-A).

[k] Lower doses of antidepressants are often effective if the intent is to treat hot flashes (SHRS-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 (Discussion).

[m] Drinking alcohol may cause hot flashes. 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] dehydroepiandrosterone [DHEA][r]) • Consider referral to appropriate specialist for management • For vaginal pain or discomfort, see SSH-2
Urogenital complaints (females)[a]	• Local estrogen treatment[p] • Referral to appropriate specialist for management

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.
[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[a]	• **Modification to ADT (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[t]** ◊ **Venlafaxine** ◊ **Gabapentin** • **Non-pharmacologic treatments[u]** ‣ **Acupuncture** ‣ **Exercise/physical activity (SPA-1)** ‣ **Lifestyle modifications[m] (HL-1)** ‣ **CBT** ‣ **Weight loss if survivor has obesity or overweight (SNWM-1)** • **If no response after 2 or 3 lines of therapy, consider referral to specialists as appropriate**
Gynecomastia	• **Prophylactic radiation (must be delivered prior to development of breast tissues)** • **Tamoxifen** • **Reduction mammoplasty**

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

[m] Drinking alcohol may cause hot flashes. Individual responses to alcohol may vary. If alcohol is a trigger, consider limiting intake.

[s] Testosterone is contraindicated in individuals with carcinoma of the breast or known or suspected prostate cancer.

[t] Non-Hormonal Pharmacologic Treatments and Dosing for Vasomotor Symptoms (SHRS-A).

[u] 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 (Discussion).

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NON-HORMONAL PHARMACOLOGIC TREATMENTS AND DOSING FOR VASOMOTOR SYMPTOMS[a]

Class	Drug	Commonly Used Daily Dose for Management 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 an 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-convulsants	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[1]	5–10 mg	Start with 2.5–5 mg BID, typically used for overactive bladder and may cause urinary retention along with other anticholinergic side effects
Selective neurokinin-3 (NK3) receptor antagonist	Fezolinetant	45 mg PO once daily with or without food	• An FDA-approved alternative to hormones for the treatment of moderate to severe vasomotor symptoms due to menopause. • Side effects: Risk for elevated LFT's. Perform LFTs prior to initiation. • In the original trials, patients with breast cancer were excluded.

Footnotes on SHRS-A 2 of 2
References on SHRS-A 2 of 2

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FOOTNOTES AND REFERENCES FOR SHRS-A 1 OF 2

Footnotes

[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.

References

[1] Leon-Ferre RA, et al. JNCI Cancer Spectr 2019;4:pkz088.

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PRINCIPLES OF MENOPAUSAL HORMONE THERAPY (MHT) USE IN FEMALE SURVIVORS[a]

- **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 tissue-selective estrogen complex (TSEC) conjugated estrogens/bazedoxifene is FDA-approved for treating menopausal symptoms in healthy post-menopausal survivors.**
    - ◊ **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**

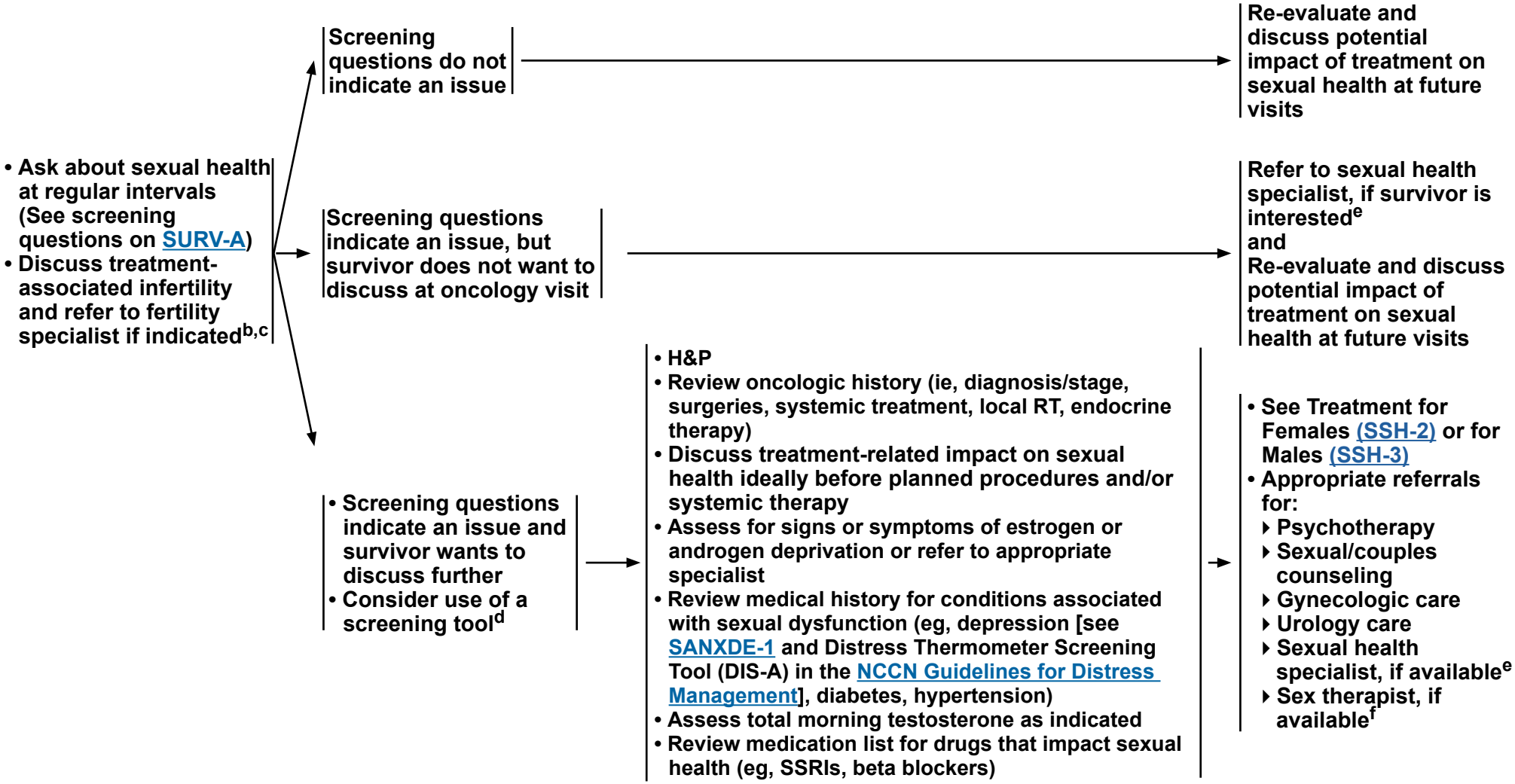
- **Caution in:**
  - **Survivors with coronary heart disease or hypertension**
  - **Survivors at increased genetic risk for cancers**
  - **Survivors who smoke, especially if >35 years**

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

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

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.

DIAGNOSTIC EVALUATION[a]



Footnotes on (SSH-1A)

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.

FOOTNOTES FOR SSH-1

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

[b] For information regarding fertility preservation for patients with cancer, see NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology and Oktay K, et al. J Clin Oncol 2018;36:1994-2001; Burns KC, et al. Cancer 2018;124:1867-1876; and Hampe ME, Rhoton-Vlasak AS. J Assist Reprod Genet 2020;37:717-729.

[c] Principles of Fertility (SF-1)

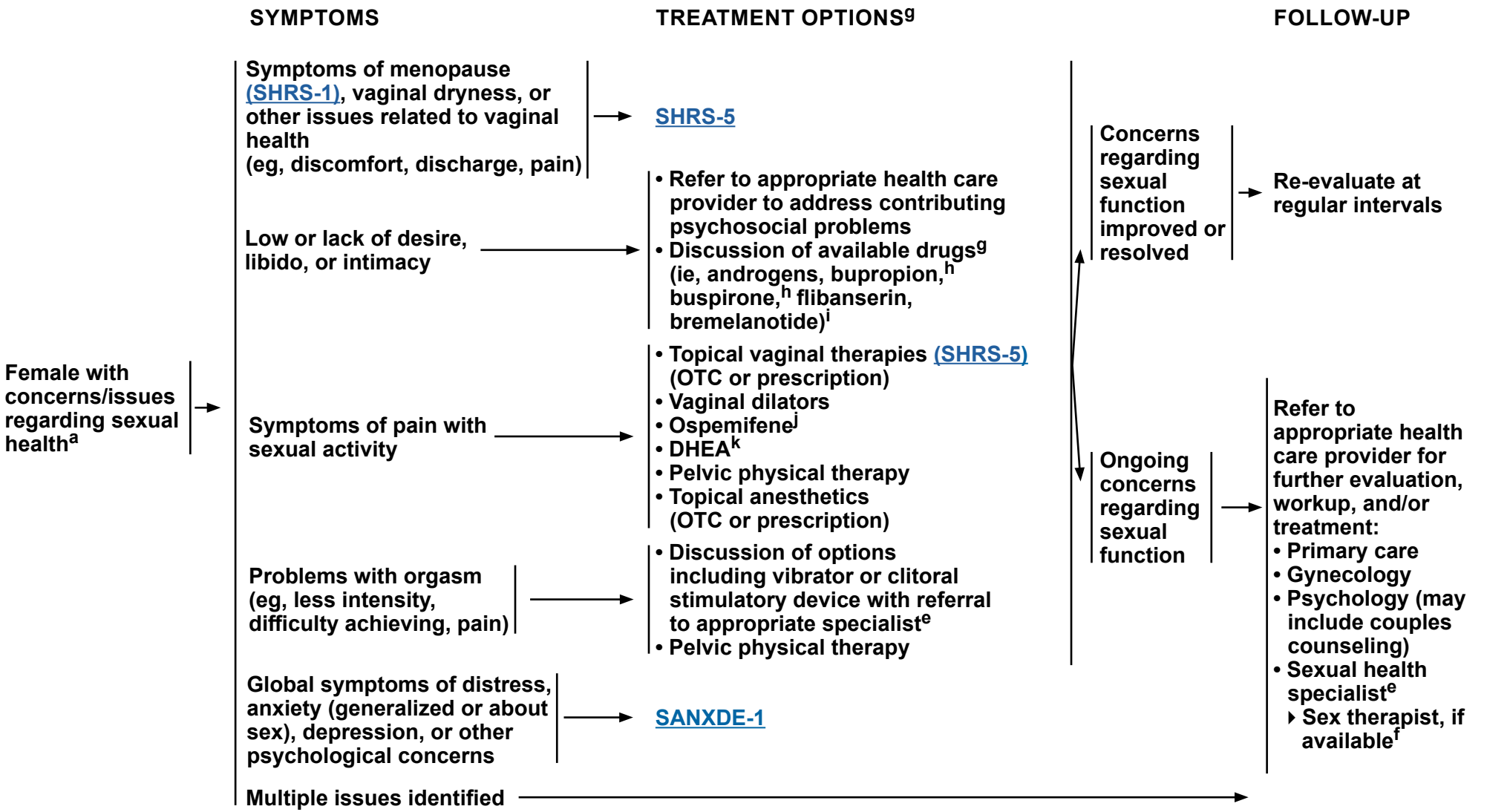
[d] There are a number of validated tools to assess sexual concerns in cancer survivors. Common tools that may be used include:

- Brief Symptom Checklist [Brief Sexual Symptom Checklist for Women (SSH-A)]
- Sexual Health Inventory for Men (SHIM) (SSH-B)
- Arizona Sexual Experience Scale
- Female Sexual Functioning Index (FSFI), including a breast-specific adaptation of the FSFI (http://www.fsfiquestionnaire.com/)
- PROMIS Sexual Function and Satisfaction Measure (SexFS)

[e] 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.

[f] Referral to a sex therapist certified by the American Association of Sexuality Educators, Counselors and Therapists (AASECT) (https://www.aasect.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.



Footnotes on (SSH-2A)

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.

FOOTNOTES FOR FEMALE WITH CONCERNS/ISSUES REGARDING SEXUAL FUNCTION

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

[e] 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.

[f] Referral to a sex therapist certified by the AASECT (https://www.aasect.org).

[g] 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.

[h] Bupropion and buspirone may be considered as off-label treatments for hypoactive sexual desire disorder, despite limited safety and efficacy data.

[i] There is a lack of data showing a benefit of sildenafil in female sexual arousal 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.

[j] Currently ospemifene is contraindicated in survivors with a history of estrogen-dependent cancers.

[k] DHEA should be used with caution in survivors with a history of estrogen-dependent cancers.

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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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Survivorship: Sexual Health

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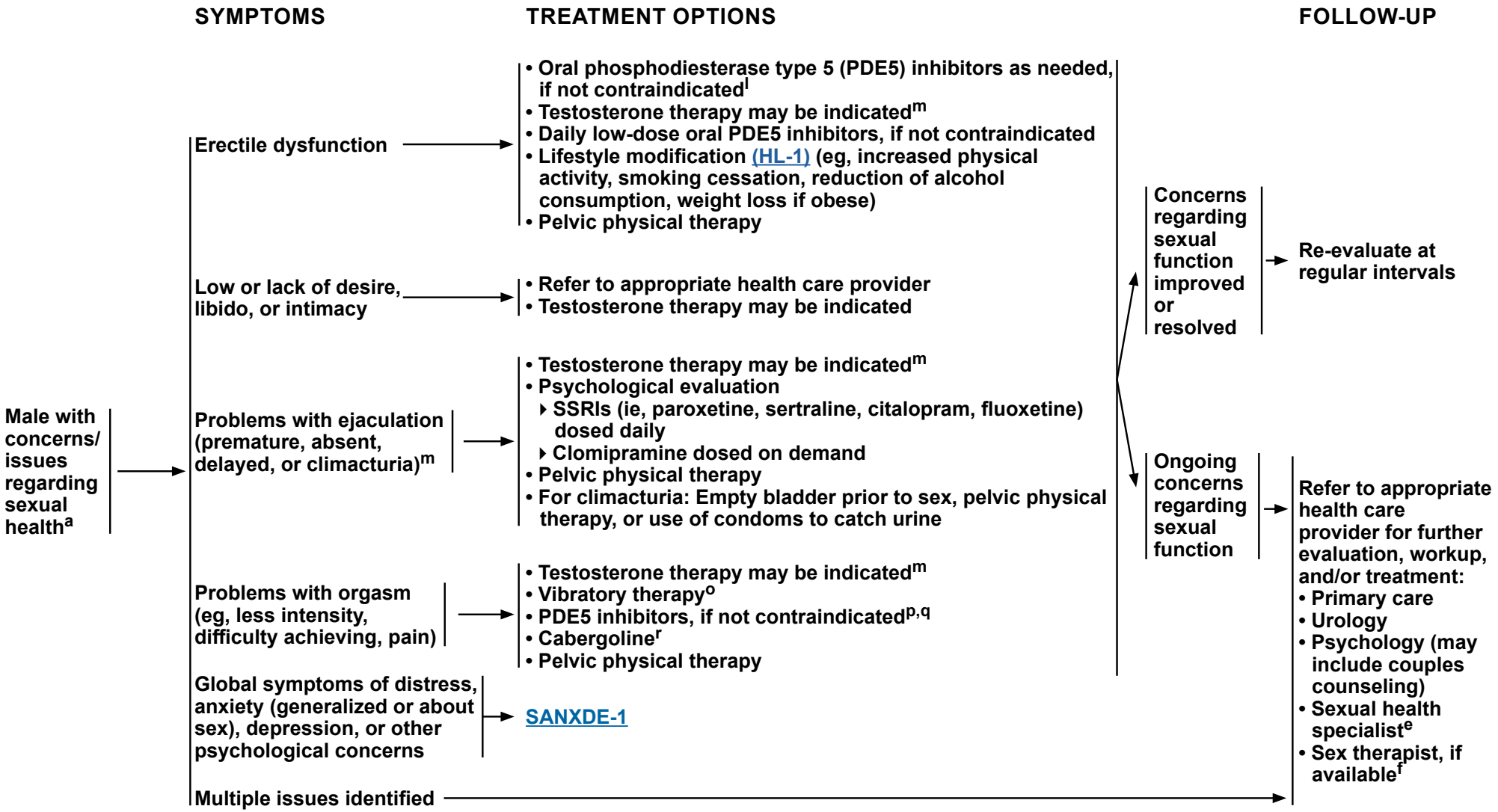

Footnotes on (SSH-3A)

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.

FOOTNOTES FOR SSH-3

[a] Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population, but should be followed for transgender and intersex survivors as applicable, with the involvement of the appropriate health care specialists.

[e] 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.

[f] Referral to a sex therapist certified by the AASECT (https://www.aasect.org/).

[l] Dosing should be titrated to optimal effect.

[m] If total morning testosterone <300 ng/dL (repeat second morning total testosterone and free testosterone, LH, and prolactin), then testosterone therapy may be indicated. 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). Exogenous testosterone therapy should not be prescribed to those who are currently trying to conceive. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility.

[n] Clavell-Hernández J, et al. Sex Med Rev 2018;6:124-134.

[o] Nelson CJ, et al. Urology 2007;69:552-555.

[p] Pavlovich CP, et al. BJU Int 2013;112:844-851.

[q] Montorsi F, et al. J Urol 2004;172:1036-1041. Erratum in: J Urol 2005;173:664.

[r] Hollander AB, et al. Sex Med 2016;4:e28-33.

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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.

BRIEF SEXUAL SYMPTOM CHECKLIST FOR WOMEN[a,b]

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

[a] 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.

[b] Sexual health and related concerns can be difficult for survivors to discuss with their providers. Examples of sexual health screeners have been provided to help facilitate a discussion regarding a survivor's symptoms and/or sexual health history.

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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.

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)[a,b]

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

[a] 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.

[b] Sexual health and related concerns can be difficult for survivors to discuss with their providers. Examples of sexual health screeners have been provided to help facilitate a discussion regarding a survivor's symptoms and/or sexual health history.

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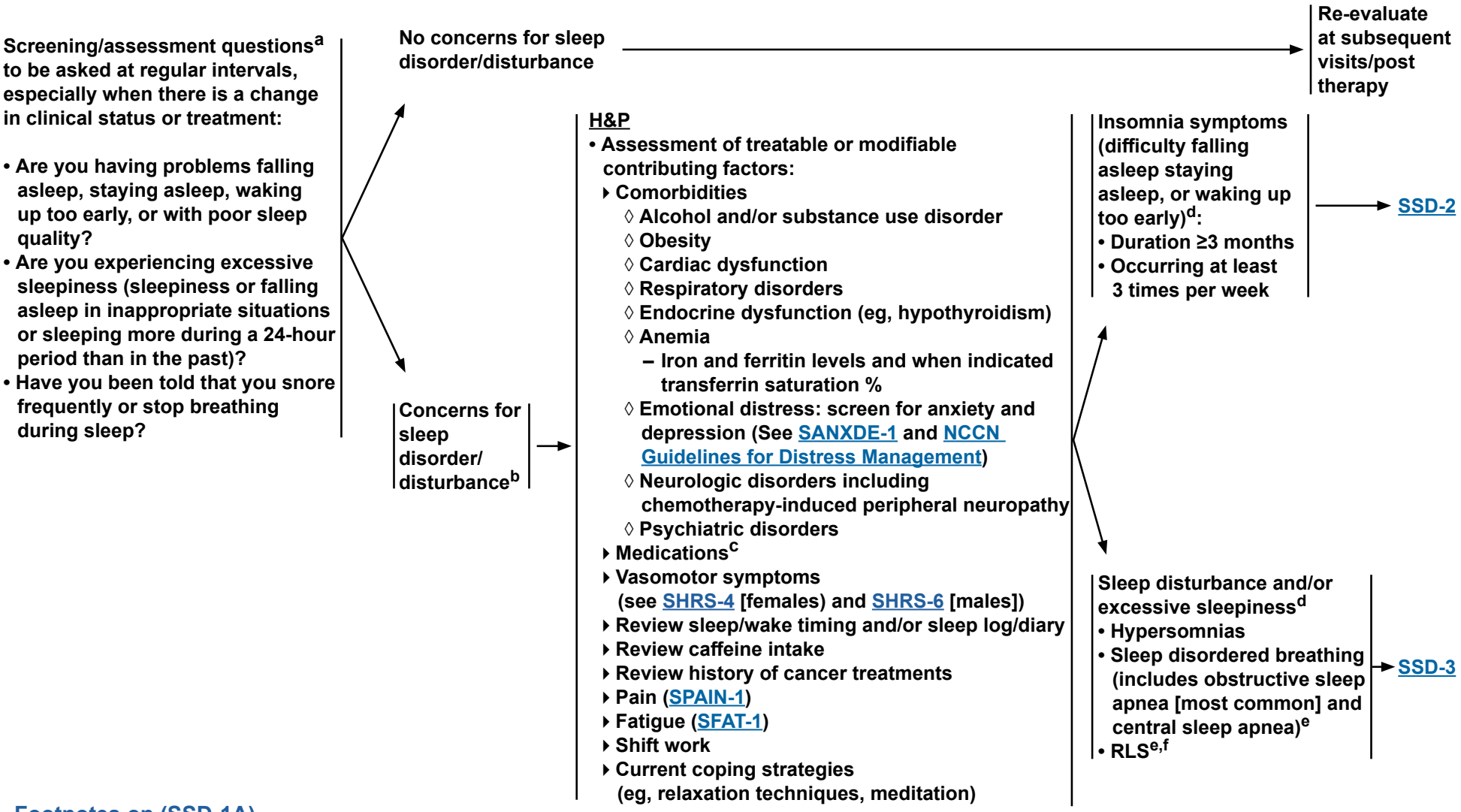
PRINCIPLES OF FERTILITY[1]

- **The risks of treatment-induced infertility should be discussed with all reproductive-aged survivors at the time of cancer diagnosis.**
- **Survivor-centered care is important. The survivor's goals regarding fertility and discussions regarding the risks of treatment-induced infertility should be discussed and documented in the medical chart.**
- **Prior to initiation of cancer treatments, available options for fertility preservation should be discussed and/or referrals made to the appropriate specialists for those patients wishing to preserve fertility.**
- **Fertility preservation procedures prior to cancer treatment are the most effective way to preserve fertility in cancer survivors.**
  - **Fertility preservation procedures include in vitro fertilization (IVF) with oocyte or embryo cryopreservation, ovarian tissue preservation, and sperm cryopreservation.**
  - **Data show that ovarian tissue cryopreservation is currently only about 40% successful. There is a much greater success with traditional IVF with oocyte or embryo cryopreservation.**
  - **In addition to fertility preservation procedures, gonadotropin-releasing hormone (GnRH) agonists should be offered during chemotherapy to breast cancer survivors in order to preserve ovarian function.**
- **If possible, reproductive organs should be shielded during RT.**
- **If survivors have a change in their cancer treatment, the impact of treatment on potential infertility should be discussed again and/or referrals made to the appropriate specialists.**
- **Once cancer treatment is complete, clinicians and survivors should not assume that the survivor is infertile, and survivors interested in fertility should be assessed by a fertility specialist.**
- **For survivors of breast cancer, pregnancy is considered safe and the hormonal environment associated with pregnancy is not thought to increase the risk of breast cancer recurrence. Prior breast cancer treatment does not increase the future risk of congenital malformations. General recommendations have traditionally been to wait until the survivor is disease free for 2 years before attempting to conceive, whether naturally or via assisted reproductive technologies, because of the higher risk of recurrence within that time.**
- **For additional information regarding fertility preservation for patients with cancer, see:**
  - **NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology**
  - **NCCN Guidelines for Breast Cancer**

[1] Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36:1994-2001.

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.

SCREENING



Footnotes on (SSD-1A)

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.

FOOTNOTES FOR SSD-1

[a] The following additional tools may be used for individual intensive screening to assess sleep quality: PSQI https://www.sleep.pitt.edu/instruments/#psqi; PROMIS SLEEP http://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=183&Itemid=992; and Epworth Sleepiness Scale, Johns MW. Sleep 1991;14:540-545.

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

[c] Medication review: Re-evaluate the need for persistent use of sleep aids, pain medications, antiemetics, stimulants, antidepressants, anti-psychotics, sedative/hypnotics, opioids, OTC sleep aids, or antihistamines.

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

[e] Note that sleep disordered breathing (eg, obstructive sleep apnea), RLS, circadian rhythm sleep wake disorders, and parasomnias may also present with symptoms of insomnia.

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

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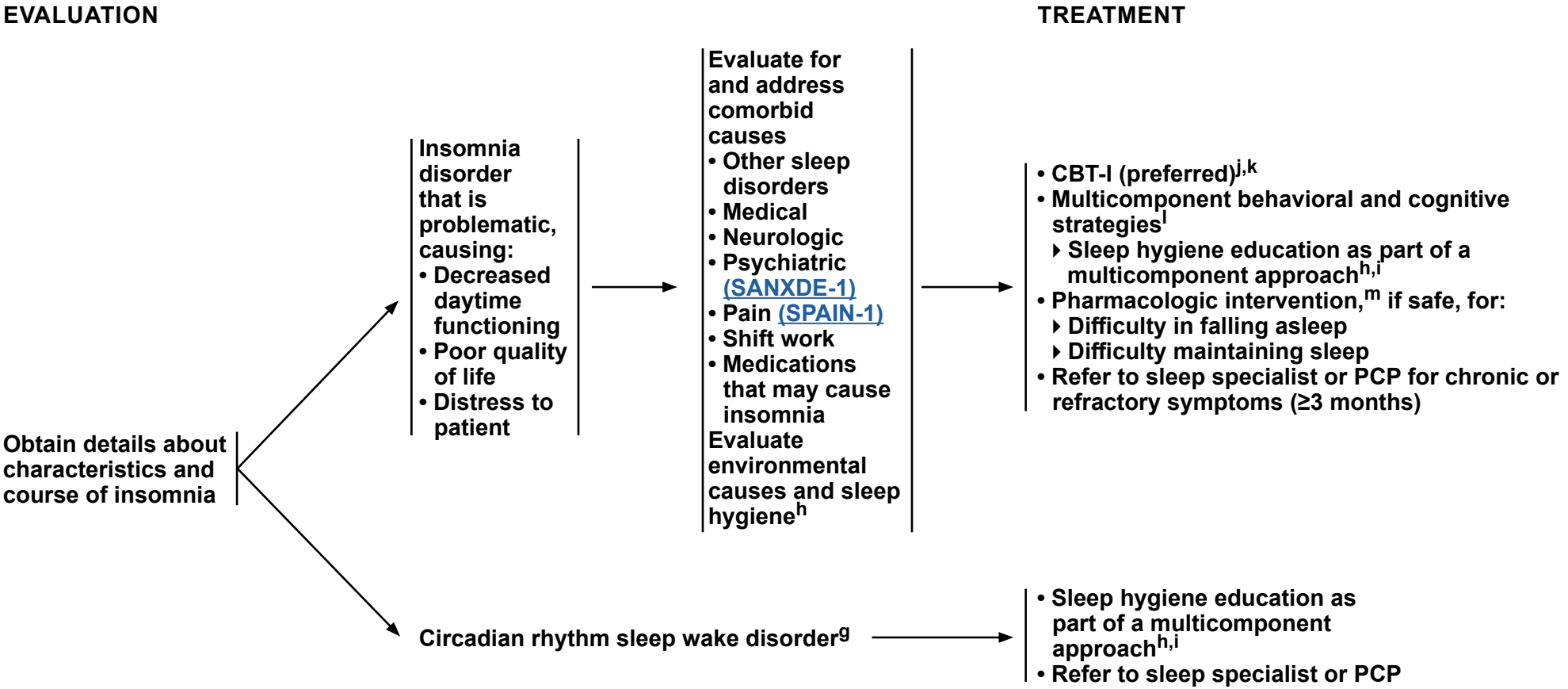

[g] Circadian rhythm sleep wake disorder: A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to an alteration of the circadian timing system or to a misalignment with the sleep-wake schedule required by an individual's physical environment or social/work schedules.
[h] General 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. Use of general sleep hygiene measures should not delay other interventions or referral to a specialist, especially if quality of life is impacted or if sleep problems (eg, insomnia) are severe. (Edinger JD, et al. J Clin Sleep Med 2021;17:255-262).
[j] Cognitive Behavioral Therapy for Insomnia (SSD-B).
[k] CBT-I is preferred over pharmacologic interventions as first-line therapy.
[l] Strategies such as tai chi and mindfulness therapy may be beneficial.
[m] Principles for Choosing an FDA-Approved Hypnotic (SSD-C).

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.

NCCN Guidelines Version 2.2024
Survivorship: Sleep Disorders

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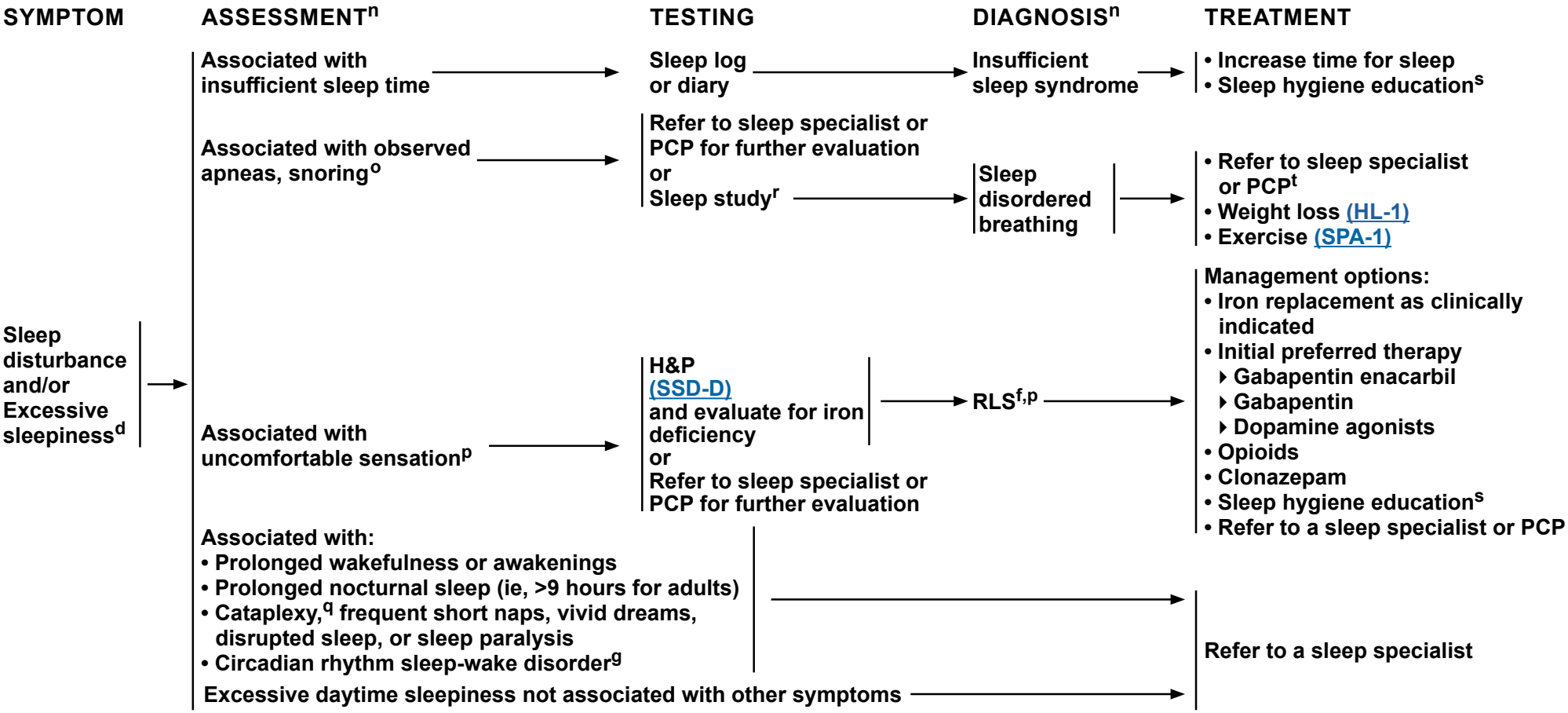

[d] In the differential diagnosis of insomnia or excessive sleepiness symptoms, consider parasomnias or circadian rhythm sleep wake disorders and referral to a sleep specialist.
[f] RLS is also known as Willis-Ekbom disease.
[g] Circadian rhythm sleep wake disorder: A chronic or recurrent pattern of 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.
[n] For other less frequent syndromes, refer to a sleep specialist.
[o] The following tools may be used to help identify individuals at high risk for obstructive sleep apneas: STOP Questionnaire (Chung F, et al. Anesthesiology 2008;108:812-821) and Berlin Questionnaire (https://www.ncbi.nlm.nih.gov/books/NBK424168/bin/appb-fm1.pdf).
[p] Essential Diagnostic Criteria for Restless Legs Syndrome (SSD-D).
[q] 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.
[r] Sleep studies can be performed as an in-laboratory polysomnography or as home sleep study. However, survivors with certain medical disorders (ie, cardiac, respiratory, neurologic), or currently on opiates for cancer-related pain, may not be good candidates for home sleep studies.
[s] General Sleep Hygiene Measures (SSD-A).
[t] The most common medical treatment fo sleep disordered breathing is continuous positive airway pressure (CPAP).

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.

GENERAL SLEEP HYGIENE[a,1,2,3]

- **Maintain a regular bedtime and waketime every day.**
- **Engage in regular physical activity in the morning and/or afternoon (SPA-1). Avoid moderate to strenuous physical activity within 3 hours of bed time.**
- **Exposure to daytime bright light, particularly in the morning.**
- **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).**
- **Avoid looking at the clock when awake during the night.**
- **If necessary, limit daytime sleep to 1 short nap per day in the afternoon (no longer than 30 min).**
- **Turn off electronics and light-emitting sources at bedtime.**

Other Sleep Interventions

- If survivor is not able to fall asleep within what feels like 20 minutes (survivor should not check the clock) or if they wake up in middle of night and can't fall back to sleep, consider using the following sleep strategy:
  - Get up, go to a different location, but stay in a darkened room and do non-stimulating activity like reading a relaxing non-stimulating book. Once survivor feels sleepy again they should try to go to bed. The goal is to help the body associate the bed with sleeping.
- Other sleep interventions include the use of:
  - Sleep apps, meditation apps, breathing exercises, and strategies to reduce worrying (ie, write a "to do" list or set aside "worry time" [eg, 10–15 mins] earlier in the day, not close to bedtime)

Footnote

[a] 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. Use of general sleep hygiene measures should not delay other interventions or referral to a specialist, especially if quality of life is impacted or if sleep problems (eg, insomnia) are severe (Edinger JD, et al. J Clin Sleep Med 2021;17:255-262).

References

[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, 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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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.

COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA (CBT-I)[a,b,1]

Strategy	Goal
CBT-I[2] or internet-based cognitive behavioral therapy for insomnia	Challenge survivor's maladaptive beliefs and misconceptions about sleep disturbances
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[c] • Maintaining a regular sleep schedule by keeping a standard bedtime and wake time every day
Relaxation training	• Reduce physiologic and cognitive arousal at bedtime • Techniques include progressive muscular relaxation, deep breathing, meditation, yoga, and biofeedback • Visualization

Footnotes

[a] The American Academy of Sleep Medicine (AASM) includes a strong recommendation for multicomponent CBT-I and conditional recommendations for stimulus control, sleep restriction, and relaxation therapy as single-component therapy options for the treatment of insomnia. Edinger JD, Arnedt JT, Bertisch SM, et al. J Clin Sleep Med 2021;17:255-262.

[b] There are paid and/or free guided, semi-guided, and unguided CBT-I digital resources available. See Survivorship Resources for Health Care Professionals and Survivors (SURV-B).

[c] Match total amount of time spent in bed to the actual amount of time spent sleeping (no less than 5 hours).

References

[1] Data from Bootzin RR and Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992;53(suppl):37-41.

[2] 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.

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.

PRINCIPLES FOR CHOOSING AN FDA-APPROVED HYPNOTIC AS SECOND-LINE THERAPY[a-f]:

- **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	+	+	+
Lemborexant	+	+	+
Daridorexant	+	+	+

[a] These agents should only be used after all other methods have been deemed unsuccessful. CBT-I is the preferred first-line treatment option (SSD-2).
[b] Data from the Physicians' Desk Reference ed 66). Montvale, NJ: PDR Network, LLC; 2012.
[c] Inform patients that taking hypnotic medications may cause complex sleep-related behaviors (eg, sleep driving, sleep eating).
[d] Other commonly used medications for insomnia include sedating medications such as antidepressants (eg, trazodone, mirtazapine), antihistamines, atypical anti-psychotics, other benzodiazepine receptor agonists, and nutritional/herbal supplements. 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. Trazodone is one of the most commonly used medications for insomnia, but due to paucity of evidence of its long-term efficacy and safety, it is not recommended for routine use (Kansagara D, et al. Ann Intern Med 2016;165:892; Sateia MJ, et al. J Clin Sleep Med 2017;13:307-349; Wilt TJ, et al. Ann Intern Med 2016;165:103-112).
[e] Most of these agents, with the exception of ramelteon, doxepin, suvorexant, and lemborexant are benzodiazepine receptor agonists and can be associated with dependence, misuse, and withdrawal. Assessment for the continued need of hypnotics is recommended every 1–3 months.
[f] Refer to package insert for specifics regarding potential for drug-drug interactions, side effects, risk of dependency, black box warnings, or other problems with these drugs.

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.

ESSENTIAL DIAGNOSTIC CRITERIA FOR RESTLESS LEGS SYNDROME[a]

- **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.**

RESTLESS LEGS 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.[b]**
  - **Consider referral to specialist for refractory symptoms** **(See NCCN Guidelines for Palliative Care)**
- **Consider modification of lifestyle factors and medications that can exacerbate RLS symptoms.[c]**

[a] 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.
[b] 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;87:2585-2593.
[c] Alcohol, nicotine, caffeine, centrally active antihistamines, SSRI, SNRI, and dopaminergic medications are associated with worsening of RLS symptoms.

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.

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 those who do not 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.[1]**
- **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 (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.**

[1] U.S. Department of Justice, Civil Rights Division; Americans with Disabilities Act (ADA). Guide to Disability Rights Laws. https://www.ada.gov/resources/disability-rights-guide/

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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 (SFAT-1)
    - ◊ Pain/neuropathy (SPAIN-1)
    - ◊ Musculoskeletal/neurologic issues (eg, joint/extremity mobility, deconditioning/loss of muscle mass, sensory neuropathy)
    - ◊ Cognitive dysfunction (SCF-1)
    - ◊ Anxiety, depression, distress (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 (SFAT-1)
  - Pain/neuropathy (SPAIN-1)
  - Cognitive dysfunction (SCF-1)
  - Anxiety, depression, distress (See SANXDE-1 and NCCN Guidelines for Distress Management)
  - Musculoskeletal/neurologic issues
  - Vision/hearing
- Treat comorbidities

→ Additional Interventions for Survivors (SWORK-3)

[a] Organ dysfunction resulting from cancer or cancer treatment that may most impact work includes cardiac (SCARDIO-1), pulmonary, and GI.
[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 policies
- Provide resources to understand options and communicate with employer (SURV-B 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
  - Patient navigator
- Pharmacologic intervention for underlying causal symptom(s) as indicated (SWORK-2)

→ Periodic re-evaluation (SWORK-2)

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ABBREVIATIONS

AASECT	American Association of Sexuality Educators, Counselors and Therapists
AASM	American Academy of Sleep Medicine
ACOG	American College of Obstetricians and Gynecologists
ACS	American Cancer Society
ACSM	American College of Sports Medicine
ADA	Americans with Disabilities Act
ADT	androgen deprivation therapy
ADL	activities of daily living
AI	aromatase inhibitor
AICR	American Institute for Cancer Research
AMH	anti-Müllerian hormone
AML	acute myeloid leukemia
APOS	American Psychosocial Oncology Society
APTA	American Physical Therapy Association
ASCO	American Society of Clinical Oncology
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CAR	chimeric antigen receptor
CBC	complete blood count
CBT	cognitive behavioral therapy
CBT-I	cognitive behavioral therapy for insomnia
CDAP	continuous positive airway pressure
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSO	Certified Specialists in Oncology Nutrition
CVD	cardiovascular disease
DTap/ Td	diptheria, tetanus, and acellular pertussis
DHEA	dehydroepiandrosterone
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ED	erectile dysfunction
FSFI	Female Sexual Functioning Index
FSH	follicle-stimulating hormone
GI	gastrointestinal
GnRH	gonadotropin releasing hormone
GVHD	graft-versus-host disease
H&P	history and physical
HBsAg	hepatitis B surface antigen
HCT	hematopoietic cell transplant
HepA	hepatitis A
HepB	hepatitis B
HD-IIV	High-dose inactivated influenza vaccine
Hib	haemophilus influenzae type b
HPV	human papillomavirus
IIV	inactivated influenza vaccine
IPV	inactivated polio vaccine
ISSWSH	International Society for the Study of Women's Sexual Health
IVIG	intravenous immunoglobulin
IVF	in vitro fertilization
LFT	liver function test
LGBT	lesbian, gay, bisexual, transgender, and queer
LH	luteinizing hormone
LLS	Leukemia and Lymphoma Society
LV	left ventricular
LVEF	left ventricular ejection fraction

ABBREVIATIONS

MCV4	quadrivalent meningocccal conjugate vaccine
MDD	major depressive disorder
MDS	myelodysplastic syndrome
MHT	menopausal hormone therapy
MMR	measles, mumps, rubella
MMSE	Mini-Mental State Examination
NCCS	National Coalition for Cancer Survivorship
NSAID	nonsteroidal anti-inflammatory drug
NK3	neurokinin-3
OCS	Office of Cancer Survivorship
OTC	over-the-counter
OUD	opioid use disorder
PCP	primary care physician
PCV	pneumococcal conjugate vaccine
PDE5	phosphodiesterase type 5
PDQ	Physician Data Query
PPSV	pneumococcal polysaccharide vaccine
PTSD	post-traumatic stress disorder
QTc	corrected QT interval
RIV	recombinant influenza vaccine
RIV3	recombinant trivalent influenza vaccine
RLS	restless legs syndrome
RZV	recombinant zoster vaccine
SBRT	stereotactic body radiation therapy
SexFS	Sexual Function and Satisfaction Measure
SHIM	sexual health inventory for men
SMART	specific, measurable, achievable, realistic, timebound
SNRI	serotonin-norepinephrine reuptake inhibitor
SPF	sun protection factor
SSRI	selective serotonin reuptake inhibitor
TBI	total body irradiation
TCA	tricyclic antidepressant
TENS	transcutaneous electrical nerve stimulation
TLSO	thoracolumbar sacral orthosis
TSEC	tissue-selective estrogen complex
TSH	thyroid-stimulating hormone
USDA	United States Department of Agriculture
UVA	ultraviolet A
UVB	ultraviolet B
WBC	white blood cell

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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NCCN Guidelines Version 2.2024
Survivorship

Discussion

This Discussion corresponds to the NCCN Guidelines for Survivorship. Last updated on December 9, 2024.

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Overview

The number of cancer survivors in the United States increased from approximately 3 million in 1971 to more than 18 million in 2022.[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 67% of survivors were ≥65 years of age in 2022.[3] In fact, an estimated 1 of every 5 persons >65 years is a cancer survivor. Only 5% are <40 years, and survivors of childhood cancer constitute between 0.5% and 3.0% of the survivor population.[4,5] 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 years ago, whereas 15% of survivors were diagnosed ≥20 years ago, and approximately 5% have survived ≥30 years.[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] The American Society of Clinical Oncology (ASCO) 2013 statement, "Achieving High-Quality Cancer Survivorship Care," cited a need for standardized, evidence-based practice guidelines for the management of treatment effects and health promotion of survivors.[7] ASCO, NCCN, the American Cancer Society (ACS), and other groups have worked in parallel 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, dietitian, gynecologist, urologist, infectious disease specialist, cardiologist, PCP, pediatric oncologist, psychologist, nutrition scientist, nurse, neurologist, epidemiologist, radiation oncologist, surgeon, 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: cancer AND survivorship. 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; Clinical Trial, Phase IV; Guideline; 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 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 at www.NCCN.org.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[15] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

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 living long-term with chronic, incurable cancer.[16] This group includes those with unresectable or metastatic disease, who are usually receiving systemic therapy either continuously or intermittently and who often have a life expectancy measured in years. Estimates suggest that >623,000 individuals are living with metastatic cancer in the United States.[16] 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),[17] many of the recommendations in these guidelines are relevant to this population (eg, those around fatigue, anxiety, depression, healthy lifestyles). 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 by Cancer Type, 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).

The NCCN Guidelines for Survivorship focus on preventive health issues including healthy lifestyle behaviors, immunizations and prevention of infection, and cardiovascular disease (CVD) risk assessment and modification. The Guidelines also focus on several common issues of survivors: 1) anthracycline-induced cardiac toxicity; 2) anxiety, depression, trauma, and distress; 3) cognitive function; 4) fatigue; 5) lymphedema; 6) hormone-related symptoms; 7) pain; 8) sexual dysfunction and fertility; 9) sleep disorders; and 10) employment and return to work.

Cancer Survivors

The National Institutes of Health (NIH) adapted the definition of a cancer survivor from the National Coalition for Cancer Survivorship and states: "An individual is considered a cancer survivor from the time of diagnosis, through the balance of their 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."[18]

The Effects of Cancer and Its Treatment

For some survivors, the consequences of cancer are minimal; these patients can return to a relatively "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.[19,20] 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.[21,22] Other studies have similarly found that most survivors enjoy a high quality of life without a large number of cancer-related symptoms.[23,24]

However, many survivors do experience physical and/or psychosocial effects of cancer and its treatment.[25-28] Some sequelae become evident during cancer 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.[20,29]

A literature review suggests that at least 50% of survivors experience some late effects of cancer treatment.[29] The most common problems in cancer survivors are depression, pain, and fatigue.[30] 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.[20] In general, the prevalence of late effects in cancer survivors is believed to have increased over time, likely because cancer interventions have become more complex and intense with combinations of surgery, radiation, chemotherapy, hormone therapy, immunotherapy, cellular therapy, and targeted biologics.[31]

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.[20,32-35] The effects of cancer treatment on

the heart and bone are also well known.[36-39] 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.[40,41] 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).[26]

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.[42-53] In fact, subsequent cancers accounted for 18% of all cancers diagnosed in the United States between 2009 and 2013.[54] Treatment-related subsequent primary cancers vary with the type and intensity of cancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.[55-61] These subsequent malignancies are especially well studied in long-term survivors of childhood cancers.[62-65] 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).[29] Another study of >2 million cancer survivors in the Surveillance, Epidemiology, and End Results (SEER) database identified the highest risk for subsequent primary cancers in survivors of bladder cancer (34% at 20 years).[66] 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, and Risk Reduction, available at www.NCCN.org). For survivors living with metastatic disease, recommendations for screening should be tailored to the survivor's individualized risk and disease status.

Referral for genetic risk assessment, counseling, and/or testing should be considered for appropriate candidates, such as those with a cancer diagnosis at a young age, with multiple primary cancers, or those with one or more relatives with the same or related cancers, to identify those with a potential 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. 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.

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.[67-74] 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.[67,70,74,75] In fact, as many as 19% of survivors meet the criteria for post-traumatic stress disorder (PTSD).[67,70,76-78] Practical and social problems of survivors include

issues surrounding employment, finances, and health and life insurance.[67,79-83]

Fear of Recurrence

A systematic review and meta-analysis of 9311 patients showed that 59% of survivors reported a moderate fear of cancer recurrence, while an additional 19% reported a severe fear, which can cause significant and enduring distress.[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.[86] In addition, survivors with high levels of fear of recurrence are more likely to be depressed and have a lower quality of life.[87]

Financial Burden

In a survey of 1218 participants from the ACS Cancer Action Network, 51% reported incurring medical debt, while 4% filed for bankruptcy.[88] The ACS Study of Cancer Survivors II found that 20% of survivors reported unmet financial needs.[26] A study in Washington state found that patients with cancer have a 2.6-fold increased risk of bankruptcy.[89] 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.[90] 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 $4000.[91,92] 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.[92] 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.[93,94] Younger cancer survivors seem to be particularly vulnerable to the financial effects of cancer.[94-96]

Clearly, with lost wages and increased expenses, the financial burden on many cancer survivors is great. Data suggest that patients belonging to traditionally marginalized racial and ethnic groups are more likely to suffer financial hardship after cancer treatment.[97,98] A recent survey comparing financial hardships of those ≥65 years in Black and white populations post-cancer treatment found that 39% and 18%, respectively, reported material financial hardship.[99] Black patients also reported higher rates of inability to afford cancer-related costs (23% vs. 7%) and increased concern regarding affording large medical bills (27% vs. 11%). 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.[100-103]

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.”[31] The NCCN Survivorship Panel adapted the essential components of survivorship care from the report:

1. Surveillance for cancer spread or recurrence, and screening for subsequent primary cancers
2. Monitoring long-term effects of cancer, including psychosocial, physical, and immunologic effects
3. Prevention and detection of late effects of cancer and therapy

4. Evaluation and management of cancer-related syndromes, with appropriate referrals for targeted intervention
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 are less likely to adhere to recommended surveillance screenings and to exercise and quit smoking.[104] A 2008 IOM report, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs,"[105] 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, Depression, Trauma, and Distress* 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.[106] 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:

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.

More recently, the NCI partnered with the Department of Veteran Affairs and other Health and Human Services agencies to develop the National Standards for Cancer Survivorship Care. These standards were released in 2024 and include recommendations around health system policies, processes, and evaluation/assessment (see https://cancercontrol.cancer.gov/ocs/special-focus-areas/national-standards-cancer-survivorship-care).

Implementation of these standards for survivorship care has been challenging, and reasons for the difficulties have been described.[107-109] 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 guidelines to inform the personalized care pathway delivery; and 4) identifying and filling research gaps.[108]

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.[110-116] Telehealth has also become increasingly more common, even more so since the COVID-19 pandemic, and survivors show high levels of satisfaction with this model.[117,118] In each case, survivorship care is delivered by either physicians or by advanced practice clinicians such as nurse practitioners.[119] 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. A recent prospective cohort study of 951 participants showed that 91.6% of survivors had at least one annual primary care provider visit, and more than half used their primary care provider as their main provider.[120] 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.[121] 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,[6,122-128] education for primary health care providers regarding appropriate survivorship care will be increasingly important.[129]

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 ($P < .001$).[130] 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; $P < .05$),[131] 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.[31] Furthermore, a nationally representative survey by the National Cancer Institute (NCI) and the ACS found that >50% of PCPs provide survivors with cancer-related follow-up care, often with co-management by oncologists.[132]

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.[133] 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.[134,135] 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.[136,137]

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.

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.[138,139] 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.[140,141] Criticisms of this trial, including the relevance of its outcome measures, have been published.[142-144] 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.[145] 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.[146] No differences in satisfaction with information or care were evident. A systematic review and meta-analysis published in 2020 came to the conclusion that while care plans are reasonable to provide to survivors, they did not improve patient-reported outcomes.[147] More research is needed to determine whether this is due to the inefficacy of the care plan, difficulties with implementation, or inappropriate research design of comparative effectiveness studies.

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.[148] 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 (HCT) survivors and briefly reviewed in a telehealth call by a trained non-professional.[139] The study randomized 458 HCT 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.[149] A third trial did not see an increase in survivors' knowledge after provision of a survivorship care plan.[150]

Overall, definitive data supporting the benefits of survivorship care plans are still insufficient.[147,151]

A survey that included a nationally representative sample of 1130 oncologists published in 2014 found that <5% of them provide a written survivorship care plan to survivors.[152] 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. More recent surveys have reported that 35% to 40% of survivors receive a written follow-up care plan and/or a written treatment summary.[153,154]

ASCO released a clinical expert statement on cancer survivorship care planning in 2014.[155] 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.[156] 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.[157] 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 auto-population systems will require manual double-checking to ensure accuracy.[158] Thus, providing a survivorship care plan is time-consuming and resource-intensive and could have unforeseen harms.[144,159]

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 by Cancer Type)
- 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 by Cancer Type (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.[160,161]

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.[162-167] 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. Fertility concerns for adults of reproductive age
10. Disease-specific recommendations for surveillance/follow-up (see NCCN Guidelines for Treatment by Cancer Type, 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, and improved adherence to guideline recommendations for health behaviors.

Survivorship Research

In 2017, the National Cancer Policy Forum of the National Academies of Sciences, Engineering, and Medicine held a workshop to evaluate advances in long-term survivorship care as a follow up to the 2006 IOM survivorship report, which cited 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.[168] Outcomes from the workshop suggest a tiered approach to survivorship based on the risk of disease recurrence and morbidity related to late effects of treatment and comorbidities, and proposed that patients at higher risk for late/long-term effects be followed by a multidisciplinary team with oncology expertise, while individuals with lower risk can be followed by their PCP. However, the workshop also concluded that more research is needed, and until risk stratification models are operationalized and evaluated, they will not be widely implemented due to ineffective patient triage.

An ASCO survey report highlighted several key gaps in current survivorship research.[169] For instance, more research pertaining to survivors >65 years of age, survivors of cancers other than breast, and 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, longer-term survivors, those >65 years, and more ethnoculturally diverse populations of survivors.[170]

In June 2012, the ACS, the Centers for Disease Control and Prevention (CDC), LIVESTRONG Foundation, and NCI held a joint meeting and created an action plan to facilitate the translation of survivorship research into survivorship care.[171] 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, have obesity, do not meet the recommended daily intake for fruits/vegetables, and/or do not engage in physical activity.[172] Analysis of data from other studies, including the National Health Interview Survey (NHIS) (2008–2012), showed similar results.[173-176] A more recent analysis of data from the 2013–2017 NHIS indicates that cancer survivors are less likely than those without a history of cancer to have a healthy body mass index (BMI) (31.6% vs. 34.7%) or meet physical activity recommendations (14.2% vs. 21.1%), although they are less likely to smoke (14.1% vs. 16.8%) or engage in moderate/heavy drinking (18.8% vs. 21.9%).[177] Results from the 2022 ACS/NCI SEER projections and 2021 NHIS found that 10% and 11.4% of survivors ≥18 years continue to smoke, respectively, and an additional 3% continue to smoke e-cigarettes.[3,178,179] Furthermore, many survivors forego recommended cancer screenings (ie, colorectal and cervical screening) and follow-up surveillance[180-182] or demand more intense surveillance than evidence supports.[86]

Healthy Lifestyles

Healthy lifestyle habits, such as engaging in routine physical activity, maintaining a healthy diet and weight, and avoiding cigarettes, tobacco

products (including hookah), e-cigarettes, and secondary exposure to cigarette smoke have been associated with improved health outcomes and quality of life.[183,184] For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.[185-192] In fact, the maintenance of a healthy lifestyle is associated with a decrease in premature death in cancer survivors.[193] 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 or avoid alcohol intake and avoid or stop using cigarettes, tobacco products (including hookah), e-cigarettes, and secondary exposure to cigarette smoke, with emphasis on tobacco cessation if the survivor currently smokes or uses smokeless tobacco products (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[194] Clinicians should also advise survivors to practice sun safety habits as appropriate, such as using a broad-spectrum sunscreen with a minimum SPF of 30, avoiding peak sun hours, avoiding tanning beds and sunburns, and using physical barriers. Survivors should also be encouraged to get an adequate amount of sleep (7–10 hours per night, depending on age).[195-197] Finally, survivors should be encouraged to see a PCP regularly and adhere to age-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 survivors with overweight or obesity or small increases in physical activity among sedentary individuals are thought to yield meaningful improvements in cancer-specific outcomes and overall health.[198] Clinicians should assess individual and community-level barriers to meeting the healthy lifestyle recommendations and support patients in developing strategies to overcome challenges, including referrals to community or medical center-based support programs.

Physical Activity

During cancer treatment, many survivors become deconditioned and can develop impaired cardiovascular fitness because of the direct and secondary effects of therapy.[199] 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.[200-213] The effectiveness of exercise is especially well studied in patients 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.[210,211,214-216] 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.[217] In fact, the finding was dose-dependent, and survivors who reported ≥9 metabolic equivalent (MET) h/wk – the equivalent of 3 to 5 sessions per week with a duration of ≥ 20 minutes of moderate or vigorous exercise – 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.[218]

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.[205,219-236] 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% ($P = .00001$).[223] 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.[221,224,233,237] 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.[234] Evidence in other disease sites is less robust, but also suggests survival benefits associated with exercise in survivors after treatment.[237]

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.[185,238-244] 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.[185]

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.[245,246]

For survivors who are not meeting the guideline recommendations (see later discussion), barriers to physical activity should be discussed and addressed. 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.[247] Alleviation of modifiable barriers (eg, pain, fatigue, distress, nutritional deficits) can facilitate the initiation of an exercise program.

Risk Assessment for Exercise-Induced Adverse Events

Exercise is considered safe for most survivors.[210,211,248] However, a significant portion of survivors may have comorbid conditions or risk factors that make them unable to safely exercise without trained supervision.[249] Therefore, a risk assessment is required for all survivors before prescribing a specific exercise program.[210,250] The type of cancer, treatment modalities received, and the number and severity of comorbidities determine risk levels.[248] 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+),[251] 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, lymphedema, presence of prosthesis, 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. Survivors at moderate risk for adverse events 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;

https://www.acsm.org/certification/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).[252-257] Progressive resistance training under supervision is recommended as part of treatment for survivors with lymphedema (see *Treatment of Lymphedema*, below).

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.[248] 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.[208,258] In addition, the Panel also 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.[259-261] 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, prolonged screen-based activities) 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 prior to aerobic/endurance exercises and at least 2 days per week on days that on those muscle groups are not 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.[172,262] However, the evidence suggests that even light-intensity physical activity can improve physical functioning in survivors.[263] For survivors who are inactive, clinicians should not advise the immediate initiation of a high-intensity, high-frequency program.[264,265] Instead, the Panel suggests that clinicians provide sufficient information to encourage survivors to avoid a sedentary lifestyle.[250] 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 per week), with progression based on tolerance.[264] 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.[266-271] A recent systematic review of 16 trials including resistance training interventions in breast cancer survivors concluded that meaningful improvements in physiologic and quality-of-life outcomes can be achieved.[272] A similar review of 11 randomized controlled trials came to similar conclusions.[271] One 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.[273]

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 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. If there is a concern that peripheral neuropathy may increase the risk of dropping free weights, patients should consider using resistance weight machines and/or training with resistance bands.

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.[207,210,274-276] However, data comparing different interventions are limited, and there is currently no “best” physical activity program for cancer survivors.[277-280] 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.[281-283]

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.[284-286] In addition, participation in supervised exercise programs or classes or enlisting the support of an exercise group or buddy may be helpful for survivors.[287-290] In addition, setting short- and long-term SMART (specific, measurable, attainable, relevant, time-bound) goals and considering the use of a pedometer or wearable activity tracker to monitor these goals (eg, achieving 7,000–10,000 steps per day) can be helpful.[291-303] 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.[288,295,304-309] Combination approaches (eg, oncologist recommendation plus exercise DVDs, pedometers, exercise diaries, exercise education sessions) may also increase exercise participation in survivors.[310]

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.[311-313] 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 having overweight or obesity can exacerbate a survivor's risk for functional decline, comorbidity, and cancer recurrence or death, and can reduce quality of life.[261,311,314-322] For example, a systematic review and meta-analysis of studies in survivors of endometrial cancer found a correlation between higher BMI (≥30 kg/m^2) and increased all-cause mortality.[323] Additionally, a meta-analysis demonstrated that this risk for increased breast cancer mortality is predominantly confined to the pre- and perimenopausal, hormone receptor (HR)-positive population.[324] A third systematic review and meta-analysis of 203 studies, which included more than 6.3 million cancer survivors, demonstrated reduced cancer-specific survival (CSS) and increased risk of recurrence in patients with a BMI ≥30 kg/m^2.[325]

ASCO published a position statement on obesity and cancer.[326] 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 have underweight (BMI <18.5), overweight (BMI = 25–29.9), or obesity (BMI ≥30), and discuss the importance of interventions to attain or maintain a BMI between 18.5 to 24.9 kg/m^2. The Panel notes, however, that BMI should be considered in context of body composition and metabolic health. For more muscular survivors, waist circumference may be a better measure of overall disease risk. A larger waist circumference increases risk for diabetes, hypertension, and CVD.[327]

Current dietary and physical activity habits and potential barriers to physical activity or a healthful diet should be ascertained either by the oncologist or other appropriate allied health personnel (eg, nurses, registered 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 and goal setting to prevent weight gain in survivors with BMI between 18.5 to 24.9 kg/m^2, intentional weight loss for survivors with overweight/obesity, and intentional weight gain for those who have underweight. Clinicians should reinforce the importance of maintaining a healthy body weight throughout life and encourage all cancer survivors to achieve and maintain a BMI between 18.5 to 24.9 kg/m^2 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.[328]

For additional information, see Resources from ASCO (https://society.asco.org/news-initiatives/current-initiatives/prevention-survivorship/obesity-cancer) and the World Cancer Research Fund International (https://www.wcrf.org/diet-activity-and-cancer).

Recommendations for Survivors with Healthy Weight

In addition to discussing nutrition, weight management, and physical activity, clinicians should reinforce the importance of weight maintenance throughout life in survivors with a BMI between 18.5 to 24.9 kg/m^2. In

particular, the importance of limiting high-calorie foods, particularly those that provide relatively few nutrients (eg, regular soft drinks, sugary desserts, fried foods), and focusing on nutrient-dense foods (eg, non-starchy vegetables, whole grains, lean meats/fish, broth-based soups, fresh fruit for desserts, and beverages such as water, unsweetened tea, and black coffee) is especially important.

Recommendations for Survivors with Overweight/Obesity

Survivors with a BMI ≥25 kg/m^2 should be engaged in discussions about nutrition, weight management, and the importance of regular 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 survivors with BMI ≥30 kg/m^2 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) and/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, pharmacologic agents or bariatric surgery can be considered as appropriate with 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. Lifestyle modifications are preferred over pharmacologic therapy.

Randomized trials have shown that intensive behavioral weight loss interventions can lead to weight loss in survivors with overweight or obesity.[329-334] For example, the ENERGY trial used a group-based 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.[334] 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.[329]

Recommendations for Survivors with Underweight

Survivors with a BMI <18.5 kg/m^2 should be engaged in discussions about nutrition (see below) and contributing psychosocial factors should be assessed and addressed. In addition, advising survivors with underweight to increase their frequency of eating and to avoid fluid intake with meals may help with weight gain. Foods that are both high in calories and nutrient-dense (eg, avocados, nuts) should be encouraged. Appetite stimulants can be considered as appropriate. Furthermore, smoking status, dental health (including risk factors for poor oral intake), swallowing and taste/smell disorders, gastrointestinal motility, and socioeconomic barriers to access of healthy food (food deserts, transportation, lack of resources to prepare food) should be assessed and addressed as appropriate. Consideration can also be given to refer the survivor 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.[335-338] 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).[339] 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).[340] 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).[341] In the Women's Health Initiative (WHI) Dietary Modification trial, nearly 49,000 postmenopausal individuals 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.[342] After an average follow-up of 8.1 years, 655 (0.42%) individuals in the intervention group and 1072 individuals (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).[343]

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.[208,344-346] 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.[347] 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.[348] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by 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 (relative risk [RR], 1.79; 95% CI, 1.11–2.89).[349] For survivors of non-colorectal cancers, the evidence linking a healthy diet 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.[350]

Unfortunately, cancer survivors often do not follow recommendations for a healthy diet and, in some studies, show worse patterns than non-cancer controls.[351,352] For example, a national survey of 1533 adult cancer survivors and 3075 matched controls found that cancer survivors had worse dietary patterns.[352] Other studies show that survivors may make improvements to their diet quality post-diagnosis.[353-355]

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, beans/legumes, olive or canola oil, avocados, seeds, and nuts. Fish and poultry are recommended, whereas red meats should be limited to no more than 18 oz (cooked) per week 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.[356,357]

In addition, survivors should be advised to avoid alcohol, or if partaking, limit alcohol intake to one drink per day for women and two drinks per day for men.[261] Evidence suggests a direct correlation between the amount of

alcohol consumed and risk of developing cancer, with the highest risk in individuals <40 years of age.[358-364] Abstaining from alcohol is especially important for survivors of liver, esophageal, kidney, and head and neck cancers, due to an increased risk of mortality with alcohol consumption.[345,365,366] Current evidence suggests no association between alcohol consumption and overall mortality in survivors of breast cancer; however, data are limited. There are also mixed data on alcohol consumption and the risk of recurrence as well as developing a second primary breast cancer.[261] 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 as noted above.[345,367,368]

Soybeans and soy foods are popular vegetarian protein sources. The fact that they contain phytoestrogens has caused some survivors of hormone-sensitive cancers to be concerned about consumption of these foods. Nonetheless, several large studies have found no adverse effects on breast cancer recurrence or total mortality related to the intake of soy food.[369-373] In fact, trends towards decreased recurrence and mortality were observed. However, no consensus regarding the role of soy foods in cancer control exists. 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 registered dietitian should be considered. The United States Department of Agriculture (USDA) approximate food plate volumes (www.myplate.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 cold-water fish
- Carbohydrates: vegetables, fruits, whole grains, and legumes
- Protein: poultry, fish, legumes, low-fat dairy foods, eggs, and nuts

The use of healthy recipes, such as those found in resources such as the ACS “Find Healthy Recipes” website (https://www.cancer.org/cancer/risk-prevention/diet-physical-activity/eat-healthy/find-healthy-recipes.html) should be encouraged.

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.[374-388] No clear evidence supports an effect of dietary supplements for cancer prevention, control, or recurrence, although a few exceptions may warrant further studies.[389,390] 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.[391]

Although the FDA regulates dietary supplement products under the Dietary Supplement Health and Education Act of 1994 (DSHEA),[392] 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.[393,394] Furthermore, dietary supplements may remain available to consumers even following FDA class I drug recalls.[393]

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.[391,395-397] 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 or previous gastrointestinal surgeries [eg, Roux-en-Y gastric bypass]), inadequate diet, or comorbid indications (eg, osteoporosis,[398] ophthalmologic disorders,[399] cirrhosis[400,401]). 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, or other cancer care team members such as integrative medicine or clinical pharmacist, 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 levels of motivation are often heightened among cancer survivors, especially close to the time of diagnosis.[201,284,402]

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.[284-286,403] However, data show that oncologists are less likely to discuss healthy lifestyle changes than other physicians. A cross-sectional study of 1460 cancer survivors (≥65 years) evaluated how often providers (oncologists, other physicians, and/or nurses) discussed healthy lifestyle topics during visits.[404] Oncologists were found to be less likely than other providers to discuss exercise (25% vs. 38%), smoking cessation (64% vs. 74%) and healthy diet (20% vs. 41%). In a mixed-method study, 91 providers (comprising approximately one-third of each: PCPs, oncologists, and other specialists) were surveyed on their health-promotion practices/beliefs and likelihood of discussing healthy lifestyle modifications with cancer survivors.[403] Most PCPs (90%) reported healthy lifestyle counseling to at least some cancer survivors, while only 26.7% of oncologists reported doing so.

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.[288,295,306-309,330,405] In fact, a trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer.[307,406] Moreover, results of the completed Reach Out to Enhance Wellness (RENEW) trial showed that an intervention of telephone counseling and mailed materials in 641individuals >65 years, with overweight/obesity, who are 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.[288] The Exercise and Nutrition Routine Improving Cancer Health (ENRICH) intervention, which includes six theory-based 2-hour sessions, has also shown a positive effect on physical activity, diet, weight, and BMI.[407]

Another strategy, motivational interviewing, may be an effective technique for increasing physical activity and other healthy behaviors in cancer survivors.[304,305] 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.[408] 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),

self-monitoring, and setting SMART goals.[302,409,410] Clinicians can also 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 HCT. In fact, antibody titers to vaccine-preventable diseases decrease after cancer treatment.[411-413] In addition, survivors are at increased risk of complications from vaccine-preventable diseases, such as those caused by HPV and influenza viruses.[412,414]

Many infections in survivors can be prevented or mitigated using vaccines. However, data analysis from the NHIS reported that only 63.8% of survivors (N = 5053) received an influenza vaccination during the 2016–2017 and 2017–2018 season.[415] A separate review of NHIS data determined that only 66.6% of cancer survivors had received two or more COVID-19 vaccinations.[416] The prevalence of HPV vaccination among cancer survivors in the pediatric and AYA population also remains low. A cross-sectional survey of 982 participants indicated 23.8% of cancer survivors aged 13 to 26 years received at least one dose of the HPV vaccine, compared to 40.5% of individuals without cancer in the same age range.[417]

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.[418-420] 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 in those with underlying disease/certain comorbidities or 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.[421-428] Contact with pets did not increase the risk of fever, bacteremia, pneumonia, and gastroenteritis in children with acute myeloid leukemia (AML),[429] and the Panel believes that contact with pets is generally safe for most survivors. However, survivors should wash their 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 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.[430] 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).[431] The Infectious Diseases Society of America (IDSA) has outlined guidance for vaccination in immunocompromised patients, including those with cancer and those post-HCT.[432] The NCCN Survivorship Panel outlined immunization guidelines specific to survivors of hematologic malignancies and solid tumors and those post-transplant, 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.[433] 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,[420] their administration is likely worthwhile to achieve some protection in the absence of known harm.

Vaccination against COVID-19 is recommended for all individuals ≥6 months of age as per CDC guidelines.[434] Some data show the efficacy of COVID-19 immunization in cancer survivors (especially those on certain active treatment regimens) is likely to be less than in individuals without cancer.[435] However, due to increased risk of severe infection, longer hospital stays, and death, it is recommended that all cancer survivors receive the COVID-19 vaccine. One cohort study looked at the seroconversion rate in 200 patients with cancer after completing a series of an FDA-approved COVID-19 vaccine.[436] Of the 200 participants, those

with solid tumors showed a 98% positive anti-SARS-CoV-2 spike IgG while those with hematologic malignancies showed an 85% positive anti-SARS-CoV-2 spike IgG. The level of immunogenicity also varied based on treatment regimen. High rates of seroconversion were seen in those on hormonal and immune checkpoint inhibitor therapy, with 100% and 97% seropositivity, respectively, while individuals receiving anti-CD20 therapy and HCT resulted in lower seroconversion rates, with 70% and 73% seropositivity, respectively. A systematic review with meta-analysis looked at seroconversion >2 weeks post-completion of the COVID-19 vaccine series in individuals with solid tumors and hematologic malignancies.[437] Approximately 80% of individuals with cancer showed antibody production and seroconversion after completing COVID-19 vaccine series; however, levels of humoral immunity varied based on cancer type. The seroconversion rate in solid tumors was 88% (95% CI, 81%–92%) as compared to 70% (95% CI, 60%–79%) in hematologic malignancies.

Please refer to the CDC Guidelines for vaccination recommendations and schedules at https://www.cdc.gov/vaccines/hcp/imz-schedules/index.html. For guidance on the management of concurrent COVID-19 and cancer, please refer to the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections (available at www.NCCN.org).

Pneumococcal conjugate vaccine (PCV20/PCV15) is recommended for all adults aged ≥65 years and those at any age with immunocompromising conditions.[438,439] Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. Adults with previous PCV13 who have not completed their recommended pneumococcal vaccine series with PPSV23 can receive one dose of PCV20 if PPSV23 is not available. 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 PPSV23 to ≥5-year survivors of cancer reduced hospitalization for pneumonia.[440]

Other vaccines, as listed in the guidelines, should be recommended if some special circumstance or risk factor is present. These vaccines 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; 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 months after chemotherapy or ≥6 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 disease specialist. For all survivors, when other vaccine options exist, they are preferred over live-attenuated vaccines.

Healthy immunocompetent individuals who live in a household with immunocompromised survivors can receive the following live vaccines

with caution: MMR, varicella zoster, yellow fever, rotavirus, nasal influenza vaccine, and oral typhoid vaccines.[432] However, severe complications have followed vaccination with live-attenuated vaccines among patients who are immunocompromised. 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. 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.[441] Live attenuated influenza vaccines should be avoided in some survivors (see *Live Viral Vaccines*, above).[442] Therefore, preferred vaccines include inactivated influenza vaccines or recombinant influenza vaccine.[442] Administration of the influenza vaccine to survivors with egg allergy symptoms (other than hives) should be done at centers that are equipped to recognize and manage severe allergic reactions, as currently recommended for all individuals.[442] No studies have addressed the superiority of any influenza vaccine in the cancer survivor population specifically.

Zoster (Shingles) Vaccine

The recombinant zoster vaccine, RZV, is the only zoster vaccine available in the United States and is >90% effective when administered according to schedule.[443] It is recommended that individuals who had previously been immunized with the live-attenuated vaccine receive RZV as well. However, the recombinant vaccine should not be given <2 months after administration of the live-attenuated vaccine. In 2021, the FDA expanded its indication to include individuals ≥18 years of age who are immunocompromised secondary to disease or therapeutic agents.[444] The ACIP recommends 2 doses of RZV in those ≥19 years of age who fit the above criteria.[444]

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.[445] 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 38.4% of deaths in 2020.[446] 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.[447] In fact, survivors of most cancers have a markedly increased risk of developing CVD compared with non-cancer populations.[448-451] A prospective community-based study looked at the risk of developing CVD in cancer survivors versus persons without cancer.[452] Of the 3250 participants, incidence rates (per 1000 people) of developing CVD were 23.1 in

survivors and 12.0 in persons without cancer. Survivors were also at a 52% higher risk for developing heart failure. As a result, a new field, called "Cardio-Oncology," has been established that focuses on the cardiovascular health of patients with cancer and survivors.[453-455]

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.[456-464] Cardiovascular sequelae of cancer treatment can include arrhythmias, pericardial disease, hypertension, thrombosis, cardiomyopathy/heart failure, and vascular and metabolic issues.

In addition to the cardiotoxic effects of cancer treatment, 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 risk factors. For example, somatic mutations in blood cells cause clonal hematopoiesis of indeterminate potential (CHIP) and increase the risk of hematologic malignancies.[465] Increasing evidence also shows that individuals with solid tumors are more likely to have CHIP than those without cancer.[466] CHIP is also emerging to be an important causal risk factor for CVD.[465] Other well-defined CVD risk factors (eg, hypertension, hyperlipidemia, diabetes) are more common in populations with cancer than populations without cancer.[467,468] 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 years after diagnosis and completion of curative therapy.[453]

Control of CVD and shared CVD/cancer risk factors can decrease the risk of subsequent cardiovascular events.[453,469] Data show that attention to and counseling about CVD/cancer risk factors may improve cancer- and cardiovascular-related outcomes.[470]

Tools exist to help quantify atherosclerotic CVD risk (eg, ASCVD risk score[471]) and help determine appropriate risk reduction strategies. However, 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. 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 at any stage of the cancer journey for survivors deemed to be at high risk for the development of CVD.[472]

The *ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors* table in the algorithm above was adapted from a paradigm developed to address CVD risk factors in survivors of breast and prostate cancer.[473,474] 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

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.[475-477] 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.[478,479] A role for topoisomerase-IIβ in cardiomyocytes in the production of ROS in response to anthracyclines has been suggested.[480]

Some data suggest that the incidence of clinical CHF after anthracycline-based therapy for adult-onset cancer is <5%.[481-484] Other studies suggest that number may be closer to 10% (≤20 years after receiving anthracyclines).[485] A retrospective, population-based, case-control study evaluated the incidence of new-onset heart failure in individuals with breast cancer or lymphoma who received anthracyclines over a 25-year period compared with a matched healthy control group. Of the 2196 participants, those with cancer (n = 812) were at greater risk of developing heart failure (HR, 2.86; 95% CI, 1.90–4.32; *P* < .001). After 10 years, 5.36% of individuals who had received anthracyclines developed heart failure versus 1.74% in the comparator group. After 20 years, individuals who developed heart failure after receiving anthracyclines nearly doubled when compared to the non-anthracycline group at 10.75% versus 4.98%, respectively. 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-based chemotherapy and trastuzumab and 1.3% in those treated with anthracycline-based chemotherapy alone.[483] 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.[481,486-488]

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,[457,489,490] 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.[457] 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.[491]

Panel Considerations Regarding Anthracycline-Induced Cardiac Toxicity

Anthracycline-induced heart failure may take years or decades to manifest. Established principles have 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.[492] Additionally, data from these other types of cardiac injury suggest that early intervention with cardioprotective medications results in better long-term cardiac function.[493-495] It is possible that if anthracycline-induced cardiac dysfunction is detected early, it may also be responsive to cardioprotective medications.[457,492-494,496] 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.[486] 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,[497-499] dietary modification (either through correcting dietary deficiencies or increasing intake of various nutrients),[500] and exercise,[217,218,501-503] may also be helpful at these early stages, prior to the onset of heart failure symptoms, although more research is necessary.[504,505]

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 twenty years 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.[506] In 2001, the AHA/ACC guidelines proposed a new classification for heart failure.[506] 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. In 2022, AHA and ACC joined with the Heart Failure Society of America (HFSA) and released guidelines that included updated treatment approaches for individuals with symptomatic heart failure including the use of SGLT2i medications and the importance of involving a heart failure specialty team in the coordination of care.[507] In addition, recommendations for the management of cardiac amyloidosis, comorbidities in individuals with heart failure, complications related to cardio-oncology, and discussion regarding implantable devices and advanced therapy options for those with stage D heart failure have been included in their guidance.

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 within one year after completion of anthracycline therapy, with the additional consideration of an ECHO screen in survivors at high risk for heart failure, as discussed in more detail below. The Panel also believes that early involvement of a

cardio-oncologist, cardiologist, survivorship specialist, or PCP for serial surveillance based on the cardiotoxicity risk associated with the cancer treatment regimen is important. 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.[508] Overall, there should be a low threshold for referral to a cardiovascular specialist (ie, cardio-oncologist or cardiologist).

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).[506] 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.[457,486,492-494,496] 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.[509] 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 survivors with a history of anthracyclines for cardiotoxicity.[510] The review also found no direct evidence showing the effectiveness of cardiac treatment on outcomes of asymptomatic survivors.[510] 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.[511] Some reasons for the lack of data on screening survivors for cardiotoxicity have been discussed,[512] 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 ECHOs or comparable imaging to evaluate cardiac anatomy and function for survivors of pediatric cancer at the conclusion of treatment and then every 2 to 5 years for life depending on age at treatment, anthracycline dose, and chest irradiation (http://www.survivorshipguidelines.org).[513] An international collaborative supports lifelong echocardiographic surveillance

at least every 5 years in survivors of childhood cancer treated with anthracyclines.[514] Although the frequency of cardiac assessment using ECHOs 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.[515,516]

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.[517] The groups recommend ECHO 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.[472] The ASCO panel gave a moderate-strength recommendation (as based on evidence and the balance between harms and benefits) that ECHO 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).[518] 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 ECHO. 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 cardiovascular specialist (ie, cardio-oncologist or cardiologist).

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.[453,456,462,519] The addition of other cardiotoxic therapies (eg, HER2-targeted agents, TKIs, fluoropyrimidines, taxanes) to anthracyclines can further increase the risk of heart failure over that seen with the use of anthracyclines alone.[520,521] Survivors >65 years, those with a higher cumulative anthracycline dose (cumulative doxorubicin dose of 250 mg/m^2 or equivalent[522]), 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. Data also showed that having overweight or obesity and visceral and intramuscular adiposity are risk factors for

cardiotoxicity from anthracyclines in breast cancer survivors.[523,524] 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.[525]

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 ECHO 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.[486] 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.[526] 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 ACE inhibitor enalapril reduced left ventricular end-systolic wall stress compared to placebo (P = .03).[496] 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.[494] 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.[492] 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.[486] 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).[493]

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 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, physical inactivity) 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, cardiotoxicity developed within the first year after treatment in 98% of patients.[486] 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 by Cancer Type, at www.NCCN.org, for specific monitoring recommendations).

The Panel recommends two-dimensional ECHO, 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.[527,528] It can recognize early stages of heart failure by revealing abnormalities of the pericardium, myocardium, and heart valves.[518] 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.[527,529]

In agreement with these guidelines, ASCO's guidelines that address monitoring of cardiac toxicity after treatment in survivors of adult-onset cancer indicate that ECHO can be considered for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction, including survivors with a history of anthracycline therapy.[472]

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 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.[530] 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.[531] While there are some promising data on the use of natriuretic peptides (in addition to troponins) in the prediction of cardiac dysfunction, larger, better designed studies, with more diverse populations, are needed to support the use of biomarker testing as a measurement of cardiotoxicity.[532]

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.[533] 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 cardiomyopathy, 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 cancer systemic therapies are potentially cardiotoxic and may increase the risk of cardiac disease.[521] Involvement of the survivor's PCP in the management of cardiac risk factors in survivors 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 cardiovascular specialist (ie, cardiologist, cardio-oncologist) for all survivors with stages B, C, or D heart failure. The sooner treatment is initiated, the more likely it is to be successful.[492]

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.[534] 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.[535]

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 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 extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis." Distress, often related to fear of recurrence, is common in survivors

and can negatively impact quality of life.[21,70,536-538] 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.[104] 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.[539-544]

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.[545]

Fear of recurrence, with persisting worry and distress sometimes reaching levels of clinical anxiety, is common, occurring in up to 80% of cancer survivors.[545] 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.[21,70,536-538,546] 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.[67,70,75,538,547] These challenges are accentuated by the usual decreased medical and interpersonal support following completion of treatment and transition to the surveillance phase of care.[445]

Anxiety and/or depression affect up to 29% of survivors.[67,70,76-78,548,549] 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.[545] A meta-analysis determined the log odds ratio (OR) for a PTSD diagnosis in cancer survivors compared with non-cancer controls to be 1.66 (95% CI, 1.09–2.53).[550] 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.[77] Another study found that 22% of survivors had PTSD symptoms at 6 months, and 6% had such symptoms at 4 years.[551] 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, as part of routine care, especially when there is a change in clinical status or treatment or if survivors present with multiple somatic complaints.

Survivors should be screened using validated measures such as the PHQ-9 for depression, GAD-7 for anxiety, PC-PTSD-5 for trauma, or PROMIS measures. 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.[552-559] 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.[557] 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-TR[560]). 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. 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 use disorder, 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.[561]

Protective factors also should be considered to balance against risk factors.[562] 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 with 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 themself may also indicate an elevated safety risk. Survivors judged to be at elevated risk require an emergency intervention that includes arranging to have firearms, weapons, medications, and other potentially lethal methods of suicide secured. In addition, maintaining direct observation of the individual, and calling 911 or calling, texting or chatting 988 Suicide & Crisis Lifeline, along with following other state mental health emergency plans or referring the person to emergency psychiatric evaluation procedures onsite should be implemented as appropriate.

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; call, text, or chat 988 Suicide & Crisis Lifeline; 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 use disorder should be referred to a substance use disorder 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.[563-565] In fact, evidence suggests that exercise and antidepressants (discussed below) may be equally effective in the treatment of depression.[566]

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.[567-572] Therapy, including CBT, has also been shown to be effective at reducing anxiety, depression, and distress in the survivorship population.[445,573-581] One study found that a psychoeducation program that included three telephone-based psychotherapy sessions reduced the severity of fear of recurrence in melanoma survivors.[582] 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.[583] 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.

Other alternative treatments (eg, yoga, tai chi, mindfulness) may also be helpful to survivors suffering from distress, although data showing their effectiveness are limited.[584-588] Mindfulness is possibly the best-studied

alternative treatment for psychological problems in cancer survivors.[589-593] 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.[593] In non-cancer settings, weight loss interventions have improved depression in individuals with obesity,[594] 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.[595] A population-based study in Canada found that 44% of cancer survivors were using an anxiolytic, and 22% were using an antidepressant.[596] Antidepressants and antianxiety drugs have been shown to be beneficial for the treatment of depression and anxiety in patients with cancer.[595,597-604] 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*).[605] 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 cytochrome P450 2D6 (CYP2D6) and should be used with caution for patients on tamoxifen. Antidepressants that are strong CYP3A4 inhibitors or inducers may also interact with some cancer prevention or maintenance drugs other than tamoxifen, such as TKIs, monoclonal antibodies, or mTOR inhibitors (see *Hormone-Related Symptoms* for a discussion of psychotropics and cytochrome P450 interactions).[606-608]

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 Function

Cognitive impairment is a common concern 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.[609] For some survivors, symptoms persist long-term.[610] An estimated 20% to 35% of survivors may experience cognitive impairments for months to years post-treatment.[611] 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.[612-622] 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.[623]

Younger age; female gender; being separated, divorced or widowed; working part-time or being unemployed; and having a lower household income are all associated with an increased likelihood that a survivor perceives cognitive dysfunction.[624]

Cancer-related cognitive changes have primarily been studied in patients with CNS cancer, breast cancer, and lymphoma and in those who have undergone HCT, with a reported incidence ranging widely from 19% to 78%.[610,625-640] In the 2010 LIVESTRONG survey of 3108 post-treatment survivors of a variety of cancer types, approximately 46% of respondents perceived cognitive deficits.[624] 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.[641]

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.[610,621,638,642,643] In one meta-analysis of 17 studies, individuals previously treated with chemotherapy for breast cancer (n = 807) had lower functional abilities than those not treated with chemotherapy (n = 291).[629] 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.[644] The chemotherapy group did significantly worse on several neuropsychological tests (eg, immediate and delayed verbal memory, executive functioning, psychomotor speed). Another study looked at various cognitive domain scores in 115 patients who underwent HCT as compared to the general population.[645] The HCT survivors were 2.4 times more likely to develop cognitive dysfunction than the control group. Adjusted for age, sex, and education level, HCT survivors scored worse overall in cognitive impairment when compared to the control group, resulting in 9 years of faster cognitive aging. Although no significant differences in cognitive dysfunction were identified at 2-year follow-up, patients who underwent HCT 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 cancers (eg, in intellectual capacity, concentration/short-term attention, verbal memory, executive function) and survivors with a history of HCT (eg, in fine motor dexterity, verbal speed, processing speed, auditory memory, executive function).[646,647]

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.[638,648-650] Some evidence suggests that survivors often report cognitive dysfunction, despite receiving normal scores on neuropsychological evaluations.[651] This discrepancy may be attributed to perceived cognitive deficits secondary to anxiety, depression, fatigue, or sleep disorders. Other reasons for the weak correlation between perceived and objective cognitive decline have been proposed. These include the fact that perceived cognitive decline is influenced by patient expectations, whereas expectations do not affect objective assessments. These objective assessments assess cognitive performance under optimal rather than real-life conditions.[652] 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.[650] 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 (OR, 4.51; $P < .001$), with the largest effects seen in complex processing speed, attention/working memory, and verbal learning efficiency.[617] 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.

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.[653] Structural studies have supported the hypothesis that neurotoxicity resulting in damage to white and/or gray matter of the brain may play an important role in cognitive deficits after chemotherapy treatment,[610,614,628,645,654-657] and functional MRI studies show that changes in brain activity accompany cognitive complaints or cognitive deficits in survivors.[655,658,659] 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.[644,660,661] 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.[662] 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.[609,663,664]

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 was 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. The group published recommendations regarding neuropsychological testing, defining cognitive impairment/changes, neuroimaging, and future study design.[664,665]

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, delirium, 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[666]) 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.[613] 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 sections. Additional recommendations for cognitive dysfunction in adults ≥65 years can be found in *Assessment of Cognitive Function* in 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.[667] 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.[668] 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.[669]

Routine physical activity should be encouraged. Substantial evidence shows that physical activity enhances cognitive function in people in general as they age, although only few studies specific to cancer survivors have been reported.[670-674] A small randomized controlled trial of an exercise intervention versus control in breast cancer survivors evaluated objective and self-reported cognition.[674] 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.[671,675] One study randomized 157 breast cancer survivors to web-based cognitive training with telephone support or to wait-list control.[676] 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.[677] 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.[678] 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 function.[679] A larger study also found improvements in cognitive symptoms after a mindfulness-based approach.[591] Two studies have assessed the effects of yoga on cognition in survivors.[680,681] Both reported improvements in patient-reported cognitive dysfunction.

Evidence has also shown the benefit of social support systems on the management of cognitive dysfunction in survivors. In a study of 3351 patients with breast cancer, social support, social ties, and cognitive function were assessed using a modified Medical Outcomes Study (MOS) Social Support Survey and Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG).[682] Results showed that patients who were married were likely to have better cognitive function than those who were divorced/separated or widowed ($P = .01$). Significant associations were found in individuals who reported having close friends ($P < .001$) or relatives ($P < .001$), with higher scores in those who reported having at least one friend or relative, compared to those who reported having none.

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.[683] 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.[684] For example, a randomized, placebo-controlled, double-blind trial found that d-methylphenidate had no effect on neuropsychological test scores.[685] 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.[686]

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.[687] 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.[688] Benefits with treatment were also noted among patients with primary brain tumors.[689]

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.[690,691] Donepezil was also studied in a randomized trial of 62 breast cancer survivors who had received adjuvant chemotherapy.[692] 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."[693] Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, HCT, or treatment with biological response modifiers.[694-696] According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[697,698] Cancer survivors report that fatigue continues to be a disruptive symptom after treatment ends,[699-707] with studies showing that 17% to 29% of cancer survivors experience persistent fatigue for years after the completion of active therapy.[708-710] 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.[711] A cross-sectional cohort study of 350 breast cancer survivors (median 10 years after diagnosis) reported higher rates of multidimensional fatigue (26%) when compared to the reference population (15.4%) using the Multidimensional Fatigue Inventory (MFI-20).[712]

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.[701,713] In fact, severe fatigue in survivors of Hodgkin lymphoma is associated with a decreased likelihood of employment.[714] 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.[715-720] 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.[699,721-723] 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 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 on the 0 to 10 scale.[724,725]

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, renal, or hepatic dysfunction; and endocrine disorders, should also be assessed. Disease and treatment considerations also affect recommendations for screening, such as the inclusion of ECHOs 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.[726]

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.[727]

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.[200,206,211,214,216,586,728-734] 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.[200,734-737] 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.[738]

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.[593,739-744] Several meta-analyses have evaluated the role of psychosocial interventions in reducing fatigue.[734,739,743,745] For example, Kangas et al[743] 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[745] 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[739] 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.[746-750] 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.[740,741,751] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[746,749] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[750,752] 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.[753]

Acupuncture and acupressure have been studied for the treatment of fatigue in patients with cancer and survivors.[754-761] A pilot study in 30 breast cancer survivors found that acupuncture resulted in a significant reduction in fatigue after 2 weeks.[759] 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.[761] 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.

Bright white light therapy may also be utilized in managing fatigue in cancer survivors. It is most frequently self-administered in the early morning for 30 to 40 minutes; however, timing may need to be adjusted for those who sleep during the day.[762] A recent randomized control trial of 81 survivors compared the effects of bright white light versus dim red light usage for 30 minutes immediately upon waking for 28 days on cancer-related fatigue and other psychosocial factors.[763] Those in the bright white light group reported a 17% greater decrease in fatigue compared to the control group. Clinically significant improvements in quality of life, mood, and depressive symptoms ($P < .01$) were also reported.

Massage therapy is a category 1 recommendation for survivors in the management of cancer-related fatigue. Multiple studies conclude that massage therapy is an effective technique at mitigating fatigue. One meta-analysis of 11 randomized control trials looked at the effects of massage therapy on 789 patients.[764] Results showed a significant improvement in cancer-related fatigue [SMD = - 1.69; 95% CI (- 2.46, - 0.93); $P < .01$], especially in individuals with breast cancer [SMD = - 1.62; 95% CI (- 2.18, - 1.05); $P < .01$]. Results also indicated a duration and frequency of 20 to 40 minutes, twice weekly for 3 to 5 weeks to achieve maximum benefit.

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.[765] A randomized trial in 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the dexmethylphenidate arm.[766] A meta-analysis of five randomized controlled trials of patients with cancer found limited evidence for the efficacy of ≥4 weeks of methylphenidate treatment for cancer-related fatigue (mean difference, −3.70; 95% CI, −7.03 to −0.37; $P = .03$).[767] However, another meta-analysis identified seven trials of methylphenidate and concluded that it was superior to placebo for the treatment of cancer-related fatigue.[768] A Cochrane review found that methylphenidate was likely effective for cancer-related fatigue and warrants further study.[769] 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.[734]

Other drugs, including modafinil, have also been studied for post-treatment fatigue.[770,771] In particular, a large phase III trial of 631 patients receiving chemotherapy suggested that modafinil is beneficial in patients with severe fatigue.[771] 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.[772] 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 placebo.[768] 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 after other interventions are attempted, although they acknowledge the limited data supporting the use of this agent in this setting, especially in cancer survivors.

Small pilot studies and one randomized controlled trial have evaluated the impact of supplements, including ginseng and vitamin D, for cancer-related fatigue.[773] 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. Approximately 75% of those with lymphedema are diagnosed within 3 years 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.[25] 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.[774] In a study of survivors of gynecologic cancers, the incidence of lymphedema in one or both legs 2 years after surgery was 37%.[775] 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%.[776]

Lymphedema may cause or exacerbate psychological distress.[777-779] In a study that included 692 breast cancer survivors with lymphedema, almost half reported moderate to extreme distress related to their lymphedema.[780] Lymphedema can also affect social roles, employment, medical expenses, physical function, and quality of life and can cause disability.[781-784] Unfortunately, only 55% of cancer survivors with self-reported lymphedema in the LIVESTRONG study said that they received care for lymphedema. However, lymphedema is suboptimally managed for many survivors, with evidence of racial and ethnic inequities.[785-787]

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.[788-791] Sentinel lymph node biopsy also appears to increase the risk of lymphedema, although it poses less risk than axillary lymph node dissection alone or with regional lymph node radiation.[792] Other treatment-related factors that have been associated with an increased risk of lymphedema are receipt of chemotherapy and the extent of lymph node dissection.[774,775,788-791,793-796] 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.[774,775,788,789,791,794,795,797,798]

Assessment and Workup for Lymphedema

Survivors at risk for lymphedema should be asked about swelling or feelings of heaviness, fatigue, or fullness at regular intervals. 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 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, a clinical examination should be performed and survivors should be asked about the frequency and severity of swelling, pain and/or discomfort, any issues with strength or range of motion, sensation, and functional mobility (ie, bending, stretching, flexibility), and whether symptoms interfere with daily activities.

If lymphedema symptoms are present, a recurrence of cancer, infection, or deep vein thrombosis (DVT) of an extremity 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.[34,799-801] 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. For select patients, referral to a lymphedema surgeon can be considered, in consultation with a certified lymphedema therapist and/or physiatrist who specializes in lymphedema.

Compression garments have been shown to reduce limb volume, and are often used with other modalities such as manual lymphatic drainage.[801-804] 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.[805,806] 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 resistance training and physical activity are not associated with exacerbation or development of lymphedema, and may improve lymphedema symptoms.[210,252-256,807-810] The WISER Survivor trial randomized 351 breast cancer survivors with BMI ≥25 kg/m^2 and 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.[811] 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 resistance under supervision is recommended for survivors with lymphedema. However, survivors with or at risk for lymphedema should consider discussing physical activity plans with a lymphedema specialist before starting a program that involves strength or resistance training of the affected limb. Survivors with lymphedema should work with trained exercise professionals with knowledge of cancer-related physical activity principles. 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.[808]

Survivor Lymphedema Education

Early detection and diagnosis are 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.[812,813] Consideration of compression garments, manual lymphatic drainage, and pneumatic compression for ongoing home management should also be discussed.

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.[788,790,797,798,814-817] For instance, in one study of 632 patients 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.[798] 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.[818] 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.[252-257] 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), patients randomized to the education plus exercise arm were more likely to report full range of motion at 12 months after lymph node dissection compared with patients in the education only arm (right arm: 90% vs. 83%, $P = .02$; left arm: 91% vs. 84%, $P = .16$).[819] By 18 months, 93% of participants in both groups reported full range of motion. 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.[820] In a controlled clinical intervention study, 88 patients with lymphedema secondary to cancer participated in either a water-based or land-based exercise program.[820] A higher proportion of those who performed water

exercises experienced a reduction in their secondary arm limb volume (*P* = .03) and self-reported frequency of swelling (*P* = .03).

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.

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.[821-825] 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.[826,827]

Pain has two predominant mechanisms: nociceptive and neuropathic.[828,829] 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.[821] Arthralgias, characterized by joint pain and stiffness, occur in roughly half of patients taking aromatase inhibitors as adjuvant therapy for breast cancer.[830] Pelvic pain often occurs after pelvic radiation, resulting from fractures, fistulae, proctitis, cystitis, dyspareunia, or enteritis.[821]

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.[831] ASCO also has a clinical practice guideline for the management of chronic pain in survivors of adult cancers.[832]

Screening for and Assessment of Pain

All cancer survivors should be screened for pain at regular intervals. If pain is related to cancer, the intensity should be quantified, and quality should be characterized 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).[833-836] 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 or other specialist can be made for non-cancer or non-cancer-treatment–related pain workup and management (eg, rheumatoid arthritis).

Management of Pain

The goals of pain management are to increase comfort, maximize function, and improve quality of life. A multimodality/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. 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 specialist, physical therapy, physical medicine and rehabilitation, palliative care, 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.[822,837-839] 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.[840] 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 inhibitor. 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.[841,842] 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.[843,844] 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.[838,845-847] In fact, data on the long-term safety and effectiveness of opioids in the non-cancer setting are scarce as well.[848]

Opioid prescribing rates among cancer survivors are substantially higher compared to controls, even long after attaining cancer survivorship.[849,850] 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).[849] 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 180 days after surgery, suggesting that aberrant opioid use or diversion of pain medication may be an issue in the survivor population.[851]

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.[852-856] 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 the risks of opioids through provider, patient, and family/caregiver education.[857-859] 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.

In 2022, the CDC released updated guidelines for prescribing opioids for chronic pain.[860] In May 2016, ASCO released a policy statement describing principles to help balance concerns for opioid misuse with concerns for appropriate access to opioids for pain management in patients with cancer and survivors.[861] The NCCN Survivorship Panel shares these concerns and supports ASCO's statement. Overall, the Panel believes that the concerns for opioid misuse must be balanced with concerns for appropriate access to opioids for pain management in patients with cancer and survivors.[861-863]

Adjuvant Analgesics: Adjuvant analgesics include antidepressants (eg, SNRIs, tricyclic antidepressants) and anticonvulsants (eg, gabapentin, pregabalin).[840] These are recommended for the treatment of survivors with neuropathic pain, post-radiation pain, chronic pain syndromes, myofascial pain, 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.[838] Another review found that antidepressants and anticonvulsants may provide additional neuropathic pain relief when added to opioids in patients with cancer.[864]

Tricyclic antidepressants have been shown to relieve neuropathic pain in the non-cancer setting.[865,866] 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.[867] The ASCO clinical practice guidelines for the prevention and management of CIPN in survivors of adult cancers recommend duloxetine in this setting.[868] 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.[869] 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 arthralgias.[870] Both drugs have also demonstrated efficacy in diabetic and postherpetic neuropathy,[871-873] but have not been well-studied in the cancer or survivorship settings.[868] One randomized, placebo-controlled, crossover trial in 115 survivors found that gabapentin did not effectively treat CIPN.[874] 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.[868] 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.[875] 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.[876]

Nonsteroidal Anti-Inflammatory Drugs: NSAIDs, including COX-2 inhibitors, and acetaminophen are recommended for the treatment of myofascial and skeletal 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 pain control in patients with advanced cancer are limited and weak but suggest some efficacy at reducing pain and opioid dose requirement.[877]

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.[878,879] 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.[823,880-886] 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.[887] Quality of life was also improved in the intervention arm, but distress was not reduced.

Psychosocial support and education should be provided.[888] 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.[882,889] 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.[890]

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 their intact limb in a mirror while trying to move the amputated limb. In a small randomized trial, mirror therapy reduced 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).[891] One case report suggests that this therapy can be effective in survivors.[892]

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.[893] 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.[206,823,894,895] Several randomized controlled trials have reported a reduction of neck and shoulder pain associated with exercise or therapy programs.[896-900] 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.[898] 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.[896] 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).[899] 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.[290] 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.[901]

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.[823] 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. 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,[902-908] but the evidence for the effectiveness of lidocaine and capsaicin is stronger.[902,904-906] 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.[909] 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.[910,911] 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.[905] A larger trial with a similar population of 92 patients found no effect of topical amitriptyline, ketamine, or a combination of the two.[912] Another study found that a higher dose of amitriptyline had some efficacy in reducing peripheral neuropathy, but also showed systemic effects.[913] 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.[914] 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.[915]

TENS is a noninvasive procedure in which electrodes are placed on or around the painful area.[823] A systematic review demonstrated that data supporting the efficacy of TENS for reducing cancer-related pain are inconclusive.[916] 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.[823] The data on these interventions are also limited.[823]

Acupuncture

Acupuncture is recommended as a possible option for the treatment of myalgias, arthralgias, and myofascial or neuropathic pain in survivors. Evidence supporting the efficacy of this technique for reducing cancer-related pain is evolving.[917-919] A small randomized controlled trial compared electroacupuncture (EA) to white light cystoscopy (WLC) and sham acupuncture in 67 postmenopausal patients with breast cancer and aromatase inhibitor-associated arthralgia.[920] 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 patients with early-stage breast cancer and aromatase inhibitor-induced joint pain 2:1:1 to acupuncture, sham acupuncture, or waitlist.[921] 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.[922]

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.

Hormone-Related Symptoms

Sexual function and management of hormone-related symptoms are important aspects of quality of life for all cancer survivors. The recommendations here are intended for cisgender survivors based on the availability of data in this population but should be followed for gender-diverse survivors as applicable, with the involvement of the appropriate health care specialists.

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.[923-927] In one study of breast cancer survivors diagnosed at age <40 years, 46% of participants reported hot flashes, 51% reported vaginal dryness,

and 39% reported dyspareunia.[926] Similarly, about 50% to 80% of patients on ADT experience hot flashes, which can persist after treatment.[928-933] The incidence of gynecomastia in patients on ADT varies with the method of ADT used and can be as high as 80% in those on estrogen therapy.[930,934]

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 individuals reach menopause at a mean age of 51 years, with 95% reaching menopause between 45 and 55 years of age.[935] Many cancer survivors experience menopausal symptoms without meeting the definition of menopause, including survivors on tamoxifen or aromatase inhibitors or with a history of oophorectomy or chemotherapy and 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 patients of all genders. Individuals assigned male at birth may experience many of the same symptoms as those assigned female at birth, as well as gynecomastia, decreased testicle size, and thinning of body hair. Hormonal symptoms can have a profound impact on quality of life.[925,936]

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.[937-939] If appropriate and desired, referral for fertility preservation should be considered before chemotherapy, because studies report that 33% to 73% of premenopausal patients treated for breast cancer become peri- or postmenopausal after treatment.[925] Younger survivors with irregular menses may have primary ovarian insufficiency and may develop menopausal symptoms.[940] These patients may or may not be fertile, and should be counseled on the need for contraception to prevent unintended pregnancy if they do not meet the definition of menopause and if their sexual activity could result in pregnancy. In non-cancer populations, primary ovarian insufficiency or early menopause may be associated with specific menopause-related health risks. However, data in cancer survivors are limited.

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 premenopausal 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.[941,942] In male survivors, total testosterone and free testosterone may also be checked if hypogonadism is suspected.[943] For survivors 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 Cisgender 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 certain antidepressants, anticonvulsants, neuropathic pain relievers, certain antihypertensives, antimuscarinic anticholinergic agents, and selective neurokinin-3 (NK3) receptor antagonists.[944-949] 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.[950-952] A randomized clinical trial in healthy postmenopausal individuals showed that low-dose paroxetine reduces the frequency and severity of hot flashes.[952] Small studies have shown that SSRIs and SNRIs also reduce the severity and frequency of hot flashes in female cancer and survivor populations.[953-962] One of these studies was a randomized, double-blind, placebo-controlled study in 80 survivors of gynecologic cancers.[954] 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 survivors on tamoxifen, because these drugs block the conversion of tamoxifen to active metabolites through inhibition of CYP2D6.[607,963] 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 those on concurrent tamoxifen and antidepressants, including SSRIs such as paroxetine.[606] In contrast, a study of 2430 breast cancer survivors found an increased risk of cancer death in those taking tamoxifen and an SSRI.[964] 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 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.[965-970] 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.[969] 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 individuals.[971,972] Randomized controlled trials in breast cancer survivors also show that clonidine can reduce hot flash frequency and severity in postmenopausal survivors taking tamoxifen.[973,974] Side effects include sleep difficulties, dry mouth, fatigue, dizziness, and nausea.

Oxybutynin, an antimuscarinic anticholinergic agent, has been shown to reduce the quantity and severity of hot flashes in perimenopausal and postmenopausal individuals.[948] A randomized, multicenter, double-blind study of 150 patients (65% of participants were taking tamoxifen or an

aromatase inhibitor) showed a greater reduction in hot flash frequency in those on twice-daily dosing (5 mg twice a day: -7.5 [SD, 6.6], 2.5 mg twice a day: -4.8 [SD, 3.2], placebo: -2.6 [SD, 4.3]; *P* < .003 for both oxybutynin doses vs. placebo). Individuals on oxybutynin also reported overall improved quality of life. Side effects of oxybutynin include urinary retention, dry mouth, and other known anticholinergic effects.

Fezolinetant, an NK3 receptor antagonist, may also be considered as a non-hormonal treatment option for vasomotor symptoms in menopausal individuals. In a randomized, double-blind, placebo-controlled, phase 3 trial, the safety and efficacy of fezolinetant was studied in 2205 menopausal individuals who reported at least 7 moderate to severe hot flashes per day.[949] Those who received doses of 30 mg and 45 mg fezolinetant showed a significant reduction in vasomotor symptoms at 4 weeks (-0.15 [0.06; *P* = .012], -0.19 [0.06; *P* = .002]) and 12 weeks (-0.24 [0.08; *P* = .002], -0.20 [0.08; *P* = .007]), respectively, when compared to the control arm. Side effects of fezolinetant include risk of elevated liver enzymes; however, they were found to be transient and resolved without intervention.

Several studies have compared non-hormonal pharmacologic treatments. For example, venlafaxine has been compared with clonidine in breast cancer survivors.[975-977] 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.[970] 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 (for survivors who have overweight or obesity), hypnosis, and CBT may help survivors manage hot flashes.[311,944,946,947,978-982] 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.[945,983-990] 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.[991] Limited data show a possible benefit of black cohosh for vasomotor symptoms in the general population.[992-994] However, randomized data in breast cancer survivors show no benefit.[995] 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.[996,997] Several studies in people with cancer or survivors have shown acupuncture to be a safe and effective option for managing vasomotor symptoms.[998-1001] 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.[998,1000,1001]

Yoga may also help survivors manage hot flashes. A randomized trial in 355 healthy peri- and postmenopausal individuals found that yoga improved quality of life associated with menopause, including an improvement in the vasomotor symptom domain.[1002] Another randomized controlled trial showed that yoga improved sleep but did not affect the frequency of symptomatic burden of vasomotor symptoms.[1003]

Evidence that exercise/physical activity helps manage hot flashes in postmenopausal individuals is inconclusive.[944,1002,1004-1010] In fact, a

randomized controlled trial of 261 peri-menopausal and postmenopausal individuals found no difference in the frequency of hot flashes between those randomized to an exercise intervention and the control group.[1005] A similar trial involving 248 participants also found that physical activity did not improve vasomotor symptoms.[1008] 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.[1011] 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 individuals 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.[980] Data in breast cancer survivors also suggest that weight loss may help alleviate hot flashes in this population.[311,982] 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.[1012] Although studies of this sort have not been done in survivor populations, data suggest that survivors who currently smoke are more likely to experience hot flashes.[1013] Individual vasomotor responses to alcohol vary.[1014] 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.[1015,1016] 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, to receive CBT plus an exercise intervention, or to a control group.[1011] Results suggested that CBT lessened the perceived burden of hot flashes. Another study randomized 96 survivors with hormonal symptoms after breast cancer treatment to a group CBT intervention or a usual care group.[1017] 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, or wait-list control.[1018] 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 individuals.[935,1019-1024] However, the use of long-term MHT is controversial because, for many, the health risks associated with MHT are thought to outweigh the potential benefits. In the past, MHT was typically given to postmenopausal individuals 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 postmenopausal individuals aged 50 to 79 years 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.[1025] In the WHI, estrogen plus progestin in postmenopausal individuals aged 50 to 79 years 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.[1026] The participants 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 those who received placebo.[1027-1029] MHT was also associated with an increase in breast cancer incidence and the cancers were more likely to be lymph node positive.[1030,1031] 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.[1032] 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 individuals taking estrogen and progestins combined.[1033]

Data from retrospective studies and an incomplete randomized controlled trial suggest that MHT is safe to use in survivors of early-stage endometrial cancer.[1034-1038] 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.[1039] In the Stockholm trial, no difference was seen in breast cancer recurrence after 10.8 years of follow-up.[1040]

Overall, based on these data, the Panel believes that MHT can be used in appropriate 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 those who currently smoke, 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 include combination estrogen and progestins (for survivors with an intact uterus) or estrogen alone (for survivors assigned female at birth 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.[1041] 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,[1042] and is FDA-approved for treating menopausal symptoms in healthy postmenopausal individuals. 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.[1043,1044] 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 they are not contraindicated.

Treatment of Vaginal Dryness

Vaginal dryness can be treated with over-the-counter vaginal moisturizers, gels, oils (category 2B), and hyaluronic acid (category 2B).[1045-1047] Lubricants can be used for sexual activity.[1048,1049] In one study of breast cancer survivors, the control group used a non-hormonal moisturizer and saw a transient improvement in vaginal symptoms.[1045] Survivors should be cautioned that some lubricants may be irritating to the area of application.

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.[1026,1050-1056] Furthermore, some controversy exists regarding their safety in survivors of hormone-dependent cancers.[1057] However, evidence suggests that local estrogen does not increase the risk of breast cancer recurrence.[1058] Vaginal estrogen preparations include rings, suppositories, and creams and have been shown to be effective for managing symptoms of vaginal dryness in menopausal individuals.[1056,1059] 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.[1057,1060] Other topical hormones (ie, testosterone, dehydroepiandrosterone [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.[1051] 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 individuals. Significant improvements in symptoms were observed in as many as 84% of participants, although sample sizes are small.[1061-1063] Studies suggest that adverse events are infrequent and include pelvic pain, vaginal infections, genital herpes reactivation, and postmenopausal bleeding.[1061,1064,1065] Some trials have shown a benefit of laser therapy in improving symptoms of genitourinary syndrome of menopause in cancer survivors, but data on the overall safety and effectiveness of these types of devices in cancer populations are limited.[1066-1069] Furthermore, 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. Overall, the Panel believes that although preliminary data look promising, additional studies in cancer survivors are needed before this technique can be recommended.

Treatment of Urogenital Complaints

Patients 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.[1059,1070] See *Treatment of Vaginal Dryness*, above, for a discussion on the safety of vaginal estrogen.

Management of ADT-Related Symptoms

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, 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 those 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.[1071-1074] Individuals

with vasomotor symptoms should be offered medication for symptomatic improvements. Options include venlafaxine, MPA, cyproterone acetate, and gabapentin.[1075]

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 patients with prostate cancer in two randomized controlled trials.[1076-1078] Case reports and small pilot studies have shown that venlafaxine may improve hot flash symptoms in patients with prostate cancer undergoing ADT.[1079] The Panel lists venlafaxine as the preferred antidepressant and gabapentin as the preferred anticonvulsant for hormone-related symptoms.

Survivors with ADT-related symptoms can try non-pharmacologic treatments, including acupuncture, exercise/physical activity, yoga, lifestyle modifications, weight loss (if individual has overweight or obesity), hypnosis, and CBT.[1075] 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.[1080,1081] 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.[1082]

Phytoestrogens, botanicals, and dietary supplements are often used. However, data are limited on the effectiveness and safety of these nonpharmacologic treatments in survivors on ADT.[1083] Furthermore, there are concerns that supplemental vitamin E may increase the risk for prostate cancer.[1084,1085] 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 individuals with anemia, bone density loss, diabetes, exposure to chemotherapy or testicle radiation, HIV/AIDS, chronic narcotic use, infertility, pituitary dysfunction, and chronic corticosteroid use.[1086] 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.[1075] 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 PCP (ie, surgeon, oncologist, radiation oncologist). Patients still receiving ADT should not receive androgens (eg, testosterone).

Androgens are contraindicated in patients with prostate cancer on active surveillance or observation, in patients actively being treated for prostate cancer, and in those with advanced prostate malignancy on ADT. The 2018 AUA Guidelines Committee found insufficient evidence to quantify the risk-benefit ratio of testosterone therapy in survivors with a prior history of prostate cancer.[1086] 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 patients on ADT by prophylactic radiation (must be delivered prior to development of breast tissue), tamoxifen, or reduction mammoplasty.[934,1087,1088]

Anemia

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

Guidelines for Hematopoietic Growth Factors (available at www.NCCN.org).

Sexual Health

Cancer treatment, especially hormonal therapy with induced menopause 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.[1089] It is also important to note that individuals with past trauma are more likely to experience sexual dysfunction, although data in cancer populations are lacking.[1090]

Sexual dysfunction may be especially common in certain populations of cancer survivors. For example, 24% to 100% of head and neck cancer survivors reported a negative effect of head and neck cancer on their sexuality.[1091,1092] Other populations that are likely to experience sexual dysfunction include survivors of anal or colorectal cancer and gay and bisexual men who engage in receptive anal sex after treatment for prostate, anal, or colorectal cancer.[1093-1098] The causes of sexual dysfunction in these populations include pain, physical barriers, decreased libido, changes in emotional functioning, fatigue, and body image distress.[1093,1095-1099]

Sexual dysfunction can cause increased distress and have a significant negative impact on quality of life.[1100-1105] Nonetheless, sexual function is often not discussed with survivors.[1106-1110] 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.[1100] However, effective strategies for treating 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 cancer that ASCO has endorsed.[1075,1111] 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 for treatment of menopausal changes, erectile dysfunction (ED), or incontinence (ie, vaginal rejuvenation by lasers or ED by shock waves). 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.

Sexual Function in Gender-Diverse Survivors

Gender diverse individuals include those who are transgender, non-binary, agender, intersex, and gender queer. Unfortunately, there is a lack of research regarding sexual function following cancer treatment in this population.[1112,1113] The Panel therefore developed the recommendations within these Guidelines for cisgender survivors based on the availability of data, but the Panel believes they should be followed for gender-diverse survivors as applicable, with involvement of appropriate health care specialists. The Panel notes that studies on the unique sexual health issues faced by gender-diverse cancer survivors are greatly needed.

Sexual Health in Cisgender Women

Sexual problems related to issues with sexual desire, arousal, orgasm, and pain are common after cancer treatment.[1114-1116 33,1104,1117-1123] 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; $P < .001$).[1121] A survey of survivors of ovarian germ cell tumors and age-, race-, and education-matched controls found that survivors reported a significant decrease in sexual pleasure.[1124]

Sexual dysfunction varies with cancer site and treatment modalities.[1118,1119] 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.[1118] A systematic review of sexual functioning in cervical cancer survivors found similar results, except that no differences in orgasm/satisfaction were observed.[1125] Chemotherapy seems to be linked to sexual dysfunction in breast cancer survivors,[1119] possibly related to the prevalence of chemotherapy-induced menopause in this population.[1115] Furthermore, body image changes related to breast cancer surgery and reconstruction can affect sexual health and well-being.[1126] In addition, survivors with a history of HCT may have multiple types of sexual dysfunction even 5 to 10 years after diagnosis.[1127-1129] Some of the sexual dysfunction associated with HCT is related to GVHD, which can result in vaginal fibrosis, stenosis, mucosal changes, vaginal irritation, bleeding, and increased sensitivity of genital tissues.[1128,1130] 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 Health in Cisgender Men

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) defines ED as a condition in which someone is unable to get or keep an erection firm enough for satisfactory sexual intercourse.[1131] 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.[1132] In one community-based study, 33% of participants aged ≥75 years reported moderate or worse ED.[1133] ED is also very common in cancer survivors. Cancer 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%,[1095,1101,1134,1135] and it has been reported in up to 90% of survivors of prostate cancer.[1135-1140]

Male cancer survivors exposed to radiation or chemotherapy often experience hypogonadism—usually primary hypogonadism—resulting in decreased libido and sexual function.[1141] Hypogonadism refers to a decrease in the production of sperm and/or testosterone. Primary hypogonadism results when the testes do not produce enough testosterone; 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 survivors 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 the absence of an adequate compensatory response. In these individuals, low testosterone levels are associated with normal or low levels of gonadotropins, suggesting physiologic problems of both the testicles and hypothalamic-pituitary system.[1142]

Cancer therapies can also cause a variety of ejaculatory dysfunctions (premature, absent, delayed, or climacturia) or problems with orgasm (eg, less intensity, difficulty achieving, pain).[1143-1146]

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. 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.[1147-1149] 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.[1150] For more information regarding fertility in cancer survivors, see *Fertility*, below.

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 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).[1151-1154] 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.[1132,1155,1156] The FSFI has been validated in patients with cancer and cancer survivors.[1157,1158] The FSFI and ASEX were also identified in a systematic review as tools that have acceptable psychometric properties in patients with breast cancer.[1159] 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 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 excessive alcohol use, 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, total morning testosterone should be measured if indicated by concerns regarding hypogonadism.[943]

Interventions for Sexual Dysfunction in Cisgender Women

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 sexual dysfunction. Referrals to specialists (ie, psychotherapy, sexual/couples counseling, gynecologic care, sexual health specialist [sex therapist, if available]) should be made if appropriate and available. For sexual concerns that may be related to menopause (eg,

vaginal dryness, discomfort, discharge, pain), MHT can lead to improvements in sexual function (see *Hormone-Related Symptoms*, above).

Overall, the evidence base for interventions to treat sexual dysfunction in survivors is weak and high-quality studies are needed.[1160,1161] Based on evidence from other populations, evidence from survivors when available, recommendations from the American College of Obstetricians and Gynecologists (ACOG),[1162] and consensus among NCCN Survivorship Panel members, the Panel made recommendations for treatment of sexual dysfunction in cisgender female 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 survivors with sexual dysfunction because they can help alleviate associated symptoms like anxiety that can impact sexual functioning.[1002,1163] In addition, CBT has been shown to be effective at improving sexual functioning in breast cancer survivors.[1164]

Vaginal moisturizers, vaginal gels, oils, and topical vitamin D or E can help alleviate symptoms such as vaginal dryness and sexual pain,[1046,1165] 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.[1166]

Many survivors with sexual dysfunction may have associated pelvic floor dysfunction that can be treated with pelvic physical therapy (ie, pelvic floor muscle training). Alleviating pelvic floor dysfunction may improve sexual pain, arousal, lubrication, orgasm, and satisfaction. In fact, a small study of 34 survivors of gynecologic cancers found that pelvic floor training significantly improved sexual function.[1167]

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. Although evidence for the effectiveness of dilators is limited,[1168] they may be useful for increasing vaginal depth and accommodation and may allow a survivor to discover what hurts and what does not in a non-sexual setting.

Several topical prescription medications can also be considered for survivors with sexual dysfunction (also see *Treatment of Vaginal Dryness*, under *Hormone-Related Symptoms* above). Vaginal estrogen (pills, rings, or creams) is the most effective treatment for vaginal dryness leading to sexual dysfunction, and it has been shown to be effective in treating itching, discomfort, and painful intercourse in postmenopausal individuals.[1026,1052-1056] A study in 76 postmenopausal survivors of HR-positive breast cancer on aromatase inhibitor therapy found that intravaginal testosterone cream or an estradiol-releasing vaginal ring were safe and improved vaginal atrophy and sexual function.[1169] Furthermore, a large cohort study of almost 50,000 patients with breast cancer followed for up to 20 years showed no evidence that there was a higher risk of breast cancer-specific mortality in those using vaginal estrogen.[1170] 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 also 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 individuals.[1171-1175] However, a systematic review and meta-analysis published in 2015 concluded that it is uncertain whether vaginal DHEA improves vaginal dryness.[1176] 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.[1051] 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 those with a history of breast cancer. The Panel cautions that DHEA should be used with caution in survivors on aromatase inhibitor therapy, because vaginal DHEA increases levels of circulating androgens,[1177] which have the potential to impact aromatase activity. Overall, the safety of vaginal hormones has not been firmly established in survivors of estrogen-dependent cancers. Therefore, first-line vaginal therapy for survivors of estrogen-sensitive cancers should be over-the-counter options.

In 2013, the FDA approved the SERM ospemifene for treating moderate to severe dyspareunia in postmenopausal individuals without known or suspected breast cancer and without a history of breast cancer.[1178] Ospemifene has been studied in several large trials of individuals with postmenopausal vulvar and vaginal atrophy and was found to effectively treat vaginal dryness and dyspareunia.[1179-1181] 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.[1182] The Panel recommends consideration of ospemifene for dyspareunia in survivors without a history of estrogen-dependent cancers.

In August 2015, the FDA approved flibanserin to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. Meta-analyses have shown that flibanserin resulted in approximately 1 additional satisfying sexual event every 2 months in premenopausal individuals.[1183,1184] Preliminary results from a small study of 37 survivors with breast cancer on adjuvant endocrine therapy showed that flibanserin may also be effective in this population.[1185] Although it is not FDA approved for use in postmenopausal individuals, some data suggest that it can be effective and safe in the postmenopausal setting as well.[1186,1187]

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. The safety and efficacy of bremelanotide in premenopausal individuals with HSDD was evaluated in two phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trials (RECONNECT; BMT-301, and BMT-302).[1188] 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. Participants 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 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 cisgender female survivors with low or lack of desire, libido, or intimacy include bupropion and buspirone.[1189] These drugs have been studied in a few trials involving non-cancer populations.[1190-1192] 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 limited data regarding their effectiveness in this setting. Although thought to increase pelvic blood flow to the clitoris and vagina,[1193,1194] PDE5i showed contradictory results in randomized clinical trials of various non-cancer populations of women being treated for sexual arousal disorder.[1195-1200] More research is needed before a recommendation can be made regarding the use of sildenafil for the treatment of female sexual dysfunction.

Interventions for Sexual Dysfunction in Cisgender Men

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 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 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 [sex therapist, if available]) should be made if appropriate and available. Treatment of sexual dysfunction should be guided by the specific type of problem.

Treatment for 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 this population.[1201-1204] In fact, one study found that PDE5i treatment with an aerobic activity program was more effective than PDE5i treatment alone in 60 patients with ED.[1205] 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 sexual dysfunction.[1206-1210] Small studies in survivors of prostate cancer suggest that these approaches can be helpful in the survivorship population as well.[1211,1212] Therapy is often offered in conjunction with medical therapy.

PDE5i treatment has been shown to improve the symptoms of ED and be well tolerated.[1213,1214] The 2017 ASCO Practice on Interventions to Address Sexual Problems in People with Cancer recommends PDE5i medications be used to help patients with ED.[1075] Many studies have also shown the efficacy and tolerability of PDE5i for treating ED in patients with cancer and survivors.[1215,1216] Importantly, PDE5i are contraindicated in patients taking oral nitrates, because together they can lead to a dangerous decrease in blood pressure.[1217,1218] The timing and dose of on-demand PDE5i should be started conservatively, and it should be titrated to the maximum dose as needed.[1219] 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.[1220-1223]

If total morning testosterone is <300 ng/dL, then hypogonadism is diagnosed and testosterone therapy may relieve symptoms of ED, problems with ejaculation, or problems with orgasm.[1224] A randomized

controlled trial in 470 patients >65 years of age with testosterone levels <275 ng/dL found that testosterone gel led to improvements in sexual function, desire, and activity.[1225,1226] Other studies have shown that the addition of testosterone to PDE5i therapy in individuals with low serum testosterone levels helps improve ED.[1227-1232] Testosterone therapy should not be used if contraindicated by the primary oncologic diagnosis (eg, prostate cancer on active surveillance, prostate cancer on ADT). Furthermore, the Panel cautions that exogenous testosterone therapy should not be prescribed to those who are currently trying to conceive because it can cause short-term suppression of sperm production.[1233] Although evidence is conflicting, testosterone may also have a long-term impact on spermatogenesis, which should be discussed with those interested in future fertility.[1233]

Other treatments may help with ED and with ejaculation and orgasm issues. Although evidence in the general population is lacking,[1234] studies in prostate cancer survivors suggest that pelvic physical therapy (ie, pelvic floor muscle training) may improve sexual function in this population.[1235,1236] Vibratory therapy may reduce problems with premature ejaculation.[1237] Cabergoline, a dopamine agonist, has been shown to have subjective improvement in orgasm.[1238] A retrospective pilot analysis of 131 men with orgasmic disorder who took cabergoline 0.5 mg twice weekly showed subjective improvement in two-thirds of participants. Other options to treat problems with ejaculation include a psychological evaluation and use of SSRIs or on-demand clomipramine, although data in cancer populations are lacking.[1145,1146]

Cancer therapies can also result in a variety of ejaculatory dysfunctions (premature, absent, delayed, or climacturia), and these are best addressed with urology specialist consultation.[1143-1146]

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 (SMSNA) does not recommend the use of restorative therapy in routine clinical practice, citing an absence of robust clinical trial data supporting their efficacy.[1239] Although they strongly support the development of novel erectogenic therapies, they note: “…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/SVF are investigational and platelet rich plasma is experimental and should only be conducted under research protocols in compliance with Institutional Review Board approval at little or no cost to the patient. Specifically, the SMSNA does not feel that it is appropriate or ethical for providers to advertise or otherwise make implicit or explicit claims of efficacy for these therapies pending further data. Similarly, patients considering such therapies should be fully informed as to the lack of data demonstrating clinically relevant efficacy and consented regarding the potential benefits and risks.”[1239]

Fertility

Cancer treatments, particularly chemotherapy and radiation, can be gonadotoxic and can result in impaired fertility.[1148] Fortunately, fertility preservation techniques can be effective and are widely available.[1148,1240,1241] In addition, radiation planning techniques can be used to spare or minimize dose to reproductive organs and thus minimize the impact of radiation on fertility.[1242] Thus, for survivors in their reproductive years, fertility preservation is of crucial importance and should be an integral part of their cancer care.[1240,1243-1245] Importantly, the population of survivors of reproductive age is increasing. The incidence of cancer in individuals <50 years of age has risen over the last decade.[1246] In fact, in

2019, 56,468 people in the United States were diagnosed with cancer before the age of 49 years.[1246]

Unfortunately, however, there are barriers to fertility preservation in patients with cancer, including those at the patient level (eg, not receiving or remembering adequate information; concerns about delaying cancer treatment), the clinician level (eg, limited knowledge, training, and confidence; discomfort with the topic), and the system level (eg, lack of insurance coverage; scarcity of fertility resources; absence of standardized referral mechanisms).[1247,1248] Rates of counseling on the infertility risks of chemotherapy in patients of reproductive age was only 44% in a large cross-sectional study, and range from 34% to 70% in other studies.[1149,1249]

Ideally, the survivor's goals regarding fertility and the risks of treatment-induced infertility should be discussed with all reproductive-aged survivors at the time of cancer diagnosis and before cancer treatment is initiated. Available options for fertility preservation should be discussed and/or referrals made to the appropriate specialists for those patients wishing to preserve fertility prior to initiation of cancer treatments, because fertility preservation procedures such as oocyte, embryo, or ovarian tissue cryopreservation and sperm banking before treatment are the most effective way to preserve fertility. In addition, limited evidence suggests that luteinizing hormone-releasing hormone (LHRH) agonists and antagonists given during chemotherapy may help preserve ovarian function and thus lead to improved fertility.[1250] The NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at www.NCCN.org) have more information on pretreatment fertility preservation.

These conversations should be performed by a multidisciplinary team that can include oncologists, reproductive endocrinologists and urologists, and reproductive surgeons with fertility preservation training.[1241] Ongoing collaboration between specialists is also recommended. Conversations surrounding fertility, especially for younger survivors, can have a strong emotional impact, and there may be concerns about the cost of fertility preservation or the transmission of heritable diseases. Therefore, mental health professionals, ethicists, genetic counselors, and financial counselors may also be needed to assist survivors in the decision-making process about fertility preservation.[1240,1241]

Fertility After Cancer Treatment

Premenopausal cancer survivors who received chemotherapy may experience transient or permanent menopause, dependent on the age of the patient and the type of chemotherapy.[937-939] For example, 33% to 73% of premenopausal patients treated for breast cancer become peri- or postmenopausal after treatment.[925] However, clinicians and survivors should not assume that an amenorrheic survivor is infertile, as menses may resume. A discussion regarding the need for contraception may be needed in some cases, because the incidence of unplanned pregnancies is approximately three times higher in cancer survivors than in the general population.[1150]

Cancer treatment can also cause low sperm counts (oligospermia), an absence of sperm (azoospermia), and diminished sperm quality and can have effects on erection and ejaculation.[1251,1252] For example, in one study of survivors treated for testicular cancer between 1979 and 1999, 67.1% of patients who attempted to impregnate their partners succeeded compared with 91.2% before treatment.[1253] Radiation was more detrimental to fertility than chemotherapy. More recent data showed that only 56.5% of posttreatment testicular cancer survivors successfully impregnated their partners.[1254]

Addressing Fertility After Cancer Treatment

A survey of 484 cancer survivors who wanted to have children before treatment showed that the majority maintained that desire 3 to 7 years

post-treatment, but about one third of respondents reported difficulty conceiving.[1147] Furthermore, an unfulfilled desire to have children was associated with poorer mental health.

Survivors and clinicians should be aware that there are approaches that can be undertaken after cancer treatment to aid in fertility for those who did not receive fertility preservation before treatment. For example, some evidence suggests that ovarian tissue cryopreservation and oophorectomy after aggressive cancer treatment can result in viable tissue and live births following transplantation, and testicular sperm extraction and intracytoplasmic sperm injection are methods that can help post-treatment survivors with minimal sperm achieve pregnancy.[1149] Furthermore, pregnancy is usually considered safe for survivors and their offspring post treatment, although the majority of data is in those treated for breast cancer.[1255] Similarly, although there can be mutagenic effects of chemotherapy and radiation on sperm and data on safety of conception during or shortly after cancer treatment are limited, conception post cancer treatment can result in healthy offspring.[1256,1257]

Therefore, it is important for clinicians caring for survivors to be aware that fertility issues should be discussed in the survivorship phase, regardless of if they were not addressed prior to treatment. The Panel recommends that post-treatment survivors interested in fertility should be assessed by a fertility specialist.

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.[1258] Sleep disturbances are common, affecting 30% to 50% of patients with cancer and survivors, often in combination with pain, fatigue, anxiety, and/or depression.[1258-1269] In fact, sleep disorders have been shown to be a risk factor for suicide.[561] Improvements in sleep quality lead to improvements in fatigue, mood, and overall quality of life.[751] Most clinicians, however, do not know how best to evaluate and treat sleep disorders.[1258]

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).[1270] 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.[1270]

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.

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.[1271-1274] It is important to note that survivors may have more than one 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.[1275-1280] 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 use disorder, obesity, cardiac dysfunction, endocrine dysfunction, respiratory disorders, anemia, neurologic disorders (including CIPN), pain, fatigue, and emotional distress. Screening for common sleep disorders such as sleep disordered breathing (eg, 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 3 months. 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 sleep disordered breathing.[1281] Other screening tools for OSA risk have also been validated.[1282,1283] Sleep studies can confirm the diagnosis of sleep disordered breathing; 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, sleepwalking, 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.[1284,1285] Alternatively, referral can be made to a sleep specialist or PCP for further evaluation.

Evaluation for Insomnia

If insomnia is diagnosed, details should be obtained regarding the course of insomnia, including the duration of symptoms. Insomnia is considered chronic if symptoms have been ongoing for ≥3 months. It should also be determined whether the insomnia symptoms are causing distress, impacting daytime functioning, or affecting the survivor's quality of life.

Management of Sleep Disorders

In all survivors, 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.[1258,1286,1287] Referral to a sleep specialist can be considered in most cases, especially for sleep disordered breathing, RLS, parasomnias, circadian rhythm disorders, narcolepsy, and chronic or refractory insomnia. Referral to a PCP can also be considered, except for survivors with 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 case 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.[1288-1290] Key points are listed in the guidelines and include regular morning or afternoon physical activity; daytime exposure to bright light, particularly in the morning; 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 adults in non-cancer settings.[1291-1294] Physical activity may also improve sleep in patients with cancer and survivors.[206,1295-1300] 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.[1296] 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.[1301] Another randomized controlled trial assessed the effects of a 3-month physical activity behavior change intervention on 222 breast cancer survivors.[1302] 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, internet-based CBT, relaxation therapy, stimulus control, and sleep restriction are recommended to treat sleep disturbances in survivors.[1303-1305] 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.[740-742,750,1306-1308] 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 treat insomnia as they would in normal clinical practice) had no effect on wakefulness.[740] Another trial randomized 96 survivors (68% breast cancer; 87% female) to a 7-week intervention of CBT, armodafinil, CBT plus armodafinil, or placebo.[1308] 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 meta-analysis identified 8 studies, including 752 cancer survivors, and found large effect sizes for self-reported insomnia severity (d = .77) following CBT.[1309] 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.[1309] In fact, the American College of Physicians

recommends that CBT be the initial treatment for all adults with chronic insomnia disorder.[1303]

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.[1310] 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.[1311]

A randomized, partially blinded, noninferiority trial compared CBT with MBSR in 111 patients with cancer.[1312] 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.[1313]

Pharmacologic Interventions

Many pharmacologic treatments for sleep disturbances are available, including hypnotics for insomnia (eg, zolpidem, ramelteon).[1314,1315] Many of the FDA-approved hypnotics are BZD receptor agonists and can be associated with dependence, misuse, 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 are often used off-label for the treatment of insomnia, even though limited to no efficacy or effectiveness data are available for this use. Trazadone is one of the most commonly used medications for insomnia but due to paucity of evidence of its long-term efficacy and safety, it is not recommended for routine use.[1316-1318] 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.[1319] A 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; $P < .001$).[990] Overall, however, data on pharmacologic interventions aimed at improving sleep in patients with cancer and survivors are lacking.[1268]

Treatment of Sleep Disordered Breathing

Weight management should be recommended to survivors with sleep disordered breathing (ie, OSA [most common]; central sleep apnea), because studies have shown weight loss to be associated with reduced hypoxia and excessive sleepiness in patients with sleep disordered breathing.[1320] Small randomized studies have also shown that physical activity can improve sleep disordered breathing symptoms independent of weight loss.[1321,1322] In addition, survivors with sleep disordered breathing should be referred to a sleep specialist or PCP. The most common medical treatment for sleep disordered breathing is continuous positive airway pressure (CPAP).[1323]

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 gabapentin enacarbil.[1324-1332] Two separate 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.[1332,1333]

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.[1334] The American Academy of Neurology also has clinical practice guidelines for the treatment of adults with RLS.[1335]

Employment Issues and Return to Work

Cancer and its treatment often have an adverse effect on work status, performance, and satisfaction.[1336] 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.[1336-1340] 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.[1336,1341,1342]

Several studies have addressed factors that predict a delayed return to work.[1343-1349] 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.[1347] In addition, a systematic review of cohort studies that included survivors aged 18 to 65 years found that more advanced age, lower education level, and lower income were associated with a reduced likelihood of returning to work.[1348] 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.[1350]

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.[1351-1354] 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.

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.

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