Childhood Cancer Survivor Long-Term Follow-Up Guidelines

Version 1.1 - September 2003

DISCLAIMER

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The following guidelines were developed by the Children's Oncology Group as a collaborative effort of the Late Effects Committee and Nursing Discipline. These guidelines provide recommendations for screening and management of late effects potentially arising as a result of therapeutic exposures used in the treatment of childhood malignancies, and are designed for use beginning two or more years following the completion of therapy. The guidelines are **not** intended to provide guidance for follow-up of the cancer survivor's primary disease.

Children's Oncology Group is a research organization, and these guidelines were developed within the context of clinical research involving long-term follow-up of childhood cancer survivors. These guidelines are provided as a courtesy. They are an informational and educational service and are derived from in-depth review and assessment of current scientific and clinical information. They are not intended as a sole source of guidance in the evaluation of childhood cancer survivors. Rather, they are designed to assist clinicians by providing a framework for comprehensive, focused evaluations of childhood cancer survivors based on specific risk factors.

The Children's Oncology Group assumes no liability for damage resulting from the use or review of this information. While the Children's Oncology Group intends for these guidelines to reflect state-of-the-art medical knowledge and, in this regard, diligently attempts to keep the information current, the Children's Oncology Group makes no representation or warranty about the accuracy, reliability, completeness, relevance, or timeliness of the information herein and disclaims any such representation or warranty to such effect. Further, the Children's Oncology Group makes no representation or warranty that conforming to these guidelines will ensure compliance with federal, State, and/or local law. Clinicians and others who review this information are advised to consult with legal counsel to ensure compliance with federal, State, and/or local law. Further, these guidelines are not intended to supplant the functions of an Institutional Review Board (IRB), Privacy Board, or similarly constituted body.

The guidelines are not intended to replace clinical judgment, medical advice, or to exclude other legitimate criteria for screening, health counseling, or intervention for specific complications of childhood cancer treatment. Neither are they intended to exclude other reasonable alternative follow-up procedures. The Children's Oncology Group itself does not provide individualized treatment advice to patients or their families, and strongly recommends discussing this information with a qualified medical professional. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

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- **Panel of Experts**
- **Reviewers**
- **Health Link Authors**

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Introduction & Instructions for Use

Introduction to the Childhood Cancer Survivor Long-Term Follow-Up Guidelines

The Children's Oncology Group Childhood Cancer Survivor Long-Term Follow-Up Guidelines were developed as a collaborative effort of the Nursing Discipline and the Late Effects Committee. The purpose of these guidelines is to provide recommendations for screening and management of late effects that may potentially arise as a result of therapeutic exposures used during treatment for childhood cancer. These guidelines represent a statement of consensus from a panel of experts in the late effects of treatment for pediatric malignancies. The recommendations are based on a thorough review of the literature as well as the collective clinical experience of the task force members, panel of experts, and multidisciplinary review panel (including nurses, physicians, behavioral specialists and patient/parent advocates). Implementation of these guidelines is intended to increase awareness of potential late effects and to standardize and enhance follow-up care provided to childhood cancer survivors throughout the lifespan.

These guidelines are designed for use beginning **two or more years following the completion of therapy** and provide a framework for ongoing late effects monitoring in childhood cancer survivors. However, these guidelines are **not** intended to provide guidance for follow-up of the childhood cancer survivor's primary disease.

The recommendations for periodic screening evaluations provided in this document are intended to allow for earlier identification of and intervention for complications that may potentially arise as a result of childhood cancer treatment. Although some survivors will develop complications, many will not, and it is important to put the risk of these complications into perspective. The fact that these patients have survived their primary disease is the paramount benefit of the life-saving therapies that they have received. Ongoing healthcare that promotes healthy lifestyle choices and provides ongoing monitoring of health status and timely medical intervention for potential late effects is important for all childhood cancer survivors.

The Childhood Cancer Survivor Long-Term Follow-Up Guidelines were developed as a resource for clinicians who provide ongoing healthcare to childhood cancer survivors. A basic knowledge of ongoing issues related to the long-term follow-up needs of this patient population is assumed. The screening recommendations in these guidelines are appropriate for asymptomatic childhood cancer survivors presenting for routine exposure-based medical follow-up. More extensive evaluations are presumed, as clinically indicated, for survivors presenting with signs and symptoms suggesting illness or organ dysfunction. Healthcare professionals who do not regularly care for childhood cancer survivors are encouraged to consult with a pediatric oncology long-term follow-up center if any questions or concerns arise when reviewing or using these guidelines. Healthcare professionals who have difficulty locating such a center are encouraged to contact us for assistance. These guidelines are not intended to replace clinical judgment or to exclude other

reasonable alternative follow-up procedures. The Children's Oncology Group recognizes that specific patient care decisions are the prerogative of the patient, family, and healthcare provider.

Although the information within the guidelines will certainly prove valuable to the survivors themselves, at this time the only version available is targeted to healthcare professionals. Therefore, survivors who choose to review these guidelines are strongly encouraged to do so with the assistance of a healthcare professional knowledgeable about long-term follow-up care of childhood cancer survivors. This is important in order to put the recommendations in perspective, avoid over-testing, address potential anxieties, and provide a comprehensive evaluation of the survivor's health status. The Children's Oncology Group itself does not provide individualized treatment advice to patients or their families, and strongly recommends discussing this information with a qualified medical professional.

As new information becomes available, the Guidelines will be updated periodically to reflect those changes. These guidelines will be posted on the COG website at www.childrensoncologygroup.org/disc/le/ We recommend that clinicians check the website periodically for the latest updates and revisions.

Childhood Cancer Survivor Long-Term Follow-Up Guidelines: Instructions for Use

Comprehensive Treatment Summary

The Childhood Cancer Survivor Long-Term Follow-Up Guidelines are based on therapeutic exposures received during treatment for childhood cancer. Availability of a comprehensive treatment summary, including all therapeutic agents received by the survivor, is assumed. Patients who do not have a comprehensive treatment summary should be instructed to obtain one from the institution(s) where they received their treatment. The comprehensive treatment summary should include, at minimum, the following information:

- Diagnosis, including site/stage, date, and relapse(s) if any
- List of all chemotherapy agents received during treatment (including route of administration for all agents, cumulative doses for alkylators and anthracyclines, and designation of "high dose" versus "standard dose" for methotrexate and cytarabine)
- Radiation therapy summary (including types, dates, fields, total doses, and number of fractions)
- List of all surgical procedures
- Dates and types of hematopoietic cell transplant(s), including conditioning regimen(s)
- Blood products received (including date of first exposure)
- Significant complications, including treatment required

Using the Childhood Cancer Survivor Long-Term Follow-Up Guidelines

The Childhood Cancer Survivor Long-Term Follow-Up Guidelines are organized according to therapeutic exposures, arranged by column as follows:

Therapeutic Agent: The therapeutic intervention for malignancy, including chemotherapy, radiation therapy, surgery, transfusion, or hematopoietic stem cell transplant.

Section Number: Corresponds with Reference List and Index.

Potential Late Effects: Lists the most common late treatment complications associated with the therapeutic intervention.

Risk Factors: Lists host factors (e.g., age, sex, race, genetic predisposition), treatment factors (e.g., cumulative dose of therapeutic agent, mode of administration, combinations of agents), medical conditions (e.g., pre-morbid or co-morbid conditions), and health behaviors (e.g., diet, smoking, alcohol use) that may increase risk of developing the complication.

Highest Risk: Lists conditions (host factors, treatment factors, medical conditions and/or health behaviors) associated with the highest risk for developing the complication.

Periodic Evaluations: Recommended screening evaluations including health history, clinical exams, laboratory evaluations, diagnostic imaging studies, psychosocial assessments, or other indicated evaluations.

Minimum Recommended Frequency: Recommended minimum frequency of periodic evaluations based on risk factors and magnitude of risk as supported by medical literature and/or the combined clinical experience of the reviewers and panel of experts.

Health Protective Counseling: Suggested patient counseling regarding measures to prevent/reduce risk or promote early detection of the potential treatment complication. "Health Links" listed in the document are health education materials produced specifically to accompany this document. These Health Links are included in the Appendix and are also available on the COG website at www.childrensoncologygroup.org/disc/le/

Considerations for Further Testing and Intervention: Includes recommendations for further diagnostic evaluations beyond minimum screening for individuals with positive screening tests, recommendations for consultation and/or referral, and recommendations for management of exacerbating or predisposing conditions.

Cancer Screening Recommendations are included at the end of the Guidelines. This section is organized as follows:

Organ: The organ at risk for developing malignancy.

At Risk Population: Populations generally considered at increased risk for the specified malignancy based on risk factors such as age, gender, genetic susceptibility, personal or family history, health-related behaviors or co-morbidities.

Highest Risk: Populations considered by the Panel of Experts or other evaluating bodies (such as the American Cancer Society) as being at significantly increased risk for the specified malignancy. Risk factors may include therapeutic exposures resulting from childhood cancer treatment, as well as other factors listed above (e.g., genetic susceptibility).

Periodic Evaluations:

Standard Risk: Guidelines provided under the "Standard Risk" category in this document are per American Cancer Society recommendations for standard-risk populations and are included here for reference. In addition, clinicians are encouraged to consult recommendations from other organizations, such as the U. S. Preventive Services Task Force (http://www.ahrq.gov/clinic/serfiles.htm).

Highest Risk: Recommendations for these high-risk populations, when applicable, are specified and may differ from recommendations for the standard risk groups due to the significantly increased risk of the specified malignancy within the high-risk group.

References are provided immediately following the Guidelines. The Reference section contains medical citations corresponding to each numbered section of the Guidelines. Included are references that provide evidence for the association of the therapeutic intervention with the specific treatment complication and/or evaluation of predisposing risk factors. In addition, some general review articles have been included in the Reference section for clinician convenience.

Index - due to significant overlap of toxicities between therapeutic agents, and in order to avoid an enormously lengthy document, duplicate entries have been avoided as much as possible. *Therefore, **use of the Index is imperative** in order to determine the location of each potential late effect associated with each therapeutic agent within this document.*

Scoring - Each recommendation in the Guidelines was scored by the Panel of Experts (see accompanying "Explanation of Scoring" following the Index.) A tabulation of the final scores is included in this packet.

We are hopeful that these Childhood Cancer Survivor Long-Term Follow-Up Guidelines will enhance the follow-up care provided to childhood cancer survivors. If you have questions, suggestions, or concerns regarding use of these guidelines, please contact:

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Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Any cancer experience								
Clinician Info Link Long-term follow-up guidelines apply to patients who are ≥ 2 years after completion of therapy.	1	**Psychosocial Effects** Depression Anxiety Post-traumatic stress Social withdrawal, isolation	**Host factors** Female gender Family history of depression, anxiety, or mental illness **Social factors** Lower household income Lower educational achievement	**Host factors** CNS cancer or CNS-directed therapy Premorbid learning or emotional difficulties **Social factors** Failure to graduate from high school	Clinical interview	Yearly	**Health Link** Introduction to Long-Term Follow-Up after Treatment for Childhood Cancer Emotional Issues after Childhood Cancer **Resource** "Childhood Cancer Survivors: A Practical Guide to Your Future" by Nancy Keene, Wendy Hobbie & Kathy Ruccione Sebastopol, CA: O'Reilly & Assoc., 2000	Psychological consultation in patients with emotional difficulties related to cancer experience including physical deformities or chronic disabilities following cancer treatment. Consider appropriate psychotropic medications. Social work consultation. Consider evaluation of parent for post-traumatic stress syndrome.
	2	**Limitations in healthcare and insurance access**	**Social factors** Lower household income Lower educational achievement		Clinical history	Yearly	**Health Link** Finding Appropriate Healthcare after Childhood Cancer	Social work consultation.
Any Chemotherapy								
	3	**Dental abnormalities** Tooth/root agenesis Root thinning/ shortening Enamel dysplasia	**Host factors** Any patient who has not developed permanent dentition **Cancer treatment** Any radiation treatment including oral cavity or salivary glands.	**Host factors** Younger age at treatment, especially < 5 years old	Dental exam and cleaning	Every 6 months	**Health Link** Dental Health	Regular dental care including fluoride applications. Baseline panorex prior to dental procedures to evaluate root development.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Alkylating Agents								
Mechlorethamine **Cyclophosphamide** **Ifosfamide** **Melphalan** **Chlorambucil** **Lomustine (CCNU)** **Carmustine (BCNU)** **Busulfan** **Thiotepa** **Procarbazine** **Non-classical alkylators:** **Dacarbazine** **Temozolamide** **Heavy metals:** **Cisplatin** **Carboplatin** **Clinician Info Link** Doses that cause gonadal dysfunction show individual variation. Sertoli cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function. Females can typically maintain gonadal function at higher cumulative doses. Prepubertal status does not protect from gonadal injury in males.	4	**Hypogonadism** **Infertility** **Early menopause (females)** **See related topics: Radiation – TBI, head/brain, abdomen, pelvis, or testes.** **Orchiectomy** **Clinician Info Link** Extensive information regarding infertility for physicians and patients available at American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	**Treatment factors** Higher cumulative doses of alkylators or combinations of alkylators Combined with radiation to: - abdomen/pelvis - CNS - head/neck - testes - craniospinal axis in girls (from ovarian scatter)	**Host factors** Male gender **Treatment factors** MOPP > 3 cycles Busulfan ≥ 600 mg/m^2 Cyclophosphamide ≥ 7.5 g/ m^2 cumulative or ≥ 200 mg/kg for stem cell transplant Any alkylators combined with: - testicular radiation - pelvic radiation - TBI	**Females:** Pubertal history (onset, tempo) Menstrual and pregnancy history Physical exam including height, weight, Tanner stage	Yearly	**Health Link** Female Health Issues after Childhood Cancer **or** Male Health Issues after Childhood Cancer Counsel currently menstruating women at increased risk of early menopause to be cautious about delaying childbearing. Counsel regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology/ obstetrics referral for infertility evaluation and consultation regarding assisted reproductive technologies. Consider 2 months off hormonal replacement in women with ovarian failure to assess ovarian recovery.
					FSH, LH, estradiol	Baseline at about age 11 and as clinically indicated in patients with: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency For patients who received alkylating chemotherapy for stem cell transplant conditioning, obtain baseline at age 8 and then yearly until normal puberty is established.		
					Males: Pubertal history (onset, tempo) History of sexual function (erections, nocturnal emissions, libido) History of medication use Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					FSH, LH, testosterone	Baseline at about age 11 and as clinically indicated in patients with: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency For patients who received alkylating chemotherapy for stem cell transplant conditioning, obtain baseline at age 9 and then yearly until normal puberty is established		
					Semen analysis	As requested by patient and for evaluation of infertility		
	5	**Acute myeloid leukemia** **Myelodysplasia**	**Treatment factors** Less than 10 years since exposure to agent Higher cumulative alkylator dose or combination of alkylators Note: Melphalan and mechlorethamine are more potent leukemogens than cyclophosphamide **Medical conditions**: Splenectomy (conflicting evidence)		Physical exam CBC/differential	Yearly up to 15 years after exposure to agent	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Busulfan **Carmustine (BCNU)** **Lomustine (CCNU)**	6	**Pulmonary fibrosis** **See related topics:** **Bleomycin** **Chest/thorax radiation**	**Treatment factors** Higher cumulative doses Combined with other pulmonary toxic therapy: - bleomycin - chest/thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **Medical conditions** Atopic history **Health behaviors** Cigarette smoking	**Treatment factors** BCNU ≥ 600 mg/m^2 Busulfan ≥ 500 mg (transplant doses)	Physical exam	Yearly	**Health Link** Pulmonary Health Due to the potential pulmonary toxicity of this therapy, patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist	Pulmonary consultation for symptomatic pulmonary dysfunction. Influenza and Pneumovax immunization.
					PFTs (including DLCO and spirometry) and CXR	Baseline at entry into long-term follow-up and prior to general anesthesia. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction		
Busulfan	7	**Cataracts** **See related topics:** **Prednisone** **Dexamethasone** **Head/brain radiation** **TBI**	**Treatment factors** Combined with: - total body irradiation - brain/head radiation - corticosteroids	**Treatment factors** TBI given in single daily fraction Radiation dose ≥ 10 Gy with potential scatter to eye(s) Longer interval since treatment	Eye exam including funduscopic exam and visual acuity	Yearly	**Health Link** Eye Problems after Childhood Cancer	Ophthalmology consultation if problem identified. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP).
Cyclophosphamide **Ifosfamide**	8	**Hemorrhagic cystitis** **Bladder fibrosis** **Dysfunctional voiding** **See related topics:** **Pelvic radiation**	**Treatment factors** Higher cumulative doses (decreased incidence with Mesna) Combined with pelvic radiation **Health behaviors** Alcohol use Tobacco use	**Treatment factors** Cyclophosphamide dose ≥ 3 gm/m^2	Voiding history	Yearly	Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture negative macroscopic hematura.
					Urinalysis	Yearly		
	9	**Bladder malignancy** **See related topics:** **Pelvic radiation**	**Treatment factors** Combined with pelvic radiation		Urinalysis	Yearly	**Health Link** Reducing the Risk of Second Cancers	Urology consultation for culture negative macroscopic hematuria.
Ifosfamide	10	**Renal toxicity:** Glomerular toxicity Tubular toxicity -Renal tubular acidosis -Fanconi's syndrome -Hypophosphatemic rickets **See related topics:** **Cisplatin/Carboplatin** **Methotrexate** **Abdominal/pelvic radiation** **Cystectomy** **Nephrectomy**	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Combined with other nephrotoxic agents, such as: - cisplatin/carboplatin - aminoglycosides - amphotericin - immunosuppressants - abdominal radiation **Medical conditions** Tumor infiltration of kidney(s) Pre-existing renal impairment Nephrectomy or mononephric	**Host factors** Age < 5 years at time of treatment **Treatment factors** Ifosfamide dose ≥ 60 grams/m^2	Blood pressure	Yearly	**Health Link** Kidney Health See also: Single Kidney Precautions	Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Yearly		
					Na, K, Cl, CO_2, Ca, Mg, $P0_4$	Baseline electrolytes at entry into long-term follow-up. If normal, repeat every 5 years. If abnormal, repeat as clinically indicated.		
					Creatinine clearance or GFR	Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Heavy Metals								
Cisplatin **Carboplatin**	11	**Ototoxicity:** - Sensorineural hearing loss - Tinnitus - Vertigo **See related topics:** **Ear radiation** **Clinician Info Link** Prospective studies are needed to define ototoxic dose/effect relationship for carboplatin.	**Host factors** Age <4 years at treatment **Treatment factors** Combined with: - head/neck/cranial radiation - other ototoxic drugs (e.g., aminoglycosides, loop diuretics) **Medical conditions** Chronic otitis Cerumen impaction Renal dysfunction	**Host factors** CNS neoplasm **Treatment factors** Cumulative cisplatin dose ≥ 360 mg/m^2	History and physical exam	Yearly	**Health Link** Hearing Problems after Childhood Cancer	Audiology consultation for assistive devices in patients with progressive hearing loss. Speech and language therapy for children with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources, IEP for preferential classroom seating or specialized classroom placement, FM trainer or other assistive devices, and other educational assistance as indicated.
					Audiogram or brainstem auditory evoked response (ABR, BAER)	Baseline at entry into long-term follow-up. If abnormal, follow yearly until stable. If clinical evidence of progressive hearing loss, obtain more frequently as indicated until stable.		
	12	**Peripheral sensory neuropathy** **Clinician Info Link** Neuropathy presents as persistent effect after therapy and is typically not late in onset.	**Treatment factors** Combined with vincristine	**Treatment factors** Cisplatin cumulative dose ≥ 300 mg/m^2	Neurologic exam	Yearly, until 2 to 3 years after therapy. Monitor yearly if symptoms persist.	**Health Link** Peripheral Neuropathy	Physical therapy referral for patients with symptomatic neuropathy. Physical therapy and occupational therapy assessment of hand function. Consider treatment with agent effective for neuropathic pain (e.g., gabapentin or amitriptyline).
	13	**Renal toxicity:** - Glomerular injury - Tubular injury - Renal insufficiency **See related topics:** **Ifosfamide** **Methotrexate** **Abdominal/pelvic radiation** **Cystectomy** **Nephrectomy**	**Treatment factors** Combined with other nephrotoxic agents, such as: - ifosfamide - aminoglycosides - amphotericin - immunosuppressants - cyclosporine - abdominal radiation therapy **Medical conditions** Mononephric Diabetes mellitus Familial hypertension	**Treatment factors** Cisplatin dose ≥ 200 mg/m^2	Blood pressure	Yearly	**Health Link** Kidney Health See also: Single Kidney Precautions In patients with salt-wasting tubular dysfunction, educate that low magnesium levels potentiate coronary atherosclerosis.	Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Yearly		
					Na, K, Cl, CO_2, Ca, Mg, $P0_4$	Baseline electrolytes at entry into long-term follow-up. If normal, repeat every 5 years. If abnormal, repeat as clinically indicated.		
					Creatinine clearance or GFR	Baseline at entry into long-term follow-up. If abnormal, repeat as clinically indicated		
	14	**Dyslipidemia**	**Host factors** Family history of dyslipidemia **Medical conditions** Overweight/Obesity		Fasting lipid profile	Baseline, at entry into long-term follow-up; then as per United States Preventive Task Force Recommendations http://www.ahrq.gov/clinic/prevenix.htm If abnormal, refer for management of dyslipidemia	**Health Link** Health Promotion through Diet and Physical Activity	Lipid lowering strategies including diet, exercise, weight loss, and pharmacologic therapy (e.g., statin therapy).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Antimetabolites								
Cytarabine (high-dose IV) **See related topics:** **Methotrexate** **Head/brain radiation** **Clinician Info Link** Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New deficits may emerge over time.	15	**Neurocognitive deficits:** **Diminished IQ** (combined with high dose and/or intrathecal methotrexate and/or cranial radiation.) **Functional deficits in**: **Processing speed** **Memory** (particularly visual, sequencing, temporal memory) **Sustained attention** **Visual-motor integration** **Math** **Reading** (particularly reading comprehension) **Planning and organization** **Clinician Info Link** Acute toxicity predominates if administered systemically as single agent. May contribute to late neurotoxicity if combined with intrathecal methotrexate and/ or cranial radiation.	**Host factors** Younger age at treatment CNS leukemia/lymphoma **Treatment factors** High-dose systemic administration ($\geq$ 1000 mg/m^2 dose) In combination with: - dexamethasone - cranial radiation - total body irradiation - intrathecal methotrexate	**Host factors** Age < 3 years old at time of treatment Female gender **Treatment factors** Combined with methotrexate and/or cranial radiation. Radiation $\geq$ 24 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical interview including assessment of educational or vocational progress	Baseline at entry into long-term follow-up, then yearly	**Health Link** School and Learning Issues after Childhood Cancer	Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Refer to community services for vocational rehabilitation or for services for developmentally disabled.
					Referral for formal neuropsychological evaluation	Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress		
		Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - mineralizing micro-angiopathy **Clinician Info Link** Neuroimaging changes do not always correlate with degree of cognitive dysfunction. Prospective studies are needed to define the dose/effect relationship of neurotoxic agents. Note: new deficits may emerge over time.	**Treatment factors** Combined with: - intrathecal methotrexate - dexamethasone - cranial radiation	**Treatment factors** High-dose IV administration combined with cranial radiation Radiation dose $\geq$ 24 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical evaluation	Yearly		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: microvascular injury CT: calcifications Neurology consultation and follow-up.
					Brain MRI	As clinically indicated		
					Brain CT plus MRI with MR angiography	As clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Mercaptopurine **Thioguanine** **Clinician Info Link** Acute hepatotoxicity reported with thioguanine used in CCG 1952 (regimens B1 and B2) for ALL maintenance therapy requires longer follow-up to determine long-term sequelae.	16	**Hepatic dysfunction** **Veno-occlusive disease** Acute toxicities predominate from which the majority of patients recover without sequelae. **See related topics:** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Transfusion (chronic hepatitis B & C)** **Hematopoietic cell transplant (liver toxicity)**	**Medical conditions** Viral hepatitis	**Medical conditions** Chronic viral hepatitis	Physical exam ALT, AST, bilirubin	Yearly Baseline at entry into long-term follow-up.	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunization in patients lacking immunity.
Methotrexate **(PO, IV, IM)** **Clinician Info Link** Osteopenia and osteoporosis occur more commonly after methotrexate than does osteonecrosis. **See related topics:** **Corticosteroids** **Hematopoietic cell transplant** **(continued on next page)**	17	**Osteopenia** Bone mineral density ≥ 1 and < 2.5 SD below mean **Osteoporosis** Bone mineral density ≥ 2.5 SD below mean **Clinician Info Link** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density of young adults at peak bone age and defined as a T-score. A T-score of ≥ 2.5 standard deviations below the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Host factors** Both genders at risk **Treatment factors** Corticosteroids Cranial/spinal, head/neck, gonadal radiation Hematopoietic stem cell transplantation **Medical conditions** Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism		Bone density evaluation (DEXA or quantitative CT) **Clinician Info Link** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.	**Health Link** Bone Health Resource: National Osteoporosis Foundation website www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. ** Caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency; correction of chronic metabolic acidosis that could accelerate bone loss.). Endocrine consultation for patients with bone density more than 2.5 SD below mean or patients with history of multiple fractures, for other pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Methotrexate (PO, IV, IM)	18	**Renal dysfunction** Acute toxicities predominate, from which the majority of patients recover without sequelae. **See related topics:** **Ifosfamide** **Cisplatin/Carboplatin** **Abdominal/pelvic radiation** **Cystectomy** **Nephrectomy**	**Host factors** Mononephric Combined with other nephrotoxic agents: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppresants - cyclosporine - abdominal radiation **Medical conditions** Diabetes mellitus Familial hypertension	**Treatment factors** Treatment before 1970.	Blood pressure	Yearly	**Health Link** Kidney Health See also: Single Kidney Precautions	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
					BUN, creatinine, U/A	Baseline at entry into long-term follow-up.		
					Na, K, Cl, CO_2 Ca, Mg, PO_4 Creatinine clearance or GFR.	Obtain in patients with abnormal BP, urinalysis, BUN, or creatinine. If abnormal, repeat as clinically indicated.		
	19	**Hepatic dysfunction** Acute toxicities predominate from which the majority of patients recover without sequelae. **See related topics:** **Mercaptopurine** **Dactinomycin** **Hepatic radiation** **Transfusion (chronic hepatitis B &C)** **Hematopoietic cell transplant (liver toxicity)**	**Treatment factors** Abdominal radiation **Medical conditions** Viral hepatitis	**Treatment factors** Treatment before 1970 **Medical conditions** Chronic viral hepatitis	Physical exam	Yearly	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver function on screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunization in patients lacking immunity.
					ALT, AST, bilirubin	Baseline at entry into long-term follow-up.		

Therapeutic Agent	Sec ##	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Methotrexate (IT, high-dose IV) **See related topics:** **Head/brain radiation** **Cytarabine (high-dose IV)** **Clinician Info Link** Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). Extent of deficit depends on age at treatment, intensity of treatment and time since treatment. New deficits may emerge over time.	20	**Neurocognitive deficits:** **Diminished IQ** (with high dose and/or intrathecal methotrexate and/or cranial radiation.) **Functional deficits in:** **Processing speed** **Memory** (particularly visual, sequencing, temporal memory) **Sustained attention** **Visual-motor integration** **Math** **Reading** (particularly reading comprehension) **Planning and organization**	**Host factors** Younger age at treatment CNS leukemia/lymphoma **Treatment factors** Intrathecal administration High-dose systemic administration ($\geq$ 1000 mg/m^2 dose) In combination with: - dexamethasone - cranial radiation - total body irradiation - high-dose IV cytarabine **Medical conditions** CNS leukemia/lymphoma with poor CSF reabsorption	**Host factors** Age < 3 years old at time of treatment Female gender **Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose $\geq$ 24 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical interview including assessment of educational or vocational progress	Yearly	**Health Link** School and Learning Issues after Childhood Cancer	Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual-motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Refer to community services for vocational rehabilitation or for services for developmentally disabled.
					Referral for formal neuropsychological evaluation	Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress		
		Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - mineralizing micro-angiopathy **Clinician Info Link** Neuro-imaging changes do not always correlate with degree of cognitive dysfunction. Prospective studies are needed to define the dose/effect relationship of neurotoxic agents. Note: new deficits may emerge over time.	**Host factors** Younger age at treatment CNS leukemia/lymphoma **Treatment factors** Intrathecal administration High-dose systemic ($\geq$ 1000 mg/m^2 dose) administration Triple intrathecal chemotherapy In combination with: - dexamethasone - cranial radiation - total body irradiation **Medical conditions** CNS leukemia/lymphoma with poor CSF reabsorption	**Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose $\geq$ 20 Gy TBI with daily fraction $\geq$ 2 Gy	Clinical evaluation	Yearly		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadalinium-enhanced MRI: microvascular injury CT: calcifications Neurology consultation and follow-up
					Brain MRI	As clinically indicated		
					Brain CT plus MRI with MR angiography	As clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Anthracycline antibiotics								
Doxorubicin **Daunorubicin** **Idarubicin** **Mitoxantrone** **Epirubicin** **See related topics:** **Chest/thorax radiation**	21	**Acute myeloid leukemia**	**Treatment factors** Less than 5 years since exposure to drug		Physical exam CBC/ differential	Yearly up to 15 years post exposure to anthracycline	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.
	22	**Cardiomyopathy** **Arrhythmias** **Clinician Info Link** Dose levels correlating with cardiotoxicity are derived from adult studies. Childhood cancer patients exhibit clinical and subclinical toxicity at lower levels. Certain conditions such as isometric exercise, pregnancy, and viral infections, have been anecdotally reported to precipitate cardiac decompensation. Need for prospective studies to define risk factors. Note: pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of daunomycin and doxorubicin assuming an equivalent relative cardiotoxicity per mg dose. Idarubicin and mitoxantrone are more cardiotoxic than doxorubicin/daunorubicin on a mg per mg dose basis. In limited studies, epirubicin has similar dose equivalency to daunomycin and doxorubicin.	**Treatment factors** Combined with radiation involving the heart: Mantle Mediastinal Total body irradiation Spinal ≥ 30 Gy Whole lung Whole abdomen Left hemiabdomen/flank Combined with other cardiotoxic chemotherapy: - cyclophosphamide (100-200 mg/kg as conditioning for stem cell transplantation) - amsacrine **Medical conditions** Congenital heart disease Pregnancy Febrile illness Health behaviors Isometric exercise Drug use (e.g., cocaine, diet pills, ephedra, mahuang)	**Host factors** Female Black/African American Younger than 5 years at treatment **Treatment factors** Higher cumulative doses: ≥ 550 mg/m^2 in patients 18 years or older at time of treatment ≥ 300 mg/m^2 in patients younger than 18 years at time of treatment Any dose in infant Longer time elapsed since treatment	Detailed history of exertional tolerance. **Clinician Info Link** Note: exertional intolerance is uncommon in young patients (< 25 years). Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain. EKG for evaluation of QT interval ECHO or MUGA for evaluation of systolic function	Yearly Baseline at entry into long-term follow-up Baseline at entry to long-term follow-up, then periodically, based on age at treatment, history of chest radiation and cumulative anthracycline dose (see table).	**Health Link** The Heart and Anthracyclines See also: The Heart and Radiation Counsel patients with prolonged QT interval about use of medications that may further prolong QT interval (e.g., tricyclic anti- depressants, antifungals, macrolide antibiotics, metronidazole).	Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QT interval. Additional cardiology evaluation in patients who received ≥ 300 mg/m^2 or < 300 mg/m^2 plus chest radiation or TBI who are pregnant or planning pregnancy to include an EKG and echocardiogram before and periodically during pregnancy (especially during 3rd trimester) and monitoring during labor and delivery due to risk of cardiac failure. Consider excess risk of isometric exercise program in any high risk patient defined as needing screening every 1 or 2 years.

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM OR MUGA SCAN

Age at Treatment*	Chest Radiation	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	<200 mg/m^2	Every 2 years
		≥200 mg/m^2	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
		≥100 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
≥5 years old	Yes	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
		≥200 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
Any age with decrease in serial function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Anti-Tumor Antibiotics								
Bleomycin	23	**Interstitial pneumonitis** **Pulmonary fibrosis** **Acute respiratory distress syndrome (very rare)** **See related topics:** **Chest/thorax radiation** **Busulfan** **Carmustine** **Lomustine** **Clinician Info Link** Administration of high concentrations of oxygen may result in chronic progressive pulmonary fibrosis.	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Combined with other pulmonary toxic therapy: - busulfan - carmustine (BCNU) - lomustine (CCNU) - thoracic radiation - spinal radiation ≥30 Gy - total body irradiation **Medical conditions** Renal dysfunction High dose oxygen support such as during general anesthesia **Health behaviors** Smoking	**Treatment factors** Bleomycin dose ≥ 400 U/m^2 (injury observed in doses 60-100 U/m^2 in children)	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up and prior to general anesthesia. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Bleomycin Alert SCUBA diving should be avoided. (Potential exacerbation of pulmonary fibrosis as a result of increased oxygen concentrations associated with underwater pressures). Notify healthcare providers of history of bleomycin therapy and risk of worsening fibrosis with high oxygen exposure such as during general anesthesia.	Pulmonary consultation in patients with symptomatic or progressive pulmonary dysfunction. Influenza and Pneumococcal vaccines.
Dactinomycin	24	**No known late effects** (Dactinomycin has been associated with acute veno-occlusive disease, from which the majority of patients recover without sequelae) **See related topics:** **Mercaptopurine** **Methotrexate** **Hepatic radiation** **Transfusion (chronic hepatitis B &C)** **Hematopoietic cell transplant (liver toxicity)**	**Treatment factors** Hepatic radiation		Physical exam ALT, AST, bilirubin	Yearly Baseline at entry into long-term follow-up.	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Corticosteroids								
Prednisone **Dexamethasone**	25	**Osteopenia** (Bone mineral density 1-2.5 SD below mean) **Osteoporosis** (Bone mineral density ≥ 2.5 SD below mean) **Clinician Info Link** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density of young adults at peak bone age and defined as a T-score. A T-score of ≥ 2.5 standard deviations below the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Host factors** Both genders at risk **Treatment factors** Combined with: - methotrexate - cranial or spinal radiation - other head/neck radiation - radiation to bones **Medical Conditions** Hypogonadism Premature ovarian failure Early menopause Growth hormone deficiency Hyperthyroidism **See related topics:** **Methotrexate** **Hematopoietic cell transplant**	**Host factors** Older age at time of treatment **Treatment factors** Dexamethasone effect is more potent than prednisone.	Bone density evaluation (DEXA or quantitative CT) **Clinician Info Link** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.	**Health Link** Bone Health National Osteoporosis Foundation website: www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D. ** Caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency; correction of chronic metabolic acidosis that could accelerate bone loss.). Endocrine consultation for patients with bone density more than 2.5 SD below mean, or patients with history of multiple fractures, for other pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).
	26	**Avascular necrosis (AVN)** **(Osteonecrosis)** **Clinician Info Link** AVN typically occurs during the acute treatment phase, may progress over time or resolve. Multifocal AVN is significantly more common (3:1) than unifocal.	**Host factors** Both genders at risk **Treatment factors** Dexamethasone effect is more potent than prednisone. Combined with: - high-dose radiation to any bone **Medical conditions** Sickle cell disease	**Host factors** Older age (≥10 years at time of treatment) **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	History	Yearly	**Health Link** Avascular Necrosis	Diagnostic imaging (radiograph, MRI) in patients with history of chronic pain. Orthopedic consultation for history of chronic joint pain in predisposed patient.
	27	**Cataracts** **See related topics:** **Busulfan** **Head/brain radiation** **TBI**	**Treatment factors** Combined with: - total body irradiation - brain/head radiation - busulfan	**Treatment factors** TBI given in single daily fraction Radiation dose ≥ 10 Gy with potential scatter to eye(s) Longer interval since treatment	Eye exam including funduscopic exam and visual acuity	Yearly	**Health Link** Eye Problems after Childhood Cancer	Ophthalmology consultation if problem identified. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP).

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Enzymes								
Asparaginase	28	**No known late effects.** Acute toxicities predominate, from which the majority of patients recover without sequelae.						
Plant Alkaloids								
Vincristine **Vinblastine** **Clinician Info Link** Acute toxicities most commonly occur and usually resolve prior to patients entering long-term follow-up. Neuropathy can persist after treatment and is typically not late in onset.	29	**Peripheral sensory or motor neuropathy:** - areflexia - weakness - foot drop - parasthesias	**Treatment factors** Combined with cisplatin **Medical conditions** Anorexia Severe weight loss	**Medical conditions** Charcot-Marie-Tooth disease	Neurologic exam	Yearly, until 2 to 3 years after therapy; continue to monitor yearly if symptoms persist.	**Health Link** Peripheral Neuropathy	Physical therapy referral for patients with symptomatic neuropathy. Physical therapy and occupational therapy assessment of hand function. Treatment with anticonvulsant effective for neuropathic pain (e.g., gabapentin and amitriptyline).
	30	**Vasospastic attacks** (Raynaud's phenomenon)	**Health behaviors** Tobacco use Illicit drug use		History Physical exam	Yearly	**Health Link** Raynaud's Phenomenon Counsel to wear appropriate protective clothing in cold environments and to not use tobacco or illicit drugs.	Vasodilating medications (calcium-channel blockers, alpha blockers) for patients with frequent, severe vasospastic attacks unresponsive to behavioral management.
Epipodophyllotoxins								
Etoposide (VP-16) **Teniposide (VM-26)** **Clinician Info Link** Administration schedules since ~1990 have been modified to reduce the risk of this complication.	31	**Acute myeloid leukemia**	**Medical conditions** Splenectomy (conflicting evidence)	**Treatment factors** Weekly or twice weekly administration Less than 5 years since exposure to drug.	Physical exam CBC/ differential	Yearly up to 15 years post exposure to agent	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Radiation								
All fields, including Total Body Irradiation **Clinician Info Link** General factors influencing radiation toxicity: - daily fraction size - cumulative dose - age of patient at irradiation - type of radiation used - toxicity may not be manifest until growth completed or patient ages	32	**Skin changes**: Fibrosis, telangiectasias, permanent hair loss, altered skin pigmentation	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose	**Host factors** Prepubertal at treatment **Treatment factors** Dose fraction ≥ 2 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly	**Health Link** Skin Health	
	33	**Secondary benign or malignant neoplasm** in or near radiation field	**Host factors** Cancer predisposing mutations: p53, RB1, NF1 **Treatment factors** High cumulative dose Large treatment volumes	**Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam with inspection and palpation of irradiated skin and soft tissues. Other evaluations based on treatment volumes	Yearly See recommendations for specific fields	**Health Link** Reducing the Risk of Second Cancers	Surgical and/or oncology consultation as clinically indicated.
	34	**Dysplastic nevi** **Skin cancer:** Basal cell carcinoma Squamous cell carcinoma Melanoma	**Host factors** Gorlin's syndrome (nevoid basal cell carcinoma syndrome)	**Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly	**Health Link** Skin Health Reducing the Risk of Second Cancers	Dermatology consultation for evaluation and monitoring of atypical nevi. Oncology consultation as clinically indicated.
	35	**Bone malignancies**	**Host factors** Adolescent at treatment Cancer-predisposing mutation (e.g., p53, RB1, NF1) **Treatment factors** High radiation dose Combined with alkylating agents	**Treatment factors** Radiation dose ≥ 30 Gy Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly	Counsel patient to report symptoms promptly (bone pain, bone mass, persistent fevers, etc.)	X-ray or other diagnostic imaging in patients with clinical symptoms. Oncology consultation as clinically indicated.
Total Body Irradiation (TBI)								

Potential complications related to total body irradiation (TBI) are addressed throughout this document.
In order to obtain a complete list of potential complications related to total body irradiation, with associated recommendations, refer to <u>all</u> of the following radiation sections in this document:

Radiation - All Fields, Head/Brain, Eye, Ear, Neck, Trunk, Chest/Thorax, Abdomen/Pelvis, Testicular

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Head/Brain Radiation								
Total Body Irradiation **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** (continued on next page)	36	**Neurocognitive deficits:** **Diminished IQ (< 85)** **Functional deficits in:** **Processing speed** **Memory** (particularly visual, sequencing, temporal memory) **Sustained attention** **Visual-motor integration** **Math** **Reading** (particularly reading comprehension) **Planning and organization** **Increased risk for social difficulties, psychological maladjustment.** **Clinician Info Link** Neurocognitive deficits in survivors of leukemia and lymphoma are more frequently related to information processing (e.g., learning disability). Neurocognitive deficits in brain tumor survivors treated with higher doses of cranial radiation are more global (significant decline in IQ). The extent of deficit depends on age at treatment intensity of treatment and time since treatment. New deficits may emerge over time. **See related topics:** **Methotrexate** **Cytarabine** **Neurosurgery**	**Host factors** Younger age at treatment Primary CNS tumor ALL or relapsed ALL Head/neck tumors with brain in radiation field **Treatment factors** Combined with: - methotrexate (IT, high-dose IV) - dexamethasone - cytarabine (high-dose IV) - high dose chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation.	**Host factors** Age < 3 years at time of treatment Female gender Tumor site in cerebral hemisphere **Treatment factors** Cranial irradiation **Social factors** Low SES Premorbid or family history of learning or attention problems.	Clinical interview including assessment of educational or vocational progress	Baseline and yearly	**Health Link** School and Learning Issues after Childhood Cancer	Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual-motor integration, memory, comprehension of verbal instructions verbal fluency, executive function and planning. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Refer to community services for vocational rehabilitation or for services for developmentally disabled.
					Referral for formal neuropsychological evaluation	Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress		
	37	**Clinical leukoencephalopathy** (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures) **with or without imaging abnormalities:** - leukoencephalopathy - cerebral lacunes - cerebral atrophy - dystrophic calcifications - cavernous hemangioma - mineralizing micro-angiopathy	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose Combined with: - high-dose methotrexate - intrathecal methotrexate or cytarabine **Medical conditions** Hydrocephalus requiring shunt Posterior fossa syndrome	**Host factors** Age < 2 years at time of treatment **Treatment factors** Dose ≥ 30 Gy Fraction dose ≥ 2 Gy	Clinical evaluation	Yearly		Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadolinium-enhanced MRI: microvascular injury CT: calcifications Neurology consultation and follow-up.
					Brain MRI	As clinically indicated		
					Brain CT plus MRI with MR angiography	As clinically indicated		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
(continued from previous page) **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** (continued on next page)	38	**Stroke/Moyamoya Occlusive cerebral vasculopathy** **Clinician Info Link** Moyamoya syndrome is the complete occlusion of one or more of the three major cerebral vessels with the development of small, immature collateral vessels, which reflect an attempt to revascularize the ischemic portion of the brain.	**Host factors** Hypothalamic/chiasmatic glioma **Medical conditions** Sickle cell disease Neurofibromatosis	**Treatment factors** Dose ≥ 40 Gy	Clinical evaluation Brain MRI with diffusion-weighted imaging with MR angiography	Yearly As clinically indicated		Neurology consultation and follow-up. Physical and occupational therapy as clinically indicated.
	39	**Brain tumor:** High-grade astrocytoma Meningioma Sarcoma	**Host factors** Younger age at treatment Thiopurine methyl transferase (TPMT) genetic polymorphism Neurofibromatosis **Treatment factors** Higher radiation dose	**Host factors** Age < 6 years at time of treatment Ataxia telangiectasia	History & physical Neurologic exam Brain MRI	Yearly Baseline at maturity for all patients Every other year for patients with neurofibromatosis, beginning 2 years after radiation As clinically indicated for symptomatic patients		Neurosurgical consultation for tissue diagnosis and/or resection. Neuro-oncology consultation for medical management.
	40	**Growth hormone deficiency**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation doses Surgery in suprasellar region Pretransplant radiation Total body irradiation: ≥ 10 Gy single fraction ≥ 12 Gy fractionated	**Treatment factors** Radiation dose ≥ 18 Gy Pretransplant cranial radiation Single daily fraction TBI dose	Assess nutritional status. Monitor height, weight BMI percentiles Tanner staging Bone age	Every 6 months until growth is completed. Obtain in poorly growing children.	**Health Link** Growth Hormone Deficiency See also: Hypopituitarism www.magicfoundation.org	Endocrine consultation for: - drop in %ile on growth grid - growth velocity < 4-5 cm/year during childhood - growth below 3rd %ile - lack of pubertal growth spurt. Evaluate thyroid function in any poorly growing child.
	41	**Hyperprolactinemia**	**Treatment factors** Higher radiation dose Surgery or tumor in hypothalamic area	**Treatment factors** Radiation dose ≥ 50 Gy	Review of systems: Female: - galactorrhea - menstrual history Male: - decreased libido - galactorrhea Prolactin level	Yearly In all patients with galactorrhea; females with amenorrhea; males with decreased libido	**Health Link** Hyperprolactinemia www.magicfoundation.org	CT evaluation of sella turcica for pituitary adenoma in patients with hyperprolactinemia. Endocrine consultation for patients with hyperprolactinemia, amenorrhea, or galactorrhea.
	42	**Central hypothyroidism** (thyroid-releasing and thyroid-stimulating hormone deficiency)	**Treatment factors** Higher radiation dose Total body irradiation	**Treatment factors** Radiation dose ≥ 30 Gy	Free T4, TSH	Yearly	**Health Link** Thyroid Problems after Childhood Cancer. See also: Hypopituitarism	Consider TSH surge testing. Endocrine consultation for thyroid hormone replacement.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
(continued from previous page) **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** (continued on next page)	43	**Central adrenal insufficiency**	**Treatment factors** Higher radiation dose	**Treatment factors** Radiation dose ≥ 30 Gy	Review of systems: - failure to thrive - anorexia - dehydration - hypoglycemia - lethargy - unexplained hypotension	Yearly	**Health Link** Central Adrenal Insufficiency See also: Hypopituitarism Corticosteroid replacement therapy & stress dosing. Medic Alert bracelet. www.magicfoundation.org	Endocrine consultation for further evaluation and replacement steroids.
					8:00 AM serum cortisol in patients treated with ≥ 30 Gy radiation to hypothalamic-pituitary axis	Baseline at entry into long term follow-up and periodically as clinically indicated		
	44	**Precocious puberty**	**Host factors** Female gender Younger age at treatment **Treatment factors** Radiation doses ≥ 18 Gy		Physical exam including height, weight, Tanner stage	Yearly	**Health Link** Precocious Puberty www.magicfoundation.org	Endocrine consultation for accelerated puberty (puberty in girl < 8 years old and boy < 9 years old). Consider pelvic ultrasound in females to evaluate for ovarian tumor
					LH, FSH, estradiol or testosterone	As clinically indicated in patients with signs of accelerated pubertal progression and growth.		
					Bone age	Obtain in rapidly growing children.		
	45	**Gonadotropin deficiency (LH and FSH)**	**Treatment factors** Higher radiation dose	**Treatment factors** Radiation dose ≥ 30 Gy	**Females:** Pubertal history (onset, tempo) Menstrual and pregnancy history Physical exam including height, weight, Tanner stage	Yearly	**Health Link** Female Health Issues after Childhood Cancer **or** Male Health Issues after Childhood Cancer See also: Hypopituitarism Counsel currently menstruating women at increased risk of early menopause to be cautious about delaying childbearing. Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Bone density evaluation for osteopenia/osteoporosis in hypogonadal patients. Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Hormonal replacement therapy for hypogonadal patients. Reproductive endocrinology/ obstetrics referral for infertility evaluation and consultation regarding assisted reproductive technologies. Consider 2 months off hormonal replacement in women with ovarian failure to assess ovarian recovery.
					FSH, LH, estradiol	Baseline at age 8, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency		
					Males: Pubertal history (onset, tempo) History of sexual function (erections, nocturnal emissions, libido) History of medication use Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					FSH, LH, testosterone	Baseline at age 9, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency		
					Semen analysis	As requested by patient and for evaluation of infertility		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
(continued from previous page) **Total Body Irradiation** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Orbital/Eye** **Ear/Infratemporal** **Mantle (48 & 49 only)** **Cervical Spine (48 & 49 only)** (continued on next page)	46	**Overweight/Obesity** Definition by adult standards: body mass index (BMI) = wt (kg)/ht (M^2) Overweight: BMI ≥ 25-29.9 Obese: BMI ≥ 30 BMI calculator available on-line at: http://nhlbisupport.com/bmi/ Definition by pediatric standards for < 16 years old: Overweight is defined by sex-and age-specific 95%ile cutoff points of CDC/NCHS growth charts. Growth charts available on-line at: www.cdc.gov/growthcharts/	**Host factors** Younger at treatment **Treatment factors** Higher cranial radiation dose Combined with corticosteroids **Medical conditions** Familial dyslipidemia Growth hormone deficiency Hypothyroidism	**Host factors** Age < 4 years old at time of treatment Female gender **Treatment factors** Hypothalamic dose ≥ 20 Gy **Medical conditions** Inability to exercise	Blood pressure Growth percentile or Body mass index Fasting lipid profile Fasting insulin	Yearly Yearly Every 3-5 years in overweight or obese patients Obtain baseline for patients with acanthosis nigricans. Consider testing in overweight or obese patients with dyslipidemia.	**Health Link** Health Promotion through Diet and Physical Activity Obesity-related health risks.	Consider evaluation for other co-morbid conditions including: dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, insulin resistance. Nutritional counseling. Endocrine consultation for patients with dyslipidemia or hyperglycemia.
	47	**Chronic sinusitis**	**Treatment factors** Higher cumulative radiation doses to sinuses (≥ 30 Gy) Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) **Medical conditions** Atopic history Hypogammaglobulinemia		History Physical exam CT sinuses	Yearly As clinically indicated		Otolaryngology consultation as clinically indicated.
	48	**Xerostomia** Salivary gland dysfunction	**Treatment factors** Head and neck radiation involving the parotid gland Higher radiation doses Total body irradiation Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Salivary gland dose ≥ 30 Gy **Medical conditions** Chronic GVHD	History Physical exam	Yearly	**Health Link** Dental Health	Supportive care with saliva substitutes, moistening agents, and sialogogues (pilocarpine). Regular dental care including fluoride applications.
	49	**Dental abnormalities** Tooth/root agenesis Microdontia Root thinning/shortening Enamel dysplasia Periodontal disease Tooth decay Malocclusion Temporomandibular joint dysfunction	**Host factors** Younger age at treatment Gorlin's syndrome **Treatment factors** Higher radiation dose	**Host factors** Age < 5 years at time of treatment **Treatment factors** Dose ≥ 20 Gy (may occur in young children at 10 Gy)	Dental exam and cleaning	Every 6 months	**Health Link** Dental Health	Regular dental care including fluoride applications. Consultation with orthodontist experienced in management of irradiated childhood cancer survivors. Baseline panorex prior to dental procedures to evaluate root development.
	50	**Craniofacial abnormalities**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose	**Host factors** Age < 5 years at time of treatment **Treatment factors** Dose ≥ 30 Gy	Physical exam Psychosocial assessment of adjustment	Yearly Yearly	Resource: FACES - The National Craniofacial Association www.faces-cranio.org/	Reconstructive craniofacial surgical consultation. Consultation with psychologist in patients with adjustment disorders related to facial asymmetry/deformity.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Eye radiation								
Total Body Irradiation **Orbital/Eye** **Cranial (whole brain)** **Craniospinal** **Clinician Info Link**: Complications other than cataracts are generally associated only with orbital/eye radiation. Reduced visual acuity may be associated with cataracts, retinal damage, and optic nerve damage	51	**Cataracts**	**Treatment factors** Higher radiation dose Combined with: - corticosteroids - busulfan Longer interval since treatment	**Treatment factors** Dose ≥ 10 Gy TBI given in single daily fraction Fraction dose ≥ 2 Gy	Ophthalmology evaluation including funduscopic exam and visual acuity	Yearly for patients who received ≥ 30 Gy or TBI Every 3 years for patients who received < 30 Gy (these patients also need yearly funduscopic exams during yearly long-term follow-up visits)	**Health Link** Eye Problems after Childhood Cancer Resource: FACES - The National Craniofacial Association www.faces-cranio.org/	Ongoing ophthalmology follow-up for identified problems. Consider every 6 month ophthalmology evaluation for patients with corneal damage (usually associated with xerophthalmia) or complex ocular problems. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources.
		Orbital hypoplasia	**Treatment factors** Higher radiation dose Higher daily fraction dose	**Treatment factors** Dose ≥ 30 Gy Fraction dose ≥ 2 Gy				
		Lacrimal duct atrophy (resulting in excessive tearing)	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 40 Gy Fraction dose ≥ 2 Gy				
		Xerophthalmia (severe) (resulting from atrophy of lacrimal gland)	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 30 Gy Fraction dose ≥ 2 Gy				
		Keratitis	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 40 Gy Fraction dose ≥ 2 Gy				
		Keratoconjunctivitis sicca	**Treatment factors** Higher radiation dose Corticosteroids Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	**Treatment factors** Dose ≥ 40 Gy Fraction dose ≥ 2 Gy **Medical conditions** Chronic GVHD				
		Telangiectasias	**Treatment factors** Higher radiation dose	**Treatment factors** Dose ≥ 50 Gy Fraction dose ≥ 2 Gy				
		Retinopathy	**Treatment factors** Higher radiation dose **Medical conditions** Diabetes mellitus	**Treatment factors** Dose 45-65 Gy Fraction dose ≥ 2 Gy				
		Optic chiasm neuropathy	**Treatment factors** Higher radiation dose **Medical conditions** Diabetes mellitus Hypertension	**Treatment factors** Dose 50- 65 Gy Fraction dose ≥ 2 Gy				
		Enophthalmos **Chronic painful eye**	**Treatment factors** Higher radiation dose	Fraction dose ≥ 2 Gy				

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Ear radiation								
Total body irradiation **Ear/Infratemporal** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal**	52	**Tympanosclerosis** **Otosclerosis** **Eustachian tube dysfunction** **Conductive hearing loss**	**Host factors** Younger age at treatment **Treatment factors** Higher radiation dose **Medical conditions** Chronic otitis Chronic cerumen impaction	**Treatment factors** Dose ≥ 50 Gy	History Physical exam Audiogram or brainstem auditory evoked response (ABR, BAER)	Yearly For patients who received ≥ 30 Gy: Yearly after completion of therapy for 5 years (for patients < 10 yrs old continue yearly until age 10); then every 5 years. If abnormal, follow yearly until stable. Obtain more frequently if clinical evidence of progressive hearing loss. For patients who received < 30 Gy: Baseline at entry into long term follow-up, then as clinically indicated	**Health Link** Hearing Problems after Childhood Cancer	Audiology consultation for assistive devices in patients with progressive hearing loss. Speech and language therapy for children with hearing loss. Otolaryngology consultation in patients with chronic infection, cerumen impaction, or other anatomical problems exacerbating or contributing to hearing loss. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate provision of educational resources, IEP for preferential classroom seating or specialized classroom placement, FM trainer or other assistive devices, and other educational assistance as indicated.
		Sensorineural hearing loss **Tinnitus** **See related topics:** **Cisplatin/Carboplatin**	**Host factors** Younger age at treatment CNS tumor CSF shunting **Treatment factors** Higher radiation dose Combined with other ototoxic agents, such as: - cisplatin - aminoglycosides	**Treatment factors** Doses ≥ 30-40 Gy				
Neck radiation								
Any radiation with potential impact to the neck/thyroid, including: **Total Body Irradiation** **Cervical** **Cranial (whole brain)** **Craniospinal** **Nasopharyngeal** **Oropharyngeal** **Mantle** **Mediastinal** **Whole lung** **Spinal** **Mantle & Cervical Spine, see also: Sections 48 & 49 (Xerostomia & Dental Abnormalities)**	53	**Thyroid nodules**	**Host factors** Younger age at treatment Female gender **Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 25 Gy	Physical exam	Yearly	**Health Link** Thyroid Problems after Childhood Cancer.	Ultrasound for evaluation of palpable nodule(s). Endocrine and/or surgical consultation for diagnostic biopsy or thyroidectomy.
	54	**Thyroid cancer**	**Host factors** Younger age at treatment Female gender **Treatment factors** > 5-10 years after irradiation Cervical or total body irradiation		Physical exam	Yearly	**Health Link** Thyroid Problems after Childhood Cancer.	Ultrasound for evaluation of palpable nodule(s). Surgical consultation for resection. Nuclear medicine consultation for ablation of residual disease. Endocrine consultation for postoperative medical management..
	55	**Hypothyroidism**	**Host factors** Female gender **Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 20 Gy	History Physical exam TSH, free T4 Note: must be free T4 in females on OCP	Yearly; consider more frequent screening during periods of rapid growth	**Health Link** Thyroid Problems after Childhood Cancer.	Endocrine consultation for medical management.
	56	**Hyperthyroidism**	**Treatment factors** Higher radiation dose Cervical or total body irradiation	**Treatment factors** Cervical radiation dose ≥ 35 Gy	History Physical exam TSH, free T4	Yearly	**Health Link** Thyroid Problems after Childhood Cancer.	Endocrine consultation for medical management.
	57	**Carotid artery disease**		**Treatment factors** Dose ≥ 40 Gy	Clinical evaluation Doppler ultrasound of carotid vessels	Yearly As clinically indicated		MRI with diffusion-weighted imaging with MR angiography and cardiovascular surgery consultation as clinically indicated.
	58	**Esophageal stricture**	**Treatment factors** Higher radiation dose Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin **Medical conditions** Gastroesophageal reflux	**Treatment factors** Dose ≥ 40 Gy	History	Yearly		Surgical and/or gastroenterology consultation for symptomatic patients.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Trunk radiation								
Any field from shoulders to pelvis including: **Total Body Irradiation** **Spinal (≥ 12 Gy)**	59	**Musculoskeletal growth problems:** - Hypoplasia - Fibrosis - Reduced or uneven growth - Shortened trunk height	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Larger treatment field Higher dose per fraction	**Host factors** Prepubertal at treatment **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones. Epiphysis in treatment field. Dose ≥ 20 Gy	Physical exam	Yearly		Orthopedic consultation if clinically significant or for any deficit noted in growing child. Plastic surgery consultation for reconstruction.
	60	**Scoliosis**	**Host factors** Younger age at irradiation Paraspinal malignancies Neurofibromatosis **Treatment factors** Hemithoracic or abdominal radiation Hemithoracic, abdominal or spinal surgery Radiation of only a portion of (rather than whole) vertebral body **Clinician Info Link**: With contemporary treatment approaches, scoliosis is infrequently seen as a consequence of radiation unless the patient has also undergone surgery to the hemithorax, abdomen or spine	**Treatment factors** Radiation doses ≥ 20 Gy (lower doses for infants) Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly until growth completed; may need more frequent assessment during puberty	**Health Link** Scoliosis and Kyphosis after Treatment for Childhood Cancer	Orthopedics consultation as indicated based on radiographic exam.
					Spine films	In patient with clinically apparent curve		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Chest/thorax radiation								
Any field involving the chest/thorax, including: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)** **Whole abdomen** **Any upper abdominal field**	61	**Kyphosis**	**Host factors** Younger age at irradiation Paraspinal malignancies Neurofibromatosis	**Treatment factors** Radiation doses ≥ 20 Gy (lower doses for infants) Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones.	Physical exam	Yearly until growth completed; may need more frequent assessment during puberty	**Health Link** Scoliosis and Kyphosis after Treatment for Childhood Cancer	Orthopedics consultation as indicated based on radiographic exam.
					Spine films	In patient with clinically apparent curve		
	62	**Esophageal stricture**	**Treatment factors** Higher radiation dose to esophagus Radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin **Medical conditions** Gastroesophageal reflux	**Treatment factors** Dose ≥ 40 Gy	History	Yearly		Surgical and/or gastroenterology consultation for symptomatic patients.
Chest/thorax radiation with potential impact to the breast: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)**	63	**Breast cancer**	**Host factors** Family history of breast cancer **Treatment factors** Higher radiation dose Longer time from radiation (≥ 5-9 years since radiation)	**Host factors** Female gender	**For females only:** Breast self-examination	Monthly, beginning at puberty	**Health Link** Breast Cancer after Treatment for Childhood Cancer: Are You at Risk?	Surgical consultation for diagnostic procedure. Precautions about the use of HRT.
					Clinical breast exam	Yearly, beginning at puberty until age 25, then every 6 months.		
					Mammogram **Clinician Info Link** Mammography is currently limited in its ability to evaluate premenopausal breasts.	Yearly, beginning 8 years after radiation or at age 25 (whichever occurs last)		
	64	**Breast tissue hypoplasia**	**Host factors** Prepubertal at time of breast irradiation **Treatment factors** Higher radiation dose		Physical exam	Yearly		Surgical consultation for breast reconstruction after completion of growth.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Chest/thorax radiation with potential impact to the heart: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)** **Whole abdomen** **Left hemiabdomen/ flank**	65	**Congestive heart failure** **Cardiomyopathy** **Pericarditis** **Pericardial fibrosis** **Valvular disease** **Myocardial infarction** **Arrhythmia** **Atherosclerotic heart disease** **See related topics:** **Anthracycline chemotherapy**	**Host factors** Younger age at irradiation Family history of dyslipidemia Coronary artery disease **Treatment factors** Radiation dose ≥20 Gy to chest/thorax Combined with radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin) Combined with other cardiotoxic chemotherapy: - cyclophosphamide (100-200 mg/kg as conditioning for stem cell transplantation) - amsacrine Total body irradiation **Medical conditions** Hypertension Obesity Dyslipidemia Diabetes mellitus Premature ovarian failure (untreated) **Health behaviors** Smoking	**Treatment factors** Anteriorly-weighted radiation fields Lack of subcarinal shielding Doses ≥30 Gy in patients who have received anthracyclines Doses ≥ 40 Gy in patients who have not received anthracyclines	EKG	Baseline, at entry into long-term follow-up and as clinically indicated	**Health Link** The Heart and Radiation Health Promotion through Diet and Physical Activity See also: The Heart and Anthracyclines	Cardiology consultation for patients with subclinical abnormalities on screening evaluations or with left ventricular dysfunction, dysrhythmia or prolonged QT interval. Additional cardiology evaluation for patients who are pregnant or planning pregnancy who: (1) received ≥ 30 Gy chest/thorax radiation, or (2) received TBI in combination with cardiotoxic chemotherapy (anthracyclines or high-dose cyclophosphamide). Evaluation to include echocardiogram before and periodically during pregnancy (especially during third trimester) and monitoring during labor and delivery due to risk of cardiac failure.
					ECHO	Baseline, at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose (see table).		
					Cardiology consultation for stress testing	For patients who received ≥ 40 Gy chest radiation alone or ≥ 30 Gy chest radiation plus anthracycline: obtain baseline 5-10 years after radiation		
					Fasting glucose and lipid profile	Every 3 to 5 years. If abnormal, refer for ongoing management		
					Detailed history of exertional tolerance **Clinician Info Link** Exertional intolerance is uncommon in patients younger than 25 years old. Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in young patients	Yearly		
Chest/thorax radiation with potential impact to the lungs: **Total Body Irradiation** **Mantle** **Mediastinal** **Whole lung** **Spinal (≥ 30 Gy)** **Whole abdomen** **Any upper abdominal field**	66	**Pulmonary fibrosis** **Delayed interstitial pneumonitis** **Restrictive/obstructive lung disease** **See related topics:** **Carmustine** **Lomustine** **Bleomycin** **Busulfan**	**Host factors** Younger age at irradiation **Treatment factors** Higher radiation dose to lungs Total body irradiation Combined with: - bleomycin - busulfan - carmustine (BCNU) - lomustine (CCNU) **Medical conditions** Atopic history **Health behaviors** Smoking	**Treatment factors** Whole lung radiation	Physical exam	Yearly	**Health Link** Pulmonary Health Due to the potential pulmonary toxicity of this therapy, patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations.
					PFTs (including DLCO and spirometry) and CXR	Baseline at entry into long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.		

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM

Age at Treatment*	Radiation Dose	Anthracycline Dose†	Recommended Frequency
<5 years old	Any	None	Every 2 years
		Any	Every year
≥5 years old	<30 Gy	None	Every 5 years
	≥30 Gy	None	Every 2 years
	Any	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
Any age with serial decrease in function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)
†Based on equivalent mg of doxorubicin/daunorubicin

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Abdomen/Pelvis								
≥ 30 Gy to: **Whole abdomen** **Left upper quadrant** **Entire spleen**	67	**Functional asplenia** **Life-threatening infection** with encapsulated organisms (Haemophilus influenzae, Streptococcus pneumoniae, Meningococcus).	**Treatment factors** Higher radiation dose to entire spleen	**Treatment factors** Dose ≥ 30 Gy	Physical exam Blood culture	When febrile T ≥ 101°	**Health Link** Splenic Precautions Medical alert bracelet/card noting functional asplenia. Counsel to avoid malaria and tick bites if living in or visiting endemic areas.	In patients with T ≥ 101° (38.3°C), or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC; toxic clinical appearance; fever ≥104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines. All patients should receive Pneumococcal booster 3 - 5 years after initial dose.
Total Body Irradiation **Renal** **Para-Aortic** **Whole abdominal** **Spinal (≥ 15 Gy)**	68	**Renal insufficiency** **Hypertension** **See related topics:** **Ifosfamide** **Methotrexate** **Cisplatin/Carboplatin** **Cystectomy** **Nephrectomy**	**Treatment factors** Higher radiation dose to kidneys Combined with: - doxorubicin, - dactinomycin Hyperfractionated radiation Total body irradiation Combined with other nephrotoxic agents such as: - cisplatin/carboplatin - ifosfamide - aminoglycosides - amphotericin - immunosuppressants - cyclosporine **Medical conditions** Mononephric Diabetes mellitus Hypertension	**Treatment factors** Dose ≥ 15 Gy to whole kidney 14 Gy TBI without renal shielding	Blood pressure BUN, creatinine, U/A Na, K, Cl, CO_2 Ca, Mg, PO_4 Creatinine clearance or GFR	Yearly Yearly Obtain in patients with abnormal BP, urinalysis BUN, or creatinine. If abnormal, repeat as clinically indicated.	**Health Link** Kidney Health See also: Single Kidney Precautions	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
Total Body Irradiation **Whole abdomen** **Hepatic** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Transfusion (chronic hepatitis B &C)** **Hematopoietic cell transplant (liver toxicity)**	69	**Hepatic fibrosis** **Cirrhosis**	**Treatment factors** Higher radiation dose to liver **Medical conditions** Chronic hepatitis **Health behaviors** Alcohol use	**Treatment factors** Dose ≥ 40 Gy to at least 1/3 of liver volume Dose 20-30 Gy to entire liver	Physical exam ALT, AST, bilirubin	Yearly Baseline at entry into long-term follow-up.	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity.
	70	**Hepatocellular carcinoma**	**Medical conditions** Chronic hepatitis B or C Cirrhosis **Treatment factors** Higher radiation dose to liver **Health behaviors** Alcohol use		AFP Liver ultrasound	Yearly in patients with chronic hepatitis Yearly in patients with cirrhosis	**Health Link** Reducing the Risk of Second Cancers Hepatitis after Childhood Cancer	Oncology consultation for medical management.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Total Body Irradiation **All abdominal and pelvic fields** **Spinal ≥ 20 Gy**	71	**Bowel obstruction**	**Treatment factors** Higher radiation dose to bowel Abdominal surgery **Clinician Info Link** Bowel obstruction is rarely seen in individuals treated with abdominal radiation who have not had abdominal surgery.	**Treatment factors** Dose ≥ 45 Gy (Obstruction may occur in people who received lower doses of abdominal radiation during childhood)	Physical exam KUB	With clinical symptoms of obstruction.		Surgical consultation in patients who fail medical management.
	72	**Chronic enterocolitis** **Fistula, Strictures**	**Treatment factors** Higher radiation dose to bowel Abdominal surgery	**Treatment factors** Dose ≥ 45 Gy	History Serum protein, albumin	Yearly Yearly in patients with chronic diarrhea or fistula		Surgical and/or gastroenterology consultation for symptomatic patients.
Total Body Irradiation **All abdominal and pelvic fields ≥ 25 Gy** **Spine ≥ 25 Gy**	73	**Gastrointestinal malignancy**	**Host factors** Hepatoblastoma Familial polyposis **Treatment factors** Higher radiation dose to bowel Higher daily fraction dose Combined with chemotherapy (especially alkylators)	**Treatment factors** Radiation dose ≥ 25 Gy	*The following monitoring is to begin 15 years after radiation or at age 35 years (whichever occurs last). Monitor more frequently if clinically indicated.* **Choose one of the following three options:** Fecal occult blood (minimum 3 cards) — Yearly **AND** Flexible sigmoidoscopy — Every 5 years **OR** Double contrast barium enema — Every 5 years **OR** Colonoscopy — Every 10 years		**Health Link** Reducing the Risk of Second Cancers	Surgical and/or oncology consultation as needed.
Total body irradiation **Whole abdomen** **Pelvic** **Iliac/inguinal** **Para-aortic**	74	**Uterine vascular insufficiency** resulting in adverse outcomes such as spontaneous abortion, neonatal death, low-birth weight infant, fetal malposition, and premature labor	**Host factors** Females with Wilms tumor and associated müllerian anomalies **Clinician Info Link:** 10% of girls with Wilms tumor have congenital uterine anomalies **Treatment factors** Higher radiation dose to pelvis	**Host factors** Prepubertal at treatment **Treatment factors** Dose ≥ 20-30 Gy TBI	History Consider high-level ultrasound evaluation of genitourinary tract after pubertal development.	Yearly and as clinically indicated As clinically indicated in patient contemplating pregnancy.	**Health Link** Female Health Issues after Childhood Cancer Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	High-risk obstetrical care during pregnancy. High level ultrasound in women with Wilms tumor.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Total body irradiation **Whole abdomen** **Pelvic** **Iliac/inguinal** **Para-aortic** **Spinal ≥ 24 Gy**	75	**Ovarian dysfunction:** - Delayed/arrested puberty - Primary amenorrhea - Secondary amenorrhea - Premature ovarian failure - Early menopause - Infertility **See related topics:** **Alkylating agents** **Head/brain radiation**	**Host factors** Older age at irradiation **Treatment factors** Radiation dose to pelvis 6-10 Gy Combined with: - cranial radiation Combined with alkylating agent chemotherapy	**Treatment factors** Dose ≥ 10-20 Gy TBI Combined with cyclophosphamide dose ≥ 200 mg/kg (conditioning for stem cell transplant)	Pubertal history (onset, tempo) Symptoms of menopause (hot flashes, poor libido) Menstrual history Physical exam with height, weight, Tanner stage	Yearly	**Health Link** Female Health Issues after Childhood Cancer Risks and benefits of hormonal replacement therapy Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Gynecology or endocrinology consultation for hormonal replacement therapy. Consider evaluation for conditions exacerbated by hypogonadism (e.g., osteopenia/osteoporosis). Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies.
					LH, FSH, Estradiol	Baseline at age 8, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty, irregular menses or amenorrhea - Clinical signs and symptoms of estrogen deficiency		
Whole abdomen **Pelvic** **Iliac/inguinal** **Para-aortic** **Spinal ≥ 30 Gy**	76	**Hemorrhagic cystitis** **See related topics:** **Cyclophosphamide** **Ifosfamide**	**Treatment factors** Higher radiation dose	**Treatment factors** Combined with cyclophosphamide and/or ifosfamide	Urinalysis	Yearly	Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture-negative macroscopic hematuria.
	77	**Bladder fibrosis** **Dysfunctional voiding**	**Treatment factors** Higher cumulative radiation dose (≥ 45 Gy) Combined with: - cyclophosphamide - ifosfamide		Voiding history	Yearly		Urologic consultation for patients with incontinence or dysfunctional voiding.
	78	**Bladder malignancy** **See related topics:** **Cyclophosphamide** **Ifosfamide**	**Treatment factors** Radiation to pelvis Combined with: - cyclophosphamide - ifosfamide **Health behaviors** Alcohol use Tobacco use		Urinalysis	Yearly	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report dysuria or gross hematuria	Urology consultation for culture-negative macroscopic hematuria.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Testicular radiation								
Total body irradiation **Testicular** **Pelvic** **Inguinal/femoral** **Spinal ≥ 24 Gy**	79	**Testicular dysfunction** **- Azoospermia** **- Infertility**	**Treatment factors** Radiation to testes 1 to 3 Gy: azoospermia may be reversible. 3 to 6 Gy: azoospermia possibly reversible (but unlikely)	**Treatment factors** Radiation to testes ≥ 6 Gy: azoospermia likely permanent	Semen analysis	As requested by patient and for evaluation of infertility. **Clinician Info Link** Late recovery of gonadal function has been reported.	**Health Link** Male Health Issues after Childhood Cancer Counseling regarding need for contraception since there is tremendous individual variability in gonadal toxicity after exposure to radiation therapy and alkylating agents. Recovery of fertility may occur many years after therapy. Resources: American Society for Reproductive Medicine website: www.asrm.org See also: www.fertilehope.org	Refer to endocrinologist for delayed clinical signs of puberty or persistently abnormal hormone levels Urology or endocrinology consultation for hormonal replacement therapy. Consider evaluation for conditions exacerbated by hypogonadism: e.g., osteopenia/osteoporosis. Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies.
		-Hypogonadism **-Delayed/arrested puberty** **See related topics:** **Alkylating agents** **Head/brain radiation**	Testicular irradiation combined with head/brain irradiation	Radiation to testes ≥ 20 Gy: Leydig cell damage (affecting testosterone production) Radiation combined with alkylating agents Combined with cyclophosphamide dose ≥ 200 mg/kg (conditioning for stem cell transplant) TBI	History of sexual function (erections, nocturnal emissions, libido).	Yearly		
					History of medication use.	Yearly		
					Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					LH, FSH, Testosterone	Baseline at age 9, and then yearly until normal puberty is established, AND as clinically indicated in patients with: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency		
Extremity radiation								
	80	**Musculoskeletal growth problems:** - Hypoplasia - Fibrosis - Reduced or uneven growth - Limb length discrepancy	**Host factors** Younger age at treatment **Treatment factors** Higher cumulative dose Larger treatment field Higher dose per fraction	**Host factors** Prepubertal at treatment **Treatment factors** Orthovoltage radiation (commonly used before 1970) due to delivery of greater dose to skin and bones. Epiphysis in treatment field. Dose ≥ 20 Gy	Physical exam	Yearly	Counsel regarding increased risk of fractures in weight-bearing irradiated bones	Orthopedic consultation if clinically significant (limb length discrepancy, chronic pain) or for any deficit noted in growing child. Reconstructive surgical consultation.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Transfusion								
Clinician Info Link Consider any blood or serum product including: Packed red cells Whole blood White cells Platelets Fresh frozen plasma Cryoprecipitate Allogeneic marrow or stem cells Immunoglobulin preparations: IVIG, VZIG Clotting factor concentrates Note dates screening of blood donors initiated: 1971 Hepatitis BsAg 1985 HIVAB HIV-1 EIA 1986 Surrogate ALT screening 1990 HCV EIA-I screening 1992 HCV EIA-II screening Note: International screening policies may not include these measures.	81	**Chronic Hepatitis B** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Chronic hepatitis C** **Hematopoietic cell transplant (liver toxicity)**	**Host factors** Living in hyperendemic area **Treatment factors** Transfusion before 1972 **Health behaviors** IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing	**Host factors** Chronic immuno-suppression	Hepatitis B surface antigen (HBsAg) AND Hepatitis B core antibody (anti HBc or HBcAb)	Once in patients who received any blood or serum product prior to 1972	**Health Link** Hepatitis after Childhood Cancer	Gastroenterology or hepatology consultation for patients with chronic infection. Hepatitis A immunization in patients lacking immunity.
		Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	**Treatment factors** Stem cell transplantation **Medical conditions** Chronic hepatitis B, C **Health behaviors** Alcohol use	**Medical conditions** Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Physical exam ALT, AST, AFP, bilirubin, prothrombin time	Yearly in patients with chronic hepatitis		
					Liver ultrasound	Yearly in patients with cirrhosis		
	82	**Chronic Hepatitis C** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Chronic hepatitis B** **Hematopoietic cell transplant (liver toxicity)**	**Host factors** Living in hyperendemic area **Treatment factors** Transfusion before 1993 **Health behaviors** IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing	**Treatment factors** Transfusion before 1986 when surrogate screening of blood donors with ALT initiated and donors with self-reported high-risk behaviors deferred. Chronic immunosuppression	Hepatitis C antibody	Once in patients who received any blood or serum product prior to 1993	**Health Link** Hepatitis after Childhood Cancer	Screen for viral hepatitis in patients with persistently abnormal liver function regardless of transfusion history. Consider HCV PCR screening in all transfused at risk patients (especially those with abnormal liver function) or in patients with persistent immunosuppression (stem cell transplant recipients). Gastroenterology or hepatology consultation for management of patients with chronic infection, progressive liver dysfunction, or other hepatitis-related sequelae. Hepatitis A and B immunization in patients lacking immunity.
					PCR to establish chronic infection	Once in patients with positive hepatitis C antibody		
		Complications related to chronic hepatitis: - Cirrhosis - Hepatic failure - Hepatocellular carcinoma	**Treatment factors** Stem cell transplantation **Medical conditions** Chronic hepatitis B, C **Health behaviors** Alcohol use	**Medical conditions** Chronic co-infection with hepatotoxic viruses: Hepatitis B, Hepatitis C, and/or HIV	Physical exam and ALT, AST, AFP, bilirubin, and prothrombin time	Yearly in patients with chronic hepatitis		
					Liver ultrasound	Yearly in patients with cirrhosis		
	83	**HIV infection**	**Treatment factors** Transfusion before 1986 **Health behaviors** IV drug use unprotected sex multiple partners high-risk sexual behavior sexually transmitted diseases tattoos, body piercing **Medical conditions** HPV infection	**Health behaviors** High-risk behaviors	HIV 1 & 2 antibodies	Once in patients who received any blood or serum product prior to 1986	Standard counseling regarding safe sex, universal precautions, exacerbating high-risk behaviors	Infectious diseases consultation for patients with chronic infection.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Surgery								
Amputation	84	**Cosmesis** **Functional and activity limitations** **Residual limb integrity problems** **Phantom pain**	**Host factors** Skeletally immature/ growing children		Physical exam Prosthetic evaluation	Yearly until completion of growth, or every 3 years if skeletally mature. Every 6 months until skeletally mature, then yearly thereafter.	Counsel regarding skin checks, signs of poor prosthetic fit, residual limb and prosthetic hygiene.	Psychological consultation in patients with emotional difficulties related to cosmesis and adaptation following amputation. Vocational rehabilitation referral.
Central venous catheter	85	**Thrombosis** **Vascular insufficiency** **Infection of retained cuff or line tract**			History Physical exam	Yearly, and as clinically indicated.		
Cystectomy	86	**Chronic urinary tract infection** **Renal dysfunction** **See related topics:** **Ifosfamide** **Cisplatin/Carboplatin** **Methotrexate** **Abdominal/pelvic radiation** **Nephrectomy**			Blood pressure BUN, creatinine, U/A Urine culture Urology evaluation Na, K, Cl, CO_2. Ca, Mg, PO_4 Creatinine clearance or GFR.	Yearly Yearly Yearly and as clinically indicated Yearly Obtain in patients with abnormal BP, U/A, BUN, or creatinine. If abnormal, repeat as clinically indicated	**Health Link** Kidney Health	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.
Enucleation	87	**Cosmesis** **Poor prosthetic fit** **Orbital hypoplasia**	**Host factors** Younger age at enucleation **Treatment factors** Combined with radiation		Physical exam Ophthalmology Ocularist	Yearly		Psychological consultation in patients with emotional difficulties related to cosmesis and visual impairment. Vocational rehabilitation referral.
Laparotomy	88	**Adhesive/obstructive complications**	**Treatment factors** Combined with radiation		Physical exam	When symptomatic		Surgical consultation for patients unresponsive to medical management.
Limb sparing procedure	89	**Functional and activity limitations** **Contractures** **Loosening of endoprosthesis** **Chronic infection** **Chronic pain** **Limb length discrepancy**	**Host factors** Younger age at surgery Rapid growth spurt **Health behaviors** Higher risk of loosening in patients with high level of physical activity. Higher risk of contractures or functional limitations in patients with low level of physical activity.		Physical exam Radiograph Orthopedic follow-up	Yearly and as needed Yearly Every 6 months until skeletally mature, and yearly thereafter	**Health Link** Limb Salvage after Bone Cancer Counsel regarding need for antibiotic prophylaxis prior to dental and invasive procedures	Psychological consultation in patients with emotional difficulties related to cosmesis and adaptation following limb-sparing procedure. Vocational rehabilitation referral. Antibiotic prophylaxis prior to dental and invasive procedures
Nephrectomy	90	**Proteinuria** **Hyperfiltration** **Renal insufficiency** **Hydrocele** **See related topics:** **Ifosfamide** **Cisplatin/Carboplatin** **Methotrexate** **Abdominal/pelvic radiation** **Cystectomy**	**Treatment factors** Combined with other nephrotoxic therapy: - cisplatin, carboplatin - ifosfamide - kidney irradiation - abdominal irradiation - aminoglycosides - amphotericin - immunosuppresants - cyclosporine - methotrexate		Blood pressure BUN, creatinine, U/A Na, K, Cl, CO_2. Ca, Mg, PO_4 Creatinine clearance or GFR.	Yearly Yearly Obtain in patients with abnormal BP, U/A, BUN, or creatinine. If abnormal, repeat as clinically indicated	**Health Link** Single Kidney Precautions See also: Kidney Health	Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Neurosurgery	91	**Neurocognitive deficits** vary with extent of surgery and postoperative complications. In general, mild delays occur in most areas of neuropsychological function compared to healthy children. **Intracranial bleed/stroke** **Motor deficits** **Paralysis** **Movement disorders** **Ataxia** **Seizures** **Hydrocephalus** **Shunt malfunction** **Clinician Info Link** Extent of deficit depends on age at treatment, intensity of treatment, and time since treatment. New deficits may emerge over time.	**Host factors** Younger age at diagnosis **Treatment factors** Combined with: - brain radiation - high-dose chemotherapy - intrathecal chemotherapy **Medical conditions** Hydrocephalus	**Host factors** Younger age at treatment (< 3 years) Supratentorial tumor **Treatment factors** High-dose and/or IT methotrexate combined with cranial radiation. Radiation dose ≥ 60 Gy **Medical conditions** Posterior fossa syndrome CNS infection **Social factors** Low SES Predisposing family history of learning or attention problems	Neurology evaluation	Yearly, until 2 to 3 years after surgery or stable; continue to monitor if symptoms persist. Every 6 months for patients with seizure disorder.	**Health Link** School and Learning Issues after Childhood Cancer	Formal neuropsychological evaluation to include tests of processing speed, computer-based attention, visual- motor integration, memory, comprehension of verbal instructions verbal fluency, executive function and planning. Consider use of psychotropic medication (stimulant). Caution: lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Refer to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources (IEP) and/or social skills training. Speech, physical, and occupational therapy in patients with persistent deficits. Consider nutrition, endocrine, and psychiatric (obsessive-compulsive behaviors) consultations in patients with hypothalamic pituitary axis tumors. Neuroimaging with preferred study based on intracranial lesion to be evaluated: MRI: White matter Gadolinium-enhanced MRI: microvascular injury CT: calcifications
					Rehabilitation medicine/ physiatrist evaluation	Yearly, or more frequently as clinically indicated in patients with motor dysfunction		
					Neurosurgery evaluation	Yearly for patients with shunts.		
					Abdominal x-ray	At puberty growth spurt for patients with shunts to assure distal shunt tubing in peritoneum		
					Clinical assessment of educational or vocational progress	Baseline and yearly		
					Referral for formal neuropsychological evaluation	Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress		
Orchiectomy	92	**Infertility** **Hypogonadism**	**Treatment factors** Bilateral orchiectomy Unilateral orchiectomy combined with pelvic or testicular radiation and/or alkylating agents		History of sexual function (erections, nocturnal emissions, libido).	Yearly	**Health Link** Male Health Issues after Childhood Cancer For patients with single testis - counsel to wear athletic supporter with protective cup during athletic activities.	Refer to endocrinologist for bilateral orchiectomy, delayed clinical signs of puberty, or persistently abnormal hormone levels Consider surgical placement of testicular prosthesis.
					History of medication use.	Yearly		
					Physical exam including height, weight, Tanner stage, testicular volume by Prader orchiometry.	Yearly		
					LH, FSH, Testosterone	For patients with bilateral orchiectomy, refer to endocrinology at about age 9. For patients with unilateral orchiectomy, obtain as clinically indicated for: - Delayed puberty - Clinical signs and symptoms of testosterone deficiency		
					Semen analysis	As requested by patient and for evaluation of infertility		

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Pelvic surgery	93	**Retrograde ejaculation** **Impotence** **Bowel incontinence** **Bladder incontinence** **Hydrocele**	**Treatment factors** Retroperitoneal node dissection		History	Yearly	**Health Link** For males: Male Health Issues after Childhood Cancer	Urologic consultation for patients with incontinence, dysfunctional voiding, or sexual dysfunction.
Pulmonary lobectomy, pulmonary wedge resection, pulmonary metastasectomy	94	**Pulmonary insufficiency**	**Treatment factors** Chest radiation Combined with pulmonary toxic therapy: - bleomycin - busulfan - carmustine (BCNU) - lomustine (CCNU) - chest/thoracic radiation - spinal radiation ≥30Gy - total body irradiation **Medical conditions** Atopic history **Health behaviors** Smoking		Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up. Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction.	**Health Link** Pulmonary Health Patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumococcal vaccinations.
Splenectomy	95	**Life-threatening infection** with encapsulated organisms (Haemophilus influenzae, Streptococcus pneumoniae, Meningococcus)			Physical exam Blood culture	When febrile T ≥ 101°	**Health Link** Splenic Precautions Medical alert bracelet/card noting asplenia. Counsel to avoid malaria and tick bites if living in or visiting endemic areas.	In patients with T ≥ 101° (38.3°C), or other signs of serious illness, administer a long-acting, broad-spectrum parenteral antibiotic (e.g., ceftriaxone), and continue close medical monitoring while awaiting blood culture results. Hospitalization and broadening of antimicrobial coverage (e.g., addition of vancomycin) may be necessary under certain circumstances, such as the presence of marked leukocytosis, neutropenia, or significant change from baseline CBC; toxic clinical appearance; fever ≥104°F; meningitis, pneumonia, or other serious focus of infection; signs of septic shock; or previous history of serious infection. Immunize with Pneumococcal, Meningococcal, and HIB vaccines. All patients should receive Pneumococcal booster 3 - 5 years after initial dose.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
Hematopoietic Stem Cell Transplantation								
Clinician Info Link Complications after hematopoietic stem cell transplantation have multifactorial etiology: - prior therapy for primary malignancy - intensity of transplant conditioning - stem cell product (e.g., marrow, cord blood, peripheral stem cells) - donor (e.g., autologous, allogeneic, unrelated) - quality of donor to recipient match - complication of transplant process (immunosuppression and GVHD.) - complications in the post-transplant period. - underlying disease - host genetic factors - lifestyle behaviors This section includes late treatment complications that may be observed in hematopoietic cell transplant recipients not covered elsewhere in these guidelines Refer to other sections of these guidelines for specific details related to late complications of radiation and of specific chemotherapeutic agents **(continued on next page)**	**Immune system**							
	96	**Secretory IgA deficiency** **Hypogammaglobulinemia** **Chronic infections,** such as conjunctivitis, sinusitis, and bronchitis	**Medical conditions** Chronic GVHD	**Host factors** Low CD4 T-cell count	History	Yearly		Immunology or infectious diseases consultation for assistance with management of chronic infections.
	Liver							
	97	**Chronic hepatitis** **Cirrhosis** **Iron overload** **See related topics:** **Mercaptopurine** **Methotrexate** **Dactinomycin** **Hepatic radiation** **Transfusion (chronic hepatitis B & C)**	**Treatment factors** History of multiple transfusions Radiation to the liver **Medical conditions** Chronic GVHD Viral hepatitis **Health behaviors** Alcohol use		ALT, AST, bilirubin Ferritin	Baseline at entry into long term follow-up, Baseline at entry into long term follow-up	**Health Link** Liver Health	Prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. Note: PCR testing for HCV may be required in immunosuppressed patients who are negative for antibody. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction. Hepatitis A and B immunizations in patients lacking immunity.
	Lungs							
	98	**Bronchiolitis obliterans** **Chronic bronchitis** **Bronchiectasis**	**Treatment factors** Allogeneic transplant Thoracic radiation Total body irradiation Pulmonary toxic chemotherapy **Medical conditions** Chronic GVHD	**Medical conditions** Prolonged immunosuppression related to GVHD prophylaxis	Physical exam PFTs (including DLCO and spirometry) and CXR	Yearly Baseline at entry into long-term follow-up Repeat as clinically indicated in patients with abnormal or progressive pulmonary dysfunction and prior to general anesthesia.	**Health Link** Pulmonary Health Patients who desire to SCUBA dive should be advised to obtain medical clearance from a diving medicine specialist	Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Influenza and Pneumovax vaccination.

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
	Muscles/Bones							
Hematopoietic stem cell transplantation (continued from previous page) **Clinician Info Link** Sources of donor stem cells for transplantation include: *Autologous* (patient's own marrow or stem cells are harvested prior to ablative therapy) *Allogeneic* (marrow or stem cells are harvested from a related or unrelated donor) *Cord blood* (stem cells harvested from umbilical cord blood) Donors are usually matched to the patient based on HLA (Human Leukocyte Antigen) typing	99	**Joint contractures**	**Medical conditions** Chronic GVHD		Physical exam	Yearly		Consultation with rehabilitation medicine/physiatrist.
	100	**Osteopenia** Bone mineral density 1-2.5 SD below mean **Osteoporosis** Bone mineral density ≥2.5 SD below mean **Clinician Info Link** The World Health Organization definition of osteoporosis in adults is based on comparison of a measured bone mineral density of young adults at peak bone age and defined as a T-score. A T-score of ≥ 2.5 standard deviations below the mean is consistent with a diagnosis of osteoporosis. T-scores are not appropriate to assess skeletal health in pediatric patients who have not achieved peak adult bone mass. Instead, pediatric bone mineral density reference data sets calculate z-scores based on age and gender, but do not account for variations related to sexual maturation and ethnicity. The ideal reference data should provide assessment relative to body size, pubertal status, and age. Currently available pediatric reference data sets are not large enough to accurately characterize the normal variability in bone mineral density. Consequently, there are no evidence-based guidelines for classification of bone health in children.	**Treatment factors** Corticosteroids **Medical conditions** Hypogonadism **Behavioral factors** Physical inactivity	**Treatment factors** Prolonged corticosteroid therapy for chronic GVHD	Bone density evaluation (DEXA or quantitative CT) **Clinician Info Link** The optimal method of measuring bone health in children is controversial. Existing technologies have limitations. Dual energy x-ray absorptiometry (DEXA) provides an estimate of total bone mass at a given site. Quantitative CT provides distinct measures of trabecular and cortical bone dimension and density.	Baseline screening at 18 years old; consider earlier screening if clinically indicated. Repeat as clinically indicated.	**Health Link** Bone Health National Osteoporosis Foundation website: www.nof.org	Nutritional supplements in cases of osteopenia unresponsive to behavioral and dietary management: Calcium 1000-1500 mg daily plus RDA for vitamin D ** Caution regarding calcium supplementation in patients with history of renal lithiasis. Treatment of exacerbating or predisposing conditions (e.g., hormonal replacement therapy for hypogonadism, growth hormone deficiency; correction of chronic metabolic acidosis that could accelerate bone loss.). Endocrine consultation for patients with bone density ≥ 2.5 SD below mean, or patients with history of multiple fractures, for other pharmacologic interventions (e.g., bisphosphonates, calcitonin, selective estrogen receptor modulators).

(continued on next page)

Therapeutic Agent	Sec #	Potential Late Effects	Risk Factors	Highest Risk	Periodic Evaluation	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Intervention
	Second Cancers							
Hematopoietic stem cell transplantation (continued from previous page)	101	**Myelodysplasia** **Acute myeloid leukemia**	**Treatment factors** Radiation therapy Stem cell priming with etoposide Alkylating agent chemotherapy Epipodophyllotoxins Anthracyclines Autologous transplant	**Host factors** Autologous transplant for non-Hodgkin's lymphoma and Hodgkin's disease	Physical exam CBC/differential	Yearly up to 15 years after exposure to agent.	**Health Link** Reducing the Risk of Second Cancers Counsel to promptly report fatigue, pallor, petechiae, or bone pain.	Bone marrow exam as clinically indicated.
		Solid cancers most common are: - Basal/squamous cell - Melanoma - Oral cavity cancers - Liver cancer - CNS cancer - Thyroid cancer - Connective tissue - Cervical cancer	**Host factors** Younger age at transplant Fanconi's anemia **Treatment factors** Radiation therapy **Medical conditions** Hepatitis C infection Human papilloma virus infection Chronic GVHD of skin	**Treatment factors** Higher dose TBI	Physical exam	Yearly	**Health Link** Reducing the Risk of Second Cancers	Oncology consultation as clinically indicated.
		Lymphoma	**Treatment factors** Chemotherapy Stem cell transplant		Physical exam	Yearly		Oncology consultation as clinically indicated.
	Skin							
	102	**Alopecia** **Nail dysplasia** **Vitiligo** **Scleroderma**	**Treatment factors** Radiation therapy **Medical conditions** Chronic GVHD		Physical exam	Yearly	**Health Link** Skin Health	
General Health Screening								
	103	**Refer to United States Preventive Services Task Force recommendations at http://www.ahrq.gov/clinic/uspstfix.htm**						

Cancer Screening Guidelines

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Note to Clinicians: "Highest Risk" guidelines below include suggested periodic evaluations for childhood cancer survivors who are at increased risk of a specific cancer due to prior therapy, co-morbid conditions, family history, genetic susceptibility or other factors. "Standard Risk" guidelines below are per American Cancer Society recommendations for standard-risk populations and are provided here for reference. In addition, clinicians are encouraged to consult recommendations from other organizations, such as the U.S. Preventive Services Task Force (http://www.ahrq.gov/clinic/serfiles.htm). Specific decisions regarding cancer screening are the prerogative of the patient, family, and healthcare provider.							
Breast	104	Over age 40 Family history of breast cancer in first degree relative Early onset of menstruation Late onset of menopause (age 55 or older) Older than 30 at birth of first child Never pregnant Obesity Previous breast biopsy with atypical hyperplasia Hormone replacement therapy	Chest/thorax radiation with potential impact to the breast including : Total Body Irradiation Mantle Mediastinal Whole lung Spinal ≥30 Gy BRCA1, BRCA2, ATM mutation	**For females only:** **Standard Risk:** Breast self-examination Clinical breast exam Mammogram **Highest Risk:** Breast self-examination Clinical breast exam Mammogram **Clinician Info Link** Mammography is currently limited in its ability to evaluate premenopausal breasts..	 Monthly, beginning at age 20 Every 3 years between ages 20-40; then yearly beginning at age 40 Every year beginning age 40 Monthly beginning at puberty. Yearly, beginning at puberty until age 25, then every 6 months Yearly, beginning 8 years after radiation or at age 25 (whichever occurs last)	**Health Link** Breast Cancer after Treatment for Childhood Cancer: Are You at Risk?	Surgery and/or oncology consultation as clinically indicated.
Cervical	105	Early age at first intercourse Multiple lifetime sex partners Cigarette smoking Sexually transmitted diseases	Personal history of cervical dysplasia. Prenatal DES exposure HPV infection Immunosuppression Chronic steroid use	*Begin screening 3 years after first vaginal intercourse, or at age 21, whichever comes first* **Standard Risk:** Pelvic exam Cervical PAP smear **Highest Risk:** Pelvic exam Cervical PAP smear	 Every 1-2 years Yearly for regular PAP test; Every 2 years for liquid-based PAP test. After age 30: If patient has had 3 normal PAP tests in a row, may screen every 2-3 years. Yearly Yearly	**Health Link** Reducing the Risk of Second Cancers	Gynecology and/or oncology consultation as clinically indicated.

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Colorectal	106	High fat/low fiber diet Age 50 to 75 years Obesity	Total body irradiation Abdominal or pelvic radiation ≥25 Gy Spinal radiation ≥25 Gy Personal history of ulcerative colitis, gastrointestinal malignancy, adenomatous polyps or hepatoblastoma Familial polyposis Family history of colorectal cancer or polyps	**Standard Risk:** Fecal occult blood (minimum of 3 cards)	Yearly, beginning at age 50	**Health Link** Reducing the Risk of Second Cancers	Gastroenterology, surgery and/or oncology consultation as clinically indicated.
				AND/OR			
				Flexible sigmoidoscopy	Every 5 years beginning at age 50.		
				Note: The combination of yearly fecal occult blood testing and every 5 year flexible sigmoidoscopy is preferable to either test done alone.			
				OR			
				Double contrast barium enema	Every 5 years beginning at age 50.		
				OR			
				Colonoscopy	Every 10 years beginning at age 50		
				Highest Risk: Monitoring to begin 15 years after radiation or at age 35 years (whichever occurs last). Monitor more frequently if clinically indicated. **Choose from one of the following three options:**			
				Fecal occult blood (minimum of 3 cards)	Yearly, beginning 15 years after radiation or at age 35 (whichever occurs last).		
				AND			
				Flexible sigmoidoscopy	Every 5 years		
				OR			
				Double contrast barium enema	Every 5 years		
				OR			
				Colonoscopy	Every 10 years		
Endometrial	107	Obesity Older age Unopposed estrogen therapy	History of or at risk for hereditary nonpolyposis colon cancer (HNPCC)	**Highest Risk:** Endometrial biopsy	Yearly, beginning at age 35 for patients at highest risk.	**Health Link** Reducing the Risk of Second Cancers	

Organ	Sec #	At Risk Population	Highest Risk	Periodic Evaluations	Minimum Recommended Frequency	Health Protective Counseling	Considerations for Further Testing and Interventions
Lung	108	Cigarette smoking Workplace exposures to asbestos, arsenic, radiation Second hand smoke (in non- smokers)	Chest/thorax radiation with potential impact to the lungs, including Total body irradiation Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Any upper abdominal field	**Highest Risk:** History and Physical exam Imaging	 Yearly As clinically indicated	**Health Link** Reducing the Risk of Second Cancers	Surgery and/or oncology consultation as clinically indicated.
Oral	109	Tobacco use (smoking cigars cigarettes, or pipe; dipping, chewing), Alcohol abuse Excessive sun exposure increases risk of cancer of lower lip.	Head/brain radiation Neck radiation	**Highest Risk:** Oral cavity exam	Yearly if smoker or history of head/neck radiation	**Health Link** Reducing the Risk of Second Cancers Dental Health	Head and neck/otolaryngology consultation as indicated.
Prostate	110	Older age, with steadily increasing risk after age 40.	African-American race Family history of prostate cancer in first degree relative	**Standard Risk:** Digital rectal exam Prostate specific antigen (PSA)	 Yearly, beginning at age 50 Yearly, beginning at age 50	**Health Link** Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
				Highest Risk: Digital rectal exam Prostate specific antigen (PSA)	 Yearly, beginning at age 45 Yearly, beginning at age 45		
Skin	111	Light skin color Chronic exposure to sun Atypical moles or > 50 moles	Any history of radiation Personal history of melanoma or skin cancer. Dysplastic nevi Family history of melanoma or skin cancer. History of severe sunburn at young age	**Standard Risk:** Clinical skin exam	 Every 3 years, from ages 20-39 Yearly, beginning at age 40.	**Health Link** Reducing the Risk of Second Cancers Skin Health	Surgery, dermatology, and/or oncology consultation as clinically indicated.
				Highest Risk: Skin self exam Clinical skin exam with attention to pigmented nevi in radiation field.	 Monthly Yearly		
Testicular	112	Young males	History of undescended testicle History of testicular cancer or carcinoma- in-situ in contralateral testis. History of gonadal dysgenesis Klinefelter's syndrome Family history of testicular cancer	**Standard Risk:** Testicular self-exam Clinical testicular exam	 Not indicated Every 3 years, ages 20-39, then yearly.	**Health Link** Reducing the Risk of Second Cancers	Urology and/or oncology consultation as clinically indicated.
				Highest Risk: Testicular self-exam Clinical testicular exam	 Monthly, beginning at puberty Yearly		

Childhood Cancer Survivor
Long-Term Follow-Up Guidelines

Version 1.1 – September 2003

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Scoring

Explanation of Scoring for the Long-Term Follow-Up Guidelines

These guidelines represent a statement of consensus from a multidisciplinary panel of experts in the late effects of treatment for pediatric malignancies. The guidelines outline minimum recommendations for specific health screening evaluations in order to detect potential late effects arising as a result of therapeutic exposures received during treatment for childhood cancer. The recommendations are based on identified risk factors supported by the literature as well as by collective clinical experience.

Each score relates to the **strength of the association of the identified late effect with the specific therapeutic exposure based on current literature**, and is **coupled with a recommendation for periodic health screening based on the collective clinical experience of the panel of experts.** This is due to the fact that there are no randomized clinical trials (and none forthcoming in the foreseeable future) on which to base recommendations for periodic screening evaluations in this population; therefore, the Guidelines should not be misconstrued as representing conventional "evidence-based clinical practice guidelines" or "standards of care".

Each item was scored based on the level of evidence currently available to support it. Scores were assigned according to the following categories:

> **Category 1**: There is uniform consensus that the recommendation is appropriate based on high-level evidence of an association between the therapeutic agent and the late effect.
>
> **Category 2A**: There is uniform consensus that the recommendation is appropriate based on lower-level evidence, including clinical experience, of an association between the therapeutic agent and late effect.
>
> **Category 2B**: There is non-uniform consensus that the recommendation is appropriate based on lower-level evidence, including clinical experience, of an association between the therapeutic agent and late effect.
>
> **Category 3**: There is major disagreement that the recommendation is appropriate.

"High-level evidence" was defined as evidence derived from high quality case control or cohort studies. "Lower-level evidence" was defined as evidence derived from non-analytic studies, case reports, case series and clinical experience.

All "Category 1" recommendations reflect uniform consensus among the reviewers. "Category 2" recommendations are designated as "2A" (there is uniformity of consensus among the reviewers regarding strength of evidence for the association/recommendation) or "2B" (there is non-uniform consensus among the reviewers regarding the strength of evidence for the association/recommendation).

Rather than submitting recommendations representing major disagreements, items scored as "Category 3" were either deleted or revised by the panel of experts to provide at least a "Category 2B" score for all recommendations included in the guidelines.

SCORING

THERAPY	LATE EFFECT	SCORE
Any cancer experience	Psychosocial effects	2A
	Limitations in healthcare access	2A
Any chemotherapy	Dental abnormalities	1
Alkylating agents		
Classical alkylators: Mechlorethamine Cyclophosphamide Ifosfamide Melphalan Chlorambucil Lomustine (CCNU) Carmustine (BCNU) Busulfan Thiotepa Procarbazine	Hypogonadism Infertility Early menopause (females)	1
	AML/MDS	1
Non-classical alkylators: Dacarbazine Temozolamide Cisplatin Carboplatin	Hypogonadism Infertility Early menopause (females)	2A
	AML/MDS	2A
Heavy Metals		
Cisplatin Carboplatin	Ototoxicity	1
	Peripheral neuropathy	2A
	Renal toxicity	1
	Dyslipidemia	2B
Busulfan Carmustine (BCNU) Lomustine (CCNU)	Pulmonary fibrosis	1
Busulfan	Cataracts	2B

THERAPY	LATE EFFECT	SCORE
Cyclophosphamide Ifosfamide	Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding	1
	Bladder malignancy	1
Ifosfamide	Renal toxicity	1
Antimetabolites		
Methotrexate (po, IV, IM)	Osteopenia, Osteoporosis	2B
	Renal dysfunction	2A
	Hepatic dysfunction	2A
Methotrexate (IT, high-dose IV)	Neurocognitive deficits Clinical leukoencephalopathy (with or without imaging abnormalities)	1
Cytarabine (high-dose IV)	Neurocognitive deficits Clinical leukoencephalopathy (with or without imaging abnormalities)	2A
Mercaptopurine Thioguanine	Hepatic dysfunction Veno-occlusive disease	2A
Anthracyclines		
Doxorubicin Daunorubicin Idarubicin Mitoxantrone Epirubicin	AML	1
	Cardiomyopathy Arrhythmia	1
Anti-tumor antibiotics		
Dactinomycin	No known late effects	1
Bleomycin	Interstitial pneumonitis Pulmonary fibrosis	1
	Acute respiratory distress syndrome	2B

SCORING

THERAPY	LATE EFFECT	SCORE
Corticosteroids		
Prednisone Dexamethasone	Osteopenia, Osteoporosis	1
	Avascular necrosis (AVN)	1
	Cataracts	1
Enzymes		
Asparaginase	No known late effects	1
Plant alkaloids		
Vincristine Vinblastine	Peripheral sensory or motor neuropathy	2A
	Vasospastic attacks (Raynaud's phenomenon)	2A
Epipodophyllotoxins		
Etoposide Teniposide	AML	1
Radiation		
All fields including TBI	Skin changes	1
	Secondary benign or malignant neoplasms	1
	Dysplastic nevi Skin cancer	1
	Bone malignancies	1
TBI	Complications scored under individual radiation fields	N/A

THERAPY	LATE EFFECT	SCORE
Head and brain radiation		
TBI Cranial (whole brain)	Neurocognitive deficits	1
	Clinical leukoencephalopathy (with or without neuro-imaging abnormalities)	1
	Stroke/moyamoya Occlusive cerebral vasculopathy	1
	Brain tumor	1
	Growth hormone deficiency	1
	Hyperprolactinemia	1
	Central hypothyroidism	1
	Central adrenal insufficiency	1
	Precocious puberty	1
	Gonadotropin deficiency	1
	Overweight/obesity	1
	Chronic sinusitis	1
	Craniofacial abnormalities	1
TBI Cranial (whole brain) Craniospinal Nasopharyngeal Oropharyngeal Orbital/Eye Ear/Infratemporal Mantle Cervical spine	Dental abnormalities	1
	Xerostomia	1

SCORING

THERAPY	LATE EFFECT	SCORE
Eye radiation		
TBI Orbital/Eye Cranial (whole brain) Craniospinal	All adverse effects on eye: Cataracts Orbital hypoplasia Lacrimal duct atrophy Xerophthalmia (severe) Keratitis Keratoconjunctivitis sicca Telangiectasias Retinopathy Optic chiasm neuropathy Endophthalmos Chronic painful eye	1
Ear radiation		
TBI Ear/Infratemporal Cranial (whole brain) Craniospinal Nasopharyngeal	Tympanosclerosis Otosclerosis Eustachian tube dysfunction Conductive hearing loss	1
	Sensorineural hearing loss Tinnitus	1
Neck radiation		
Any radiation to the neck, including: TBI Cranial (whole brain) Craniospinal Nasopharyngeal Oropharyngeal Cervical Mantle Mediastinal Whole lung Spinal	Thyroid nodules	1
	Thyroid cancer	1
	Hypothyroidism	1
	Hyperthyroidism	1
	Carotid artery disease	2A
	Esophageal stricture	1

THERAPY	LATE EFFECT	SCORE
Trunk radiation		
Any field from shoulders to pelvis including: TBI Spinal (≥12 Gy)	Musculoskeletal growth problems	1
	Scoliosis	1
Chest/thorax radiation		
Any field involving the chest/thorax, including: TBI Mantle Mediastinal Whole lung Spinal ≥ 30 Gy Whole abdomen Any upper abdominal field	Kyphosis	1
	Esophageal stricture	1
Chest/thorax radiation with potential impact to the breast: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy	Breast cancer	2A
	Breast tissue hypoplasia	1
Chest/thorax radiation with potential impact to the heart: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Left hemiabdomen/ Left flank	Congestive heart failure Cardiomyopathy Pericarditis Pericardial fibrosis Valvular disease Myocardial infarction Arrhythmia Atherosclerotic heart disease	1

SCORING

THERAPY	LATE EFFECT	SCORE
Chest/thorax radiation with potential impact to the lungs: TBI Mantle Mediastinal Whole lung Spinal ≥30 Gy Whole abdomen Any upper abdominal field	Pulmonary fibrosis Delayed interstitial pneumonitis Restrictive/obstructive lung disease	1
Abdominal/Pelvic radiation		
≥30 Gy to: Whole abdomen Left upper quadrant Entire spleen	Functional asplenia Life-threatening infection	1
TBI Renal Para-aortic Whole abdomen Spinal (≥15 Gy)	Renal insufficiency Hypertension	1
TBI Whole abdomen Hepatic	Hepatic fibrosis Cirrhosis	1
	Hepatocellular carcinoma	2A
TBI All abdominal and pelvic fields Spinal (≥20 Gy)	Bowel obstruction	1
	Chronic enterocolitis Fistula, strictures	1
TBI ≥25 Gy to: All abdominal and pelvic fields Spine	Gastrointestinal malignancy	2A

THERAPY	LATE EFFECT	SCORE
TBI Whole abdomen Pelvic Iliac/Inguinal Para-aortic	Uterine vascular insufficiency	2B
TBI Whole abdomen Pelvic Iliac/Inguinal Para-aortic Spinal ≥24 Gy	Ovarian dysfunction	1
Whole abdomen Pelvic Iliac/Inguinal Para-aortic Spinal ≥30 Gy	Hemorrhagic cystitis	2A
	Bladder fibrosis Dysfunctional voiding	1
	Bladder malignancy	1
Testicular radiation		
TBI Testicular Pelvic Inguinal/femoral Spinal ≥24 Gy	Testicular dysfunction	1
Extremity radiation		
	Musculoskeletal growth problems	1
Transfusion		
	Chronic Hepatitis B	1
	Chronic Hepatitis C	1
	Complications related to chronic hepatitis	1
	HIV infection	1

SCORING

THERAPY	LATE EFFECT	SCORE
Surgery		
Amputation	Cosmesis Functional and activity limitations Residual limb integrity problems Phantom pain	1
Limb sparing procedure	Functional and activity limitations Contractures Loosening of endoprosthesis Chronic infection Chronic pain Limb length discrepancy	1
Enucleation	Cosmesis Poor prosthetic fit Orbital hypoplasia	1
Neurosurgery	Neurocognitive deficits Intracranial bleed/stroke Motor deficits Seizures Hydrocephalus Shunt malfunction	1
Laparotomy	Adhesive/obstructive complications	1
Orchiectomy	Infertility Hypogonadism	1
Pelvic surgery	Retrograde ejaculation Impotence Bowel incontinence Bladder incontinence Hydrocele	1
Splenectomy	Life-threatening infection	1
Nephrectomy	Proteinuria Hyperfiltration Renal insufficiency Hydrocele	1
Cystectomy	Chronic urinary tract infection Renal dysfunction	1
Placement of central venous catheter	Thrombosis Vascular insufficiency Infection of retained cuff or line tract	1
Hematopoietic stem cell transplantation		
Hematopoietic stem cell transplantation	Secretory IgA deficiency Hypogammaglobulinemia Chronic infection	1
	Alopecia Nail dysplasia Vitiligo Scleroderma	1
	Myelodysplasia AML	1
	Solid cancers	1
	Lymphoma	1
	Bronchiolitis obliterans Chronic bronchitis Bronchiectasis	1
	Chronic hepatitis Cirrhosis Iron overload	1
	Joint contractures	1
	Osteopenia Osteoporosis	1

SCORING

GENERAL HEALTH SCREENING	
General Health Screening	Not scored

CANCER SCREENING		
Organ	**Standard Risk**	**Highest Risk - Score**
Breast	Not scored (ACS recommendation)	2A
Cervical	Not scored (ACS recommendation)	2A
Endometrial	N/A	Not scored (ACS recommendation)
Colorectal	Not scored (ACS recommendation)	2A
Lung	N/A	1
Prostate	Not scored (ACS recommendation)	Not scored (ACS recommendation)
Testicular	Not scored (ACS recommendation)	2A
Skin	Not scored (ACS recommendation)	2A
Oral	N/A	1

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Appendix

Health Links

Healthy living after treatment for childhood cancer

All 34 Health Links may be downloaded in a single pdf file "Appendix" or the Health Links may be downloaded individually at

www.childrensoncologygroup.org/disc/le