VOLUME 30 · NUMBER 35 · DECEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Yield of Screening for Long-Term Complications Using the Children's Oncology Group Long-Term Follow-Up Guidelines

*Wendy Landier, Saro H. Armenian, Jin Lee, Ola Thomas, F. Lennie Wong, Liton Francisco, Claudia Herrera, Clare Kasper, Karla D. Wilson, Meghan Zomorodi, and Smita Bhatia*

Listen to the podcast by Dr Oeffinger at www.jco.org/podcasts

All authors: City of Hope, Duarte, CA.

Submitted April 9, 2012; accepted August 22, 2012; published online ahead of print at www.jco.org on October 22, 2012.

Supported in part by Grant No. P30 CA033572 from the National Institutes of Health; and by the Lincy, Bandai, Hearst, Graham Family, Rite Aid, Altschul, and Newman's Own Foundations; and by the Sam Bottleman Estate.

Presented in part at the European Symposium on Late Complications After Childhood Cancer, Amsterdam, the Netherlands, September 29-30, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Smita Bhatia, MD, MPH, City of Hope, 1500 East Duarte Rd, Duarte, CA 91010-3000; e-mail: sbhatia@coh.org.



0732-183X/12/3035-4401/$20.00

DOI: 10.1200/JCO.2012.43.4951

## ABSTRACT

### Purpose
The Children's Oncology Group Long-Term Follow-Up (COG-LTFU) Guidelines use consensus-based recommendations for exposure-driven, risk-based screening for early detection of long-term complications in childhood cancer survivors. However, the yield from these recommendations is not known.

### Methods
Survivors underwent COG-LTFU Guideline–directed screening. Yield was classified as negligible/negative (< 1%), intermediate (≥ 1% to < 10%), or high (≥ 10%). For long-term complications with high yield, logistic regression was used to identify subgroups more likely to screen positive.

### Results
Over the course of 1,188 clinic visits, 370 childhood cancer survivors (53% male; 47% Hispanic; 69% leukemia/lymphoma survivors; median age at diagnosis, 11.1 years [range, 0.3 to 21.9 years]; time from diagnosis, 10.5 years [range, 5 to 55.8 years]) underwent 4,992 screening tests. High-yield tests included thyroid function (hypothyroidism, 10.1%), audiometry (hearing loss, 22.6%), dual-energy x-ray absorptiometry scans (low bone mineral density [BMD], 23.2%), serum ferritin (iron overload, 24.0%), and pulmonary function testing/chest x-ray (pulmonary dysfunction, 84.1%). Regression analysis failed to identify subgroups more likely to result in high screening yield, with the exception of low BMD (2.5-fold increased risk for males [$P = .04$]; 3.3-fold increased risk for nonobese survivors [$P = .01$]). Screening tests with negligible/negative (< 1%) yield included complete blood counts (therapy-related leukemia), dipstick urinalysis for proteinuria and serum blood urea nitrogen/creatinine (glomerular defects), microscopic urinalysis for hematuria (hemorrhagic cystitis, bladder cancer), ECG (anthracycline-related conduction disorder), and hepatitis B and HIV serology.

### Conclusion
Screening tests with a high yield are appropriate for risk groups targeted for screening by the COG-LTFU Guidelines. Elimination of screening tests with negligible/negative yield should be given consideration.

*J Clin Oncol 30:4401-4408. © 2012 by American Society of Clinical Oncology*

## INTRODUCTION

One third of childhood cancer survivors report severe or life-threatening complications 30 years after diagnosis.[1] Clear relationships exist between specific therapeutic exposures and long-term complications[2-5]; surveillance for and early detection of these complications in high-risk populations can potentially reduce morbidity, given availability of appropriate interventions.[6]

In 2002, the Institute of Medicine called for guidelines to direct long-term follow-up care of childhood cancer survivors.[7] The Children's Oncology Group (COG) responded by developing the COG Long-Term Follow-Up (COG-LTFU) Guidelines, using the known association between therapeutic exposures and long-term complications to create risk groups that would need screening; although the definition of at-risk populations was evidence based, the modality and intensity of screening were consensus based (Table 1).[8] The COG-LTFU Guidelines have been in use since 2003. However, the yield from these consensus-based screening recommendations is not known. It is also not known whether there are certain subgroups of survivors who could benefit from lower or higher intensities of screening.

**Table 1.** COG Long-Term Follow-Up Screening Recommendations and Definitions of Positive Screening Tests

| Therapeutic Exposure | Potential Late Effect | COG-Recommended Screening | Positive Screening Test Definition Used for This Study |
|---|---|---|---|
| Alkylators, topoisomerase II inhibitors, autologous HCT | t-MDS/AML | CBC yearly × 10 years after exposure | Abnormal CBC (WBC < 4,000/$\mu$L, hemoglobin < 10 gm/dL, platelet count < 150,000/$\mu$L, or blasts present on differential) and pathology report confirming diagnosis of therapy-related myelodysplastic syndrome or AML |
| Cisplatin, carboplatin, ifosfamide, methotrexate, radiation to kidney (any dose) | Renal insufficiency | BUN/creatinine: baseline | Calculated GFR < 60 mL/min per 1.73 $m^2$ according to Schwartz et al[9] formula (for patients age ≤ 18 years) or Cockroft-Gault formula[10] (for patients age > 18 years) |
| | | UA for protein: yearly | Proteinuria ≥ 2+[11] |
| Cyclophosphamide, ifosfamide, pelvic irradiation (any dose) | Hemorrhagic cystitis | UA for microscopic hematuria: yearly | > 5 RBCs/high power field[12] |
| | Bladder cancer | UA for microscopic hematuria: yearly | > 5 RBCs/high power field and pathology report confirming diagnosis of bladder cancer[12] |
| Antimetabolites, abdominal irradiation ≥ 30 Gy | Hepatic toxicity | LFTs (ALT, AST, bilirubin): baseline | ALT ≥ 2× ULN or AST ≥ 2× ULN or total bilirubin > 1.5 mg/dL (ULN: ALT, 56 U/L; AST, 46 U/L)[13] |
| Cisplatin, carboplatin, ifosfamide | Renal tubular injury | Potassium/magnesium/phosphorous: baseline | ≥ 2 of following: serum potassium < 3.5 mmol/L, serum magnesium < 1.6 mg/dL, and serum phosphorus < 2.6 mg/dL[14] |
| Neck irradiation (any dose) | Hypothyroidism | TSH, free T4: yearly | TSH > 4.5 mIU/L[15] |
| Cisplatin, myeloablative carboplatin, ear irradiation ≥ 30 Gy | Hearing loss | Audiometry: baseline (and every 5 years for irradiation; yearly if age < 10 years) | Chang et al[16] grade 1 to 4 hearing loss in better ear |
| Anthracyclines | Cardiac conduction disorder (prolonged QT interval) | ECG: baseline and as clinically indicated | Corrected QT interval: males: > 450 msec; females: > 470 msec |
| Anthracyclines | Cardiac left ventricular systolic dysfunction | Echocardiogram: periodically (every 1 to 5 years) as indicated based on anthracycline dose and age at treatment | Ejection fraction < 55% or fractional shortening < 28% |
| Bleomycin, busulfan, nitrosoureas, chest irradiation (any dose), allogeneic HCT with cGVHD | Pulmonary fibrosis | Chest x-ray: baseline | Radiology report indicates scarring of pulmonary parenchyma and/or pleura per chest x-ray report[17] |
| | Pulmonary dysfunction (restrictive, obstructive, and/or diffusion defect) | PFTs: baseline | ≥ 1 of following: obstructive defect (FEV1 < 80% predicted), restrictive defect (TLC < 80% predicted), diffusion defect (DLCO < 80% predicted)[17] |
| Methotrexate, corticosteroids, HCT | Low bone mineral density | DEXA scan | Patients age < 20 years: Z score > 2 SD below mean; patients age ≥ 20 years: T score > 1 SD below mean[18] (screening limited to patients age ≥ 18 years; 65 patients age < 18 years not tested) |
| HCT | Iron overload | Serum ferritin: baseline | Serum ferritin > 500 ng/mL[19] |
| Blood products before 1972 | Chronic hepatitis B infection | Hepatitis B surface antigen and core antibody: baseline | Positive hepatitis B surface antigen and core antibody |
| Blood products before 1993 | Chronic hepatitis C infection | Hepatitis C antibody and PCR: baseline | Positive hepatitis C antibody with confirmatory PCR |
| Blood products between 1977 and 1985 | HIV infection | HIV serology: baseline | Positive HIV 1 and 2 antibody screen (ELISA) confirmed by Western blot |
| Alkylators, pelvic irradiation (any dose) | Gonadal dysfunction (females): premature menopause | FSH: baseline at age 13 years and as clinically indicated | FSH ≥ 13 mIU/mL[20] |
| Alkylators, pelvic irradiation ≥ 20 Gy | Gonadal dysfunction (males): Leydig cell dysfunction | Serum testosterone: baseline at age 14 years and as clinically indicated | Serum testosterone < lower limit of normal based on Tanner stage: 1, < 11; 2, < 18; 3, < 100; 4, < 200; and 5/adult, < 275 ng/mL[21] |
| Chest/thorax irradiation ≥ 20 Gy | Breast cancer | Mammogram: yearly | Abnormal mammogram (BI-RADS category 3 to 5) and pathology report confirming diagnosis of breast cancer[22] |

Abbreviations: AML, acute myeloid leukemia; BI-RADS, Breast Imaging Data Reporting System; BUN, blood urea nitrogen; CBC, complete blood count; cGVHD, chronic graft-versus-host disease; COG, Children's Oncology Group; DEXA, dual-energy x-ray absorptiometry; DLCO, diffusion capacity of lung for carbon monoxide; ELISA, enzyme-linked immunosorbent assay; FEV1, forced expiratory volume in 1 second; FSH, follicle-stimulating hormone; GFR, glomerular filtration rate; HCT, hematopoietic cell transplantation; LFT, liver function test; PCR, polymerase chain reaction; PFT, pulmonary function test; SD, standard deviation; T4, thyroxine; TLC, total lung capacity; t-MDS/AML, therapy-related myelodysplastic syndrome/acute myeloid leukemia; TSH, thyroid-stimulating hormone; UA, urinalysis; ULN, upper limit of normal.

  

In this study, we aimed to determine the yield of the COG-LTFU Guidelines in identifying key long-term complications in a cohort of childhood cancer survivors who underwent guideline-directed screening during routine follow-up care. Specifically, we aimed to identify populations of survivors with high, intermediate, or low yield and to use the information obtained to refine the COG-LTFU Guidelines.

## METHODS

### Study Participants

Participants were childhood cancer survivors enrolled in the institutional review board–approved City of Hope LTFU Clinic for Childhood Cancer Survivors (LTFU Clinic) aimed at providing comprehensive long-term follow-up care for childhood cancer survivors. Eligibility for inclusion in the current analysis was as follows: diagnosis of pediatric cancer at age $\leq$ 21 years, treatment with radiation and/or chemotherapy and/or hematopoietic cell transplantation (HCT), $\geq$ 5 years from diagnosis, remission for $\geq$ 2 years after completion of cancer therapy, and participation in the LTFU Clinic. Written informed consent was obtained from each participant or his or her legal representative.

### Procedures

*Risk-based screening.* Medical records were reviewed to determine each participant's therapeutic exposures, including cumulative doses of chemotherapy, radiation doses/fields, surgical procedures, and HCT-related details. A computerized algorithm was used to generate a list of screening tests, tailored to each patient's specific therapeutic exposures, sex, age, and time since exposure; the list of recommendations was reviewed and confirmed by a clinician to assure precise adherence to COG-LTFU Guidelines. Participants underwent screening evaluations in the LTFU Clinic and were invited to return annually for follow-up.

*Identification of long-term complications.* Results of all screening tests were defined a priori (Table 1) and classified as positive, negative, or indeterminate by two study team members (W.L., O.T.). Participants were excluded from the analysis for the targeted complication if they had been diagnosed with the targeted complication before their first screening visit (the outcome was excluded from the screening yield analysis but included in the prevalence report), if the positive screening test was inevaluable (eg, hematuria in urine specimen obtained from menstruating female survivor), or if the positive screening result was because of an unrelated condition (eg, thrombocytopenia related to immune thrombocytopenic purpura). Medication records were reviewed to clarify false-negative screening (eg, normal thyroid-stimulating hormone in patient receiving thyroid replacement therapy for previously diagnosed hypothyroidism). Indeterminate test results that could not be classified after a second level of review were referred to the senior researcher (S.B.) for final arbitration.

### Statistical Analyses

*Screening yield.* Screening yield was defined as the ratio of the number of positive screening tests in evaluable at-risk previously undiagnosed patients to the total number of evaluable screening tests completed. Screening yield was classified as negligible/negative ($<$ 1%), intermediate ($\geq$ 1% to $<$ 10%), or high ($\geq$ 10%) based on the prevalence of the targeted late effects reported in the literature (detailed rationale for the classification is provided in the Appendix, online only). Clinical and demographic characteristics (sex, race, diagnosis, age at diagnosis, age at testing, time since diagnosis, therapeutic exposures that triggered screening) were summarized for the screened population for each complication. For long-term complications with high yield, logistic regression techniques were used to identify subgroups (defined by relevant demographic and clinical characteristics) most likely to screen positive. The following variables were examined for their association with yield: primary cancer diagnosis, age at diagnosis, time since diagnosis, age at participation, sex, race/ethnicity, and HCT (none, autologous, allogeneic with or without chronic graft-versus-host disease) for all analyses; in addition, the following variables were examined for specific outcomes: platinum chemotherapy and radiation field involving the ear (ototoxicity); body mass index (pulmonary dysfunction, low bone mineral density [BMD]); bleomycin, lomustine, carmustine, busulfan, and chest irradiation/total-body irradiation (pulmonary dysfunction); prednisone, dexamethasone, methotrexate, and gonadal dysfunction (low BMD); and number of relapses (iron overload). The final multivariate regression models always included primary diagnosis, time since diagnosis, sex, race/ethnicity, and age at diagnosis or study participation; additional variables that were significant at $P < .2$ in the univariate analysis were also retained in the final models.

*Prevalence.* Prevalence was defined as the ratio of at-risk survivors newly identified with the targeted complication by screening, plus the number of at-risk survivors diagnosed with the complication before their first screening visit (but after receiving cancer therapy), to the total number of at-risk survivors.

## RESULTS

### Participant Characteristics

Between October 1, 2003, and October 31, 2010, 370 childhood cancer survivors underwent COG-LTFU Guideline–directed evaluations; of these, 59 underwent one evaluation, 89 underwent two evaluations, and 222 underwent more than two annual evaluations. Median age at diagnosis was 11.1 years (range, 0.3 to 21.9 years); median follow-up was 10.5 years (range, 5 to 55.8 years); median age at first evaluation was 23.9 years (range, 5.3 to 57.2 years). Fifty-three percent of participants were male; 47% were Hispanic; 69% had a primary diagnosis of leukemia or lymphoma. Participant characteristics are summarized in Table 2 and detailed by time from diagnosis (in 5-year increments) in Appendix Table A1 and Appendix Figure A1 (online only).

### Screening Yield

A total of 5,062 screening recommendations were generated by the computerized algorithms for the 370 participants over the course of 1,188 annual evaluations in the LTFU Clinic. All survivors in the cohort underwent at least one screening test. Of the 5,062 recommended tests, 4,992 (98.6%) were completed, and 4,954 (99.2%) of the 4,992 completed tests were evaluable (Appendix Table A2, online only). Eight of the evaluable tests (0.16%) were deemed indeterminate during the initial two levels of review and were referred to the senior researcher, who provided final arbitration. Screening yield is shown in Figures 1A to 1C and in Appendix Table A3 (online only). Clinical characteristics of the at-risk populations and corresponding screening results are summarized in Appendix Table A4 (online only).

*High yield.* Screening per COG-LTFU Guidelines resulted in high yield ($\geq$ 10%) for the following complications: hypothyroidism (10.1%), hearing loss (22.6%), low BMD (23.2%), iron overload (24%), and pulmonary dysfunction (84.1%).

*Intermediate yield.* Screening resulted in intermediate yield (1% to $<$ 10%) for the following complications: renal tubular dysfunction (2.4%), chronic hepatitis C infection (HCV; 2.9%), breast cancer (2.9%), hepatic dysfunction (3.8%), left ventricular (LV) systolic dysfunction (6.0%), premature menopause (6.6%), and Leydig cell dysfunction (8.2%).

*Negligible/negative yield.* Screening resulted in negligible/negative yield ($<$ 1%) for the following: renal glomerular dysfunction (0.2% by urinalysis; 0% by serum blood urea nitrogen/creatinine),

**Table 2.** Demographic and Clinical Characteristics of Study Participants

| Characteristic | No. | % |
|---|---|---|
| Cohort size | 370 | |
| Age, years | | |
| Diagnosis | | |
| Median | 11.1 | |
| Range | 0.3-21.9 | |
| Study participation | | |
| Median | 23.9 | |
| Range | 5.3-57.2 | |
| Time from diagnosis to study entry, years | | |
| Median | 10.5 | |
| Range | 5-55.8 | |
| Male sex | 195 | 52.7 |
| Race | | |
| Asian | 30 | 8.1 |
| Black | 12 | 3.2 |
| Hispanic | 174 | 47.0 |
| Non-Hispanic white | 141 | 38.1 |
| Other | 13 | 3.5 |
| Diagnosis | | |
| Acute lymphoblastic leukemia | 124 | 33.5 |
| Acute myeloid leukemia | 29 | 7.8 |
| CNS tumor | 17 | 4.6 |
| Hodgkin lymphoma | 58 | 15.7 |
| Non-Hodgkin lymphoma | 39 | 10.5 |
| Germ cell tumor | 15 | 4.1 |
| Wilms tumor | 15 | 4.1 |
| Bone and soft tissue sarcoma | 46 | 12.4 |
| Other | 27 | 7.3 |
| Any chemotherapy | 351 | 94.9 |
| Any radiation | 206 | 55.7 |
| HCT | 96 | 25.9 |

Abbreviation: HCT, hematopoietic cell transplantation.

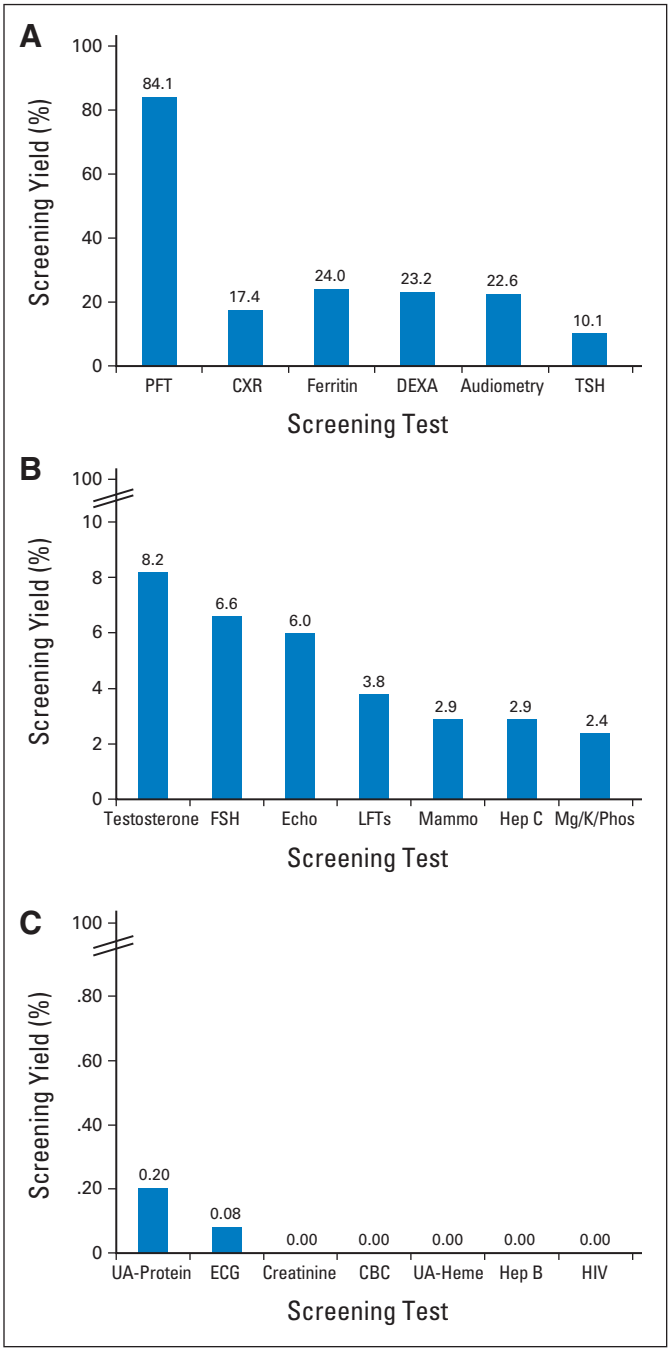


**Fig 1.** Screening yield (A) ≥ 10%, (B) ≥ 1% to < 10%, and (C) < 1%. CBC, complete blood count; CXR, chest x-ray; DEXA, dual-energy x-ray absorptiometry; Echo, echocardiogram; FSH, follicle-stimulating hormone (females only); Heme, microscopic hematuria; Hep B, hepatitis B surface antigen and core antibody; Hep C, hepatitis C antibody and confirmatory polymerase chain reaction; LFTs, liver function tests; Mammo, mammogram; Mg/K/Phos, magnesium/potassium/phosphorous; PFT, pulmonary function test; TSH, thyroid-stimulating hormone; UA, urinalysis.

anthracycline-related cardiac conduction disorder (0.08%), therapy-related myelodysplasia/acute myeloid leukemia [t-MDS/AML] (0%), hemorrhagic cystitis (0%), bladder cancer (0%), chronic hepatitis B infection (0%), and HIV (0%).

### *Populations With the Highest Probability for High Yield From Screening*

Multivariable logistic regression analyses performed for complications with high yield failed to identify subgroups more likely to result in high screening yield, with the exception of low BMD (2.5-fold increased risk for male compared with female survivors [27.2% *v* 18.4%; $P = .04$]; 3.3-fold increased risk for nonobese compared with obese survivors [29.2% *v* 10.5%; $P = .01$].

### *Prevalence*

Pre-existing conditions diagnosed in > 5% of at-risk participants before initiation of screening included chronic HCV infection (6.2%), pulmonary dysfunction (8.2%), low BMD (10%), hearing loss (12.7%), breast cancer (16.7%), gonadal dysfunction (female, 20.8%; male, 25.6%), and hypothyroidism (29.6%). Conditions with high (> 10%) overall prevalence (pre-existing conditions plus conditions newly identified by screening) in at-risk patients included LV systolic dysfunction (15.0%), breast cancer (23.3%), iron overload (24.0%), gonadal dysfunction (female, 26.0%; male, 31.7%), low BMD (30.8%), hearing loss (32.4%), hypothyroidism (36.7%), and pulmonary dysfunction (85.4%). Prevalence of long-term complications is summarized in Figures 2A to 2C and Appendix Table A3 (online only).

  

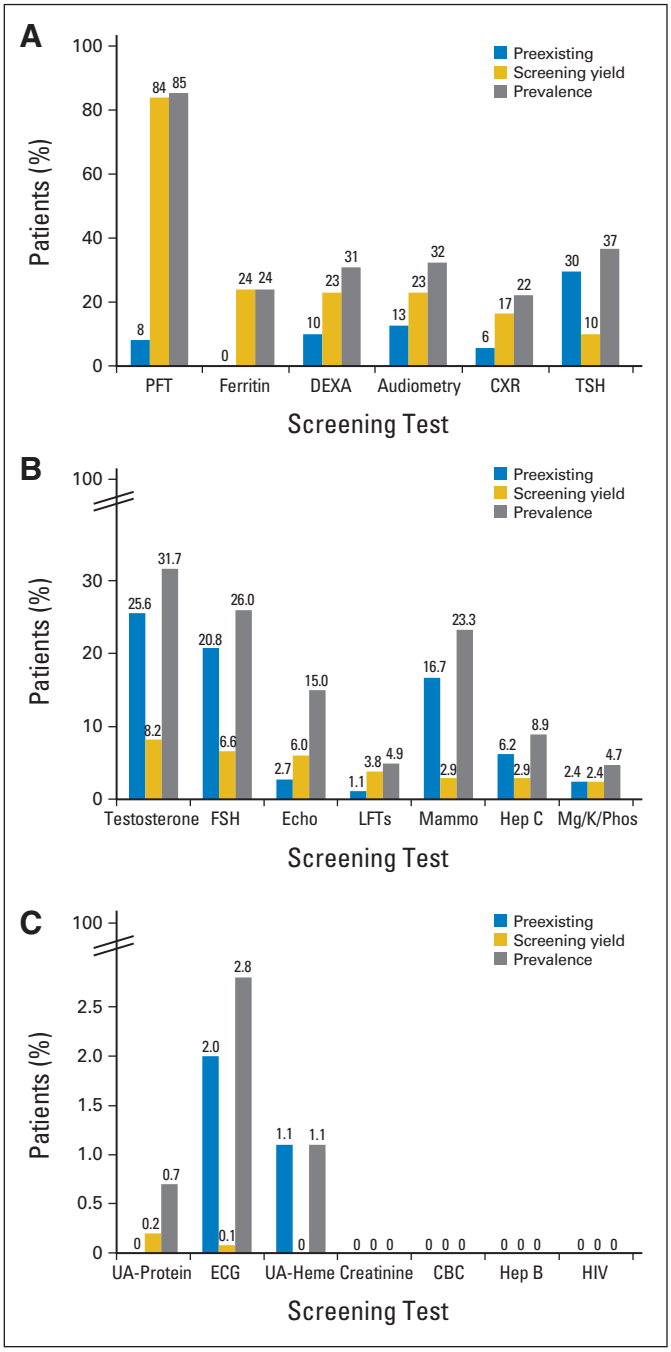


**Fig 2.** Pre-existing conditions, screening yield, and overall prevalence for (A) high-yield (≥ 10%), (B) intermediate-yield (≥ 1% to < 10%), and (C) negligible/negative-yield (< 1%) screening tests. CBC, complete blood count; CXR, chest x-ray; DEXA, dual-energy x-ray absorptiometry; Echo, echocardiogram; FSH, follicle-stimulating hormone (females only); Heme, microscopic hematuria; Hep B, hepatitis B surface antigen and core antibody; Hep C, hepatitis C antibody and confirmatory polymerase chain reaction; LFTs, liver function tests; Mammo, mammogram; Mg/K/Phos, magnesium/potassium/phosphorous; PFT, pulmonary function test; TSH, thyroid-stimulating hormone; UA, urinalysis.

## DISCUSSION

To our knowledge, this is the first study that reports the yield of nearly 5,000 screening tests following meticulous application of COG-LTFU screening guidelines in a cohort of childhood cancer survivors. Using this approach, we were able to identify screening tests with high and low yield in the context of the prevalence of these conditions in the at-risk populations, with implications for guideline refinement. Conditions with a high prevalence included LV systolic dysfunction (15%), iron overload (24%), low BMD (31%), hearing loss (32%), hypothyroidism (37%), and pulmonary dysfunction (85%); these findings are consistent with previous reports (pulmonary toxicity [13% to 87%],[4,23-28] iron overload [40% to 93%],[29-31] low BMD [21% to 65%],[32-34] hearing loss [25% to 83%],[35-39] and hypothyroidism [21% to 57%][40-45]). However, in our study, we differentiated screening yield from pre-existing conditions, with both contributing to the overall prevalence.

Screening according to the COG-LTFU Guidelines resulted in high yield for several conditions, likely a reflection of the generally asymptomatic nature of these conditions in the early stage and the fairly long latency after exposure to specific therapeutic agents. Thus, although pulmonary dysfunction had already been diagnosed in 8% of the patients before screening in this clinic, it was newly identified in 84% of at-risk patients screened, demonstrating the necessity to screen those at risk so that appropriate preventive/interventional measures can be instituted to decelerate the progression and, in some, reverse the process. Similarly, low BMD had been previously diagnosed in 10% of the at-risk population, but screening resulted in identification of low BMD in 23% of the remaining patients at risk. Hypothyroidism generally has a short latency after irradiation, but cancer survivors remain at risk for many years. In the current study, 30% of at-risk patients had already been diagnosed with hypothyroidism at the time of study entry, and screening resulted in a diagnosis of hypothyroidism in 10% of the remaining at-risk patients. Iron overload is generally an asymptomatic condition until organ (eg, cardiac, liver) dysfunction occurs as a result of high iron burden over a prolonged period of time. It is therefore not surprising that no patients were identified with iron overload before study entry, and screening resulted in identification of 24% with iron overload. Hearing loss, generally related to platinum agents with or without radiation, typically has a short latency, but it can be diagnosed several years after therapeutic exposure, because platinum-related hearing loss initially affects the higher frequencies, and patients/families may not identify the hearing loss unless it affects day-to-day activities. In our study, 13% of the patients were diagnosed with hearing loss before study entry; screening resulted in 23% of the remaining at-risk patients being newly identified with hearing loss. Although standard therapeutic interventions are readily available and likely to benefit survivors with some of these high-yield conditions (eg, thyroid replacement therapy for hypothyroidism,[46] auditory amplification for hearing loss,[47] calcium supplementation and bone loading for low BMD[48]), interventions for asymptomatic patients with other conditions (eg, iron overload,[29] pulmonary dysfunction[49]) are currently under investigation. In particular, for the 84% of survivors who received potentially pulmonary toxic therapy and were identified with previously unrecognized subclinical pulmonary dysfunction on screening evaluation, the implications of these findings are as yet unknown. However, because pulmonary function declines with age, these findings may portend future symptomatic pulmonary dysfunction as this population ages[50] and thus may have implications for the need to develop interventions to preserve or enhance pulmonary function in this vulnerable population.

Screening determinations used in this study were based on therapeutic exposures already identified by the COG-LTFU Guidelines as placing patients at risk for the targeted complications. The generally negative findings for subgroups with a higher likelihood to screen positive lend support to the appropriateness of risk groups targeted for screening by the COG Guidelines. The only exceptions were the identification of male sex and lack of obesity to be associated with an increased probability of low BMD; these findings are consistent with previously reported observations.[51-56]

The intermediate yield for renal tubular dysfunction (2%), chronic HCV infection (3%), breast cancer (3%), hepatic dysfunction (4%), LV systolic dysfunction (6%), premature menopause (7%), and Leydig cell dysfunction (8%) is probably a reflection of the low overall incidence of some complications (eg, hepatic dysfunction); the long latency of others (eg, breast cancer, LV systolic dysfunction; the yield will likely increase as follow-up matures); the short latency associated with some conditions (eg, gonadal dysfunction), such that the conditions were diagnosed before study entry; or the combination of short latency and self-resolving course (eg, renal tubular dysfunction), such that by the time the patients entered this study, the condition was no longer present. These scenarios are confirmed by the wide range of the overall prevalence of the intermediate-yield conditions (renal tubular injury, 5%; Leydig cell dysfunction, 32%).

The prevalence of renal tubular and LV systolic dysfunction in our cohort is comparable to that reported by others. In contrast, the higher prevalence of breast cancer (23%) in our cohort, compared with other studies (6% to 12%),[57] may be the result of inclusion of patients in the previous studies regardless of age or therapeutic exposure, whereas patients included in our study were targeted for screening based on therapeutic exposures (chest irradiation dose $\geq$ 20 Gy), current age ($\geq$ 25 years), and time from therapy ($\geq$ 8 years after irradiation).

The low prevalence of hepatotoxicity (5%) in our study is similar to that reported by others.[58,59] The risk for acquisition of transfusion-related HCV infection in the United States extended through 1992,[60] and reports of seroprevalence have ranged from 2% to 53%.[61-64] The prevalence of chronic HCV infection (9%) seen in our study is comparable to that reported by St Jude Children's Research Hospital.[64] Given the potential morbidity associated with this complication and the availability of effective treatments, continuation of this screening may be prudent.[65]

The prevalence of Leydig cell dysfunction in childhood cancer survivors has ranged from 2% to 23%,[66-69] lower than the prevalence identified in our study (32%). This may reflect the higher proportion of at-risk patients with a history of HCT (52%) in our cohort, a large proportion of whom received testicular irradiation (48%), and the fact that our cohort included only those at risk for the complication because of gonadotoxic therapeutic exposure.

All seven conditions with negligible yield also had a low prevalence (anthracycline-related cardiac conduction disorder, 2.8%; hemorrhagic cystitis, 1.1%; glomerular dysfunction, 0.7% by urinalysis and 0% by serum BUN/creatinine; t-MDS/AML, 0%; bladder cancer, 0%; chronic hepatitis B, 0%; HIV, 0%). Our findings are similar to the extremely low prevalence of t-MDS/AML[70] and bladder cancer[71] reported by others. Glomerular injury after ifosfamide and platinum-based chemotherapy,[72,73] improves over time.[74,75] No reports of late-onset hemorrhagic cystitis in cohorts of childhood cancer survivors were identified in the literature. Recent studies have found a low prevalence of prolonged QT interval after anthracycline exposure.[76] Finally, complete blood counts obtained during the first 10 years after exposure and annual lifelong urinalyses accounted for the vast majority of the screening tests that resulted in negligible/negative yield.

The study needs to be considered within the context of certain limitations. The study population was limited to survivors who participated in the LTFU Clinic. Bias could potentially result from clinical and sociodemographic differences between those who did and did not attend the LTFU Clinic and differences in lifestyle exposures (ie, high-risk health behaviors). However, the yield of complications for a given screening test is driven by therapeutic exposures, thus minimizing the impact of any participation bias. Additionally, the sample was drawn from participants who entered the study at varying lengths of time from cancer diagnoses. Because latency varies by long-term complication, it is possible that not all complications had become detectable at screening, and conversely, it is possible that some complications with shorter latency that were already diagnosed before entry into the LTFU Clinic (deemed pre-existing conditions) would have been detected by screening had the affected participants presented for their initial screening at an earlier time point. Interpretation of our data in the context of both prevalence and screening yield addresses the varying length of follow-up.

In this uniformly screened cohort of childhood cancer survivors using the COG-LTFU Guidelines, we found that screening yield was high for pulmonary dysfunction, hypothyroidism, iron overload, hearing loss, and low BMD. Screening tests with negligible/negative yield included complete blood counts (therapy-related leukemia), dipstick urinalysis for proteinuria and serum blood urea nitrogen/creatinine (glomerular defects), microscopic urinalysis for hematuria (hemorrhagic cystitis, bladder cancer), and ECG (anthracycline-related conduction disorder). Elimination of these screening tests should be given consideration. Although the period of elevated risk for acquisition of transfusion-related hepatitis B and HIV infections in the United States ended with initiation of screening of blood products for hepatitis B (1972)[77] and HIV (1985),[78] the serious implications of undetected occult HIV and hepatitis B virus infection, and the availability of effective therapy for these conditions, suggest that screening may be prudent, despite low yield.[79,80]

Information related to the yield of the screening tests recommended by the COG-LTFU Guidelines has several practical implications. This information is useful for primary care providers, because they carry an increasing burden of caring for childhood cancer survivors at risk for complex health conditions. The high yield of certain screening tests demonstrates the need for referral to subspecialists for appropriate interventions and hence a need for increased awareness of these complications by the specialists. Finally, the incidence of treatment-related complications will likely increase with time from diagnosis, making it imperative to continue follow-up of our childhood cancer survivors, using standardized recommendations, such as those offered by the COG-LTFU Guidelines. However, given the fact that the recommendations in the COG-LTFU Guidelines are consensus based, this study serves as an example of how application of the COG-LTFU Guidelines in a clinical setting can be used to refine them. The results of this study support the need for additional research to contribute to ongoing refinement of the recommendations for screening frequencies and modalities within the COG-LTFU Guidelines.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

  

## AUTHOR CONTRIBUTIONS

**Conception and design:** Wendy Landier, Saro H. Armenian, Smita Bhatia
**Financial support:** Smita Bhatia
**Administrative support:** Smita Bhatia
**Provision of study materials or patients:** Smita Bhatia
**Collection and assembly of data:** Wendy Landier, Jin Lee, Ola Thomas, Liton Francisco, Claudia Herrera, Clare Kasper, Karla D. Wilson, Meghan Zomorodi, Smita Bhatia
**Data analysis and interpretation:** Wendy Landier, Saro H. Armenian, Jin Lee, Ola Thomas, F. Lennie Wong, Smita Bhatia
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

## REFERENCES


1. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572-1582, 2006
2. Armenian SH, Meadows AT, Bhatia S: Late effects of childhood cancer and its treatment, in Pizzo PA, Poplack DG (eds): Principles and Practice of Pediatric Oncology (ed 6). Philadelphia, PA, Lippincott Raven, 2010, pp 1431-1462
3. Landier W, Bhatia S: Cancer survivorship: A pediatric perspective. Oncologist 13:1181-1192, 2008
4. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al: Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705-2715, 2007
5. Diller L, Chow EJ, Gurney JG, et al: Chronic disease in the Childhood Cancer Survivor Study cohort: A review of published findings. J Clin Oncol 27:2339-2355, 2009
6. Hennekens CH, Buring JE: Screening, in Mayrent SL (ed): Epidemiology in Medicine. Boston, MA, Little, Brown and Company, 1987, pp 327-347
7. Hewitt M, Weiner SL, Simone JV: Childhood Cancer Survivorship: Improving Care and Quality of Life. Washington, DC, National Academies Press, 2003
8. Landier W, Bhatia S, Eshelman DA, et al: Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 22:4979-4990, 2004
9. Schwartz GJ, Furth SL: Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol 22:1839-1848, 2007
10. Pierrat A, Gravier E, Saunders C, et al: Predicting GFR in children and adults: A comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. Kidney Int 64:1425-1436, 2003
11. Beetham R, Cattell WR: Proteinuria: Pathophysiology, significance and recommendations for measurement in clinical practice. Ann Clin Biochem 30:425-434, 1993
12. Kersun LS, Wimmer RS, Hoot AC, et al: Secondary malignant neoplasms of the bladder after cyclophosphamide treatment for childhood acute lymphocytic leukemia. Pediatr Blood Cancer 42:289-291, 2004
13. McIntosh S, Davidson DL, O'Brien RT, et al: Methotrexate hepatotoxicity in children with leukemia. J Pediatr 90:1019-1021, 1977
14. Bianchetti MG, Kanaka C, Ridolfi-Lüthy A, et al: Persisting renotubular sequelae after cisplatin in children and adolescents. Am J Nephrol 11:127-130, 1991
15. Aoki Y, Belin RM, Clickner R, et al: Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). Thyroid 17:1211-1223, 2007
16. Chang KW, Chinosornvatana N: Practical grading system for evaluating cisplatin ototoxicity in children. J Clin Oncol 28:1788-1795, 2010
17. Kreisman H, Wolkove N: Pulmonary toxicity of antineoplastic therapy. Semin Oncol 19:508-520, 1992
18. Kaste SC: Bone-mineral density deficits from childhood cancer and its therapy: A review of at-risk patient cohorts and available imaging methods. Pediatr Radiol 34:373-378, 2004; quiz 443-444
19. Knovich MA, Storey JA, Coffman LG, et al: Ferritin for the clinician. Blood Rev 23:95-104, 2009
20. Bath LE, Wallace WH, Critchley HO: Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. BJOG 109:107-114, 2002
21. Sklar C: Reproductive physiology and treatment-related loss of sex hormone production. Med Pediatr Oncol 33:2-8, 1999
22. Saslow D, Boetes C, Burke W, et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75-89, 2007
23. Motosue MS, Zhu L, Srivastava K, et al: Pulmonary function after whole lung irradiation in pediatric patients with solid malignancies. Cancer 118:1450-1456, 2012
24. Inaba H, Yang J, Pan J, et al: Pulmonary dysfunction in survivors of childhood hematologic malignancies after allogeneic hematopoietic stem cell transplantation. Cancer 116:2020-2030, 2010
25. Wasilewski-Masker K, Mertens AC, Patterson B, et al: Severity of health conditions identified in a pediatric cancer survivor program. Pediatr Blood Cancer 54:976-982, 2010
26. Mulder RL, Thönissen NM, van der Pal HJ, et al: Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. Thorax 66:1065-1071, 2011
27. Weiner DJ, Maity A, Carlson CA, et al: Pulmonary function abnormalities in children treated with whole lung irradiation. Pediatr Blood Cancer 46:222-227, 2006
28. Kaplan E, Sklar C, Wilmott R, et al: Pulmonary function in children treated for rhabdomyosarcoma. Med Pediatr Oncol 27:79-84, 1996
29. Chotsampancharoen T, Gan K, Kasow KA, et al: Iron overload in survivors of childhood leukemia after allogeneic hematopoietic stem cell transplantation. Pediatr Transplant 13:348-352, 2009
30. Kornreich L, Horev G, Yaniv I, et al: Iron overload following bone marrow transplantation in children: MR findings. Pediatr Radiol 27:869-872, 1997
31. McKay PJ, Murphy JA, Cameron S, et al: Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. Bone Marrow Transplant 17:63-66, 1996
32. Kaste SC, Shidler TJ, Tong X, et al: Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. Bone Marrow Transplant 33:435-441, 2004
33. Kaste SC, Ahn H, Liu T, et al: Bone mineral density deficits in pediatric patients treated for sarcoma. Pediatr Blood Cancer 50:1032-1038, 2008
34. Holzer G, Krepler P, Koschat MA, et al: Bone mineral density in long-term survivors of highly malignant osteosarcoma. J Bone Joint Surg Br 85: 231-237, 2003
35. Lewis MJ, DuBois SG, Fligor B, et al: Ototoxicity in children treated for osteosarcoma. Pediatr Blood Cancer 52:387-391, 2009
36. Schell MJ, McHaney VA, Green AA, et al: Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 7:754-760, 1989
37. Macdonald MR, Harrison RV, Wake M, et al: Ototoxicity of carboplatin: Comparing animal and clinical models at the Hospital for Sick Children. J Otolaryngol 23:151-159, 1994
38. Li Y, Womer RB, Silber JH: Predicting cisplatin ototoxicity in children: The influence of age and the cumulative dose. Eur J Cancer 40:2445-2451, 2004
39. Kushner BH, Budnick A, Kramer K, et al: Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer 107: 417-422, 2006
40. Bhatia S, Ramsay NK, Bantle JP, et al: Thyroid abnormalities after therapy for Hodgkin's disease in childhood. Oncologist 1:62-67, 1996
41. Baker KS, Ness KK, Weisdorf D, et al: Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: A report from the Bone Marrow Transplant Survivor Study. Leukemia 24:2039-2047, 2010
42. Bonato C, Severino RF, Elnecave RH: Reduced thyroid volume and hypothyroidism in survivors of childhood cancer treated with radiotherapy. J Pediatr Endocrinol Metab 21:943-949, 2008
43. Steffens M, Beauloye V, Brichard B, et al: Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). Clin Endocrinol (Oxf) 69:819-827, 2008
44. Bailey HK, Kappy MS, Giller RH, et al: Time-course and risk factors of hypothyroidism following allogeneic hematopoietic stem cell transplantation (HSCT) in children conditioned with fractionated total body irradiation. Pediatr Blood Cancer 51:405-409, 2008
45. Miyoshi Y, Ohta H, Hashii Y, et al: Endocrinological analysis of 122 Japanese childhood cancer survivors in a single hospital. Endocr J 55:1055-1063, 2008
46. Nandagopal R, Laverdière C, Mulrooney D, et al: Endocrine late effects of childhood cancer therapy: A report from the Children's Oncology Group. Horm Res 69:65-74, 2008
47. Grewal S, Merchant T, Reymond R, et al: Auditory late effects of childhood cancer therapy: A report from the Children's Oncology Group. Pediatrics 125:e938-e950, 2010
48. Wasilewski-Masker K, Kaste SC, Hudson MM, et al: Bone mineral density deficits in survivors of childhood cancer: Long-term follow-up guidelines

and review of the literature. Pediatrics 121:e705-e713, 2008

**49.** Liles A, Blatt J, Morris D, et al: Monitoring pulmonary complications in long-term childhood cancer survivors: Guidelines for the primary care physician. Cleve Clin J Med 75:531-539, 2008

**50.** Huang TT, Hudson MM, Stokes DC, et al: Pulmonary outcomes in survivors of childhood cancer: A systematic review. Chest 140:881-901, 2011

**51.** Tillmann V, Darlington AS, Eiser C, et al: Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Miner Res 17:1073-1080, 2002

**52.** Arikoski P, Komulainen J, Voutilainen R, et al: Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 20:234-240, 1998

**53.** Kaste SC, Jones-Wallace D, Rose SR, et al: Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: Frequency of occurrence and risk factors for their development. Leukemia 15:728-734, 2001

**54.** Müller HL, Schneider P, Bueb K, et al: Volumetric bone mineral density in patients with childhood craniopharyngioma. Exp Clin Endocrinol Diabetes 111:168-173, 2003

**55.** Benmiloud S, Steffens M, Beauloye V, et al: Long-term effects on bone mineral density of different therapeutic schemes for acute lymphoblastic leukemia or non-Hodgkin lymphoma during childhood. Horm Res Paediatr 74:241-250, 2010

**56.** NIH Consensus Development Panel on Osteoporosis Prevention Diagnosis and Therapy: Osteoporosis prevention, diagnosis, and therapy. JAMA 285:785-795, 2001

**57.** De Bruin ML, Sparidans J, van't Veer MB, et al: Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. J Clin Oncol 27:4239-4246, 2009

**58.** Floyd J, Mirza I, Sachs B, et al: Hepatotoxicity of chemotherapy. Semin Oncol 33:50-67, 2006

**59.** Castellino S, Muir A, Shah A, et al: Hepatobiliary late effects in survivors of childhood and adolescent cancer: A report from the Children's Oncology Group. Pediatr Blood Cancer 54:663-669, 2010

**60.** Centers for Disease Control and Prevention: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep 47:1-39, 1998

**61.** Locasciulli A, Testa M, Pontisso P, et al: Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. Blood 90:4628-4633, 1997

**62.** Aricò M, Maggiore G, Silini E, et al: Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. Blood 84:2919-2922, 1994

**63.** Cesaro S, Petris MG, Rossetti F, et al: Chronic hepatitis C virus infection after treatment for pediatric malignancy. Blood 90:1315-1320, 1997

**64.** Castellino S, Lensing S, Riely C, et al: The epidemiology of chronic hepatitis C infection in survivors of childhood cancer: An update of the St Jude Children's Research Hospital hepatitis C seropositive cohort. Blood 103:2460-2466, 2004

**65.** Ly KN, Xing J, Klevens RM, et al: The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med 156:271-278, 2012

**66.** Gerl A, Mühlbayer D, Hansmann G, et al: The impact of chemotherapy on Leydig cell function in long term survivors of germ cell tumors. Cancer 91:1297-1303, 2001

**67.** Greenfield DM, Walters SJ, Coleman RE, et al: Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. J Clin Endocrinol Metab 92: 3476-3482, 2007

**68.** Romerius P, Ståhl O, Moëll C, et al: Hypogonadism risk in men treated for childhood cancer. J Clin Endocrinol Metab 94:4180-4186, 2009

**69.** Ridola V, Fawaz O, Aubier F, et al: Testicular function of survivors of childhood cancer: A comparative study between ifosfamide- and cyclophosphamide-based regimens. Eur J Cancer 45:814-818, 2009

**70.** Bhatia S, Yasui Y, Robison LL, et al: High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. J Clin Oncol 21:4386-4394, 2003

**71.** Bassal M, Mertens AC, Taylor L, et al: Risk of selected subsequent carcinomas in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. J Clin Oncol 24:476-483, 2006

**72.** Jones DP, Chesney RW: Renal toxicity of cancer chemotherapeutic agents in children: Ifosfamide and cisplatin. Curr Opin Pediatr 7:208-213, 1995

**73.** Skinner R, Pearson AD, English MW, et al: Cisplatin dose rate as a risk factor for nephrotoxicity in children. Br J Cancer 77:1677-1682, 1998

**74.** Brock PR, Koliouskas DE, Barratt TM, et al: Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr 118:531-534, 1991

**75.** Stöhr W, Paulides M, Bielack S, et al: Nephrotoxicity of cisplatin and carboplatin in sarcoma patients: A report from the late effects surveillance system. Pediatr Blood Cancer 48:140-147, 2007

**76.** Hudson MM, Rai SN, Nunez C, et al: Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. J Clin Oncol 25: 3635-3643, 2007

**77.** Dodd RY: The risk of transfusion-transmitted infection. N Engl J Med 327:419-421, 1992

**78.** Lackritz EM, Satten GA, Aberle-Grasse J, et al: Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Engl J Med 333:1721-1725, 1995

**79.** Yuen MF, Lai CL: Treatment of chronic hepatitis B: Evolution over two decades. J Gastroenterol Hepatol 26:138-143, 2011 (suppl 1)

**80.** Camacho R, Teófilo E: Antiretroviral therapy in treatment-naive patients with HIV infection. Curr Opin HIV AIDS 6:S3-S11, 2011 (suppl 1)

  