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Efficacy and Cost-effectiveness of the Children's Oncology Group Long-Term Follow-Up Screening Guidelines for Childhood Cancer Survivors at Risk of Treatment-related Heart Failure

F. Lennie Wong, PhD¹, Smita Bhatia, MD, MPH¹, Wendy Landier, PhD, RN¹, Liton Francisco, BS¹, Wendy Leisenring, ScD², Melissa M. Hudson, MD³, Gregory T. Armstrong, MD³, Ann Mertens, PhD⁴, Marilyn Stovall, PhD⁵, Leslie L. Robison, PhD³, Gary H. Lyman, MD, MPH², Steven E. Lipshultz, MD⁶, and Saro H. Armenian, DO, MPH¹

¹City of Hope, Duarte, CA

²Fred Hutchinson Cancer Research Center, Seattle, WA

³St. Jude Children's Research Hospital, Memphis, TN

⁴Emory University School of Medicine, Atlanta, GA

⁵University of Texas MD Anderson Cancer Center, Houston, TX

⁶Wayne State University School of Medicine and Children's Hospital of Michigan, Detroit, MI

Abstract

Background—Childhood cancer survivors treated with anthracyclines are at high risk for asymptomatic left ventricular dysfunction (ALVD), subsequent heart failure (HF), and death. The consensus-based Children's Oncology Group (COG) Long-Term Follow-Up Guidelines recommend lifetime echocardiographic screening for ALVD.

Address correspondence and reprint requests to: F. Lennie Wong, Ph.D., City of Hope, 1500 E. Duarte Rd., Duarte, CA 91010, Phone: 626-256-4673 x65004; Fax: 626-471-9204, lwong@coh.org.

Current postal addresses for all authors:

F. Lennie Wong, PhD, Smita Bhatia, MD, MPH, Wendy Landier, PhD, RN, Liton Francisco, BS, Saro H. Armenian, DO, MPH, Department of Population Sciences, City of Hope, 1500 E. Duarte Rd., Duarte, CA 91010-3000

Wendy Leisenring, ScD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., D5-360, PO Box 19024, Seattle, WA 98109

Melissa M. Hudson, MD, Gregory T. Armstrong, MD, Leslie L. Robison, PhD, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 262 Danny Thomas Pl, Mail Stop 735, Memphis, TN 38105-3678

Ann Mertens, PhD, Department of Pediatrics, Emory University School of Medicine, 2015 Uppergate Dr. NE, Atlanta, GA 30322

Marilyn Stovall, PhD, Department of Radiation Physics, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030

Gary H. Lyman, MD, MPH, Hutchinson Institute for Cancer Outcome Research, University of Washington Schools of Public Health and Pharmacy, 1100 Fairview Ave. N, M3-B232, PO Box 19024, Seattle, WA 98109-1024

Steven E. Lipshultz, MD, Department of Pediatrics, Wayne State University School of Medicine, 3901 Beaubien Blvd, 1K40, Detroit, MI 48201-2196

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Conflicts of interest

We declare that we have no conflict of interest.

Objective—To evaluate the efficacy and cost-effectiveness of the COG Guidelines and to identify more cost-effective screening strategies.

Design—Simulation of life-histories using Markov health states.

Data Sources—Childhood Cancer Survivor Study; published literature.

Target Population—Childhood cancer survivors.

Time Horizon—Lifetime.

Perspective—Societal.

Intervention—Echocardiographic screening, followed by angiotensin-converting enzyme (ACE) inhibitor and beta-blocker therapies after ALVD diagnosis.

Measurements—Quality-adjusted life years (QALYs), costs, incremental cost-effectiveness ratios (ICERs) in dollars per QALY, and the cumulative incidence of HF.

Results of Base-Case Analysis—The COG Guidelines versus no screening have an ICER of \$61,500, extend life expectancy by 6 months and QALYs by 1.6 months, and reduce the cumulative incidence of HF by 18% at 30 years after cancer diagnosis. However, less-frequent screenings are more cost-effective than the Guidelines, and maintain 80% of the health benefits.

Results of Sensitivity Analysis—The ICER was most sensitive to the magnitude of ALVD treatment efficacy; higher treatment efficacy resulted in lower ICER.

Limitation—Lifetime non-HF mortality and the cumulative incidence of HF more than 20 years after diagnosis were extrapolated; the efficacy of ACE inhibitor and beta-blocker therapy in childhood cancer survivors with ALVD is undetermined (or unknown).

Conclusion—The COG Guidelines could reduce the risk of HF in survivors at less than \$100,000/QALY. Less-frequent screening achieves most of the benefits and would be more cost-effective than the COG Guidelines.

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INTRODUCTION

Anthracyclines are a class of highly effective chemotherapeutic agents incorporated into more than half of all childhood cancer treatments (1, 2). However, they are associated with a dose-dependent cardiotoxicity, which manifests along a continuum from asymptomatic left ventricular dysfunction (ALVD) to clinical heart failure (HF) (1). Five-year survival after HF diagnosis is generally poor (3-5).

The Children's Oncology Group Long-Term Follow-Up Guidelines (COG Guidelines) (6) recommend lifelong serial echocardiographic screening for survivors of childhood cancer to identify anthracycline-related ALVD and to delay the onset of HF with ALVD treatment (e.g., angiotensin-converting enzyme [ACE] inhibitors and/or beta-blockers) (7). The Guidelines recommend screening frequencies of 1 to 5 years, depending on 12 risk profiles defined by lifetime anthracycline dose, age at cancer diagnosis, and history of chest irradiation (8). These frequencies take into account the evidence for clinical and

demographic modifiers of the dose-dependent risk of ALVD or HF, but are essentially consensus-based.

Excessive screening wastes scarce financial resources, whereas inadequate screening delays ALVD treatment. The purpose of this study was to determine the efficacy and cost-effectiveness of the COG Guidelines and to explore alternative screening schedules that might be more cost-effective.

METHODS

We developed a Markov state transition model (TreeAge Software, Inc., Waltham, MA, USA) and simulated the life histories of 10 million childhood cancer survivors from 5 years after cancer diagnosis until death for each risk profile described in the COG Guidelines (Appendix 1; Appendix Table 1). Survivors included children with cancer diagnosed and treated between ages 0 and 20 years. The simulated populations mirrored the Childhood Cancer Survivor Study (CCSS) cohort (described below) in terms of sex, age at cancer diagnosis, chest irradiation, and cumulative anthracycline dose.

We compared lifetime costs and health outcomes (expected life-years, quality-adjusted life-years [QALYs], and the cumulative incidence of HF at 20, 30, and 50 years after cancer diagnosis) achieved by following the screening schedules against no screening (standard of care before the institution of the COG Guidelines) and calculated the incremental cost-effectiveness ratio (ICER) for the schedule recommended for each risk profile. The ICER of the COG Guidelines for the entire at-risk cohort was calculated by averaging the costs and QALYs calculated for each risk profile weighted by their prevalence. A 3% annual discount rate for costs and QALYs was used. The study was conducted as a reference case from the societal perspective (9).

Children's Oncology Group Long-Term Follow-Up Guidelines

The COG Guidelines recommend screening frequencies for 12 risk profiles (6). However, we excluded the first risk profile (age at diagnosis <1 year, chest irradiation, any anthracycline dose) for lack of data on HF.

Childhood Cancer Survivor Study Cohort

The CCSS data included information on 4,635 anthracycline-exposed childhood cancer survivors treated during 1970-1986 in the US and Canada and followed to December 31, 2002 (Appendix 1). Males comprised 54.5%; median age at cancer diagnosis was 7 years (range 0-20); median cumulative anthracycline dose was 292.8 mg/m²; 22% received chest radiation; and the median follow-up after cancer diagnosis was 20 years (10, 11).

Model Structure

The model comprised 4 health states (no ALVD, ALVD, HF, death) (Appendix Figure 1), which closely resembled the American Heart Association and American College of Cardiology definitions of HF (7): Stage A (No ALVD), Stage B (ALVD), and Stage C/D (HF). Individuals were ALVD-free at the start of simulation. They underwent life-time

echocardiographic screening according to the COG Guidelines with 100% adherence. The model used a 1-year cycle length.

The correct diagnosis of ALVD depended on the sensitivity and specificity of the screening echocardiography. After echocardiographic screening, individuals with ALVD were true-positive or false-negative; those without ALVD were false-positive or true-negative. True-positive cases underwent cardiac Magnetic Resonance Imaging (MRI) to confirm ALVD, followed by treatment (ACE inhibitor and beta blocker) with 76% compliance (12). Those in whom HF developed received an ACE inhibitor and a beta blocker. They could remain stable (no disease progression), become hospitalized for HF, or die of HF or of non-cardiac causes. False-positive cases underwent cardiac MRI to rule out ALVD and continued with screening per the COG Guidelines, as did the false- and true-negative cases. Survivors in any health state could die of non-HF causes.

Model Inputs

Echocardiography Performance Characteristics—Medical literature review showed the range of sensitivity and specificity for echocardiography to be 75%-94% and 90%-100%, respectively, when radionuclide angiography is the reference standard (13-18) (Table 1; Appendix 1). Thus, we used conservative values of 75% for sensitivity and 90% for specificity.

Efficacy of ALVD Treatment—Treatment for ALVD was assumed to reduce the annual HF incidence by 30% (12, 19, 20) (Table 1; Appendix 1).

Incidence of HF and ALVD—The annual incidence of HF from 5 to 30 years after cancer diagnosis was synthesized from published studies (Table 1; Appendix 1; Appendix Figure 2) (3, 21-28). Given sparse data, HF incidence beyond 20 years after diagnosis was held at the 20-year rate, but incorporated the age- and sex-specific HF incidence of the general population (29). The annual ALVD incidence was assumed to be three times that of HF (Appendix 1 for rationale). The cumulative incidences of ALVD and lifetime mortality from HF are shown in Appendix Table 2.

Annual Mortality—Non-HF mortality was estimated from 4,635 anthracycline-exposed CCSS participants (30) up to age 30 years for age at cancer diagnosis <5 years and up to age 40 years for age at cancer diagnosis ≥ 5 years. Mortality rates beyond these ages were estimated from the age- and sex-appropriate U.S. general population, by applying the multiplicative assumption and the relative risks estimated at ages 30 and 40 years (Table 1; Appendix 1; Appendix Figure 3). The annual HF mortality was derived from data in children (approximated by the rate of HF death or progression to heart transplantation) (31) and adults with HF (32, 33).

Utilities—We used health state values estimated from healthy men and women for the four heart disease classifications of the New York Heart Association for our three alive health-states (34). For ages 26-45 and 46-65 years, sex-specific means were used. For ages less than 26 or over 65 years, linearly extrapolated values at 15 and 85 years, respectively, were used. To account for side effects of ALVD treatment (35), the decrement in ALVD utility

relative to no ALVD was increased by 25% in 20% of ALVD patients (36) (Table 1; Appendix 1).

Costs—Costs (Table 2; Appendix 1) were adjusted to 2010 U.S. dollars using the medical portion of the Consumer Price Index, U.S. Bureau of Labor Statistics. Costs of a two-dimensional screening echocardiogram and a cardiac MRI were obtained from the 2010 Medicare Physician Fee Schedule (38). We used the average wholesale price for ACE inhibitors and beta blockers (39). Healthcare costs included age-dependent general health care (40), hospitalization leading to non-HF death (41), hospitalization for HF ending in discharge or death (41), and outpatient HF management (38). Patient time was valued at \$143 per day based on 2010 U.S. median annual earning (42).

Sensitivity Analyses

One-way sensitivity analyses were conducted for ALVD treatment efficacy and duration of efficacy, sensitivity and specificity of echocardiography, medication adherence rate, the cumulative incidence of HF at 20 years after cancer diagnosis, utilities for HF, discount rates, and echocardiographic screening cost (Tables 1, 2). Two-way sensitivity analyses were also conducted for echocardiographic sensitivity and specificity and ALVD treatment efficacy. Cohort values were calculated using weighted averages of QALYs and cost calculated for the risk groups using their prevalence as weights.

Identifying a Cost-effective Screening Strategy

Healthcare cost and QALYs for screening frequencies of 1 to 5 years were calculated for each risk profile. The frequencies were ordered by QALYs. The incremental cost per QALY gained by increasing the screening frequency to the next higher level was calculated (9). Frequencies providing fewer QALYs for equal or higher cost than other frequencies or frequencies gaining fewer QALYs for equal or higher cost than a combination of two other frequencies were eliminated (9, 43). The remaining frequency with the highest QALY gained at less than \$100,000 was considered the most cost-effective.

Role of the Funding Source

The study was supported in part by the Lance Armstrong Foundation and the National Cancer Institute. The funding sources had no role in the design, conduct, or the decision to publish the study findings.

RESULTS

Model Validation

Model validation procedures are detailed in the Appendix 2. External model validity was assessed by comparing model-based estimates of the cumulative incidence of HF at 20 years after cancer diagnosis with estimates reported in four large cohort studies (21-23, 28). Because the cohort characteristics were reported in aggregates, we identified specific risk profiles in the Guidelines that could correspond to the study data. The range of cumulative incidence calculated for these risk profiles (0.5%-5.8%) overlapped the estimates or the 95% confidence limits reported by the four studies (2%-7.9%) (Appendix Table 3).

Base-Case

Within each age at cancer diagnosis category, life expectancy and QALYs gained from screening increased with higher anthracycline dose. The reduction in HF risk was highest in the first two decades after cancer diagnosis and declined thereafter. The largest reduction in HF risk occurred for screening performed sooner after cancer diagnosis rather than later (Table 3).

Following the COG Guidelines for life instead of no screening increased the average cohort life-expectancy from 56.8 to 57.3 years, delayed HF onset on average by 1.5 years, increased the average QALY by 0.13, and decreased the cumulative incidence (“risk”) of HF by 23%, 18%, and 12% at 20, 30, and 50 years after cancer diagnosis, respectively. Across risk profiles 2 to 12, the average gain in life expectancy ranged from 2.6 to 11.3 months, the gain in QALYs ranged from 0.02 to 0.25, and the reduction in HF risk at 20, 30, and 50 years after cancer diagnosis ranged from 12.3% to 24.7%, 12.1% to 19.6%, and 9.2% to 15.6%, respectively. The ICER for the cohort (compared to no screening) was \$61,500 (Table 3). Depending on the risk profile 2 to 12, the ICER ranged from \$40,000 to \$138,200 (Table 3). Within any age group, the ICER was better for those at higher risk for HF due to chest irradiation or anthracycline dose, whether controlled for screening frequency or based on the frequencies in the COG Guidelines.

Screening Frequencies of 1 to 5 Years

The base-case analyses examined the frequencies recommended by the COG Guidelines; however, these screening frequencies may not be optimal. Our results indicate that the costliest—but most effective—strategy was annual screening (ICER: \$43,100 to \$368,400), and the least-expensive was screening every 5 years (ICER: \$18,300 to \$138,200). Given these observations above, we identified the most cost-effective screening frequencies costing under \$100,000 per QALY. Under this constraint (Table 3), annual screening recommendations in the COG Guidelines was reduced to every 2 to 4 years depending on the risk group, biennial screening to every 5 years, and every 5-year screening recommended for risk profiles 5 and 10 was maintained for the former and reduced to every 10 years for the latter. This overall less-frequent screening strategy maintained 80% of the health benefits of the COG Guidelines at nearly half the ICER (\$33,200, relative to no screening): life-expectancy gain was 4.9 months (vs. 6.1); QALY gain was 0.11 (vs. 0.13); and the reduction in HF risk at 30 years after diagnosis was 14.3% (vs. 17.5%). When compared to the overall less-frequent screening strategy, the COG Guidelines had an overall ICER of \$185,300.

Sensitivity Analyses

The ICER was most sensitive to ALVD treatment efficacy (percent reduction in annual HF incidence) (Figure 1). If treatment efficacy was 50%, the ICER decreased to \$34,900 (base-case: \$61,500) and the reduction in HF risk at 30 years after cancer diagnosis increased to 28.6% (base-case: 17.5%). When treatment efficacy was 10%, the HF risk at 30 years reduced by 7.8%, and the ICER was \$167,200. Limiting the duration of treatment efficacy to 6 years, as observed in one study (4), increased the ICER (\$118,100) and decreased the reduction in HF risk at 30 years after cancer diagnosis to 10.7%.

The ICER was next most sensitive to the cost of echocardiography. Doubling the cost increased the ICER (\$97,700). When the echocardiographic sensitivity and specificity were 50%, screening was more costly (ICER: \$99,600); but the effect on reducing the HF risk at 30 years was small (16.2% vs. 17.5% for the base-case). Complete adherence (100%) to ALVD treatment improved cost-effectiveness (ICER: \$46,600) and resulted in a larger reduction (22.2%) in HF risk at 30 years after diagnosis. Low adherence (50%) made screening more costly (ICER: \$89,700) and decreased the percent reduction in HF risk at 30 years (12.8%).

Screening was more cost-effective (ICER: \$47,000) if HF utilities (quality-of-life weight) were lower than assumed for the base-case, and less cost-effective (ICER: \$82,500) if they were higher. The ICER was least sensitive to changes in HF risk at 20 years after cancer diagnosis: \$44,500 and \$53,800, respectively, for a 20% higher and a 20% lower risk. The ICER for 0% and 5% discount rates were \$44,500 and \$78,900, respectively.

Two-way sensitivity analyses (Appendix Figure 4) showed that the ICER of the Guidelines remained below \$100,000 if ALVD treatment efficacy was 20% or higher and the echocardiographic sensitivity and specificity were at least 75% and 90%, respectively. If treatment efficacy was 10% or less, the ICER would exceed \$142,000 even with 100% echocardiographic sensitivity and specificity.

DISCUSSION

Echocardiographic screening for ALVD following the COG Guidelines with subsequent treatment could extend the life expectancy of a childhood cancer survivor by 6.1 months, QALYs by 1.6 months, and reduce the HF risk at 30 years after cancer diagnosis by 18%. The cost per QALY gained (compared to no screening) was \$61,500, which is lower than the \$100,000 per QALY often cited to assess the cost-effectiveness of interventions (QALY is one-year of life lived in perfect health, reflecting the quantity and the quality of life) (44). We also identified a more cost-effective screening strategy (\$33,200 per QALY) that calls for less-frequent screening than the COG Guidelines while preserving most of the health benefits.

If \$100,000 was used as the cost-effectiveness benchmark, the COG Guidelines would not be considered cost-effective for ALVD treatment efficacy equal to or lower than 10% or for treatment efficacy that was short-lived (e.g. 6 years, as suggested by one study [4]), keeping other variables fixed. However, the cost per QALY remained around \$100,000 or less for echocardiographic sensitivity and specificity as low as 50%, doubling of echocardiography cost, treatment adherence of 50% (equivalent to 15% ALVD treatment efficacy), and HF quality-of-life that was higher or HF risk at 20 years after cancer diagnosis that was lower than that assumed for the base-case. Two-way sensitivity analyses further showed that the cost per QALY of screening was around \$100,000 or less if ALVD treatment efficacy was 30% or higher even for low echocardiographic sensitivity and specificity of 50%. For a lower ALVD treatment efficacy of 20%, the cost per QALY remained under \$100,000 as long as the echocardiographic sensitivity and specificity were higher than 75% and 90%, respectively.

Heidenreich et al. (19) examined the cost-effectiveness of a one-time screen for ALVD using serum B-type natriuretic peptide and echocardiography (92% sensitivity, 96% specificity) in older adults in the general population. The efficacy of ACE inhibitor therapy for treating ALVD was assumed to be 34%. They estimated the cost per QALY of echocardiography as \$69,000 (2010 US dollars) compared to no screening. It is difficult to compare their results to ours given the differences in at-risk population (older, general population vs. anthracycline-exposed childhood cancer survivors), screening frequency (one-time vs. repeated), and confirmation diagnostics (none vs. cardiac MRI). Nevertheless, both studies suggest that echocardiographic screening for ALVD is cost-effective. We found screening to be more cost-effective for survivors exposed to higher anthracycline doses, with an attendant higher risk of anthracycline-related HF. Heidenreich et al. also showed that cost-effectiveness of screening with B-type natriuretic peptide increased as ALVD prevalence increased. Other programs for preventing HF also found screening to be more beneficial for populations with higher risks (45, 46).

Reductions in HF risk were greater sooner after cancer diagnosis than later, possibly because at younger ages the HF risk is higher than the competing risks of non-HF mortality. The burden of chronic diseases (and the attendant mortality) in this cohort increases with time since cancer diagnosis (47, 48), which we addressed by the multiplicative risk assumption. The benefit of screening one disease (ALVD) is mitigated with time because the rate of non-HF-related mortality increases. Therefore, beginning screening sooner after cancer diagnosis rather than later could better control HF risk.

Our assessment of the cost-effectiveness of the COG Guidelines are limited by two sources of uncertainty: 1) the assumptions derived largely from adult data regarding ALVD treatment efficacy, the sensitivity and specificity of echocardiography, and medication adherence; and 2) the assumptions of constant HF risk beyond 20 years after cancer diagnosis and the use of a multiplicative risk model to estimate non-HF mortality at older ages.

The implications of the first source of uncertainty can be gleaned from the results of sensitivity analyses: the COG Guidelines would not be cost-effective if the true ALVD treatment efficacy in childhood cancer survivors was lower than 20% and the sensitivity and specificity of echocardiography were lower than 75% and 90%, respectively; or if treatment efficacy (at 30%) is limited to 6-years, or medication adherence was lower than 50%. However, the treatment efficacy for therapies combining ACE inhibitors and beta-blockers as well as the duration of treatment efficacy is currently unknown, and merits future investigation.

The second source of uncertainty (holding HF risk constant beyond 20 years and assuming a multiplicative model for excess non-HF mortality) underestimates the lifetime risk of HF and, therefore, the cost-effectiveness of screening. In fact, when we applied the additive risk assumption in one risk profile setting, the estimated cost per QALY was lower than that of the multiplicative risk assumption, showing that the multiplicative model we used tends to underestimate the cost-effectiveness of screening. Finally, we did not address the cost of heart transplantation, which also may underestimate the cost-effectiveness of screening.

Strengths of our studies include simulating the entire cohort of anthracycline-exposed childhood cancer survivors and their characteristics, making our assessment of the cost-effectiveness of screening more realistic than if a narrow subgroup of individuals were examined. We also identified optimal screening frequencies for individual risk profiles, hence a more cost-effective screening strategy for the cohort.

In summary, lifetime echocardiographic screening for ALVD as recommended by the COG Guidelines would be cost-effective for decreasing the HF risk in anthracycline-exposed childhood cancer survivors, given that ALVD treatment efficacy exceeds 20%. A more cost-effective strategy involving less frequent screening, and hence less patient burden, could provide similar health benefits at half of the cost. Based on our modeling using the CCSS cohort, annual screening recommended by the Guidelines for more than 50% of survivors could be decreased to every 2 to 4 years. The biennial screening recommended for more than 30% of survivors may be decreased to every 5 years. Every 5-year screening recommended for 3% of survivors could be maintained, but the frequency could be reduced to 10 years for an additional 12% of the survivors. This study provides a rationale for decreasing the screening frequencies in the COG Guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

Appendix Figure 1.

Four-health state transition diagram.

ALVD = asymptomatic left ventricular dysfunction

HF = heart failure

A.

B.

Appendix Figure 2.

Annual incidence of HF by years since cancer diagnosis, for

A) age at cancer diagnosis < 5 years;B) age at cancer diagnosis ≥ 5 years

HF = heart failure

Appendix Figure 3.

Annual non-HF mortality by attained age

HF = heart failure

RR = relative risk (compared to the U.S. population)

Appendix Figure 4.

Two-way sensitivity analyses for ICER, by varying the efficacy of ALVD treatment and the sensitivity and specificity of echocardiography for detecting ALVD

ALVD = asymptomatic left ventricular dysfunction

ICER = incremental cost-effectiveness ratio

QALY = quality-adjusted life-year

Appendix Table 1

Children's Oncology Group Guidelines for Echocardiographic Screening for ALVD

Risk profile	Frequency in the CCSS cohort, %*	Age at cancer diagnosis, y	Chest irradiation	Anthracycline dose, mg/m ²	Recommended screening interval, y
1	1.3	< 1	Yes	Any	1
2	2.0	< 1	No	<200	2
3	2.2	< 1	No	200	1
4	5.1	1-4	Yes	Any	1
5	3.1	1-4	No	<100	5
6	12.4	1-4	No	100 to 299	2
7	12.0	1-4	No	300	1
8	9.4	5	Yes	< 300	2

Risk profile	Frequency in the CCSS cohort, % [*]	Age at cancer diagnosis, y	Chest irradiation	Anthracycline dose, mg/m ²	Recommended screening interval, y
9	7.7	5	Yes	300	1
10	11.8	5	No	<200	5
11	7.8	5	No	200 to 299	2
12	25.3	5	No	300	1

* The total is more than 100% due to rounding.

Appendix Table 2

Model-based Cumulative Incidence of ALVD and Lifetime Mortality from HF

	Years since cancer diagnosis		
	20	30	50
Cumulative incidence of ALVD, %	6.9	13.3	26.9
Lifetime mortality from HF, %	1.0	3.9	11.2

ALVD = asymptomatic left ventricular dysfunction; HF = heart failure.

Appendix Table 3

Comparison of Model-based Cumulative Incidence of HF with Published Studies

Published studies: First author [year] (reference no)	No. exposed to anthracycline	Age at cancer diagnosis, y	Cumulative anthracycline dose (mg/m ²)	RT %	Cumulative incidence of HF at 20y since cancer diagnosis		COG Guidelines risk profiles potentially represented in the published studies	Model- based cumulative incidence of HF at 20y since cancer diagnosis, % [§]
van Dalen [2006] (22)	830	Mean age at treatment 8.8	Median 280; Mean 288; range 15-900	21	5.5	1.5-9.5	4 to 12	0.5 to 5.8
Mulrooney [2009] (21)	4,765 (14,358 total in study)	Median 6.0 [*]	NG	66 [*]	NG	NG	4 to 12	0.5 to 5.8
			<250	NG	2.4	NG	4,5,6,8,10,11	0.5 to 5.8
			250	NG	3.8	NG	4,6,7,8,9,11,12	0.6 to 5.8
van der Pal [2012] (23)	565 (1,362 total in study)	Median age category 5-9 [*]	Median dose category 201-300; range 1- >500	0 100	4.0 7.9	1.8-6.2 1.4-14.0	5,6,7,10,11,12 4,8,9	0.5 to 3.6 0.6 to 5.8
Armstrong [2013] (28)	3,779 (10,724 total in study)	Median age category 5-9 [*]	NG	0 100	2 [‡] 3.8 [‡]	NG NG	5,6,7,10,11,12 4,8,9	0.5 to 3.0 0.6 to 5.8

CI = confidence interval; COG = Children's Oncology Group; HF = heart failure; NG = not given; RT = radiation therapy.

* For the total study cohort.

[‡] Determined by assuming an exposure age of 7.5y to estimate the cumulative incidence of HF at 20 and 30 years after exposure (from Fig. 2D, Armstrong [2013] (28)).

[§] Ranges shown are based on the COG Guidelines' risk profile groups potentially represented in the published study data.

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Figure 1.

Tornado diagrams of the one-way sensitivity analyses for ICER and the percent reduction in the cumulative incidence of HF at 30 years after cancer diagnosis, by varying key variables.

ACE = angiotensin-converting enzyme

HF = heart failure

ICER = incremental cost-effectiveness ratio

QALY = quality-adjusted life-year

Table 1

Model Inputs for Base-Case and Sensitivity Analyses

Characteristics of the 12 Risk Profiles in the Children's Oncology Group Guidelines												
Risk Profile group	1	2	3	4	5	6	7	8	9	10	11	12
Age at cancer diagnosis, y	<1	<1	<1	1-4	1-4	1-4	1-4	5	5	5	5	5
Chest irradiation	Yes	No	No	Yes	No	No	No	Yes	Yes	No	No	No
Anthracycline dose, mg/m ²	Any	<200	200	Any	<100	100-299	300	<300	300	<200	200-299	300
Base-Case Values [range used in sensitivity analysis]												
Cumulative incidence of HF by age [†] (3, 21-28)												
[±20% of HF incidence at age 20y], see Appendix Figures 2A, 2B (for annual incidence)												
Men	30y	*	0.026	0.076	0.113	0.019	0.024	0.077	0.017	0.046	0.004	0.008
	60y	*	0.134	0.287	0.322	0.121	0.128	0.313	0.138	0.273	0.072	0.106
Women	30y	*	0.028	0.114	0.153	0.021	0.030	0.113	0.019	0.064	0.005	0.008
	60y	*	0.139	0.371	0.382	0.128	0.145	0.404	0.157	0.360	0.073	0.114
Cumulative incidence of ALVD by age [†] (see Appendix)												
[not varied]												
Men	30y	*	0.066	0.172	0.208	0.055	0.071	0.178	0.054	0.120	0.021	0.034
	60y	*	0.243	0.422	0.423	0.225	0.254	0.445	0.226	0.377	0.169	0.214
Women	30y	*	0.070	0.238	0.263	0.060	0.081	0.246	0.064	0.168	0.023	0.039
	60y	*	0.246	0.509	0.486	0.230	0.269	0.542	0.258	0.486	0.173	0.234
Cumulative mortality from non-HF by age [†] (30)												
[not varied], see Appendix Figure 3 (for annual mortality)												
Men	35y	*	0.073	0.089	0.351	0.131	0.139	0.180	0.259	0.310	0.112	0.116
	65y	*	0.266	0.311	0.688	0.312	0.324	0.390	0.659	0.726	0.347	0.366
Women	35y	*	0.055	0.073	0.292	0.102	0.110	0.152	0.210	0.267	0.088	0.104
	65y	*	0.266	0.321	0.688	0.303	0.317	0.390	0.602	0.683	0.304	0.319
												0.366

Annual HF mortality after years since HF diagnosis (31-33) [not varied]	
1, 2, 3, 4, 5, 6, 7, 8, 9, 10y	0.300, 0.080, 0.050, 0.040, 0.030, 0.025, 0.020, 0.015, 0.010, 0.005, respectively
ALVD treatment efficacy (12, 19, 20)	
Percentage reduction in annual HF incidence	
30% [10%, 50%]	
Probability of hospitalization after HF diagnosis (12, 37) [not varied]	
First year; subsequent years	
0.33; 0.11	
Adherence to ALVD treatment (12)	
76% [50%, 100%]	
Utilities, for age<26y, 26-45y, 46-65y, >65y (34-36)	
No ALVD	
0.98, 0.947, 0.913, 0.86 [not varied]	
ALVD, without treatment	
0.96, 0.834, 0.697, 0.51 [not varied]	
ALVD, with treatment	
0.95, 0.7925, 0.6212, 0.3875 [not varied]	
HF	
0.5, 0.427, 0.366, 0.27 [(0.13, 0.065, 0, 0), (0.82, 0.79, 0.66, 0.48)] [‡]	
Echocardiography characteristics (13-18)	
Sensitivity / Specificity	
75% / 90% [50% / 50%, 100% / 100%]	
Annual discounting rate for effects and costs (9)	
3% [0%, 5%]	
ALVD = asymptomatic left ventricular dysfunction; HF = heart failure.	

* Excluded for lack of data regarding their HF risks. This group comprises 1.3% of the anthracycline-exposed Childhood Cancer Survivor Study cohort.

[‡] Sample points are shown.

[‡] Values used for sensitivity analysis, shown in brackets, are mean ± 1 standard deviation (sd) reported in reference (34) for age 26-45y and 46-65y. We assumed the sd for the extrapolated values at age <26y and age >65y to be the same as those for 26-45y and 46-65y, respectively. Negative lower bounds were set to 0.

Table 2

Costs Used for Base-Case and Sensitivity Analyses

Variable	Value, 2010 US \$	Reference [‡]
Two-dimensional echocardiography		38
First time screening	438 [halved, doubled] [*]	
Subsequent screening	343 [halved, doubled] [*]	
Cardiac MRI for confirmatory diagnosis		38
First time screening	757	
Subsequent screening	702	
ACE inhibitor (annual cost)[†]		39
Lisinopril, 10 mg/day	347	
Beta-blocker (annual cost)[†]		39
Carvedilol, 25 mg pill, twice/day for HF	1,509	
Carvedilol, 25 mg pill, once/day for ALVD	755	
General health care (annual cost)		40
Age-dependent	790 - 5,111	
Hospitalization for HF (ending in discharge)		41
Age < 20 years	15,471	
Age ≥ 20 years	8,850	
Hospitalization for HF (ending in death)		41
Age < 20 years	45,518	
Age ≥ 20 years	11,662	
Outpatient management of HF		38
First year of HF diagnosis	1,049	
Subsequent years after HF diagnosis	620	
Hospitalization leading to non-HF death		40
Age-dependent	15,964 - 75,529	
Patient time		See Appendix
ALVD screening, per screen	38	
General health care, per year (age-dependent)	58 – 206	
Hospitalization for HF ending in discharge, per episode, age < 20 years	857	
Hospitalization for HF ending in discharge, per episode, age ≥ 20 years	714	
Outpatient management of HF, per clinical visit	29	

ACE = angiotensin-converting enzyme; ALVD = asymptomatic left ventricular dysfunction; HF = heart failure; MRI = magnetic resonance imaging.

* Range used for sensitivity analyses.

[†] The cost of a one-year supply was used regardless of the medication adherence rate.

[‡] Details can be found in the Appendix.

Health Outcomes, Cost, and ICER of the COG Guidelines: Screening Intervals of 1 to 5 Years Compared to No Screening and to Immediately Preceding Less Expensive Strategy

Table 3

Risk profile No. *	COG Guidelines Risk Profile Characteristics				Per person cost, \$	Screening interval, y	(Cumulative incidence of HF without screening, %) and % reduction with screening				Compared to no screening		Compared to immediately preceding less expensive non-dominated strategy ^{††}	
	Age at Dx	Chest RT	AC dose, mg/m ²				20 y after Dx	30 y after Dx	50 y after Dx	QALY/person	Incremental QALY ^{**} /person	ICER, \$/QALY	Incremental QALY ^{**} /person	ICER, \$/QALY
2	<1 y	No	<200	None	48,388	None	56.84 (2.5)	7.7 (7.7)	19.8 (19.8)	33.41	--	--	--	--
				COG Guidelines [‡]	56,383		57.35	23.0	17.5	12.1	33.54	0.130	61,500	0.106 [§] 33,200 [¶]
				None	47,586		64.71 (0.7)	2.7 (2.7)	8.8 (8.8)	29.81	--	--	--	--
				5	50,895		65.10	12.5	14.7	11.6	29.87	0.065	50,800	0.065 50,800
				4	51,562		65.14	18.1	16.9	12.9	29.88	0.071	56,100	0.006 115,100
3	<1 y	No	200	3	52,604		65.17	18.1	18.1	13.4	29.89	0.079	63,800	0.008 135,300
				2 [§]	54,616		65.21	23.6	19.6	14.8	29.89	0.085	82,700	0.006 314,400
				1	60,438		65.24	26.4	21.4	15.7	29.90	0.091	141,900	0.006 1,058,400
				None	48,712		59.04 (2.9)	9.6 (9.6)	25.2 (25.2)	28.10	--	--	--	--
				5	52,834		59.74	12.9	13.2	9.9	28.28	0.173	23,800	0.173 23,800
4	1-4 y	Yes	Any	4	53,501		59.81	17.1	15.6	11.0	28.29	0.190	25,200	0.017 38,600
				3	54,511		59.85	18.1	16.6	11.3	28.31	0.203	28,600	0.012 81,500
				2	56,372		59.91	22.3	17.9	12.2	28.32	0.219	35,000	0.016 117,100
				1	61,576		59.98	24.7	19.2	12.9	28.34	0.238	54,100	0.019 217,000
				None	52,573		42.46 (5.8)	15.6 (15.6)	31.1 (31.1)	25.07	--	--	--	--
5	1-4 y	Yes	Any	5	55,398		42.90	12.2	10.4	6.9	25.23	0.155	18,300	0.155 18,300

COG Guidelines Risk Profile Characteristics				(Cumulative incidence of HF without screening, %) and % reduction with screening				Compared to no screening		Compared to immediately preceding less expensive non-dominated strategy ^{††}							
Risk profile No. *	Age at Dx	Chest RT	AC dose, mg/m ²	Screening interval, y	Per person cost, \$	Per person Life Expectancy, y [†]	20 y after Dx	30 y after Dx	50 y after Dx	QALY/ person	Incremental QALY ^{**} / person	ICER, \$/QALY	Incremental QALY ^{**} / person	ICER, \$/QALY			
				4	55,911	42.93	15.3	12.2	7.6	25.24	0.167	20,000	0.012	41,100			
				3	56,661	42.97	16.7	13.1	7.9	25.26	0.182	22,400	0.015	49,000			
				2	58,064	43.00	20.1	14.1	8.6	25.27	0.196	28,000	0.014	103,100			
				1	61,966	43.05	22.2	15.4	9.2	25.29	0.218	43,100	0.022	177,400			
				None	49,090	62.69	(0.7)	(2.6)	(8.9)	31.18	--	--	--	--			
5	1-4 y	No	< 100														
				5	52,238	63.06	12.5	13.7	11.4	31.25	0.061	51,300	0.061	51,400			
				4	52,868	63.08	16.7	16.4	13.0	31.25	0.065	58,400	0.003	Dominated ^{§§}			
				3	53,867	63.11	18.1	17.9	13.4	31.26	0.072	66,300	0.011	152,200			
				2	55,779	63.13	22.2	19.0	14.5	31.26	0.074	90,000	0.002	Dominated			
				1	61,323	63.18	25.0	20.5	15.5	31.27	0.083	146,700	0.009	609,200			
6	1-4 y	No	100 to < 300														
				None	48,667	61.58	(1.0)	(3.3)	(10.2)	30.70	--	--	--	--			
				5	52,081	61.94	11.3	12.9	11.0	30.76	0.060	56,900	0.060	56,900			
				4	52,706	61.97	16.5	15.3	12.5	30.77	0.066	61,300	0.006	106,000			
				3	53,702	62.00	17.5	16.5	12.8	30.78	0.074	67,800	0.008	118,500			
				2	55,580	62.03	21.6	18.3	14.1	30.78	0.079	87,100	0.005	368,200			
				1	61,004	62.06	23.7	19.5	14.8	30.79	0.086	143,600	0.006	834,500			
				None	51,280	55.48	(3.6)	(11.4)	(29.1)	28.72	--	--	--	--			
				7	1-4 y	No	300										

COG Guidelines Risk Profile Characteristics				(Cumulative incidence of HF without screening, %) and % reduction with screening				Compared to no screening		Compared to immediately preceding less expensive non-dominated strategy ^{††}				
Risk profile No. *	Age at Dx	Chest RT	AC dose, mg/m ²	Screening interval, y	Per person cost, \$	Per person Life Expectancy, y [†]	20 y after Dx	30 y after Dx	50 y after Dx	QALY/ person	Incremental QALY ^{***} / person	ICER, \$/QALY	Incremental QALY ^{***} / person	ICER, \$/QALY
				5	55,163	56.18	12.4	12.4	9.3	28.89	0.175	22,200	0.175	22,200
				4	55,776	56.23	16.1	14.8	10.3	28.91	0.190	23,700	0.015	40,600
				3	56,709	56.29	18.0	16.0	10.7	28.93	0.210	25,900	0.020	47,600
				2	58,438	56.35	22.0	17.3	11.5	28.94	0.226	31,700	0.016	104,800
				1	63,182	56.42	24.5	18.7	12.3	28.96	0.246	48,300	0.020	234,900
8	5 y	Yes	< 300	None	48,975	48.70	(1.9)	(6.1)	(15.2)	33.23	--	--	--	--
				5	51,364	48.89	12.3	12.1	9.6	33.29	0.060	40,000	0.060	40,000
				4	51,852	48.91	15.9	14.4	10.8	33.30	0.065	44,600	0.005	101,600
				3	52,613	48.92	17.4	15.7	11.4	33.30	0.070	51,700	0.006	131,200
				2	54,051	48.94	22.0	17.0	12.5	33.31	0.076	66,400	0.006	235,800
				1	58,174	48.97	24.6	18.7	13.6	33.32	0.087	106,100	0.010	400,300
9	5 y	Yes	300	None	51,048	44.84	(5.8)	(16.1)	(31.3)	31.52	--	--	--	--
				5	53,618	45.18	11.6	10.5	7.2	31.64	0.125	20,500	0.125	20,500
				4	54,104	45.21	15.0	12.5	8.0	31.66	0.139	22,000	0.014	35,500
				3	54,816	45.23	16.4	13.7	8.6	31.67	0.149	25,300	0.010	73,400
				2	56,120	45.26	20.5	15.0	9.4	31.68	0.163	31,100	0.014	91,800
				1	59,724	45.31	22.9	16.4	10.3	31.70	0.183	47,300	0.020	176,600
10	5 y	No	< 200	None	52,165	62.89	(0.5)	(1.8)	(8.0)	37.74	--	--	--	--

COG Guidelines Risk Profile Characteristics				(Cumulative incidence of HF without screening, %) and % reduction with screening					Compared to no screening		Compared to immediately preceding less expensive non-dominated strategy ^{††}	
Risk profile No. *	Age at Dx	Chest RT	AC dose, mg/m ²	Screening interval, y	Per person cost, \$	Per person Life Expectancy, y [†]	20 y after Dx	30 y after Dx	50 y after Dx	QALY/ person	Incremental QALY ^{**} / person	ICER, \$/QALY
11	5 y	No	200 to <300	5	55,084	63.11	12.8	14.2	12.8	37.76	0.021	138,200
											0.021	138,400
				4	55,677	63.12	17.0	17.5	14.9	37.76	0.022	158,800
				3	56,624	63.15	19.2	18.6	15.4	37.77	0.028	158,400
				2	58,427	63.17	23.4	20.2	17.2	37.77	0.030	210,600
				1	63,659	63.19	25.5	21.9	18.4	37.77	0.031	368,400
				None	52,767	61.81	(0.9)	(3.3)	(12.0)	37.66	--	--
				5	55,849	62.10	13.3	14.2	12.0	37.71	0.057	54,600
				4	56,438	62.11	16.7	16.6	13.6	37.71	0.057	64,700
				3	57,367	62.14	17.8	18.1	14.2	37.72	0.064	72,200
12	5 y	No	300	2	59,135	62.16	23.3	19.3	15.6	37.72	0.066	97,400
				1	64,197	62.20	24.4	21.1	16.8	37.73	0.076	151,400
				None	53,962	58.79	(3.0)	(9.6)	(25.5)	36.93	--	--
				5	57,128	59.21	12.0	11.8	8.6	37.04	0.111	28,500
				4	57,703	59.24	15.7	14.2	9.9	37.05	0.120	31,100
				3	58,607	59.27	17.1	15.3	10.2	37.06	0.127	36,500
				2	60,298	59.33	21.4	16.4	11.2	37.08	0.142	44,600
				1	64,999	59.38	23.8	18.1	12.2	37.09	0.159	69,500
											0.017	278,100

AC = anthracycline; COG = Children’s Oncology Group; Dx = diagnosis; HF = heart failure; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year; RT = radiation therapy.

* Excludes: Risk profile 1: < 1 year old, chest irradiated, exposed to any anthracycline.

[†] 0% discount.

[‡] As recommended by the COG Guidelines for each risk profile. The row values for the entire AC-exposed cohort are weighted means of the values across the 11 risk profiles, using percentages of the risk profiles in the cohort as weights. The ICER was calculated by taking the weighted mean of the cost over the 11 risk profiles divided by the weighted mean of the QALY over the 11 risk profiles.

[§] Non-italicized bolded rows correspond to screening frequencies recommended by the COG Guidelines.

// Bolded rows in italics indicate the screening frequency with an ICER under \$100,000 per QALY when compared to the immediately preceding less expensive screening frequency for the risk profile. When this is not indicated (risk profile 5), the screening frequency with an ICER under \$100,000 is the same as that of the COG Guidelines. For risk profile 10, the corresponding screening frequency is 10 years (incremental QALY=0.017, ICER=\$93,400; not shown).

¶ Shown are the incremental QALY and ICER for the entire AC-exposed cohort (compared to no screening and compared to the immediately preceding less expensive strategy) based on the screening frequency with an ICER under \$100,000 per QALY when compared to no screening for each risk profile (bolded and italicized rows, except for risk profiles 5 and 10, as explained in ||).

** Discrepancies may exist due to rounding.

^{††} Non-dominated strategies are screening frequencies that are neither less effective nor more expensive than at least one competing alternative.

§§ The frequency was removed due to extended dominance, i.e. the frequency gained fewer QALYs and was more costly than at least one other alternative frequency.