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Routine echocardiography screening for left-ventricular dysfunction in childhood cancer survivors: a model-based estimation of the clinical and economic impacts

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Abstract

Background—Childhood cancer survivors treated with cardiotoxic therapies are recommended to undergo routine cardiac assessment every 1 to 5 years, yet the long-term benefits are uncertain.

Objective—To estimate the cost-effectiveness of routine cardiac assessment to detect asymptomatic left-ventricular dysfunction (ALVD) and angiotensin-converting enzyme inhibitor (ACEI) and beta-adrenergic blocking (BB) treatment to reduce congestive heart failure (CHF) in childhood cancer survivors.

Design—Simulation model.

Data Sources—Literature, including Childhood Cancer Survivor Study data.

Target Population—Childhood cancer survivors

Time horizon—Lifetime.

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REPRODUCIBLE RESEARCH STATEMENT
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Perspective—Societal.

Interventions—Interval-based echocardiography assessment every 1, 2, 5 or 10 years, with subsequent ACEI/BB treatment for positive results.

Outcome Measures—Lifetime systolic CHF risk, lifetime costs, quality-adjusted life expectancy, incremental cost-effectiveness ratios (ICERs).

Results of Base-Case Analysis—The lifetime CHF risk among 15-year-old 5-year childhood cancer survivors was 18.8% without routine cardiac assessment (average onset age 58.8 years). Routine echocardiography reduced lifetime CHF risk by 2.3% (with assessment every 10 years) to 8.7% (annual assessment). Compared to no assessment, the ICER for assessment every 10 years was $111,600/QALY. Assessment every 5 years had an ICER of $117,900/QALY, and the ICER for more frequent assessment exceeded >$165,000/QALY. For individuals exposed to ≥250 mg/m^2 total anthracycline, the ICER for assessment every 2 years was $83,600/QALY.

Results of Sensitivity Analysis—Results were sensitive to treatment effectiveness, absolute excess CHF risk, and ALVD asymptomatic period. For the overall cohort, the probability that assessment every 10 or 5 years was preferred at a $100,000/QALY threshold was 0.33.

Limitations—Treatment effectiveness based on adult data.

Conclusions—Current recommendations for cardiac assessment may reduce CHF incidence, but less frequent assessment may be preferable.

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INTRODUCTION

Nearly 14 million Americans are cancer survivors, and the survivor population is estimated to grow by nearly one-third by 2022 (1). Better early detection methods, more effective treatments and overall population aging have all contributed to the rise in number of cancer survivors. As survivors will continue to face long-term late-effects of treatment, including second cancers and cardiac events, consensus-based guidelines can provide important guidance on surveillance and management.

Childhood cancer survivors represent less than 1% of all cancer survivors (1), yet compared to adult survivors, their late-effects risks have been well characterized by the Childhood Cancer Survivors Study (CCSS) and other cohort studies (2–9). Elevated risk for cardiac events is a leading concern, especially among survivors who were treated with cardiotoxic therapies, including anthracycline or chest radiation. At 30 to 40 years after initial cancer diagnosis (median age 27 to 29 years), the cumulative incidence of cardiac disease among adult childhood cancer survivors is considerably higher than the U.S. general population (10) ranging between 7.2 and 12.4%, with congestive heart failure (CHF) responsible for up to half of all cases (11, 12).

Routine cardiac surveillance with echocardiography (and subsequent intervention if cardiomyopathy is detected) may reduce CHF risk and is currently recommended by follow-up guidelines established by the Children's Oncology Group (COG) (13). For example, annual echocardiography is recommended for survivors who received ≥300 mg/m^2 of

doxorubicin (or equivalent doses of other anthracyclines (14)) for their original cancer treatment. However, the performance characteristics of echocardiography to detect asymptomatic left ventricular dysfunction (ALVD) in this patient population is limited (15) and clinical studies on the effectiveness of angiotensin-converting enzyme inhibitors (ACEI) and beta-adrenergic blocking agents (BB) to reduce systolic CHF risk among pediatric cancer survivors have been inconclusive (14, 16).

Consensus-based guidelines on cardiac assessment can provide guidance for childhood cancer survivors, yet their impact on long-term outcomes is unclear. By synthesizing the best available data on CHF natural history among childhood cancer survivors, we sought to estimate the clinical benefits and cost-effectiveness of routine cardiac assessment to detect ALVD and ACEI and BB treatment to reduce systolic CHF incidence and improve overall survival.

METHODS

Overview

We developed a state-transition model of the clinical course of systolic CHF in a cohort of patients similar to those in CCSS (17, 18). Using the model we estimated the lifetime risk of systolic CHF, delay in average CHF onset age, and number of per-person echocardiograms associated with interval-based cardiac assessment strategies. To assess the comparative performance of these strategies, the model projected quality-adjusted-life-expectancy, lifetime costs, and incremental cost-effectiveness ratios (ICERs). We adopted a societal perspective and discounted all future costs and clinical consequences at 3% annually (19). Costs are expressed in 2012 dollars. For the cost-effectiveness analysis, we assumed that interventions with ICERs <$100,000 per QALY gained provide good value for resources invested and are therefore cost-effective (20). We conducted sensitivity analyses to assess how key variables and assumptions might influence results, including probabilistic sensitivity analysis to account for uncertainty. The model was constructed using TreeAge Pro Suite 2009™ (TreeAge Software, Inc., Williamstown, MA).

CHF simulation model

At the start of the simulation, a cohort of 15-year-old 5-year childhood cancer survivors (diagnosed with cancer at age 10) enters the state-transition model and faces a monthly risk of developing ALVD (defined as left ventricular ejection fraction (LVEF) <50%) (Figure 1). Individuals with ALVD may develop symptomatic systolic CHF, upon which they face disease-specific mortality risks. Each month, all individuals face a risk of dying from late-effects (late-recurrence of original cancer and non-cardiac late-effects, including second cancers) and other causes.

We simulated systolic CHF risk among childhood cancer survivors using data on baseline general population risk (based on the Framingham Study (21)) and absolute excess risk (AER) (estimated from CCSS (11)). We assumed that 1) all CCSS AER of CHF was due to systolic left ventricular dysfunction and 2) as follow-up data for the CCSS are limited, the AER for CHF increased to and then remained at the 25-to-30-years-since-diagnosis rates for

the remainder of each survivor's lifetime. Based on epidemiologic studies, we assumed that ALVD progressed at a constant rate to CHF after a median interval of 5.9 years (22). Once CHF developed, individuals received guideline-based care (details below).

Strategies

Compared to no cardiac assessment, we evaluated routine assessment with 2-dimensional (2D) biplane echocardiography every 1, 2, 5 or 10 years. Test characteristics of an echocardiogram to detect ALVD were based on a CCSS study that compared 2D echocardiography to cardiac magnetic resonance imaging (cMRI) (reference standard for comparing measurement of cardiac structure and function) (15). We assumed that all individuals with reduced LV function on echocardiography received ALVD treatment (details below).

Other clinical data

Table 1 shows select model variables and their plausible ranges (7, 11, 15, 21–37). As data on ACEI and BB effectiveness among childhood cancer survivors has been inconclusive (16, 38–40), we based treatment effectiveness on the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial post hoc analysis (27). We assumed that among individuals with ALVD, ACEI and BB reduced the risks of developing systolic CHF (relative risk (RR) = 0.64) and mortality from cardiac causes (RR = 0.67). We also assumed negligible mortality risks associated with echocardiograms or ACEI and BB treatment. To estimate quality-adjusted life years (QALYs), we incorporated age-specific (29) and disease-specific weights (30).

Cost data

We used 2012 U.S. average Medicare reimbursement rates (31) as a proxy for direct medical costs associated with routine cardiac assessment, follow-up care for reduced LV function on echocardiography, and ALVD and CHF treatment (Table 1). Individuals with reduced LV function on echocardiography received guideline-based care for ALVD (ACEI (lisinopril 20 mg daily) and BB (carvedilol 25 mg twice daily) treatment, physician visit every 6 months, and annual echocardiogram) (37). Upon developing symptomatic CHF, all individuals received guideline-based care for CHF (i.e., ACEI (lisinopril 20 mg daily) and BB (carvedilol 25 mg twice daily) treatment, physician visit every 3 months, and annual echocardiogram). We assumed that abnormal echocardiograms did not result in any additional diagnostic tests or procedures that would incur additional costs (nor detect other types of cardiac abnormalities). Drug costs were based on mean Wholesale Acquisition Cost among manufacturers (32). Indirect patient costs were based on time lost from work and the 2011 median hourly wage (33).

Sensitivity analysis

To evaluate parameter uncertainty, we conducted sensitivity analyses on key model parameters, including ACEI and BB treatment effectiveness, echocardiography test performance, AER of CHF, and screening and treatment costs, as well as probabilistic sensitivity analysis (Table 1).

Subgroup analyses

We conducted analyses for subgroups based on the total anthracycline dose received for the original cancer treatment (none, <250 mg/m^2 and ≥250 mg/m^2) using data from the CCSS (11) (Table 1).

Role of the Funding Source

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RESULTS

Reduction in CHF incidence

For the overall cohort of 15-year-old 5-year childhood cancer survivors, at 30 to 35 years since diagnosis, the model estimated a cumulative systolic CHF incidence of 3.6% to 5.0%, which approximates published CCSS estimates (4.1%) (11). The expected lifetime systolic CHF risk was 18.8% (Table 2). Compared to the general population (which faced zero risk of AER for CHF or late-effects mortality and had a lifetime systolic CHF risk of 9.4%), childhood cancer survivors had a 2.0-fold greater lifetime risk of developing CHF (Figure 2). For the modeled cohort, the lifetime risk of developing ALVD was 22.6% and the lifetime risk of dying from CHF was 11.1%.

Routine cardiac assessment every 10 years with 2D echocardiography (beginning 5 years after diagnosis and repeated at 10-year intervals) reduced lifetime systolic CHF risk by 2.3%, and more frequent assessment further reduced this risk (Table 2). With no screening, the average age of CHF onset was 58.8 years (compared to 75.5 years for the general population). Routine assessment every 10 years delayed the average age of CHF onset by 0.2 years and annual assessment by 0.9 years (Table 2).

For the subgroups, the lifetime systolic CHF risk was 12.6% for no anthracycline exposure, 19.8% for the low risk anthracycline subgroup (<250 mg/m^2), and 31.8% for the high-risk anthracycline subgroup (≥250 mg/m^2) (Figure 2). With no screening, the average CHF onset age differed by subgroup, and the delay in average age of CHF onset for each assessment schedule was greater for the high-risk subgroup (≥250 mg/m^2 anthracycline) (Table 2).

Number of echocardiograms

The average lifetime per-person number of echocardiograms prior to CHF diagnosis (including evaluations for routine screening and standard ALVD care) varied by assessment strategy. For assessment every 10 years, the number of echocardiograms was 8.2 (range 5.5 to 15.5). For assessment every 5, 2 or 1 years, the numbers were 14.7 (range 10.4 to 24.6), 30.2 (range 24.0 to 39.4), and 48.0 (range 45.6 to 49.7) echocardiograms, respectively. Results were similar among subgroups.

Cost-effectiveness of routine cardiac assessment

Compared to no assessment, cardiac assessment of childhood cancer survivors every 10 years had an ICER of $111,600 per QALY gained (Table 2). Compared to assessment every 10 years, assessment every 5 years had an ICER of $117,900 per QALY gained. ICERs for more frequent assessment exceeded $165,000 per QALY gained. ICERs were more favorable for females and individuals diagnosed with cancer at ages younger than 5 (mean age 2) (Appendix Table 1).

For a subgroup that received no anthracycline, ICERs for all assessment strategies exceeded $196,000 per QALY gained (results not shown). For the anthracycline-treated subgroups, assessment every 2 years was the preferred strategy for the high-risk subgroup (≥250 mg/m^2), and no assessment for the low-risk subgroup (<250 mg/m^2). The ICER for assessment every 1 year was unattractive for both anthracycline subgroups (>$139,000 per QALY gained),

Sensitivity analysis

Results were most sensitive to ACEI and BB treatment effectiveness, AER of CHF among childhood cancer survivors, and ALVD asymptomatic period (Figure 3). Results were moderately sensitive to echocardiogram test characteristics and costs. Results were insensitive to CHF mortality risk, CHF treatment costs, and disutility associated with ACEI and BB treatment adverse events. For example, if ALVD remained asymptomatic for a longer period of time (10.4 years vs. 5.9 years in the base case), ICERs for assessment every 10 and 5 years fell from over $100,000 per QALY gained to less than $80,000 per QALY gained. In contrast, if all persons with CHF required hospitalization that cost 10-fold more than base-case estimates, the ICER for assessment every 10 years fell only to $103,500 per QALY gained.

To understand how the optimal frequency of 2D echocardiography assessment depended on the assumption of treatment effectiveness, we identified threshold values of relative risk for specific strategies (Figure 4, Panel B). Given a cost-effectiveness threshold of $100,000 per QALY gained, the relative reduction in CHF risk required for assessment every 1 year to be the preferred strategy fell within the 95% CI of the SOLVD Prevention trial (RR=0.49–0.83) (27) for only the high-risk subgroup (RR=0.53).

Given the low sensitivity of 2D echocardiography, we explored how ICERs varied if cardiac magnetic resonance imaging (cMRI), with perfect sensitivity and specificity for ALVD, was used instead. At a cost of $815 (based on Current Procedural Terminology code 75557), cMRI assessment dominated nearly all 2D echocardiography strategies (was more effective and either less costly or more cost-effective). At a $100,000 per QALY gained threshold, cMRI assessment every 10 years was preferred for the overall cohort and low-risk subgroup, and assessment every 5 years for the high-risk subgroup (Appendix Table 2). Even if ACEI and BB treatment could completely reduce CHF risk (RR=0), assessment every 1 year would still not be the preferred strategy for any subgroup (Figure 4, Panel B). See Appendix Figure 1 for additional sensitivity analyses.

Based on probabilistic sensitivity analysis, the probability that assessment every 10 or 5 years was the preferred strategy at a cost-effectiveness threshold of $100,000 per QALY gained was 0.33 for the overall cohort and 0.34 for the low-risk subgroup. For the high-risk subgroup, the probability that assessment every 2 years was preferred was 0.57. Table 2 and Appendix Figure 2 provide additional details.

DISCUSSION

Although five-year survival rates have increased over the past several decades, childhood cancer survivors continue to face complex health challenges as they enter adulthood. Follow-up guidelines may help survivors navigate their health needs and physicians determine optimal screening strategies. Incorporating the best available data on CHF risk and other late-effects mortality, our model-based approach suggests that follow-up routine cardiac assessment may improve overall survival and reduce systolic CHF risk in as many as 1 in every 12 survivors. However, less frequent assessment than the schedule currently recommended by COG guidelines (See Table 3 and (13)) may be more reasonable for preventing CHF among childhood cancer survivors.

While previous studies have focused on ALVD screening for the general population (41), our study focuses on identifying the optimal interval of assessment among childhood cancer survivors and understanding the inherent tradeoffs among clinically-relevant strategies. For example, our model estimates that the lifetime per-person number of echocardiograms varied by 6-fold between annual and every 10 year assessment, suggesting that in addition to societal costs, the patient burden associated with recommended guidelines may be an important factor for survivors and their providers to consider in designing a survivorship care plan.

Our analysis suggests that routine assessment for ALVD is less cost-effective compared with results from an unpublished model-based study evaluating currently recommended COG screening guidelines (42). As results from that study are only available in abstract form, direct comparison is difficult. However, since both studies report similar clinical benefit in terms of delay in average CHF age onset, differences in cost-effectiveness likely stem from different screening scenarios evaluated; we compared different schedules of assessment whereas the abstract refers only to comparison of assessment to no assessment.

Our findings are based on two major assumptions: all CHF reported in the CCSS cohort is related to systolic LV dysfunction and ACEI and BB treatment effectively reduces CHF risk among childhood cancer survivors. As such, our estimates should be considered very optimistic. Specifically, our findings assume that the treatment effectiveness of ACEI and BB to prevent progression of ALVD to CHF observed in older adults is generalizable to childhood cancer survivors despite evidence from clinical studies that question this assumption (38–40, 43). Furthermore, childhood cancer survivors (particularly those treated with cardiac radiation) can present with a restrictive phenotype (44) for which ACEI is not effective in reducing the risk of progression to CHF. Hence, while routine cardiac assessment may be a reasonable strategy for monitoring survivors' health, screening at currently-recommended intervals is likely not needed for most survivors and revision of

guidelines is warranted. For high-risk survivors treated with anthracycline (≥250 mg/m^2), assessment every 2 years would be suggested, and for low-risk individuals (<250 mg/m^2), no screening or infrequent screening may be the preferred strategy (Table 3).

Our findings provide several additional important insights. First, given the low sensitivity of echocardiography, better methods to detect ALVD are needed. Yet even with cMRI, less frequent screening than currently recommended may still be reasonable as our model suggests that assessment every 1 or 2 years would not be cost-effective for all anthracycline subgroups (Appendix Table 2).

Second, initiating ACEI and BB treatment before ALVD develops may improve long-term outcomes. We found that more than one-third of the benefit of ACEI and BB treatment associated with routine assessment stemmed from individuals who received treatment after false-positive studies. In fact, our model estimates that if all survivors treated with ≥250 mg/m^2 anthracycline dose received ACEI and BB treatment at 5 years after original cancer diagnosis (in lieu of routine assessment), the reduction in lifetime CHF risk would be greater (8.9%) that the reduction attributable to screening (5.9%), but at a more favorable ICER ($18,500 per QALY for ‘treat all’ versus $83,600 per QALY for assessment every 2 years).

Limitations to our study include basing AER of CHF risk on published estimates for the overall CCSS cohort and assuming that the AER of CHF increased to and remained at 25-to-30-years-since-diagnosis rates. If we assumed that rates increased by 50% beyond 30 years since diagnosis, nearly 24% of all survivors would develop systolic CHF in their lifetime and assessment every 5 years would be attractive for the overall cohort (ICER = $85,700 per QALY gained). We derived subgroup-specific estimates using hazard ratios that controlled for gender, age at diagnosis, treatment era, and cardiac radiation dose (11), but other risk factors and interactions between risk factors may influence CHF risk. In particular, we could not incorporate the added effects of radiation in our model to anthracycline subgroups because data that could inform the magnitude were not available. While further analysis of the effects of radiation dose on ALVD will be needed, our model suggests that for routine assessment every 2 years to be cost-effective for the low-dose anthracycline subgroup, cardiac radiation would have to increase the relative AER for CHF by more than 75%, an increase that has not been observed. For example, among Dutch cancer survivors, the cumulative CHF incidence at 30 years after diagnosis was not significantly different among individuals treated with anthracyclines alone (7.5%; 95% CI = 3.6–11.2%) and those treated with both anthracyclines and radiotherapy (7.9%; 95% CI = 1.4–14.0%) (12). Model-based estimates of age-specific ALVD prevalence for the overall cohort were also consistent with published estimates for the general population (data not shown) (22, 45). However, gender-specific models did not reflect the higher prevalence of ALVD observed among men compared to women, most likely because we did not incorporate other risk factors which influence ALVD and CHF risk, and consequently, ICERs for screening.

We assumed that the sensitivity of echocardiography remained constant even though it may improve as LVEF declines. While ICERs for assessment every 10 and 5 years were more favorable with higher sensitivity (80%) for the overall cohort (ICERs <$86,000 per QALY),

more frequent assessment was still associated with high ICERs (>$210,000 per QALY), and the optimal strategy remained unchanged for the high-risk subgroup at a $100,000 per QALY threshold.

Our model also did not include refractory heart failure, which is associated with poorer prognosis and heart transplantation (46). While this exclusion may underestimate the cost-effectiveness of screening, ICERs were largely insensitive to CHF treatment costs. Our findings do not account for the costs or benefits associated with the annual physical exams currently recommended by follow-up guidelines or the impact of clinically-indicated echocardiograms associated with these visits. We also did not incorporate other clinical benefits from routine cardiac assessment, nor costs associated with additional diagnostic tests. However, we assumed that in addition to reducing the risk of ALVD progressing to CHF, ACEI and BB treatment also reduced mortality from other cardiac causes, accounting for some benefit on other cardiac risk types through the management of ALVD (47). Similarly, by assuming that ACEI and BB treatment reduced cardiac mortality risk among individuals with ALVD and CHF, we potentially overestimated treatment benefit, though the impact was small (ICERs varied ~5%).

Consensus-based guidelines can help childhood cancer survivors manage their late-effects risks. Because randomized clinical trials to evaluate these guidelines are unlikely, model-based analyses can provide a useful framework to inform policy and practice. Our findings suggest that current recommendations for cardiac assessment may reduce systolic CHF incidence, but less frequent screening than currently recommended may be preferred, and possible revision of current recommendations is warranted.

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REFERENCES

1. de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev. 2013; 22(4):561–570. [PubMed: 23535024]
2. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol. 2001; 19(13):3163–3172. [PubMed: 11432882]
3. Moller TR, Garwicz S, Barlow L, Falck Winther J, Glattre E, Olafsdottir G, et al. Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries. J Clin Oncol. 2001; 19(13):3173–3181. [PubMed: 11432883]
4. Cardous-Ubbink MC, Heinen RC, Langeveld NE, Bakker PJ, Voute PA, Caron HN, et al. Long-term cause-specific mortality among five-year survivors of childhood cancer. Pediatr Blood Cancer. 2004; 42(7):563–573. [PubMed: 15127410]
5. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. Pediatr Blood Cancer. 2007; 48(4):460–467. [PubMed: 16767717]
6. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973–2002. Int J Cancer. 2007; 121(10):2233–2240. [PubMed: 17557301]

7. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2008; 100(19):1368–1379. [PubMed: 18812549]
8. Green DM, Hyland A, Chung CS, Zevon MA, Hall BC. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. J Clin Oncol. 1999; 17(10): 3207–3215. [PubMed: 10506620]
9. Lawless SC, Verma P, Green DM, Mahoney MC. Mortality experiences among 15+ year survivors of childhood and adolescent cancers. Pediatr Blood Cancer. 2007; 48(3):333–338. [PubMed: 16453299]
10. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002; 106(24): 3068–3072. [PubMed: 12473553]
11. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ. 2009; 339:b4606. [PubMed: 19996459]
12. van der Pal HJ, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus RB, et al. High risk of symptomatic cardiac events in childhood cancer survivors. J Clin Oncol. 2012; 30(13):1429–1437. [PubMed: 22473161]
13. Children's Oncology Group. Cure search: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 3.0 - October 2008. http://www.survivorshipguidelines.org.
14. Shankar SM, Marina N, Hudson MM, Hodgson DC, Adams MJ, Landier W, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. Pediatrics. 2008; 121(2):e387–e396. [PubMed: 18187811]
15. Armstrong GT, Plana JC, Zhang N, Srivastava D, Green DM, Ness KK, et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol. 2012; 30(23):2876–2884. [PubMed: 22802310]
16. Lipshultz SE, Colan SD. Cardiovascular trials in long-term survivors of childhood cancer. J Clin Oncol. 2004; 22(5):769–773. [PubMed: 14990630]
17. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making. 1983; 3(4): 419–458. [PubMed: 6668990]
18. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993; 13(4):322–338. [PubMed: 8246705]
19. Gold, MR.; Siegel, JE.; Russel, LB.; Weinstein, MC., editors. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.
20. Neumann PJ, Sandberg EA, Bell CM, Stone PW, Chapman RH. Are pharmaceuticals cost-effective? A review of the evidence. Health affairs. 2000; 19(2):92–109. [PubMed: 10718025]
21. Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. Bethesda: National Institutes of Health, National Heart, Lung, and Blood Institute; 2006.
22. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation. 2003; 108(8):977–982. [PubMed: 12912813]
23. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. NEJM. 2003; 348(17):1647–1655. [PubMed: 12711739]
24. Centers for Disease Control and Prevention, National Center for Health Statistics. CDC WONDER On-line Database, compiled from Compressed Mortality File CMF 1968–1988. 2009 Series 20, No, 2A, 2000 and CMF 1989–1998, Series 20, No. 2E, 2003.
25. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol. 1992; 20(2):301–306. [PubMed: 1634664]
26. Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications

of different diagnostic strategies in primary care. Health Technol Assess. 2009; 13(32):1–207. iii. [PubMed: 19586584]

27. Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 1999; 33(4):916–923. [PubMed: 10091816]
28. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003; 361(9372):1843–1848. [PubMed: 12788569]
29. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making. 2006; 26(4):391–400. [PubMed: 16855127]
30. Gohler A, Geisler BP, Manne JM, Kosiborod M, Zhang Z, Weintraub WS, et al. Utility estimates for decision-analytic modeling in chronic heart failure--health states based on New York Heart Association classes and number of rehospitalizations. Value Health. 2009; 12(1):185–117. [PubMed: 18647251]
31. Centers for Medicare and Medicaid Services. [Accessed February 1, 2013] Research, Statistics, Data & Systems. 2012. http://www.cms.gov/Research-Statistics-Data-and-Systems/Research-Statistics-Data-and-Systems.html.
32. RED BOOK Online ®. Truven Health Analytics. 2013 http://www.micromedexsolutions.com.
33. Bureau of Labor Statistics, U.S. [Accessed February 15, 2013] Department of Labor. Occupational Employment and Wages. U.S. Government Printing Office. 2012. http://stat.bls.gov/oes/home.htm.
34. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis. 2005; 47(5):320–332. [PubMed: 16003647]
35. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003; 362(9386):767–771. [PubMed: 13678869]
36. Yeh JM, Nekhlyudov L, Goldie SJ, Mertens AC, Diller L. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. Ann Intern Med. 2010; 152(7):409–417. W131–W138. [PubMed: 20368646]
37. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013; 62(16):e147–e239. [PubMed: 23747642]
38. Silber JH, Cnaan A, Clark BJ, Paridon SM, Chin AJ, Rychik J, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol. 2004; 22(5):820–828. [PubMed: 14990637]
39. Sieswerda E, van Dalen EC, Postma A, Cheuk DK, Caron HN, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer. Cochrane Database Syst Rev. 2011; (9):CD008011. [PubMed: 21901716]
40. Foerster SR, Canter CE. Pediatric heart failure therapy with beta-adrenoceptor antagonists. Paediatr Drugs. 2008; 10(2):125–134. [PubMed: 18345722]
41. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol. 2004; 43(6):1019–1026. [PubMed: 15028361]
42. Wong, FL.; Bhatia, S.; Kurian, S.; Landier, W.; Francisco, L.; Leisenring, W., et al. Efficacy of the Children's Oncology Group (COG) Long-Term Follow-Up (LTFU) guidelines in reducing the risk of congestive heart failure (CHF) in long-term childhood cancer survivors (CCS) [abstract]. 2012. American Society for Clinical Oncology (ASCO) Annual Meeting; Chicago, IL. 2012.

43. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA. 2007; 298(10): 1171–1179. [PubMed: 17848651]

44. Lipshultz SE, Lipsitz SR, Sallan SE, Dalton VM, Mone SM, Gelber RD, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol. 2005; 23(12):2629–2636. [PubMed: 15837978]

45. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003; 289(2):194–202. [PubMed: 12517230]

46. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation. 2013; 128(17):1927–1995. [PubMed: 24081971]

47. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000; 342(3):145–153. [PubMed: 10639539]

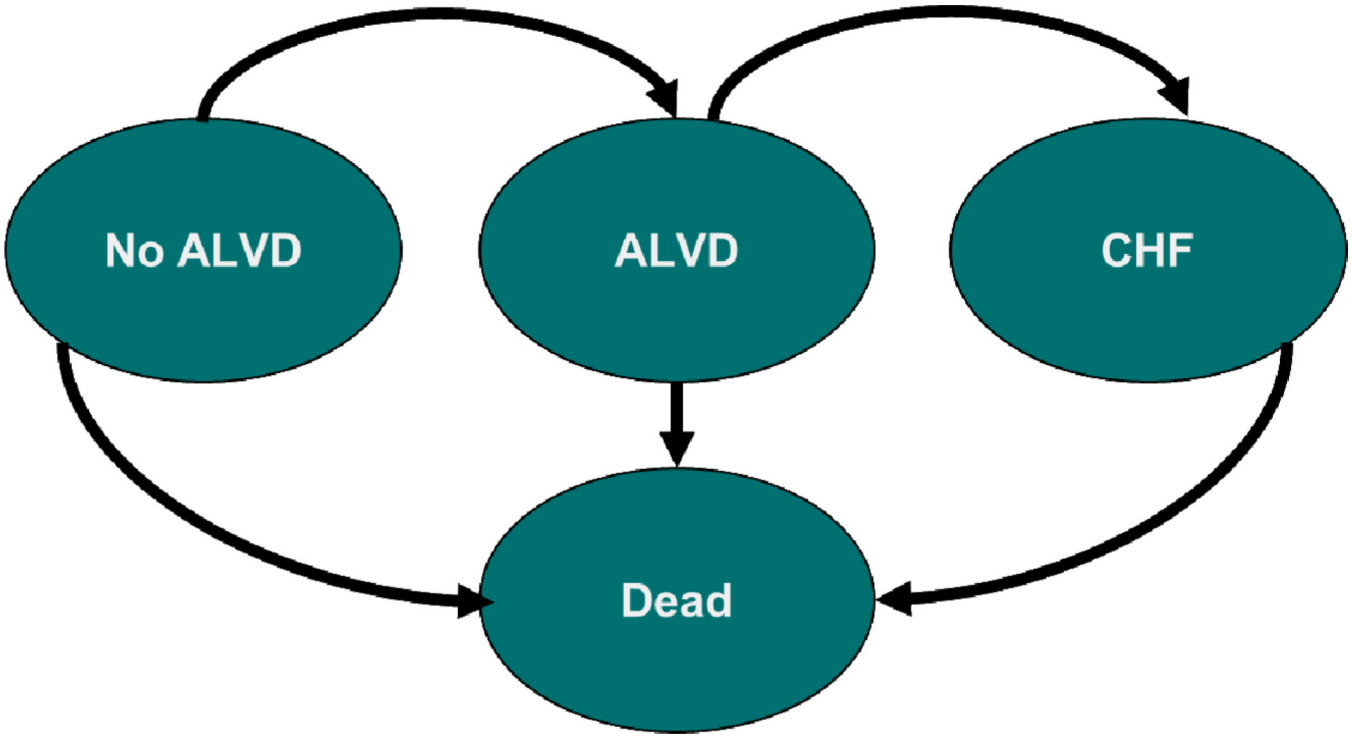


Figure 1. CHF model diagram

Health states for the CHF model are depicted in this figure. Individuals enter the model with no ALVD and face monthly rates of developing ALVD based on age-specific CHF rates. Individuals with ALVD face a risk of developing symptomatic CHF. Once CHF develops, individuals face disease-specific mortality risks. All individuals face mortality risks from background mortality rates, late-recurrence and non-cardiac late-effects (including second cancers, pulmonary, external and other causes). Individuals are followed throughout their lifetime. ALVD = asymptomatic left ventricular dysfunction; CHF = congestive heart failure.

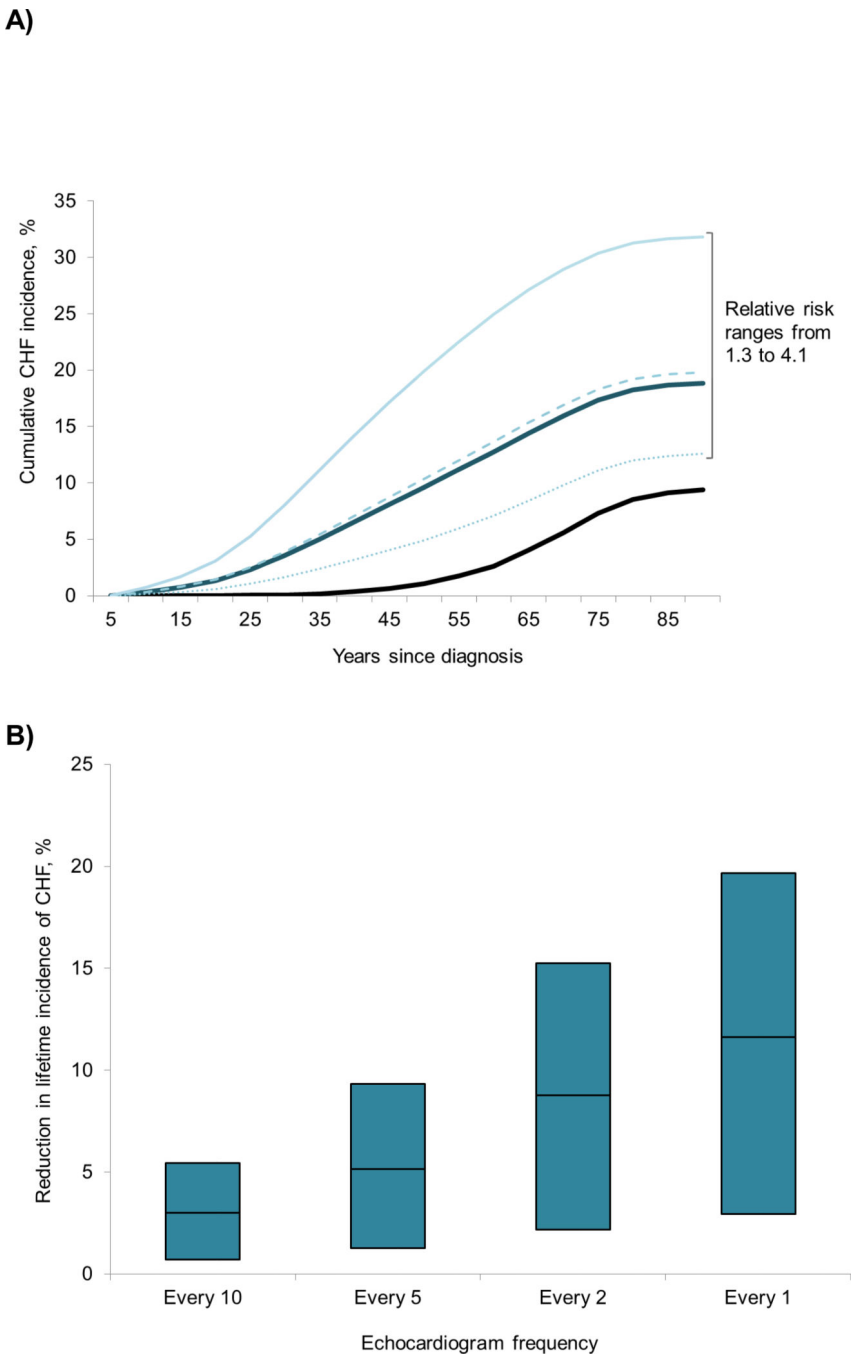


Figure 2. Cumulative CHF incidence

Panel A depicts cumulative CHF incidence by years since diagnosis for the cohort of childhood cancer survivors (overall and anthracycline subgroups) and general population. Compared to the general population, the lifetime relative risk of CHF was 1.3 (range 1.1 to 1.7) for no anthracycline, 2.1 (range 1.2 to 3.1) for <250 mg/m^2 anthracycline, and 3.4 (range 2.2 to 4.4) for ≥250 mg/m^2 anthracycline. Dark blue line indicates the overall cohort. Black line indicates the general population. Light blue lines depict anthracycline subgroups (none, <250 mg/m^2, ≥250 mg/m^2). Panel B shows the reduction in lifetime CHF risk for the

assessment strategies (vs. no assessment) for the overall cohort. The solid line represents the reduction using base case estimates, while the bars depict the 95% credible interval from probabilistic sensitivity analysis based on 1000 second-order Monte Carlo simulations. CHF = congestive heart failure.

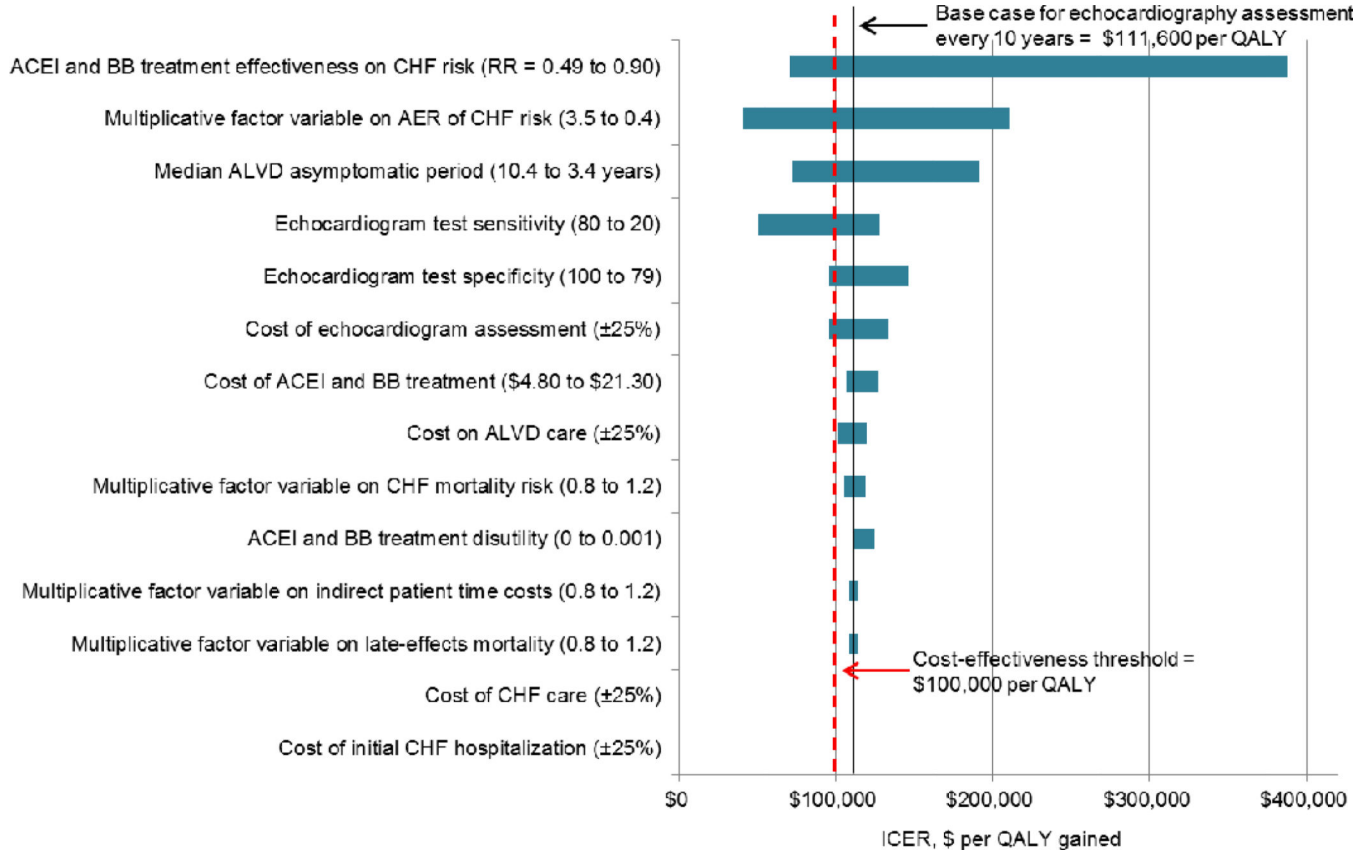


Figure 3. Tornado diagram on sensitivity analysis for select model parameters

Based on one-way sensitivity analyses, this figure depicts the relative influence of select model parameters on results for the overall cohort. The x-axis shows the effect of changes in selected variables on the ICER the assessment every 10 years (compared to no assessment). The y-axis shows the selected model parameters, with upper and lower bounds used in the sensitivity analysis in parentheses. The shaded bars indicate the variation in the ICER caused by changes in the value of the indicated variable while all other variables were held constant. Solid black line indicates the ICER for the base case. Dotted red line represents the commonly used $100,000 per QALY cost-effectiveness threshold. QALY = quality-adjusted life year.

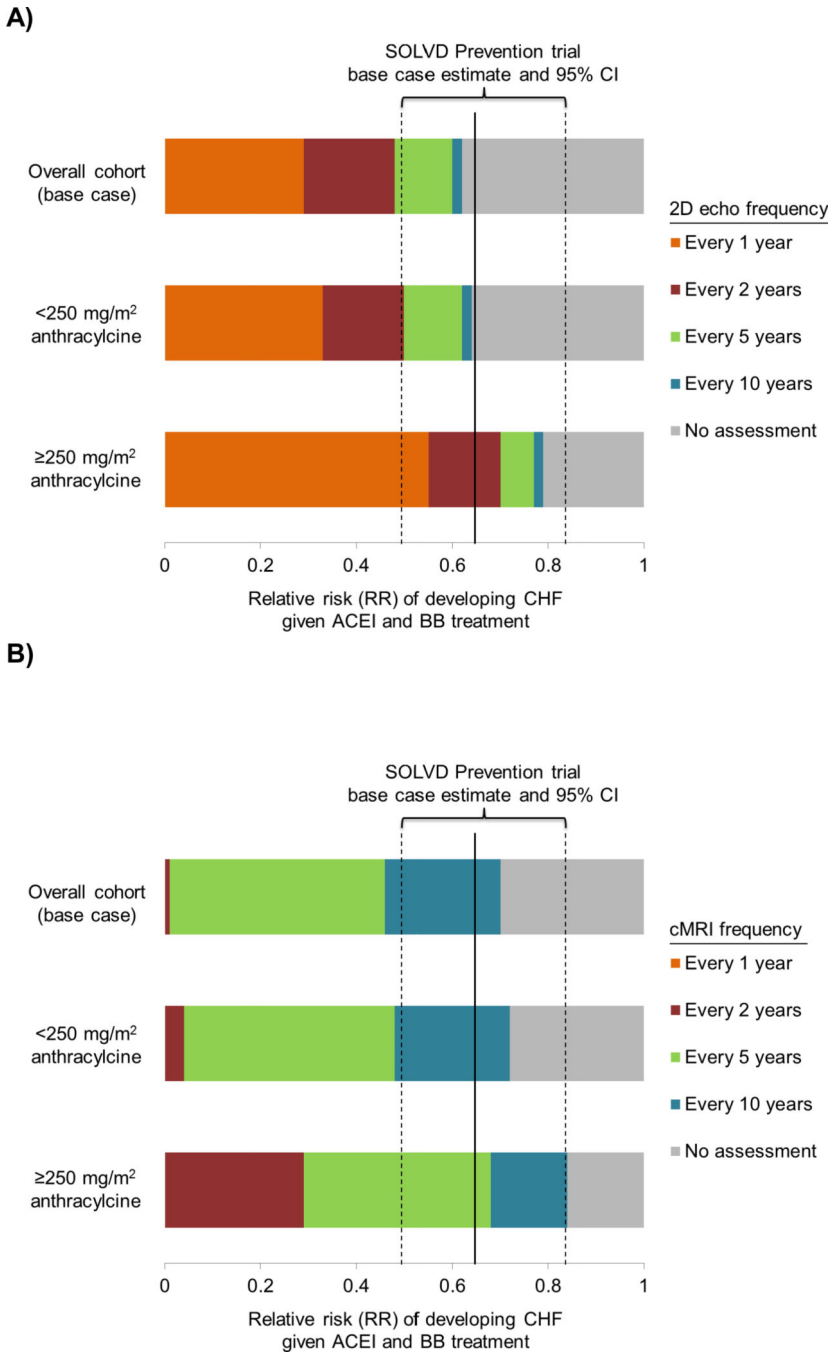
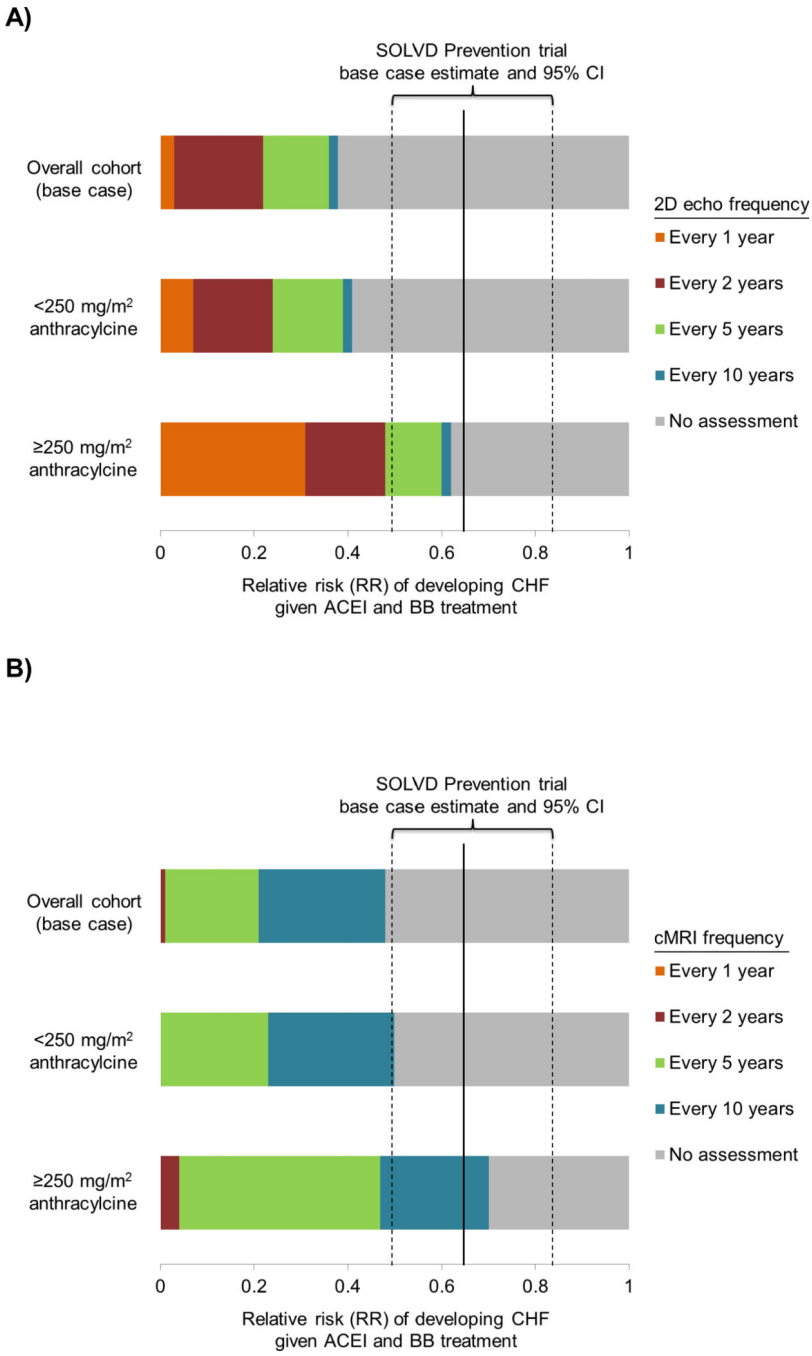


Figure 4. Threshold analysis on ACEI and BB treatment effectiveness for overall cohort and anthracycline subgroups at a $100,000 per QALY cost-effectiveness threshold

This figure depicts how effective treatment would have to be for a specific assessment strategy to be optimal from a cost-effectiveness framework for two scenarios: when only 2D echocardiography is available (Panel A) and when 2D echocardiography and cMRI are available (Panel B). On the x-axis, the relative risk of developing CHF associated with treatment is depicted, with 0 indicating complete reduction of risk, and 1 indicating no treatment effect. The colored regions indicate the range of values over which the specific strategy would be considered the optimal strategy given a willingness to pay of $100,000 per

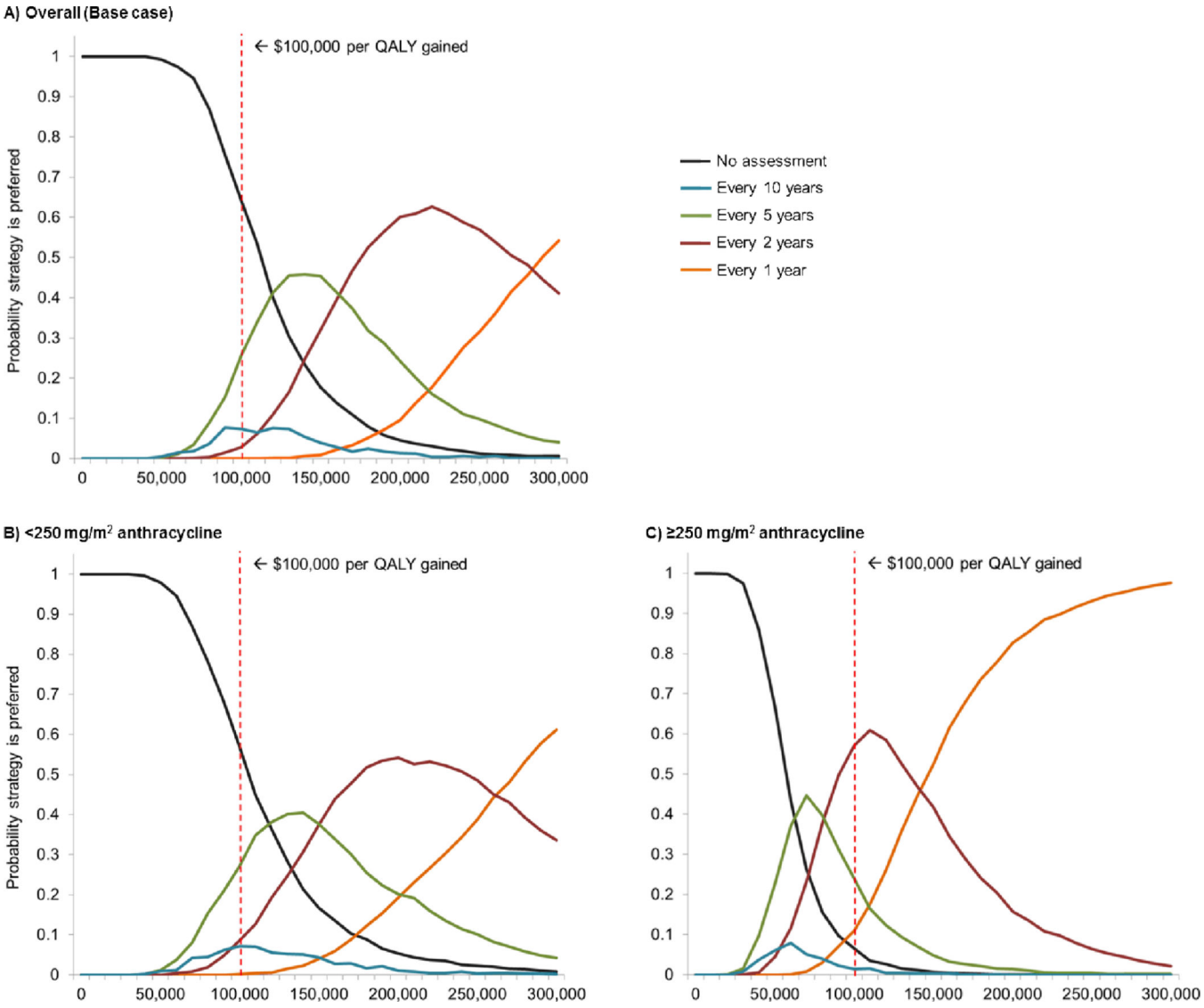
QALY gained. Black solid and dotted lines indicated the base case estimate (RR = 0.63) and 95% CI (RR = 0.49 to 0.83) from the post hoc analysis of the SOLVD Prevention trial (27). As an example, if only 2D echocardiography is available, for the ≥250 mg/m^2 anthracycline high-risk subgroup, annual assessment was the preferred strategy only if treatment reduced the risk of developing CHF by 45% (RR = 0.55); no screening or less frequent screening was preferred at all other values. In contrast, if cMRI was available, even if treatment completed reduced CHF risk, annual assessment was still not the preferred strategy. Note: the 95%CI from the SOLVD Prevention Trial is shown to depict the uncertainty in treatment effectiveness among adults. The uncertainty range among childhood cancer survivors is likely wider, including lower and negligible benefit (38–40, 43). CHF = congestive heart failure; ACEI = angiotensin converting enzyme; BB = beta-adrenergic blocking agents; SOLVD = Studies of Left Ventricular Dysfunction; 2D echo = two-dimensional echocardiography; cMRI = cardiac magnetic resonance imaging.



Appendix Figure 1. Threshold analysis on ACEI and BB treatment effectiveness for overall cohort and anthracycline subgroups at a $50,000 per QALY cost-effectiveness threshold

This figure depicts how effective treatment would have to be for a specific assessment strategy to be optimal from a cost-effectiveness framework for two scenarios: when only 2D echocardiography is available (Panel A) and when 2D echocardiography and cMRI are available (Panel B). On the x-axis, the relative risk of developing CHF associated with treatment is depicted, with 0 indicating complete reduction of risk, and 1 indicating no treatment effect. The colored regions indicate the range of values over which the specific strategy would be considered the optimal strategy given a willingness to pay of $50,000 per

QALY gained. Black solid and dotted lines indicated the base case estimate (RR = 0.63) and 95% CI (RR = 0.49 to 0.83) from the post hoc analysis of the SOLVD Prevention trial (27). Note: the 95%CI from the SOLVD Prevention Trial is shown to depict the uncertainty in treatment effectiveness among adults. The uncertainty range among childhood cancer survivors is likely wider, including lower and negligible benefit (38–40, 43). CHF = congestive heart failure; ACEI = angiotensin converting enzyme; BB = beta-adrenergic blocking agents; SOLVD = Studies of Left Ventricular Dysfunction; 2D echo = two-dimensional echocardiography; cMRI = cardiac magnetic resonance imaging.



Appendix Figure 2. Cost-effectiveness acceptability curves for the overall cohort and anthracycline subgroups

Depicted in this figure are cost-effectiveness acceptability curves, which illustrate the uncertainty surrounding the estimate of ICERs, for the overall cohort (Panel A), <250 mg/m^2 anthracycline (Panel B), and ≥250 mg/m^2 anthracycline (Panel C). In each figure, the probability that a given strategy is the preferred strategy is depicted across a range of willingness-to-pay thresholds. For example, at a threshold of $100,000 per QALY, the probability that assessment every 5 years is the preferred strategy is 0.26 for the overall cohort. In contrast, for the ≥250 mg/m^2 anthracycline subgroup, the probability that assessment every 2 years was preferred was 0.57. Results are based on 1000 second-order Monte Carlo simulations in which model variables were simultaneously varied. The red line indicates the $100,000 per QALY threshold commonly used as a benchmark in the US. QALY = quality-adjusted life year.

Table 1

Select model parameters: base case value and range

Parameter	Base Case	Range for Sensitivity Analysis	Probabilistic Sensitivity Analysis		Reference
			Distribution	Range (95% CI)	
CHF natural history*					
Baseline CHF risk (general population), annual rate†					(21, 23)
0 to 24 years old	0.000007	0.75–1.25§	Beta	0.000000–0.0000001	
25 to 34 years old‡	0.000086	0.75–1.25§	Beta	0.00002–0.0002	
35 to 44 years old	0.00017	0.75–1.25§	Beta	0.00003–0.0004	
45 to 54 years old	0.00116	0.75–1.25§	Beta	0.001–0.002	
55 to 64 years old	0.00229	0.75–1.25§	Beta	0.002–0.003	
65 to 74 years old	0.00668	0.75–1.25§	Beta	0.006–0.008	
75 to 84 years old	0.01752	0.75–1.25§	Beta	0.016–0.019	
85+ years	0.03390	0.75–1.25§	Beta	0.030–0.038	
AER of CHF (5-year childhood cancer survivors), annual rate					(11)
5 to 9 YSD	0.0008	0.4–2.4§//	Beta	0.0004–0.0014	
10 to 14 YSD	0.0010	0.4–2.4§//	Beta	0.0005–0.0015	
15 to 19 YSD	0.0012	0.4–2.4§//	Beta	0.0007–0.0018	
20 to 24 YSD	0.0018	0.4–2.4§//	Beta	0.0012–0.0026	
≥ 25 to 30 YSD	0.0037	0.4–2.4§//	Beta	0.0028–0.0048	
Anthracycline subgroup CHF risk, RR					(11)
None	1.0	--	--	--	
<250 mg/m^2	2.4	1.5–3.9	Normal¶	1.2–3.6	
≥250 mg/m^2	5.2	3.6–7.4	Normal¶	3.3–7.1	
Probability of ALVD progressing to CHF**	0.0098	0.0056–0.017	--	--	(22)
Mortality, monthly rate					
All-cause	Age-specific	--	--	--	(24)
CHF	Age-specific	0.8–1.2§	--	--	(25)

Parameter	Base Case	Range for Sensitivity Analysis	Probabilistic Sensitivity Analysis		Reference
			Distribution	Range (95% CI)	
Late-recurrence and non-cardiac late-effects	YSD-specific	0.8–1.2[§]	Normal[¶]	††	(7, 36)
Echocardiogram test characteristics, %					(15, 26)
Sensitivity	25	20–80	Beta	18–33	
Specificity	98	79–100	Beta	91–99	
Heart failure treatment (ACEI and BB) benefit, RR					(27)
CHF risk for ALVD	0.64	0.49–0.90	Normal[¶]	0.47–0.81	
Cardiac causes mortality for ALVD	0.67	0.48–0.94	Normal[¶]	0.44–0.90	
Cardiac causes mortality for CHF[‡‡]	0.82	0.59–1.00	Normal[¶]	0.55–1.00	
Quality of life, utility[§§]					
Age-related quality weight	Age-specific	--	--	--	(29)
Disease-specific weight					(30)
ALVD (NYHA Class I)	0.855	0.845–0.864	Normal[¶]	0.85–0.86	
CHF (NYHA Class III)	0.673	0.665–0.690	Normal[¶]	0.66–0.69	
Direct costs, $[///¶¶]					(31, 32)
Physician visit (CPT 99213)	50	38–63	--	--	
Echocardiogram (CPT 93308, APC 0697)[***]	250	185–315	--	--	
Monthly ACEI treatment	2.7	1.2–10.5	--	--	
Monthly BB treatment	6.0	3.6–10.8	--	--	
Hospitalization for CHF[†††](DRG 127, CPT 99222, 99232, 99238)	5830	4370–7390	--	--	
Indirect costs					
Median hourly wage, $	16.83	10.93–27.09	--	--	(33)
Lost time, hours					
Physician visit or echocardiogram	2	0–4	--	--	
CHF hospitalization and treatment	80	60–100	--	--	†††

CHF = congestive heart failure; AER = absolute excess risk; YSD = years since diagnosis; RR = relative risk; ALVD = asymptomatic left ventricular dysfunction; ACEI = angiotensin-converting enzyme inhibitor; BB = beta-adrenergic blocking agents; NYHA = New York Heart Association; DRG = diagnosis-related group; CPT = current procedural terminology; APC = ambulatory payment classifications.

[*] To account for competing risks, we proportionally adjusted the underlying risk of CHF so that model outcomes matched observed estimates of age-specific CHF risk (11, 21).

[†] Assumed 46% of all CHF systolic-related (34).

‡Assumed an annual rate equal to the average of 0–24 year and 35–44 year rate given limited CHF data on adults younger than 35 years of age.

§Value of multiplicative factor variable applied to the base case value in sensitivity analysis.

//Range based on subgroup-specific AER of CHF estimated for each anthracycline subgroup using CCSS data from Mulrooney et al. (11) on overall CHF risk, relative risk of CHF associated with each anthracycline dose, and prevalence of each anthracycline dose subgroup.

¶Truncated to values greater than or equal to 1.0 (relative risks of CHF for anthracycline subgroups), greater than or equal to 0 (late-recurrence and non-cardiac late-effects mortality rates) or less than or equal to 1.0 (heart failure treatment relative risk benefit, utility weights).

**Constant rate, based on the assumption that median time to onset for CHF is 5.9 years. Median time was varied from 3.4 to 10.4 years in sensitivity analysis.

††Distributions previously described (7, 36).

##Assumed that all individuals with CHF received ACEI and BB as part of guideline-based care (37).

§§Assumed utilities weights are multiplicative

///Range for sensitivity analysis = ±25% of base case estimate, except for drug costs, which are based on Wholesale Acquisition Cost range among leading manufacturers.

¶¶We assumed costs were fixed and did not vary them in probabilistic sensitivity analysis.

***Assumed all echocardiograms performed at an outpatient facility.

†††Assume 28% of individuals with symptomatic CHF require hospitalization (35).

‡‡‡Based on assumption.

Table 2

Clinical and economic model outcomes for 2D echocardiography assessment strategies: overall cohort and anthracycline subgroups

Cardiac assessment strategy	Lifetime systolic CHF risk, % (range)*†	Incremental reduction in lifetime systolic CHF risk†‡		Average age of systolic CHF onset (delay), years‡	Lifetime costs, $	Quality-adjusted life years	ICER, $ per QALY gained‡§	Probability strategy is preferred‡//	
		Versus No assessment, % (range)	Versus previous strategy, % (range)					$50,000 per QALY threshold	$100,000 per QALY threshold
Overall cohort									
No assessment	18.8 (16.5–21.5)	--	--	58.8	$577	21.4790	--	0.99	0.64
Every 10 years	18.4 (16.1–21.1)	2.3 (0.7–4.7)	2.3 (0.7–4.7)	58.9 (0.2)	$1,918	21.4910	$111,600	0.01	0.07
Every 5 years	18.1 (15.7–20.9)	3.9 (1.3–8.1)	1.7 (0.6–3.3)	59.1 (0.4)	$2,897	21.4993	$117,900	0.00	0.26
Every 2 years	17.6 (15.0–20.5)	6.6 (2.2–13.1)	2.7 (0.9–5.1)	59.4 (0.7)	$5,433	21.5145	$167,500	0.00	0.03
Every 1 year	17.2 (14.6–20.2)	8.7 (2.9–16.7)	2.0 (0.7–3.9)	59.7 (0.9)	$8,675	21.5261	$278,600	0.00	0.00
Anthracycline subgroups									
<250 mg/m^2									
No assessment	19.8 (14.1–25.9)	--	--	58.2	$619	21.4402	--	0.98	0.57
Every 10 years	19.4 (13.7–25.5)	2.2 (0.7–4.8)	2.2 (0.7–4.8)	58.5 (0.2)	$1,957	21.4531	$104,400	0.01	0.07
Every 5 years	19.0 (13.5–25.1)	3.9 (1.2–7.9)	1.7 (0.6–3.3)	58.6 (0.4)	$2,933	21.4619	$110,300	0.01	0.27
Every 2 years	18.5 (13.1–24.6)	6.6 (2.2–13.0)	2.7 (0.9–5.1)	58.9 (0.7)	$5,460	21.4780	$156,700	0.00	0.09
Every 1 year	18.1 (12.6–24.1)	8.6 (2.9–16.8)	2.0 (0.7–3.9)	59.2 (0.9)	$8,690	21.4904	$260,800	0.00	0.00
≥250 mg/m^2									
No assessment	31.8 (25.4–37.1)	--	--	53.8	$1,171	20.9307	--	0.67	0.07
Every 10 years	31.2 (24.9–36.4)	2.1 (0.7–4.3)	2.1 (0.7–4.3)	54.1 (0.3)	$2,471	20.9539	$56,200	0.06	0.01
Every 5 years	30.7 (24.7–36.0)	3.5 (1.2–7.2)	1.5 (0.5–2.9)	54.3 (0.5)	$3,406	20.9696	$59,300	0.23	0.24
Every 2 years	30.0 (23.9–35.4)	5.9 (2.0–11.6)	2.3 (0.8–4.6)	54.7 (0.9)	$5,814	20.9984	$83,600	0.05	0.57
Every 1 year	29.4 (23.2–35.1)	7.5 (2.7–14.7)	1.7 (0.6–3.3)	55.0 (1.2)	$8,887	21.0205	$139,500	0.00	0.11

CHF = congestive heart failure; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio.

*Results not shown for the no anthracycline subgroups for which lifetime CHF risk was less than the overall cohort (12.6%), all routine assessment strategies were associated with ICERs >$196,000K per QALY, and routine assessment is not currently recommended (13).

†Range based on 95% credible interval among 1000 second-order Monte Carlo simulations.

‡Discrepancies due to rounding errors.

§Defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared with the next least expensive strategy.

//Based on 1000 second-order Monte Carlo simulations.

Table 3

Preferred strategy: comparison between model results and consensus-based guidelines for childhood cancer survivors.

Total anthracycline dose	Preferred strategy at a $100,000 per QALY cost-effectiveness threshold*†		Children's Oncology Group (COG) guidelines‡
	With 2D echocardiography	With cMRI	
<250 mg/m^2	No assessment	Every 10 years	Every 2 or 5 years
≥250 mg/m^2	Every 2 years	Every 5 years	Every 1 or 2 years

QALY = quality-adjusted life year; cMRI = cardiac magnetic resonance imaging.

*Defined as the strategy with the highest ICER among those with ICERs less than the $100,000 per QALY threshold.

†Model-based results are based on the benefits associated with CHF risk reduction only; routine echocardiography assessment for individuals who received chest radiation may benefit from detection of other cardiac conditions, such as valvular disease, not included in our estimates but reflected in the COG guidelines.

‡Recommended assessment frequency (for individuals ≥5 years at treatment) depends by total anthracycline dose (<200 mg/m^2, ≥200 to <300 mg/m^2, ≥300 mg/m^2) and chest radiation (yes, no) (13)

Appendix Table 1

Clinical and economic model outcomes for 2D echocardiography assessment strategies: additional subgroups by gender and age at diagnosis (for original cancer)

Cardiac assessment strategy	Lifetime systolic CHF risk, % (range)*†	Incremental reduction in lifetime systolic CHF risk†‡		Average age of systolic CHF onset (delay), years‡	Lifetime costs, $	Quality-adjusted life years (QALYs)	ICER, $ per QALY gained‡§	Probability strategy is preferred‡//	
		Versus No assessment, % (range)	Versus previous strategy, % (range)					$50,000 per QALY threshold	$100,000 per QALY threshold
Gender¶									
Females									
No assessment	21.4 (1.7–24.9)	--	--	58.8	$672	21.5984	--	0.98	0.51
Every 10 years	20.9 (17.4–24.2)	2.2 (0.7–4.5)	2.2 (0.7–4.5)	59.1 (0.2)	$2,040	21.6120	$100,200	0.01	0.08
Every 5 years	20.6 (17.1–23.9)	3.8 (1.2–7.7)	1.6 (0.5–3.1)	59.2 (0.4)	$3,040	21.6214	$106,000	0.01	0.34
Every 2 years	20.0 (16.4–23.5)	6.3 (2.1–12.4)	2.6 (0.8–4.9)	59.6 (0.7)	$5,620	21.6385	$150,900	0.00	0.08
Every 1 year	19.6 (16.1–23.2)	8.3 (2.8–15.9)	1.9 (0.7–3.7)	59.8 (1.0)	$8,902	21.6517	$250,400	0.00	0.00
Males									
No assessment	16.7 (14.6–19.5)	--	--	58.6	$497	21.3274	--	0.996	0.75
Every 10 years	16.3 (14.2–19.2)	2.4 (0.7–5.0)	2.4 (0.7–5.0)	58.8 (0.2)	$1,810	21.3380	$124,200	0.004	0.08
Every 5 years	16.0 (13.9–19.0)	4.2 (1.3–8.5)	1.8 (0.6–3.4)	58.9 (0.3)	$2,765	21.3452	$130,900	0.00	0.16
Every 2 years	15.5 (13.3–18.5)	7.1 (2.3–13.8)	2.9 (1.0–5.5)	59.2 (0.6)	$5,253	21.3587	$185,400	0.00	0.02
Every 1 year	15.2 (12.8–18.3)	9.3 (3.1–17.7)	2.2 (0.7–4.2)	59.4 (0.8)	$8,449	21.3690	$308,800	0.00	0.00
Age at diagnosis (original cancer)									
0 to 4 years (mean age 2)									
No assessment	24.3 (17.2–28.8)	--	--	51.0	$845	21.2175	--	0.94	0.31
Every 10 years	23.9 (16.8–28.3)	1.9 (0.6–4.0)	1.9 (0.6–4.0)	51.3 (0.3)	$2,127	21.2333	$81,200	0.01	0.04
Every 5 years	23.5 (16.6–28.0)	3.3 (1.0–6.8)	1.4 (0.5–2.8)	51.5 (0.5)	$3,057	21.2443	$84,500	0.04	0.42
Every 2 years	23.0 (16.3–27.5)	5.5 (1.8–10.9)	2.2 (0.7–4.3)	52.0 (0.9)	$5,449	21.2640	$121,200	0.00	0.23
Every 1 year	22.6 (15.8–27.2)	7.2 (2.4–14.2)	1.7 (0.6–3.3)	52.3 (1.2)	$8,507	21.2792	$201,000	0.00	0.01
5 to 9 years (mean age 7)									
No assessment	18.0 (12.1–26.1)	--	--	57.5	$546	21.4365	--	0.99	0.67
Every 10 years	17.6 (11.8–25.7)	2.2 (0.7–4.6)	2.2 (0.7–4.6)	57.7 (0.2)	$1,869	21.4476	$119,800	0.00	0.06
Every 5 years	17.3 (11.6–25.2)	3.8 (1.2–7.8)	1.6 (0.5–3.2)	57.9 (0.4)	$2,838	21.4552	$126,000	0.01	0.22

Cardiac assessment strategy	Lifetime systolic CHF risk, % (range)[*†]	Incremental reduction in lifetime systolic CHF risk[†‡]		Average age of systolic CHF onset (delay), years[‡]	Lifetime costs, $	Quality-adjusted life years (QALYs)	ICER, $ per QALY gained[‡§]	Probability strategy is preferred[‡//]	
		Versus No assessment, % (range)	Versus previous strategy, % (range)					$50,000 per QALY threshold	$100,000 per QALY threshold
Every 2 years	16.8 (11.4–24.7)	6.4 (2.0–12.6)	2.6 (0.8–5.1)	58.2 (0.7)	$5,339	21.4692	$179,700	0.00	0.05
Every 1 year	16.4 (11.1–24.4)	8.4 (2.7–16.4)	2.0 (0.7–3.9)	58.4 (0.9)	$8,534	21.4799	$298,500	0.00	0.00
10 to 20 years (mean age 15)									
No assessment	12.3 (10.3–16.1)	--	--	66.3	$297	21.4191	--	1.00	0.98
Every 10 years	11.9 (10.0–15.6)	2.6 (0.8–5.4)	2.6 (0.8–5.4)	66.4 (0.1)	$1,653	21.4259	(Dominated)[¶]	0.00	0.00
Every 5 years	11.7 (9.8–15.4)	4.7 (1.4–9.3)	2.0 (0.6–3.8)	66.5 (0.2)	$2,655	21.4310	$197,700	0.00	0.01
Every 2 years	11.3 (9.3–14.8)	8.0 (2.6–15.2)	3.4 (1.1–6.2)	66.7 (0.5)	$5,265	21.4401	$287,600	0.00	0.00
Every 1 year	11.0 (8.9–14.5)	10.5 (3.5–19.8)	2.5 (0.8–4.7)	66.9 (0.7)	$8,625	21.4471	$481,100	0.00	0.00

CHF = congestive heart failure; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio.

[*] Subgroup-specific AER of CHF was estimated using CCSS data from Mulrooney et al. (11) on overall CHF risk, relative risk of CHF associated with each risk factor (RR = 1.4 (95% CI =1.1–1 9) for females compared to men; RR = 3.9 (95% CI = 2.1–7.3) for 0 to 4 years old and RR = 2.3 (95% CI = 1.3–4.0) for 5–9 years compared to 10 to 20 years at original cancer diagnosis) and prevalence of risk factors. For gender subgroups, gender-specific baseline CHF rates (general population), CHF mortality rates and age-specific utilities were also incorporated.

[†] Range based on 95% credible interval among 1000 second-order Monte Carlo simulations.

[‡] Discrepancies due to rounding errors.

[§] Defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared with the next least expensive strategy.

[//] Based on 1000 second-order Monte Carlo simulations.

[¶] Eliminated by extended dominance (i.e. less effective and less cost-effective than a more expensive strategy).

Appendix Table 2

Select clinical and economic model outcomes for overall and anthracycline subgroups when two-dimensional (2D) echocardiography and cardiac magnetic resonance imaging (cMRI) assessment strategies are considered

Cardiac assessment strategy*	Incremental reduction in lifetime systolic CHF risk (versus No Assessment)†	Lifetime costs, $		Quality-adjusted life years		ICER, $ per QALY gained‡§//	Probability strategy is preferred//	
		Costs	Incremental costs	QALYs	Incremental gain in QALYs		$50,000 per QALY threshold	$100,000 per QALY threshold
Overall cohort								
No assessment	--	$577	--	21.4790	--	--	0.97	0.28
Every 10 years with cMRI	4.6 (1.7–9.2)	$3,095	$2,518	21.5092	0.0302	$83,400	0.03	0.69
Every 5 years with cMRI	6.4 (2.5–12.9)	$5,050	$1,955	21.5201	0.0109	$179,600	0.00	0.02
Every 1 years with 2D echo	8.7 (2.9–16.7)	$8,675	$3,624	21.5261	0.0060	$601,000	0.00	0.00
Every 2 years with cMRI	7.5 (2.9–15.0)	$10,799	$2,124	21.5294	0.0033	$643,200	0.00	0.00
Every 1 years with cMRI	8.1 (3.1–16.4)	$20,367	$9,568	21.5336	0.0042	$2,292,500	0.00	0.00
Anthracycline subgroups								
<250 mg/m^2								
No assessment	--	$619	----	21.4402	--	--	0.91	0.26
Every 10 years with cMRI	4.6 (1.7–9.2)	$3,138	$2,520	21.4725	0.0323	$78,000	0.09	0.68
Every 5 years with cMRI	6.4 (2.4–12.9)	$5,088	$1,950	21.4842	0.0116	$167,900	0.00	0.06
Every 2 years with cMRI	7.4 (2.8–14.9)	$10,813	$5,725	21.4941	0.0100	$574,400	0.00	0.00
Every 1 years with cMRI	8.1 (3.1–16.3)	$20,336	$9,524	21.4986	0.0044	$2,150,000	0.00	0.00
≥250 mg/m^2								
No assessment	--	$1,171	--	20.9307	--	--	0.32	0.01
Every 10 years with cMRI	4.5 (1.7–9.1)	$3,707	$2,536	20.9909	0.0602	$42,100	0.65	0.38
Every 5 years with cMRI	6.1 (2.3–12.4)	$5,582	$1,875	21.0118	0.0209	$89,800	0.03	0.61
Every 2 years with cMRI	7.0 (2.7–14.4)	$10,995	$5,412	21.0299	0.0181	$298,400	0.00	0.00
Every 1 years with cMRI	7.6 (2.9–15.4)	$19,938	$8,943	21.0376	0.0077	$1,159,800	0.00	0.00

2D echo = two-dimensional echocardiography; cMRI = cardiac magnetic resonance imaging; CHF = congestive heart failure; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio.

*A total of 9 strategies were comparatively evaluated for each subgroup (no assessment; 2D echocardiogram assessment every 10, 5, 2, or 1 year; cMRI assessment every 10, 5, 2, or 1 year). We assumed cMRI has perfect sensitivity and specificity for detecting ALVD.

[†] Lifetime CHF risk = 18.8% for overall cohort, 19.8% for <250 mg/m^2 anthracycline, and 31.8% for ≥250 mg/m^2 anthracycline subgroups.

[‡] Defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared with the next least expensive non-dominated strategy.

[§] Only non-dominated strategies (i.e. those that are more effective and less costly than another strategy (strong dominance) or more effective and more cost-effective than another strategy (weak dominance) are shown).

[//] Discrepancies due to rounding errors.

[¶] Based on 1000 second-order Monte Carlo simulations.

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