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CCSS Analysis Concept Proposal

Study Title: Cost-effective cardiomyopathy surveillance strategies in childhood cancer survivors.

Working Groups:
Epidemiology/Biostatistics – Primary
Cancer Control and Intervention – Secondary
Chronic Disease – Secondary

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BACKGROUND AND SIGNIFICANCE

Childhood cancer survivors treated with anthracycline chemotherapy or chest radiation are at an increased risk of developing heart failure (HF).[1,2] In this population, HF is well-recognized as a progressive disorder, with a variable period of asymptomatic cardiomyopathy which precedes signs and symptoms.[3-5] As a result, a number of practice guidelines have been developed to facilitate detection and treatment of asymptomatic cardiomyopathy.[6-9] These guidelines differ with regards to definitions of at risk populations, surveillance modality and frequency, and recommendations for interventions. These differences may hinder the effective implementation of surveillance recommendations. Recognizing the importance for collaboration, an international effort was recently organized to harmonize existing cardiomyopathy screening recommendations for survivors of childhood cancer.[10] This effort incorporated studies published through 2012, and graded the quality of the evidence (e.g. Level A: high level of evidence; Level C: very low level of evidence; or no evidence), to formulate recommendations for cardiomyopathy risk categorization, screening, and duration of follow-up. Cardiomyopathy risk (High, Moderate, Low) was based on cumulative anthracycline exposure and chest radiation exposure, and supported by high quality (Level A) evidence. On the other hand, there were no data to support different screening frequencies (e.g. annual, every five years) or duration of screening (e.g. lifelong vs. time-limited) by cardiomyopathy risk. As such, the harmonized cardiomyopathy screening strategies are largely consensus based, recommending a minimum of every 5-year echocardiographic screening, with consideration for more frequent (not specified) screening per patient risk strata. Studies are needed to examine the cost-effectiveness of different screening frequencies and its duration by cardiomyopathy risk. Given the long latency of disease and large numbers needed for follow-up, clinical trials evaluating efficacy of different screening frequencies would be cost-prohibitive. Therefore we propose decision-modeling to estimate the

economic and health impact of different screening strategies and interventions in childhood cancer survivors with asymptomatic cardiomyopathy.

Two recent studies relied on the Childhood Cancer Survivor Study (CCSS) to derive decision-modeling estimates of the economic and health impact of echocardiographic screening.[11,12] The first, utilized patient-reported outcomes from the original cohort (treated between 1970 and 1986) to determine the cost effectiveness of screening according to the COG Long-term Follow-up Guidelines (Version 4).[11] The second, simulated the cost-effectiveness of cardiomyopathy surveillance in a population that mirrored the characteristics of the CCSS cohort, albeit without direct access to CCSS data.[12] Data were extrapolated from published hazard ratios, adjusted for known cardiomyopathy risk factors (i.e. radiation and anthracycline exposure). These studies found that when using established cost-effectiveness thresholds (e.g. $50,000 and $100,000 per QALY gained), screening for cardiomyopathy would be considered cost-effective when compared to no screening, and that less frequent screening may be preferable to current (COG LTFU Guidelines V.4) recommendations. However, both studies reflect HF risk for an older cohort of childhood cancer survivors, perhaps missing an opportunity to capitalize on the CCSS expansion cohort, which represents a much larger population of survivors treated with more contemporary approaches. Moreover, International Cardiomyopathy Screening Harmonization Guidelines are now available, as well as a clinical risk prediction model for HF based on the CCSS data (Chow and colleagues).[13] The clinical benefits and economic consequences associated with both have not been evaluated.

Therefore, the objective of the current study is to evaluate the clinical benefits and cost effectiveness of risk-based cardiomyopathy surveillance strategies that correspond more closely with contemporary risk factors found within the existing literature. To achieve this goal, we propose the following aims:

> **Specific Aim 1:** Evaluate the benefits, costs and cost-effectiveness of cardiomyopathy screening recommendations established by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) for specific cardiomyopathy risk groups
>
> *Hypothesis:* More frequent screening will be the preferred strategy for intermediate and high risk groups, while less frequent screening will be optimal for the low risk group.
>
> **Specific Aim 2:** Assess various interval-based echocardiography screening strategies to identify the optimal frequency for each of the cardiomyopathy risk groups established by Chow and colleagues.
>
> *Hypothesis:* Surveillance strategies will vary by cardiomyopathy risk groups.

As an exploratory aim, we will investigate the cost-effectiveness of risk-based screening groups defined by heart dose, rather than field or site dose, radiation. These results will be of interest, however we recognize that they will not be applicable to the broader screening community. The results of Specific Aims 1 and 2 will directly inform the upcoming Version 5.0 of the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer.[6] This approach will mark the first time that model-based analyses will be used to help inform new guideline recommendations for an outcome where latency to disease onset precludes utilization of clinical trials.

ANALYSIS FRAMEWORK

This study will be paired with the ongoing analysis (Proposal #16-18) by Dr. Mulrooney and colleagues entitled "Incidence of Cardiac Outcomes by Treatment Era and Temporal Trends in Treatment Exposure in Adult Survivors of Childhood Cancer." The results of Proposal #16-18 will provide contemporary cumulative incidence and heart failure risk estimates that will be incorporated into the subsequent simulation models. The CCSS statistical team will develop the incidence and risk data (Proposal #16-18), while the simulation models will be developed and programmed by Dr. Yeh and colleagues.

1. **Outcomes of interest**:

a. Vital status (alive, dead, lost)
b. Date of vital status
c. Cause of death
d. Congestive heart failure (per CTCAE v4.03 criteria, Grades 3 [severe] – 5 [death]

2. **Research Population:**
    a. Inclusion Criteria:
        i. All CCSS survivors (diagnosed 1970-1999) and siblings (baseline, Follow-Up 2003, Follow-Up 2007, or on the Expanded cohort baseline).
    b. Exclusion Criteria:
        i. Cases and/or siblings reporting a cardiac event prior to cohort entry at five years from primary diagnosis

3. **Explanatory Variables:**
    a. Age at diagnosis
    b. Age at follow up
    c. Gender
    d. Primary cancer diagnosis
    e. Year of diagnosis
    f. Race/ethnicity
    g. Obesity (body mass index [BMI])
        i. Underweight BMI <18.5 kg/m^2
        ii. Normal weight BMI=18.5-24.9 kg/m^2
        iii. Overweight BMI=25-29.9 kg/m^2
        iv. Obese BMI ≥ 30 kg/m^2
    h. Household income
    i. Education level (baseline and follow-up)
    j. Tobacco use
    k. Hypertension (requiring medication and above)
        i. CTCAE v4.03 criteria, Grades 2 – 4
    l. Dyslipidemia (requiring medication and above)
        i. CTCAE v4.03 criteria, Grades 2 – 4
    m. Diabetes (requiring medication and above)
        i. CTCAE v4.03 criteria, Grades 2 – 4
    n. Cumulative anthracycline exposure
        i. <250 mg/m_2, 250 mg/m^2 to <350 mg/m^2, 350 mg/m^2 to <450 mg/m^2, 450 mg/m^2 to <550 mg/m^2, and ≥550 mg/m^2
    o. Cardiac radiation exposure
        i. None, <500 cGy, 500 to <1500 cGy, 1500 to <3500 cGy, and ≥3500 cGy

Aim 1: Identify cost-effective screening echocardiography intervals for the cardiomyopathy risk groups established by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG).

We will develop a microsimulation model of the clinical course of HF for a cohort of childhood cancer survivors. In a microsimulation model, individuals transition among health states one at a time and the detailed information for each individual is continuously tracked, allowing the natural history, prognosis, and course of disease to be conditional on that individual's risk factor profile and history of treatment. The model tracks individuals from entry into the model until death. By examining the clinical course of a disease, represented by the particular pathway an individual took through the health states prior to dying, the model can generate a survival time for that individual. By running large numbers of simulated cases, a distribution of survival values can be obtained. Therefore, the model will have the ability to reflect patient variability in disease clinical course and long-term outcomes.

At the start of the model simulation, 5-year cancer survivors will enter the model and face a risk of developing asymptomatic left-ventricular dysfunction (ALVD). Risk for ALVD will be estimated from existing literature using a similar approach to that of Wong and Yeh.[11,12] Persons with ALVD face the risk for symptomatic HF. Estimated risk for HF in association with the explanatory variables listed above will be evaluated following the ongoing CCSS analysis by Mulrooney and subsequently incorporated into the model as risk ratios and/or by analyzing specific populations of interest (e.g. those with hypertension). Once HF develops, persons face disease-specific death risks. All persons face death risks from background mortality (based on US lifetables), late recurrence (based on disease specific CCSS estimates), and noncardiac late effects (including second cancer diagnoses and pulmonary, external, and other causes based on CCSS estimates). Survivors will be followed throughout their lifetime.

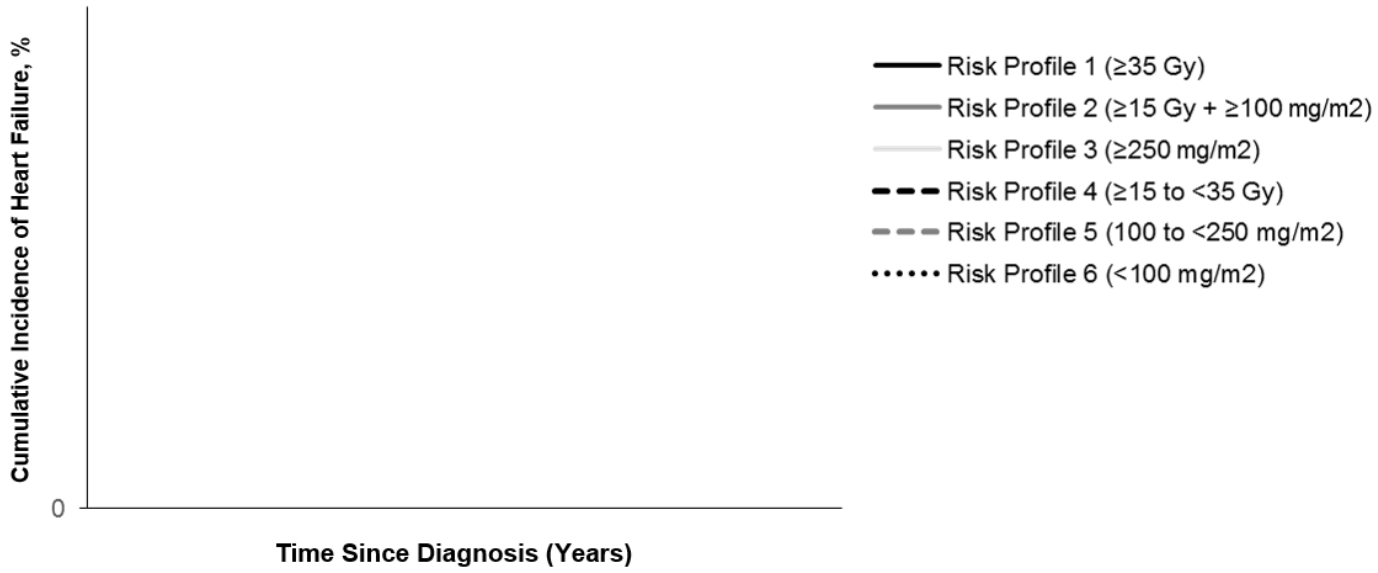
The model will simulate a cohort of survivors that mirrors the patient, cancer and treatment characteristics (i.e. sex, age at cancer diagnosis, chest irradiation, cumulative anthracycline dose, etc.) of the IGHG or Chow et al clinical risk subgroups described above. Strategies will include no screening and screening every 1, 2, 3, 5 and 10 years. Medical costs associated with routine cardiac assessment, follow up care for reduced left ventricular function, ALVD, and HF will be based on Medicare reimbursement rates as a proxy. To estimate quality-adjusted life years, we will incorporate age-specific and disease-specific utility weights.[14] Model outcomes will include reduction in lifetime HF risk, life expectancy, quality-adjusted life expectancy, and lifetime costs. To evaluate the relative performance of each screening strategy, we will calculate the incremental cost-effectiveness ratios, defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared with the next least expensive strategy, and expressed as cost per quality-adjusted life year (QALY) gained. We will use the commonly used thresholds of $50,000 and $100,000 per QALY gained to identify the preferred strategy.

Aim 2: Identify cost-effective screening echocardiography intervals for cardiomyopathy risk groups established by Chow and colleagues.

As in Aim 1, we will use the above described simulation cohort and corresponding incidence and risk data as the basis for estimating the benefits, costs and cost-effectiveness for various screening strategies for each risk profile (low, moderate, high, very high [heart dose only]) within each heart failure prediction model (simple, standard, heart dose) put forth by Chow, et al. (Supplemental Table 1). We will use the commonly used thresholds of $50,000 and $100,000 per QALY gained to identify the preferred strategy. As with any simulation analysis, sensitivity and uncertainty analysis (1-way, 2-way, and probabilistic) will be a key component to understand how results vary across the plausible range of model parameters (e.g. echo sensitivity, treatment efficacy) and under alternative assumptions. These investigations will: 1) better characterize the impact of parameter uncertainty on modeled outcomes, 2) strengthen our conclusions, and 3) identify knowledge gaps, prioritizing future investigations.

PROPOSED FIGURES AND TABLES

Figure 1. A) Cumulative incidence of heart failure and **B)** reduction in lifetime heart failure incidence



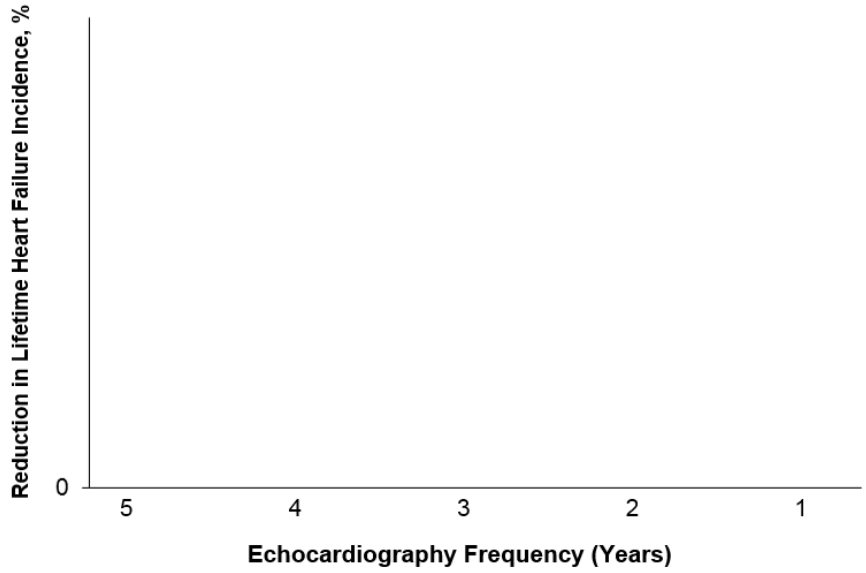
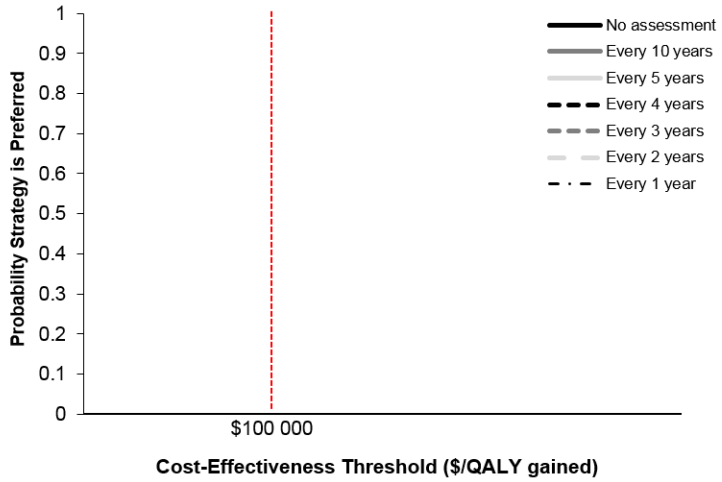
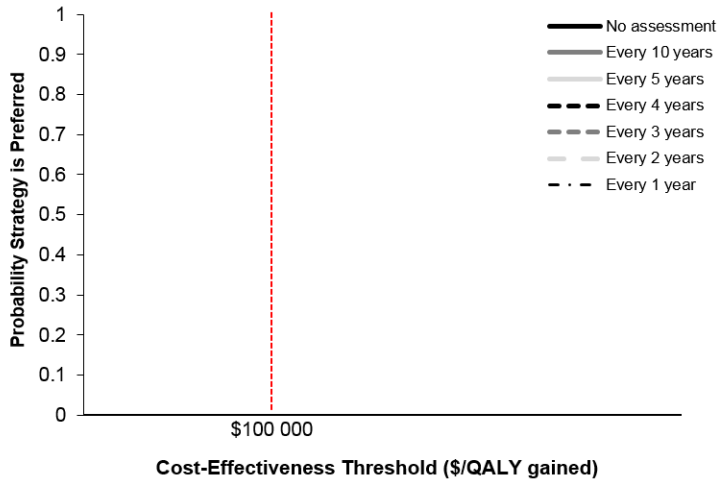


Figure 2. Cost effectiveness acceptability curves for **A)** high risk, **B)** intermediate risk, and **C)** low risk IGHG profiles.

A



B



C

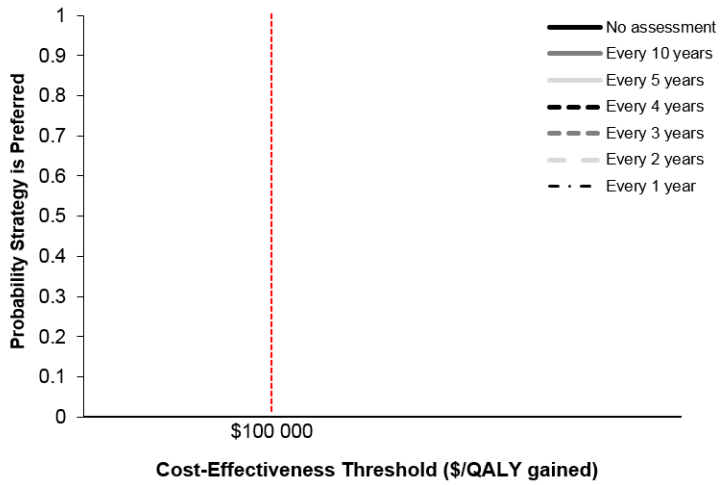


Table 2. Cost and ICER of the IHGH risk profiles intervals

Risk Profile IGHG Risk Group			Screening Interval (years)	Lifetime Cost Per-Person ($)	(Cumulative Incidence of Systolic HF without Screening), Percent Reduction with Screening (years from diagnosis)			Incremental Reduction (vs. no screening) in Lifetime Systolic HF Risk (%)	Lifetime Cost ($)	QALY/Person	ICER, Compared with No Screening ($/QALY gained)	ICER, Compared with Immediately Preceding Less Expensive Nondominated Strategy ($/QALY gained)	Probability Strategy is Preferred ($100,000/QALY Threshold)
	Profile	Chest RT (Gy)	AC Dose (mg/m^2)		20	30	50						
High Risk	1	≥35	-	None 5 4 3 2 1									
	2	≥15	≥100	None 5 4 3 2 1									
	3	-	≥250	None 5 4 3 2 1									
	1-3	Overall High Risk (Any of profiles 1-3)		None 5 4 3 2 1									
Intermediate Risk	4	≥15 to <35	-	None 5 4 3 2 1									
	5	-	100 to <250	None 5 4 3 2 1									
	4-5	Overall Intermediate Risk (Any of profiles 4-5)		None 5 4 3 2 1									
Low Risk	6	-	<100	None 10 5 4 3 2 1									

Table 3. Cost and ICER of the Chow, et al. risk profiles (risk score 0-4) assigned by simple, standard, and heart dose prediction models

	Risk	Screening Interval (years)	Lifetime Cost Per-Person ($)	(Cumulative Incidence of Systolic HF without Screening), Percent Reduction with Screening (years from diagnosis)			Incremental Reduction (vs. no screening) in Lifetime Systolic HF Risk (%)	Lifetime Cost ($)	QALY/Person	ICER, Compared with No Screening ($/QALY gained)	ICER, Compared with Immediately Preceding Less Expensive Nondominated Strategy ($/QALY gained)	Probability Strategy is Preferred ($100,000/QALY Threshold)
				20	30	50						
Simple Model	Low	None										
		5										
		4										
		3										
		2										
		1										
	Moderate	None										
		5										
		4										
		3										
		2										
		1										
	High	None										
		5										
		4										
		3										
		2										
		1										

Table 3 (continued). Cost and ICER of the Chow, et al. risk profiles (risk score 0-4) assigned by simple, standard, and heart dose prediction models

	Risk	Screening Interval (years)	Lifetime Cost Per-Person ($)	(Cumulative Incidence of Systolic HF without Screening), Percent Reduction with Screening (years from diagnosis)			Incremental Reduction (vs. no screening) in Lifetime Systolic HF Risk (%)	Lifetime Cost ($)	QALY/Person	ICER, Compared with No Screening ($/QALY gained)	ICER, Compared with Immediately Preceding Less Expensive Nondominated Strategy ($/QALY gained)	Probability Strategy is Preferred ($100,000/QALY Threshold)
				20	30	50						
Standard Model	Low	None										
		5										
		4										
		3										
		2										
		1										
	Moderate	None										
		5										
		4										
		3										
		2										
		1										
	High	None										
		5										
		4										
		3										
		2										
		1										

Table 3 (continued). Cost and ICER of the Chow, et al. risk profiles (risk score 0-4) assigned by simple, standard, and heart dose prediction models

	Risk	Screening Interval (years)	Lifetime Cost Per-Person ($)	(Cumulative Incidence of Systolic HF without Screening), Percent Reduction with Screening (years from diagnosis)			Incremental Reduction (vs. no screening) in Lifetime Systolic HF Risk (%)	Lifetime Cost ($)	QALY/Person	ICER, Compared with No Screening ($/QALY gained)	ICER, Compared with Immediately Preceding Less Expensive Nondominated Strategy ($/QALY gained)	Probability Strategy is Preferred ($100,000/QALY Threshold)
				20	30	50						
Heart Dose Model	Low	None										
		5										
		4										
		3										
		2										
		1										
	Moderate	None										
		5										
		4										
		3										
		2										
		1										
	High	None										
		5										
		4										
		3										
		2										
		1										
	Very High	None										
		5										
		4										
		3										
		2										
		1										

Supplemental Table 1. CHF risk scores

Characteristic	Simple Model	Standard Model	Heart Dose Model
Sex			
Male	0	0	0
Female	1	1	1
Age at diagnosis, years			
<5	1	2	2
5-9	0	1	1
10-14	0	0	1
≥15	0	0	0
Anthracycline, mg/m^2			
None	0	0	0
Any	3	–	–
<100	-	1	2
100-249	-	3	3
≥250	-	4	4
Chest or heart RT, Gy			
None	0	0	0
Any	3	–	–
<5	–	0	0
5-14	–	2	1
15-34	–	2	3
≥35	–	4	4
	Total Score	**Total Score**	**Total Score**
Risk Group			
Low	<3	<3	<3
Moderate	3-4	3-5	3-5
High	≥5	≥6	6-8
Very High	NA	NA	≥9

Risk scores 0, 1, 2, 3, and 4 correspond to relative risks (for heart failure) <1.3, 1.3 to 1.9, 2.0 to 2.9, 3.0 to 4.9, and ≥5.0, respectively.

Modified from Chow, et al, J Clin Oncol 2015;33:394-402

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