1. <u>STUDY TITLE</u>:
   Cost Effectiveness of Cardiac Guideline for Survivors of Pediatric Cancers

2. <u>WORKING GROUP</u>:
   CCSS Epidemiology & Biostatistics

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3. <u>BACKGROUND AND RATIONALE</u>:
   Advances in cancer treatment have resulted in a growing number of childhood cancer survivors. The current five-year survival rates approach 80% for most pediatric malignancies. By 2010, one in every 570 young adults is projected to be a survivor of a childhood cancer, increasing the need to focus on long-term consequences of cancer therapy in these individuals. Cardiomyopathy is an unfortunate consequence of certain cancer therapies and if left untreated can progress to congestive heart failure (CHF). Studies have found that long-term survivors of childhood cancer are at a 6-fold

increased risk of reporting CHF – thus making CHF the second most likely morbidity in this population. Through effective screening, the goal is to diagnose cardiomyopathy at an early subclinical stage and slow the progression to CHF. Several guidelines currently exist, with recommendations for screening for cardiomyopathy in childhood cancer survivors; the most comprehensive of these guidelines is available through the Children's Oncology Group (COG), and takes into account the cumulative dose of therapeutic exposures, the age at exposures, and exposure to radiation therapy. However, these Guidelines are consensus-based, and lack the backing of rigorous scientific evidence which can be used to support these consensus-driven recommendations.

The objective of this study is to examine the cost-effectiveness of the Children's Oncology Group screening guideline for detecting subclinical CHF using echocardiogram (ECHO) in pediatric cancer survivors treated with anthracycline. The guideline recommends varying screening frequencies using echocardiogram according to age at treatment, anthracycline dose, and exposure to chest radiation. This study will examine the cost-effectiveness of implementing the screening guideline to determine whether the recommended frequencies are appropriate from a cost-effective perspective. First, a Markov model consisting of four Markov states (no CHF, symptomatic CHF, heart transplant survivor, death) will be set up to simulate the natural history of cardiac dysfunction (Figure). A simulated patient will transition from one Markov state to another according to the transition probabilities between states. This will enable calculation of the expected (quality-adjusted) life years. Second, echocardiogram screening will be incorporated into the Markov model according to frequencies recommended in the guideline. This will augment the Markov model by adding another state, asymptomatic CHF detected (by echocardiogram). Third, various costs, including those associated with screening, treatment of CHF, and other consequences, will be assessed in the same Markov model to estimate the expected cost. Finally, incremental cost-effectiveness ratio (ratio of the difference in the monetary costs of two screening schedules and the difference of quality-adjusted life years of the two schedules) will be computed to determine the most cost-effective screening intervals. The CCSS data will be used to estimate the probabilities of death as a function of the years of follow-up for pediatric cancer survivors exposed to anthracycline, with or without chest radiation, according to sex and age at diagnosis for various types of childhood cancer. These mortality estimates will be applied in the Markov model as transition probabilities between no CHF and death. The direct estimates obtained from the CCSS data will offer more credibility to the Markov model and the results.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES

Specific Aim 1: Identify the optimal cost-effective frequency of screening ECHO for the assessment of therapy-related cardiomyopathy when comparing frequencies ranging from never, to annual, to every two, three or five years for ***cancer patients who were under the age of 1 year*** at the time of first cardiotoxic therapy and were exposed to:
   a. Varying anthracycline doses (<200 mg/m^2, ≥ 200 mg/m^2), without chest radiation
   b. Any anthracycline with exposure to chest radiation

Hypothesis 1: The optimal screening frequency for cancer patients diagnosed at <1 year of age will be:
a) annual if exposed to any anthracycline and also exposed to chest radiation;

b) every 2 years if exposed to <200 mg/m^2 of anthracycline without chest radiation;
c) annual if exposed to ≥200 mg/m^2 of anthracycline without exposure to chest radiation.

Specific Aim 2: Identify the optimal cost-effective frequency of screening ECHO for the assessment of therapy-related cardiomyopathy when comparing frequencies ranging from never, to annually, to every two, three, or five years for *cancer patients who were between 1 and 4 years of age* at the time of first cardiotoxic therapy and were exposed to:
   a. Varying anthracycline doses (<100≥100   to <300, ≥ 300 mg/m^2) without chest radiation
   b. Any anthracycline with exposure to chest radiation

Hypothesis 2: The optimal screening frequency for cancer patients diagnosed between 1 and 4 years of age will be:
a) annual if exposed to any anthracycline and also exposed to chest radiation;
b) every 5 years if exposed to <100 mg/m^2 of anthracycline without chest radiation;
c) every 2 years if exposed to ≥100 mg/m^2 and <300 mg/m^2 of anthracycline without chest radiation;
d) annual if exposed to ≥200 mg/m^2 of anthracycline without chest radiation.

Specific Aim 3: Identify the optimal cost-effective frequency of screening ECHO for the assessment of therapy-related cardiomyopathy when comparing frequencies ranging from never, to annually, to every two, three, or five years for *cancer patients who were ≥ 5 years of age* at the time of first cardiotoxic therapy and were exposed to:
   a. Varying anthracycline doses (<200, ≥ 200 to <300, ≥ 300 mg/m^2) without chest radiation
   b. Varying anthracycline levels (<300, ≥300mg/m^2) with exposure to chest radiation

Hypothesis 3: The optimal screening frequency for cancer patients diagnosed at ≥5 years of age will be:
a) every 2 years if exposed to <300 mg/m^2 of anthracycline with chest radiation;
b) every 5 years if exposed to <200 mg/m^2 of anthracycline without chest radiation;
c) every 2 years if exposed to ≥200 to <300 mg/m^2 of anthracycline without chest radiation;
d) annual if exposed to ≥300 mg/m^2 of anthracycline without chest radiation.

5.   ANALYSIS FRAMEWORK
      a. Outcome of interest:
         Vital status (alive, dead, lost)
         Date of vital status
         Cause of death
         Congestive heart failure or cardiomyopathy, including age at occurrence

      b. Subject population:
         CCSS baseline cohort from the first questionnaire, exposed to anthracycline

      c. Exploratory variables:
         Birthday
         Sex

Race
Ethnicity
Education at baseline
Education at follow-up
Congestive heart failure or cardiomyopathy, including age at occurrence
Anthracycline dose
Date of 1st anthracycline exposure
Radiation exposure to the chest
Date of 1st radiation exposure
Cancer type
Age at diagnosis of cancer

d. Examples of specific tables and figures:

Table 1. Probability of death due to non-CHF by age, sex, chest irradiation, anthracycline dose for survivors of ALL without CHF at baseline

Cancer type		ALL							
Age at treatment		< 1 year old							
Chest irradiation		No				Yes			
Anthracycline dose		<200 mg/m^2		≥200 mg/m^2		<200 mg/m^2		≥200 mg/m^2	
Sex		M	F	M	F	M	F	M	F
Attained age (y)	5								
	6								
	7								
	8								
	…								
	80								

6. <u>SPECIAL CONSIDERATIONS</u>
The CCSS Statistical Center will provide the data. F.L. Wong will conduct the statistical analyses with input and review by the collaborators listed in the WORKING GROUP.

Markov Model

ALL 5-y Survivor

ChildhoodCancer(1)

Stratify on:
XRT, sex, age at
Dx.

No screening strategy

- no CHF — 1
  - no CHF
  - Sympt CHF
  - dies → Dead
- Sympt CHF — 0
  - Pharm trtmt
    - stable → Sympt CHF
    - Heart transplant
      - successful → Heart Transplant survivor
      - not successful → Dead
    - dies → Dead
- Heart Transplant survivor — 0
  - stable → Heart Transplant survivor
  - dies → Dead
- Dead — 0

Screening w/ ECHO

- No CHF — 1
  - Echo -
    - No CHF
    - Sympt CHF
    - Dead
  - Echo +
    - Sees cardiologist (intervention)
      - false + → No CHF
      - Asympt CHF detected
      - Sympt CHF
      - Dead
- Asympt CHF detected
  - Asympt CHF detected
  - Sympt CHF
  - Dead
- Sympt CHF — 0
  - Pharm trtmt
    - stable → Sympt CHF
    - Heart transplant
      - successful → Heart Transplant survivor
      - not successful → Dead
    - dies → Dead
- Heart Transplant survivor
  - stable → Heart Transplant survivor
  - dies → Dead
- Dead — 0