Childhood Cancer Survivor Study

Analysis Concept Proposal

Study title: Efficacy and Cost-effectiveness of the Children's Oncology Group Long-term Follow-up Screening Guidelines for Childhood Cancer Survivors at Risk of Colorectal Cancer

Working groups
Epidemiology/Biostatistics (primary)
Cancer Control (secondary)
Second Malignancy (secondary)

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A. Background and rationale

Importance of studying the cost-effectiveness of colorectal cancer screening strategies for childhood cancer survivors

In the US, there are 13,500 new childhood cancer cases annually.[2] This number continues to increase,[3] placing a high illness and economic burden on society. Medical advances have markedly improved the life expectancy of childhood cancer survivors.[4] However, childhood cancer survivors are at a high risk of subsequent morbidity including subsequent malignant neoplasms (SMNs) including gastrointestinal cancers.[5,6] SMNs are the leading cause of non-relapse mortality in childhood cancer survivors.[7] According to the Childhood Cancer Survivor Study (CCSS), childhood cancer survivors carry a higher risk of developing gastrointestinal cancer, including colorectal cancer (CRC), and at a younger age compared with the general population.[7]

Survivors of childhood cancer are at a 10.9-fold higher risk of developing CRC when compared with the general population.[8] Friedman and colleagues reported a latency of 23.1y between the first neoplasm and CRC cancer in childhood cancer survivors.[6] The risk of CRC is associated with exposure to abdominal radiation for treatment of the first neoplasm, and family history of colorectal cancer or polyps in the first-degree relative.[7,9-12] Previous studies underscore the important role of pre-emptive screening and surveillance of vulnerable subpopulations of childhood cancer survivors, facilitating early detection of and timely intervention for CRC.[9,13]

In the 2018 version of the Children's Oncology Group (COG) Long-term Follow-up Guidelines,[14] childhood cancer survivors with radiation to the abdomen, pelvis, spine or to total body irradiation are recommended to initiate CRC screening at age 30, with subsequent screenings at intervals of 3 to 5y depending on the screening modality used. However, childhood cancer survivors often do not adhere with these recommendations. In a recent national study, less than 40% of the "at risk" childhood cancer survivors underwent screening for CRC.[12,15] Furthermore, this screening rate was as low as 11.5% in certain regions.[12,16]

Rigor of prior research examining cost-effectiveness of CRC screening in childhood cancer survivors

Studies examining cost-effectiveness of CRC screening guidelines for the general population have become a useful tool for policy-makers in making resource allocation choices to improve population health. Knowledge regarding cost-

effectiveness of CRC screening in childhood cancer survivors is scarce. Recently, Gini and colleagues examined the cost-effectiveness of the CRC screening guidelines for childhood cancer survivors.[17] However, this study did not incorporate all available screening modalities (i.e., only comparing colonoscopy-based screening strategies), did not adjust for quality of life in clinical outcomes, and may not address the elevated background mortality for this specific childhood survivor population.[18] Also, this study used data on medical care services for the older population (Medicare); this may not provide us with the most appropriate clinical and financial estimates in the context of childhood cancer survivors.

Significance of studying the cost-effectiveness of colorectal cancer screening strategies for childhood cancer survivors

We propose to examine the cost-effectiveness of all available CRC screening strategies recommended by COG. We will include the "No Screening" strategy as the comparison anchor. Our study will address an important gap in knowledge by providing evidence for the cost-effectiveness of the CRC screening strategies that will help reduce cancer mortality and morbidities for childhood cancer survivors. Within the proposed research, we will develop, validate, and utilize a model simulating the disease progression to CRC in a cohort of childhood cancer survivors through their lifetime. Findings from our study will help policy-makers and healthcare professionals develop appropriate screening interventions for their target population (based on clinical presentation of the population, patient's adherence to the recommendations, etc.) and make better decisions in selecting competing choices for healthcare resource allocation.[19,20]

Expected outcomes

We will determine the incremental cost-effectiveness ratio (ICER) comparing a given CRC screening strategy against its next best available strategy. We will compare this ratio against the standard willingness-to-pay threshold as $100,000 per quality-adjusted life year (QALY) to assess the cost-effectiveness. The given CRC screening strategy will be deemed as cost-effective compared to its next best available strategy if the ICER is less than $100,000 per QALY. Our findings can help policy makers with select competing choices for healthcare interventions. In addition, the outcomes from our research can help identify the best CRC screening strategy in patients-specific contexts.

Innovation

Our proposal will

- Include all CRC screening strategies currently recommended by COG
- Stratify risk based on exposure to abdominal radiation for the first neoplasm and family history of CRC or polyps in the first-degree relative
- Use the resources offered by CCSS data for important input parameters: demographics, therapeutic exposures (radiation to the abdomen/pelvis, alkylating agents), lifetable
- Incorporate adherence information
- Develop alternative, more cost-effective strategies

B. Specific aims/objectives/research hypotheses

Aim 1: Examine the efficacy and cost-effectiveness of the COG colorectal cancer screening strategies. We will build a model to simulate the natural history of developing CRC specific for childhood cancer survivors through their lifetime. Information on the operating characteristics (sensitivity, specificity) of the screening strategies along with the real-world data on U.S. patient utilization of these strategies will be incorporated. A comparative cost-effectiveness ratio between a given screening strategy to its next best alternative will be the primary outcome of interest.

Aim 2: Explore alternative CRC screening strategies that may be more cost-effective. We aim to identify feasible options of CRC screening to best use medical care resources by making adjustments (addressing factors of utilization, screening frequency, patients' elevated risk for CRC due to exposure to abdominal radiation and chemotherapy), to the existing screening strategies. We will continue to rely on the cost-effectiveness analysis tools to determine the best option of CRC screening.

C. Conceptual framework

We will estimate the clinical and economic outcomes of childhood cancer survivors using their clinical background and

patterns of screening utilization and adherence to recommended treatments. Specifically, in the base-case analysis, we will examine clinical and economic outcomes of patients following two screening strategies plus the no screening. We will create a model that simulates the natural history of developing CRC in childhood cancer survivors through their lifetime. The outcome will be ICER (numerator: difference in cost for the two screening strategies; denominator: difference in health outcomes when using the two screening strategies [effectiveness]). We will deem the given screening strategy cost-effective against a willingness-to-pay threshold if the ratio lies below $100,000 per QALY. In the sensitivity analysis, we will evaluate the cost-effectiveness of all available CRC screening modalities to develop alternate and more cost-effective screening strategy (see Table 1.)

Analytical briefing
Outcomes of interest: Incremental cost-effectiveness analysis ratios comparing CRC screening strategies
Study population: childhood cancer survivors through their lifetime
Exploratory variables: abdominal radiation, alkylating agents, genetic factors, age, race, gender, frequency of screening, patient's utilization of medical services (i.e., screening)

D. Approach

Modeling the natural history of developing CRC: Figure 1 presents the transition state diagram of a childhood cancer survivor in developing CRC. At a given time and a given state, the patient is subject to a quantified risk of transitioning into the next state or remaining in the same state (no progression). Our model will include six health states as follows: a) Disease-free, b) Adenoma, c) Preclinical CRC, d) CRC, e) CRC-related death, and f) Non-CRC death. We follow the patients from the time of screening until death and observe the risk at annual intervals.

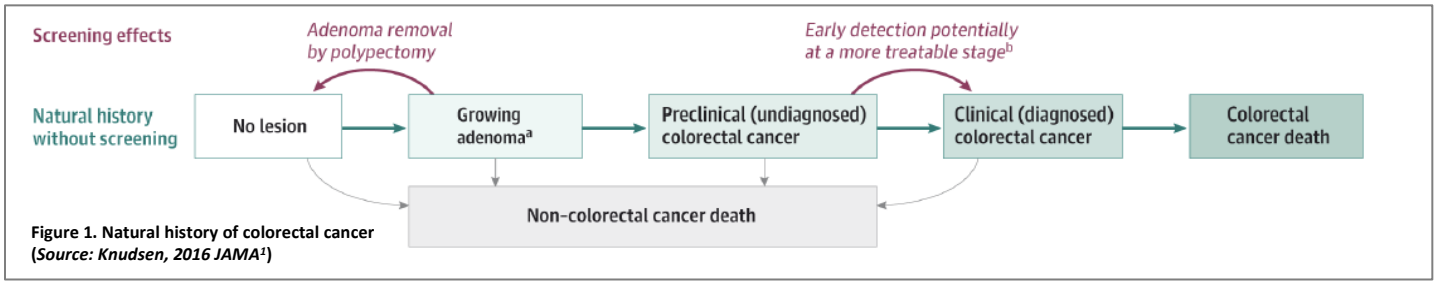


Figure 1. Natural history of colorectal cancer (*Source: Knudsen, 2016 JAMA*[1])

Comparisons: CRC screening guidelines recommended by COG; we will include "No Screening" strategy as the comparison anchor (**Table 1**).

Table 1. COG-recommended CRC screening for childhood cancer survivors (Screening start age = 30)	
A. Base-case analysis	**Screening frequency**
Structural examinations, colonoscopy	Every 5 years
Stool-based testing, multitarget stool DNA test	Every 3 years
No screening	
Sensitivity analysis	___
Stool-based testing, fecal immunochemical test	Every 1 year
Stool-based testing, high-sensitivity, guaiac-based fecal occult blood test	Every 1 year
Stool-based testing, multitarget stool DNA test	Every 3 years
Structural examinations, colonoscopy	Every 5 years
Structural examinations, CT colonography	Every 5 years
Structural examinations, Flexible sigmoidoscopy	Every 5 years
No screening	___

Screening operating characteristics and disease progression: We will derive information on the operating characteristics of the screening strategies from the literature.[1,10,21-24] We use the CCSS dataset for estimating the probability of developing CRC from being disease-free. This probability will also be moderated by several risk factors including abdominal radiation and chemotherapy exposure and family history of CRC or polyps in the first-degree relative. We will account for additional moderating factors including demographics, socioeconomics, and patients' clinical history, such as age, gender, race/ethnicity, and age at diagnosis of primary cancer. Our model build will also be informed by other disease transition

probabilities (from disease-free to adenoma; disease-free to preclinical CRC). Due to lack of availability of such data from CCSS, we will utilize these probabilities from the general population, which have been used in previous studies – we will conduct a comprehensive literature search for this (Table 2). We will adjust the life-expectancy, in comparison with the general population,[25] for the childhood cancer survivor population using the CCSS data.[26] Additionally, we will calibrate the incidence of CRC for this specific patieng group based on the information on previous treatments, doses of radiation,[8] and clinical-demographic factors using the CCSS data.

Costs: In this proposed study, we will estimate medical cost data using healthcare services claims from 2011-2018 MarketScan Commercial Claims and Encounters (CCE) database. The MarketScan CCE database includes reimbursed healthcare claims from more than 100 nationwide private health insurance plans. This database includes claims from inpatient admissions, outpatient visits, and prescriptions. The estimation of the total medical direct cost will be based on a yearly unit determined by the patient enrollment profile in the database. We will rely on the ICD-9 and ICD-10 codes to determine the target patients, whose recorded primary diagnosis code was CRC under these two coding systems. All costs will be converted to USD 2020 (Table 2).

Utility: We will use health state values derived from literature for patients aged 45 to 85.[27-29] We will gather quality data points for this age range, then linearly extrapolate values for ages 30 to 45, in order to obtain the health state values for ages less than 45. Using this strategy, we will incorporate the life-years gained and utility measure to arrive at the primary health outcome, quality-adjusted life year (QALY).

Model validation: We will validate our model against other select relevant models[1,10,21-24] and longitudinal late effects study among childhood cancer survivors, such as the SJLIFE.[30]

Analysis: The analysis will be conducted from a health-system perspective using a lifetime horizon. Our base-case analysis (Aim 1) will present the estimated total cost, total effectiveness and the ICER for each comparator against its next best alternative (see Table 3), including the no screening. A screening strategy will be deemed as the most cost-effective strategy if it is both cost-effective under the willingness-to-pay threshold of $100,000/QALY and has the highest effectiveness. We will select important parameters for the sensitivity analyses (Aim 2) based on their potential impact on the assessment of cost-effectiveness (Table 2.) To this end, possible candidates for the important parameters in the sensitivity analyses will include abdominal radiation exposure, family history of CRC, age at primary cancer diagnosis and utilization of medical care services (including frequency of CRC screening). In a one-way sensitivity analysis, we will individually vary the selected parameters throughout their plausible ranges. Table 4 is an example of the one-way sensitivity analysis on the CRC screening frequency. A two-way sensitivity analysis will investigate the robustness of the ICER given two important parameters are simultaneously varied within their own ranges. Examples of the planned two-way sensitivity analyses are presented in Tables 5 and 6. We will vary the patient's utilization of the recommended screening and the frequency of screening at the same time in Table 5, meanwhile, the frequency of screening and the stratified risk of developing CRC due to radiation exposure are simultaneously varied in Table 6. Also, we will assess the robustness of the ICER of the select CRC screening strategies when we simultaneously vary the frequency of CRC screening and the type of chemotherapy exposure for the primary neoplasm in Table 7. We will run the probabilistic sensitivity analysis (with 100,000 iterations) to account for all possible variation in the input parameters after fitting relevant distributions of each of the parameter. To this end, we will fit beta distributions for parameters bound between 0 and 1 (e.g., disease progression, medical service utilization), and gamma distribution for costs. Results from this probabilistic sensitivity analysis will be displayed in a cost-effectiveness acceptability curves in Figure 2. The model and analysis will be programmed and performed in TreeAge Pro 2020 software (TreeAge Software Inc., Williamstown, MA, USA.) We will use 3% as the discount rate for both cost and health outcome.

Expected Results: We will project the number of CRC incidence by age throughout the patient's lifetime. Primary results will be ICERs of the screening strategies in US dollars per QALY gained. The ICER will present the comparative value of a given screening strategy against its next best available. The ICER will also be explored in given scenarios which represent elevated CRC risk subject to radiation exposure, family history of CRC, etc.

Table 2. Input parameters Parameters	Point estimate	Range	Source
Background of disease prevalence			
Disease-free			
Adenoma			
Preclinical CRC			
Clinical CRC			
Operating characteristics of the tests			
Fecal immunochemical test, sensitivity			
Adenomas ≤5mm, 6-9mm, ≥10mm, cancer			
Fecal immunochemical test, specificity			
High-sensitivity guaiac-based fecal occult blood test, sensitivity			
Adenomas ≤5mm, 6-9mm, ≥10mm, cancer			
High-sensitivity guaiac-based fecal occult blood test, specificity			
Multitarget stool DNA test, sensitivity			
Adenomas ≤5mm, 6-9mm, ≥10mm, cancer			
Multitarget stool DNA test, specificity			
Colonoscopy, sensitivity			
Adenomas 0-5mm, 6-9mm, ≥10mm, malignant neoplasia			
Colonoscopy, specificity			
CT colonography, sensitivity			
Adenoma ≤5mm, 6-9mm, ≥10mm, cancer			
CT colonography, specificity			
Flexible sigmoidoscopy, sensitivity			
Adenomas ≤5mm, 6-9mm, ≥10mm, cancer			
Flexible sigmoidoscopy, specificity			
Adherence			
Screening, fecal immunochemical test			
Screening, guaiac-based fecal occult blood test			
Screening, multitarget stool DNA test			
Screening, colonoscopy			
Screening, CT colonography			
Screening, flexible sigmoidoscopy			
Treatment, sub-category 1			
Treatment, sub-category 2			
Disease progression/regression probability			
Regression, adenoma to disease-free			
Progression, disease-free to adenoma			
Progression, adenoma to pre-clinical CRC			
Progression, adenoma to clinical CRC			
Progression, disease-free to CRC			CCSS estimate
Progression, clinical CRC to CRC			
Progression, clinical CRC to CRC-related death			
Progression, disease-free to death			CCSS estimate
Disease progression probability intensified by			
Exposure to abdominal radiation			CCSS estimate
Family history of CRC or polys in the first-degree relative			CCSS estimate
Medical services utilization			
CRC screening (%)			CCSS estimate
Treatment adherence			
Costs			
Screening, fecal immunochemical test			
Screening, guaiac-based fecal occult blood test			
Screening, multitarget stool DNA test			
Screening, colonoscopy			
Screening, CT colonography			
Treatment, sub-category 1			
Treatment, sub-category 2			
Utilities			
Adenoma			
Pre-clinical CRC			
Clinical CRC			

Table 3. Base-case analysis of discounted costs, discounted quality-adjusted life expectancy, and incremental cost-effectiveness ratios (ICERs) for the screening strategies at the COG-recommended frequency, every number of years

Strategy	(Sens, Spec)	Cost ($)	Incr. cost ($)	Eff. (QALYs)	Incr. Eff. (QALYs)	ICER	Notes
No screening							
Fecal immunochemical test, 1y							
Guaiac-based fecal occult blood test, 1y							
Multitarget stool DNA test, 3y							
Colonoscopy, 10y							
CT colonography, 5y							
Flexible sigmoidoscopy, 5y							
Cost in 2020 USD							

Table 4. Sensitivity analyses on screening frequencies

Strategy	(Sens, Spec)	Cost ($)	Incr. cost ($)	Eff. (QALYs)	Incr. Eff. (QALYs)	ICER	Notes
No screening							
Fecal immunochemical test, 1y							
Fecal immunochemical test, 2y							
Fecal immunochemical test, 3y							
Guaiac-based fecal occult blood test, 1y							
Guaiac-based fecal occult blood test, 2y							
Guaiac-based fecal occult blood test, 3y							
Multitarget stool DNA test, 3y							
Multitarget stool DNA test, 4y							
Multitarget stool DNA test, 5y							
Colonoscopy, 10y							
CT colonography, 5y							
CT colonography, 3y							
CT colonography, 2y							
Flexible sigmoidoscopy, 5y							
Flexible sigmoidoscopy, 3y							
Flexible sigmoidoscopy, 2y							
Cost in 2020 USD							

Table 5. Sensitivity analyses of the cost-effectiveness of the select screening strategies (S1, S2, S3, S4) compared to No Screening with respect to the screening frequency and patient's utilization ($/QALY)

	Frequency 1	Frequency 2	Frequency 3	Frequency 1	Frequency 2	Frequency 3	Notes
Utilization 20%	9 values of for comparing S1 vs. No Screening			9 values of for comparing S2 vs. No Screening			
Utilization 30%							
Utilization 50%							
Utilization 20%	9 values of for comparing S3 vs. No Screening			9 values of for comparing S4 vs. No Screening			
Utilization 30%							
Utilization 50%							

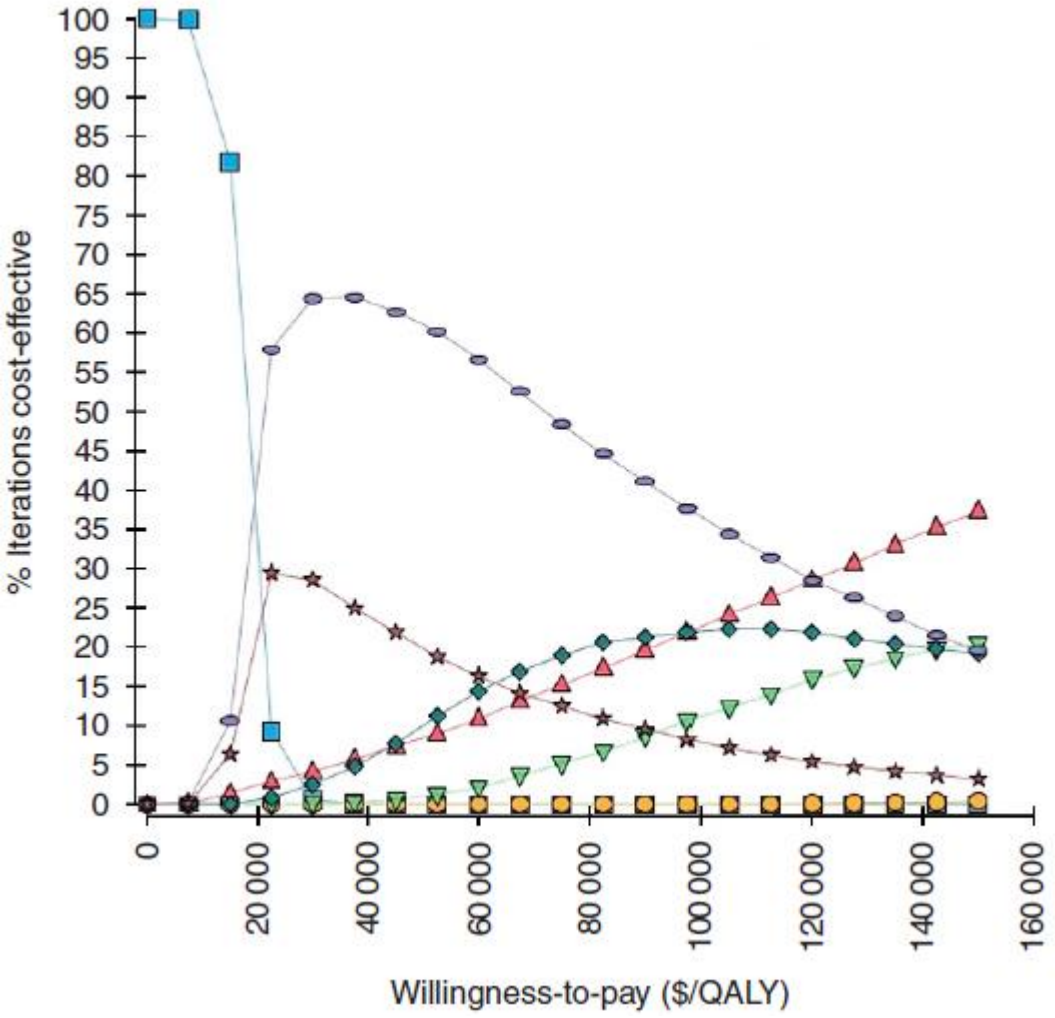
Table 6. Sensitivity analyses of the cost-effectiveness of the select screening strategies (S1, S2, S3, S4) compared to No Screening with respect to the screening frequency and risk of adverse events from radiation ($/QALY)

	Frequency 1	Frequency 2	Frequency 3	Frequency 1	Frequency 2	Frequency 3	Notes
Radiation low risk	9 values of for comparing S1 vs. No Screening			9 values of for comparing S2 vs. No Screening			
Radiation medium risk							
Radiation high risk							
Radiation low risk	9 values of for comparing S3 vs. No Screening			9 values of for comparing S4 vs. No Screening			
Radiation medium risk							
Radiation high risk							

Table 7. Sensitivity analyses of the cost-effectiveness of the select screening strategies (S1, S2, S3, S4) compared to No Screening with respect to the screening frequency and level of chemotherapy exposure ($/QALY)

	Frequency 1	Frequency 2	Frequency 3	Frequency 1	Frequency 2	Frequency 3	Notes
Chemotherapy low level	9 values of for comparing S1 vs. No Screening			9 values of for comparing S2 vs. No Screening			
Chemotherapy medium level							
Chemotherapy high level							
Chemotherapy low level	9 values of for comparing S3 vs. No Screening			9 values of for comparing S4 vs. No Screening			
Radiation medium level							
Chemotherapy high level							

Figure 2. Cost-effectiveness acceptability curves comparing multiple CRC screening strategies



Special consideration: none.

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