CCSS Concept Proposal

1. Study Title

Estimating the burden of disease associated with late-effects among childhood cancer survivors

2. Working Group and Investigators

This proposed research will be conducted within the Chronic Diseases Working Group

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3. Background and Rationale

While the elevated risks for chronic diseases and premature death among childhood cancer survivors are well established, the impact of late-effects on long-term outcomes and the benefit of follow-up care are uncertain. Using a model-based approach, we propose to estimate the "burden of disease" associated with late-effects to characterize their impact on survivors' long-term health and establish an analytical framework for evaluating follow-up guidelines that aim to mediate late-effects. Understanding not only the risk, but the burden, of specific late effect profiles may inform changes to current therapies, informing clinicians' and patients' choice between therapies which might be equally effective in terms of cancer cure rate, but different in terms of disease burden in the future. These estimates can also help inform recommended screening schedules.

Mathematical models are effective tools for simulating the underlying disease process, synthesizing data from multiple sources and projecting the impact of health risks and interventions for a population. Disease simulation models have been used by the NCI-

sponsored Cancer Intervention and Surveillance Modeling Network (CISNET) consortium to better understand cancer control interventions for breast, prostate, lung, and colorectal cancers (www.cisnet.cancer.gov) (1-4). Aside from a recent model-based study that estimated the combined impact of late-effects mortality risks on survivor life expectancy (5), the application of model-based studies to childhood cancer survivorship has been limited.

Model-based burden of disease studies aim to estimate the morbidity and mortality associated with a specific health condition into a single outcome metric: quality-adjusted years (QALYs) lost (6). A QALY is based on the assumption that health is a function of length of life and quality of life, and combines the value of these two attributes into a single number (7). To calculate QALYs, preference weights, or utilities, are used to characterize a given health state relative to perfect health and death, on a 0 to 1 scale. These utility weights can be derived from SF-36 survey responses using established methods (8, 9). To calculate quality-adjusted life expectancy (QALE), utility weights are multiplied by the time spent in each health state and summed up over an individual's lifetime. Other standard measures of burden include incidence of a health condition, prevalence of a health condition, mortality, years of potential life lost, attributable risk (i.e. burden of disease attributable to a risk factor or health condition), and avertable burden (i.e. burden of disease avertable via targeted interventions).

The prevalence of chronic health conditions among childhood cancer survivors is high, with over one-fourth reporting a severe, disabling or life-threatening condition (10). As these late-effects encompass a wide range of conditions (i.e., major hip replacement, congestive heart failure (CHF), renal failure, etc.), the burden of disease likely varies by original cancer diagnosis and treatment received. In addition, nearly 40% of survivors report having at least two chronic health conditions (10). Many survivors therefore have competing health needs and face competing mortality risks. As the risk of severe health conditions is also significantly higher among females and other subpopulations, disparities in burden may exist and raise concern.

To date, no study has used the CCSS data to derive utility weights for childhood cancer survivors. In addition, our proposed research is the first to employ a simulation model to estimate the burden of disease associated with late-effects among survivors.

4. Specific Aims/Objectives/Research Hypotheses

To characterize the burden of disease associated with late-effects among childhood cancer survivors, we propose to estimate risk factor profiles and utility weights for select chronic health conditions from the CCSS data and integrate them into a mathematical simulation model capable of generating estimates of QALE. Our specific aims are:

Aim 1. Estimate risk factor profiles and utility weights for select serious, life-threatening or disabling health conditions from the CCSS data.

Aim 2. Develop a simulation model of the lifetime clinical course of the selected health conditions by incorporating estimated risk factor profiles and utility weights.

Aim 3. Characterize the magnitude and distribution of burden using estimates generated by the simulation model.

This proposed research will be the first to leverage the wealth of CCSS data in an innovative modeling framework to characterize late-effects-related burden of disease among childhood cancer survivors. By incorporating preference-based utilities to reflect quality of life among survivors, this work will establish an analytic framework that can be used to evaluate the clinical benefits and consequences associated with follow-up guidelines and identify effective strategies and screening schedules to improve long-term outcomes among survivors.

5. Analysis Framework

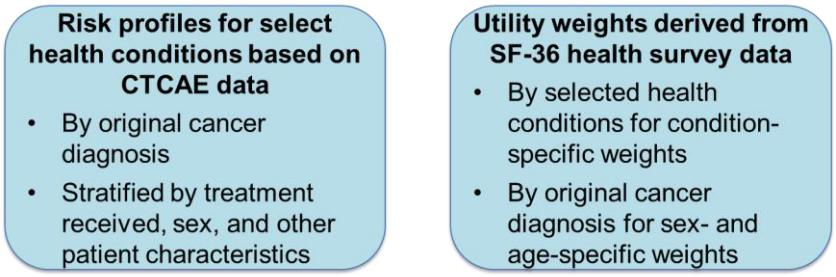
a. Outcome(s) of interest:

The main outcomes of interest will be life expectancy (LE), QALE, proportion of QALYs lost attributable to select health conditions, and proportion of QALYs lost avertable through interventions quality-adjusted life expectancy (QALE). These outcomes will be estimated using the following 3-step approach:

Aim 1. Estimate risk factor profiles and utility weights for select serious, life-threatening or disabling health conditions from the CCSS data.

Leveraging the wealth of data from the CCSS, we will estimate risk factor profiles and derive health state utility rates for select Common Terminology Criteria for Adverse Events (CTCAE 4.0) health conditions (grade 3, 4 and 5) (10, 11) (Figure 1). Organ-based health conditions (subsequent neoplasms, hearing, vision, speech, endocrine, respiratory, cardiac, gastrointestinal, renal, musculoskeletal, neurologic, hematologic, and infection diseases) will include (but are not limited to) joint replacement, renal failure, stroke, heart attack, congestive heart failure, blindness, gonadal failure, and lung fibrosis. To fully reflect the burden of severe late-effects among childhood cancer survivors, in addition to all CTCAE grade 3, 4 and 5 events, we will also include grade 1 and 2 conditions that are associated with considerable morbidity (e.g. diabetes, epilepsy). For grade 5 events, the burden of disease associated with the condition prior to death (length of time, magnitude of loss) will be based on assumptions and/or CCSS data among individuals with the condition who are still alive.

Figure 1. Outcomes measures to be estimated using CCSS data



Risk profiles. We will estimate risk profiles for the selected health conditions from the CCSS for the overall cohort, treatment exposure groups and original cancer diagnosis subgroups. Risk profiles, defined as the yearly risk of developing a specific health condition

by years since diagnosis, will be based on CTCAE data. In addition to overall risk profiles for subgroups, profiles stratified by sex and other patient characteristics will be estimated to reflect underlying differences. For cancer subgroups, we will also estimate profiles stratified by treatment received.

Utility weights. Reflecting the decrement in quality of life associated with a specific health condition, we will derive utility weights using SF-36 data from the 2003 Follow-up Survey. For each selected health condition, we will use established methods (based on ordinary least square (OLS) regression models) (8, 9) to estimate condition-specific utility weights for survivors and siblings who completed the SF-36 after onset of their condition. While utility weights can also be derived from a subset of SF-36 questions (SF-12 Short Form Health Survey), the 2007 Follow-up Survey included only 2 of the 12 questions needed. We will therefore rely on the 2003 Follow-up Survey data for estimating utility weights. Because the 2007 Follow-up Survey, when available, collected time or age of onset of events, we will also have the ability to estimate utility weights for events that occurred prior to the time of responding to the 2003 survey (not just events reported at baseline). This will assume utility weights are similar among individuals who died from the condition before completing the 2007 Follow-up Survey and those who survived the condition for an additional 4 years.

We will also derive sex- and age-specific utility rates by treatment exposure and cancer subgroups. This will allow us to explore how factors other than the selected chronic health conditions impact survivor quality of life, whether the effects vary by treatment received or original cancer diagnosis, and how utility weights compare with published estimates for the general population, both for survivors and siblings (12).

Competing mortality risks: To reflect competing mortality risks from late-recurrence, external causes and other causes (13), we will also estimate mortality risk profiles from the CCSS for each treatment exposure and cancer subgroup.

Because the CCSS data will serve as model inputs into the microsimulation model (see Aim 2 below), we are requesting raw, individual-level data, which Dr. Yeh will then incorporate into the microsimulation model with input and review by the collaborators listed in the Working Group. The list of data variables requested is listed in Part D. Tables and Figures.

Aim 2. Develop a simulation model of the lifetime clinical course of the selected health conditions by incorporating estimated risk factor profiles and utility weights.

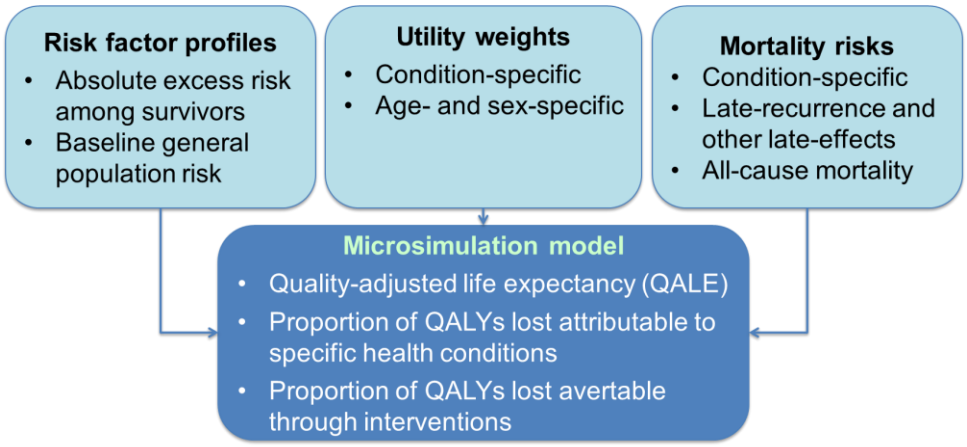
To simulate the clinical course of selected health conditions, we will develop a Monte Carlo microsimulation model which allows for flexibility in capturing multiple dimensions of heterogeneity (e.g., risk profiles for multiple health conditions), reflecting variability and uncertainty, and allowing the risk of future events to depend on risk factors or prior events. Figure 2 provides an overview of the model inputs and outcomes, which is described in further detail below.

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. Specifically, events are simulated for a sequence of individuals using random numbers based on event probabilities (e.g., the probability of developing congestive

heart failure), thus producing individual “case histories”. Characteristics (e.g., age, sex) of each person are randomly drawn from distributions derived from data. 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 (e.g., 1,000,000), a distribution of survival values can be obtained. Therefore, the model will have the ability to reflect patient variability in disease natural history and long-term outcomes.

Microsimulation model overview. At the start of the simulation, representative cohorts of 5-year childhood cancer survivors will enter the model. Movement through the health states, based on risk factor, will occur in yearly increments. Individuals will be allowed to develop multiple health conditions. Once individuals develop a chronic condition, they will also face condition-specific mortality risks. Each year, individuals will face mortality risks for late-recurrence of original disease, excess late-effects mortality risks (e.g. external causes, other causes) and competing mortality risks.

Figure 2. Overview of microsimulation model inputs and outcomes



Model inputs. Risk for developing each health condition will be based on the risk profiles estimated in Aim 1. Each risk will consist of two components: 1) baseline risk for the general population, and 2) the absolute excess risk (AER) among survivors. The AER risk will be estimated by subtracting the baseline risk from the overall risk profiles estimated in Aim 1, based on the equation below:

Overall risk = Baseline risk (general population) + AER (CCSS)

Risk factor profiles for each health condition will be estimated by the cumulative incidence method, accounting for other health conditions and death as competing risks (14, 15). To extrapolate risk factor profiles beyond the 2007 Follow-up Survey, we will explore various methods (e.g., constant, declining, increasing hazard rates) and make assumptions based on input from the clinical, epidemiological, statistical experts in the Working Group. As risk profiles will be based on self-reported data from the Follow-up Surveys, we will also consider the robustness and quality of the data for each health condition and incorporate conservative assumptions as needed to avoid overestimating risks.

Examples of the data that will be used to inform baseline risk estimates include the Framingham Heart Study (16) and Surveillance, Epidemiology, and End Results (SEER) program (17). Condition-specific and all-cause mortality rates will be based on CCSS mortality data (as available) and the published literature and US life tables (18) (as needed).

For each health state, utility weights estimated in Step 1 will be assigned to individuals with the condition. For individuals who develop more than 2 conditions, we will assign utility weights using established methods (e.g., minimum, multiplicative, additive) (19).

To allow comparisons of modeled outcomes with the general population, we will use the model to generate estimates using baseline risk profiles and published sex- and age-specific utility weights for the US population (12).

Model outcomes. As also described above, model outcomes will include life expectancy (LE), QALE, proportion of QALYs lost attributable to select health conditions, and proportion of QALYs lost avertable through interventions. To reflect the impact of uncertainty surrounding risk factor profile estimates from the CCSS and general population, we will conduct probabilistic sensitivity analyses, in which all parameters will be simultaneously varied based on distributions, to generate uncertainty intervals for all modeled outcomes.

Aim 3. Characterize the magnitude and distribution of burden using estimates generated by the simulation model.

The microsimulation model will then be used to generate estimates of disease burden that will allow us to characterize the impact of morbidity and mortality associated with the health conditions on survivor life expectancy. This will include: 1) calculating the loss in quality-adjusted life years (QALYs) compared to the general population; 2) describing the heterogeneity in burden among treatment and cancer subgroups; 3) portraying the magnitude and distribution of burden within a cancer subgroup (i.e. do all survivors experience a moderate loss in QALE? Or do only a small subset of individuals experience a substantial loss, with the remainder having a QALE similar to the general population?); and 4) estimating whether disparities in burden by sex and other patient characteristics exist across all subgroups. Outcomes will be reported separately (by treatment exposure, cancer subgroup, sex, etc.) or combined using weighted averages for overall summary estimates.

In addition, we will use the model to describe how the burden attributable to broad disease categories (e.g. cardiovascular, second malignancy, endocrine abnormalities) varies by treatment and cancer subgroups. Since the risk of developing and/or dying from the health conditions can be potentially mediated through interventions, we will use the model to explore the proportion of avertable burden for each cancer subgroup. Together, these analyses aim to comprehensively describe the burden associated with late-effects for childhood cancer survivors, identify subgroups for which follow-up care may be of particular priority, and establish an analytic framework which can be used to evaluate follow-up care guidelines and identify effective strategies and screening schedules to improve long-term outcomes and survivors' health.

b. Study population

The study population will include CCSS individuals diagnosed with one of the following childhood cancers between 1970 and 1986: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), other leukemia, central nervous system (CNS) tumor, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms tumor, neuroblastoma, osteosarcoma and Ewing sarcoma.

c. Exploratory variables

We will explore how model outcomes vary by 1) treatment exposure and 2) original cancer diagnosis. Analyses for each subgroup will be conducted separately. To characterize the heterogeneity in the burden associated with late-effects, we will conduct analyses using subgroup-specific estimates/inputs stratified by patient characteristics.

For the cancer subgroups, we will also stratify analyses by treatment variables. These variables will be specific to the major treatment exposures for each cancer and determined in consultation with clinical, epidemiological and statistical experts listed in the Working Group. For example, for Hodgkin's lymphoma, treatment factors may include chest radiation, abdominal/pelvic radiation, cumulative dose of anthracycline (doxorubicin equivalent dose), cyclophosphamide equivalent alkylating agents, and bleomycin, since these exposures will drive most of the outcomes. For cancer subgroups for which radiation dose and/or location will be important, we will define treatment factors accordingly. As an example, for Wilms tumor, we may stratify radiation by location (upper border at the diaphragm, at the nipple, entire chest).

Below are examples of patient characteristics and treatment variables that we will use in our analyses. As we note above, exploratory variables, in particular treatment variables, will vary by cancer subgroup.

<u>Original cancer diagnosis</u>

- cancer type

<u>Patient characteristics</u>

- sex
- race
- diagnosis age
- diagnosis year
- attained age

<u>Original cancer treatment</u>

- surgery only
- chemotherapy, no radiation
- radiation, no chemotherapy
- chemotherapy and radiation
- bone marrow transplant
- unknown

Surgery

- Any surgery
- Nephrectomy
- Splenectomy

Chemotherapy

- Chemotherapy treatment (any, alkylator, anthracycline, bleomycin, cisplatin, methotrexate, other chemotherapy)
- Anthracycline cumulative dose (doxorubicin equivalent): none, <200 mg/m^2, ≥200 to <300 mg/m^2, ≥300 mg/m^2)
- Cyclophosphamide equivalent dose alkylating agent (0, >0-<4000, 4000-<8000, ≥8000 mg/m^2)

Radiation

- Radiation therapy (any, brain irradiation, chest irradiation, abdominal or pelvic irradiation)
- Cardiac radiation dose (none, <500cGY, 500 to <1500 cGy, 1500 to <3500 cGY, ≥2500 cGY)
- Chest radiation (yes, no)

As the aim of the project will be to characterize the heterogeneity in the burden of disease associated with late-effects among childhood cancer survivors using a model-based approach, model estimates will portray the uncertainty in estimates via probabilistic sensitivity analyses (not determine statistical significance between subgroups).

D. Table and figure examples

Because these data will serve as model inputs into a microsimulation model (Aim 2), we are requesting raw, individual-level data, which Dr. Yeh will then incorporate into the model with input and review by the collaborators listed in the Working Group. CCSS variables requested for each CCSS individual will include the following (note: treatment variables will vary by cancer subgroup):

1. Original cancer diagnosis
2. Age at original cancer diagnosis
3. Age at baseline
4. Age at last completed survey
5. Interval between cancer diagnosis and last completed survey
6. Attained age
7. Sex
8. Race (non-Hispanic White, Other)
9. Treatment (surgery only; chemotherapy, no radiation; radiation, no chemotherapy; chemotherapy and radiation; unknown)
10. Surgery (none, any, nephrectomy, splenectomy)
11. Chemotherapy with alkylator, anthracycline, bleomycin, cisplatin, methotrexate (yes/no)
12. Chemotherapy (cumulative anthracycline dose)
13. Radiation (yes/no)
14. Cardiac radiation (total dose)
15. Chest radiation (yes, no)
16. Cyclophosphamide equivalent dose alkylating agent (0, >0-<4000, 4000-<8000, ≥8000 mg/m^2)
17. CTCAEs (grade 3 and 4) for each organ system (yes/no; if yes, age at first diagnosis for each organ system; organ systems include subsequent neoplasms, hearing, vision, speech, endocrine, respiratory, cardiac, gastrointestinal, renal, musculoskeletal, neurologic, hematologic, and infection diseases)
18. Late-mortality (yes/no; if yes, date of death, cause (late-recurrence or ICD-9 or ICD-10 code)
19. SF-36 survey responses (all 36 questions)

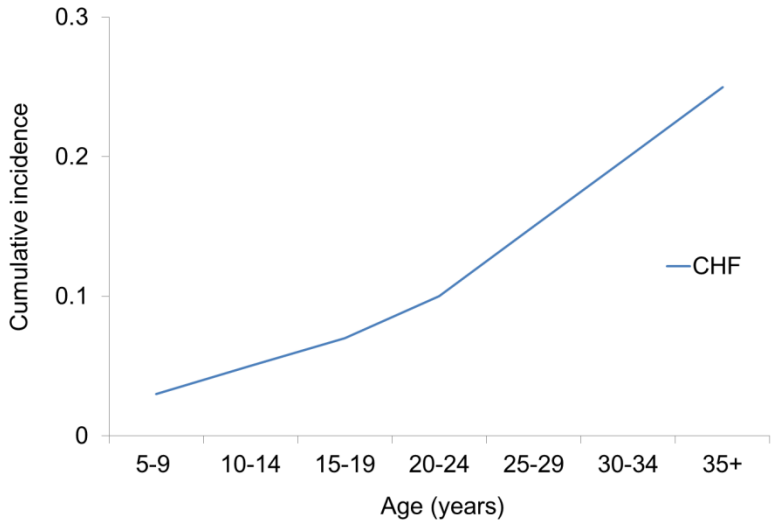
Below is an example of how risk factor profiles will be summarized and presented as model inputs for the manuscript, both in table or figure format. Please note: all tables and figures may present estimates for the overall cohort, by treatment exposure groups, by cancer subgroup, and/or stratified by other treatment and patient characteristics.

Example Table 1A. Model inputs: risk profile for selected CTCAE

Age*	Monthly probability of developing each CTCAE (note: each organ system will be subdivided into specific grade 3 and 4 conditions)												
	Subsequent neoplasms	Hearing	Vision	Speech	Endocrine	Respiratory	Cardiac	Gastrointestinal	Renal	Musculoskeletal	Neurologic	Hematologic	Infection diseases
5-9 years old													
10-14 years old													
15-19 years old													
20-24 years old													
25-29 years old													
30-34 years old													
35-39 years old													
40-44 years old													
45-49 years old													
50+ years old													

*Age interval will be based on data available. 5-year intervals are depicted as an example.
†Estimates will be based on extrapolating trends and/or expert opinion. Assumptions will be explored in sensitivity analyses.

Example Figure 1. Model inputs: Cumulative incidence of CHF*



*Hypothetical data

The manuscript will also include tables summarizing derived utility weights that will also serve as model inputs:

Example Table 2. Model inputs: Condition-specific utility weights derived from SF-36 survey response data

Examples of CTCAEs (grade 3 or 4)	Utility weights		
	Survivors (95% CI)	Siblings* (95% CI)	General population (published estimates) (95% CI)
Joint replacement			
Renal failure			
Stroke			
Heart attack			
Congestive heart failure			
Blindness			
Gonadal failure			
Lung fibrosis			

*As CCSS data allow.

Example Table 3. Model inputs: Sex- and age-specific utility weights derived from SF-36 survey response data

CTCAE	Utility weights		
	Survivors (95% CI)	Siblings (95% CI)	General population (published estimates) (95% CI)
Male			
20-29			
30-39			
40-49			
50-59			
Female			
20-29			
30-39			
40-49			
50-59			

Table 4 below is an example of how model outcomes will be presented in the manuscript.

Example Table 4. Model outcomes: life expectancy (LE), QALE, proportion of QALYs lost attributable to select health conditions, and proportion of QALYs lost avertable through interventions

Cohort	LE, years	QALE, years	QALYs		
			Total lost, QALYs	Proportion attributable to CTCAEs	Proportion avertable via interventions
General population					
Childhood cancer survivors					
Overall					
By sex					
Men					
Women					
By year of diagnosis					
1970-1973					
1974-1977					
1978-1981					
1982-1986					
By diagnosis					
ALL					
AML					
Other leukemia					
Central nervous system tumor					
Hodgkin's disease					
Non-Hodgkin's lymphoma					
Wilms tumor					
Neuroblastoma					
Osteosarcoma					
Ewing sarcoma					
By treatment					
Surgery only					
Chemotherapy, no radiation					
Radiation, no chemotherapy					
Chemotherapy and radiation					
By total anthracycline dose					
None					
<200 mg/m^2					
≥200 to <300 mg/m^2					
≥300 mg/m^2					

6. Special consideration

As noted above, the CCSS Statistical Center will provide the data. J. Yeh will incorporate the data into a mathematical microsimulation model with statistical support from Zachary Ward at the Harvard School of Public Health (staff programmer and analyst at the Center for Health Decision Science) and input and review by the collaborators listed in the Working Group. Upon completion of the primary analysis by J.Yeh, W. Leisenring will provide statistical support and review.

J. Yeh plans to submit an ACS Research Scholar Grant in April 2014 and a NCI R01 grant in June 2014 to secure funding for this project. She would like to obtain the data as soon as possible so that she can include preliminary data in the grant applications.

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