CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

1. **Study Title:** Second neoplasms in the 5th and 6th decades in long term survivors of childhood cancer

2. **Working group and Investigators:** This proposed study will be developed in cooperation with the Second Malignancy Working Group, with secondary oversight by the Epidemiology and Biostatistics Working Group. Proposed investigators include:

Lucie Turcotte	turc0023@umn.edu
Joseph Neglia	jneglia@umn.edu
Sue Hammond	sue.hammond@nationwidechildrens.org
Debra Friedman	debra.l.friedman@vanderbilt.edu
Greg Armstrong	greg.armstrong@stjude.org
Les Robison	les.robison@stjude.org
Marilyn Stovall	mstovall@mdanderson.org
Wendy Leisenring	wleisenr@fhcrc.org

3. **Background and rationale:**

Survival rates in childhood cancer have increased substantially over the past 3 decades.[1] With these improvements, several important late sequelae of cancer therapies have been recognized. One of the most studied late effects of childhood cancer is the development of second neoplasms. The current body of literature reports in detail the risk of second cancers in 5-20 year childhood cancer survivors.[2-8] There are well-established associations between specific therapeutic exposures and certain cancers. For example, epipodophyllotoxin exposure is a risk factor for secondary leukemia[5,9,10], alkylator exposure is a risk factor for secondary MDS and leukemia[9], high-dose procarbazine and platinum agent exposures have recently been associated with increased gastrointestinal SMNs[11], and therapeutic radiation is a well-documented risk factor for a wide range of second neoplasms[3,4,8,11,12,13,14,15,16], which may be further potentiated by combined chemotherapy exposure.[17] Somewhat predictable patterns also exist for the timing and types of second neoplasms that will develop in survivors based on primary cancer therapy. Secondary hematologic malignancies, such as acute myeloid leukemia (AML) occur, on average, relatively soon from the time of diagnosis (median time from initial diagnosis, 7.4 years), as compared to breast cancer (median time 21.3 years), meningioma (median time 22.9 years) or melanoma (median time 18.9 years);[8] although, more recent data suggests that leukemia risk persists beyond 15 years following the primary malignancy.[18] What has also become apparent within the survivor population is that the risk of a subsequent neoplasm does not decrease or plateau with increased follow up time.[5,8,19] In a 2001 CCSS report of second malignant neoplasms[5], a 20-year cumulative incidence of 3.2% was reported, and in an updated report from 2010[8], a 30-year cumulative incidence of 7.9% was reported, indicating both the importance of sufficiently long follow up time as well as the importance of ongoing surveillance.

Presently, minimal data exist on survivors who experience second neoplasms beyond 20 years following initial diagnosis[9,20,21,22], particularly in survivors who had not previously experienced a second neoplasm, and essentially no data are available on cancer risk in the 5th and 6th decades of life. Based on the presumed importance of this knowledge for predicting risks in the aging childhood cancer survivor population, we propose the use of CCSS data to analyze host-, disease- and treatment-related risk factors for the development of late

second neoplasms, including malignant neoplasms, meningiomas and non-melanoma skin cancers (NMSCs). This study would provide the first analysis of cancer risk beyond the 5th decade in childhood cancer survivors.

4. Specific Aims:

1. Describe the cumulative incidence and risk of second neoplasms occurring in the 5th and 6th decades in :
    a. All survivors who have reached an attained age of ≥ 40 years
    b. Survivors who have reached the attained age of ≥40 years with no prior history of second neoplasm
    c. Survivors who have reached the attained age of ≥40 years with prior history of a different second neoplasm
2. Identify the impact of host, disease and therapy characteristics on development of late second neoplasms
3. Inform surveillance and screening recommendations for the aging childhood cancer survivor population

5. Analysis framework:

A. The analysis will be restricted to survivors who are alive and have attained an age of ≥ 40 years at the time of their last follow-up within the most recent data freeze. Subsequent neoplasms will be analyzed in this population by:
    a. Descriptive characteristics:
        i. Age, gender, time from initial diagnosis, original malignancy
        ii. Therapeutic exposures
            1. Chemotherapy agents and doses
                a. Alkylating agents (yes/no/cumulative dose)
                b. Anthracyclines (yes/no/cumulative dose)
                c. Epipodophyllotoxins (yes/no/cumulative dose)
                d. Platinums (yes/no/cumulative dose)
            2. Radiotherapy (yes/no/unknown)
            3. Splenectomy (yes/no)
    b. Constructing cumulative incidence curves for:
        i. All second neoplasms
        ii. Non-melanoma skin cancers (NMSCs)
        iii. Meningioma
        iv. Malignant cancers
    c. Calculating SIRs and Absolute Excess Risk for malignancies (ICD-O, 5th digit = 3)
B. The same analysis as in part A can then be repeated, but excluding survivors who have reported a second neoplasm prior to reaching 40 years of age
C. Again, using the same analysis as in part A, but only including individuals who are ≥ 40 years of age and have reported a second neoplasm prior to age 40
D. Finally we will evaluate whether having had a first SN prior to age 40 is associated with risk of subsequent SN after age 40 in adjusted models. In addition, we will evaluate whether other factors modify that effect via interaction terms. For example, we could evaluate whether risks associated with having had a prior SN differ between the diagnosis groups.

E. Exploratory variables:
    a. Primary diagnosis: leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, soft-tissue sarcoma, bone cancer, central nervous system tumor, Wilms tumor
    b. Age at primary childhood cancer diagnosis
    c. Sex: Male/Female
    d. Race/ethnicity: White, Black, Hispanic, Other
    e. Therapeutic exposures [radiation, chemotherapy agents (alkylating agents, anthracyclines, epipodophyllotoxins, platinums), both radiation and chemotherapy]
    f. History of splenectomy: Yes/No

F. Statistical analysis:
    a. For each of the second neoplasm outcome definitions (malignant neoplasm, meningioma and NMSC), cumulative incidence will be reported from age 40 upward, using age as the time scale for presentation and treating death as a competing risk event. Subsets of subjects may be presented, divided by prior SN and/or diagnosis, for example (results from variables to be examined in Cox regression models may influence choices of subgroups).
    b. For all second malignant neoplasms reported after the age of 40, standardized incidence ratios and excess absolute risk will be reported as well using age, gender and calendar year U.S. cancer rates from SEER to evaluate expected numbers of events. SIRs will be reported by primary diagnosis as well as by type of SMN. Additionally, we will evaluate the impact of age at diagnosis and treatment, including exposure (y/n) to specific chemotherapy subgroups (anthracyclines, epipodophyllotoxins, platinums and alkylators) and to radiation therapy, on SIRs.
    c. Multivariable modeling using Cox proportional hazards model with age as the time scale will be performed to look at the impact of SN prior to age 40, diagnosis and therapeutic variables described above (in two separate models, due to the associations between diagnosis and treatment variables), along with demographic factors and allowing for the possibility of age-specific effects on the development of second malignant neoplasms. Interactions between the prior to age 40 SN variable and other risk factors will be evaluated.

G. Data summary from last frozen data set:
Total survivors ≥ 40 years of age: 3171 (median 44 years, maximum 58 years)
Total SNs occurring ≥ 40 years of age: 767 SNs in 323 survivors
Total NMSCs occurring ≥ 40 years of age: 594 NMSCs in 191 survivors (104 as 1st SN)
Total SMNs occurring ≥ 40 years of age: 173 SMNs in 156 survivors (111 as 1st SN)

6. Tables/Figures

Figure 1: Participant flow sheet

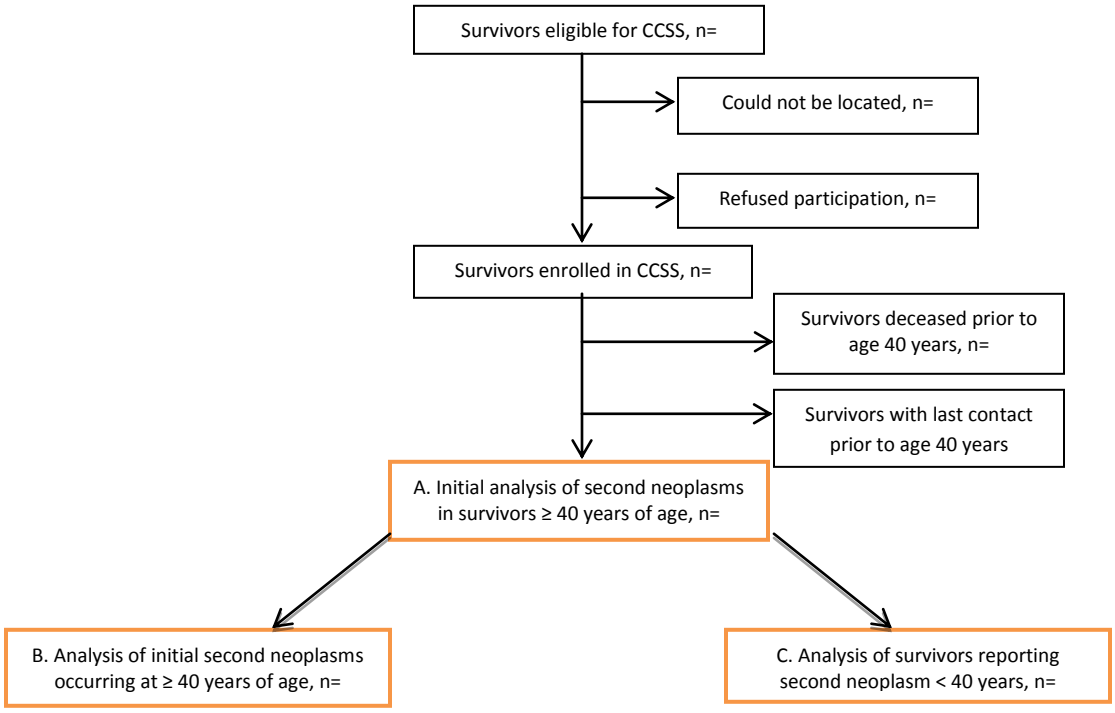

Table 1: Demographics/cohort characteristics

	Cohort members with attained age ≥ 40 years	Survivors ≥ 40 years of age with a subsequent neoplasm	Cases with first subsequent neoplasm ≥ 40 years of age	Survivors ≥ 40 years of age without subsequent neoplasm
Mean age at primary diagnosis, years				
Sex				
Male				
Female				
Race				
White				
Black				
Hispanic				
Other				
Unknown				
Primary diagnosis				
Leukemia				
CNS tumor				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
Wilms tumor				
Neuroblastoma				
Soft tissue sarcoma				
Osteosarcoma				
Other bone cancer				
Year of diagnosis of primary cancer				
1970-1974				
1975-1979				
1980-1986				
Initial therapy				
Chemotherapy only				
Radiation only				
Surgery only				
Chemo+Rad				
No treatment				
Unknown				
History of splenectomy				
Vital status				
Alive				
Deceased				
Second neoplasm				
SMN				
Meningioma				
NMSC				
Mean time from primary cancer diagnosis to development of second neoplasm, years				

Table 2: Second neoplasms after age 40 by primary diagnosis (N, %)

Primary childhood cancer diagnosis	ALL	AML	MDS	HL	NHL	Glioma	PNET	Meningioma	Melanoma	Breast	Osteosarcoma	Other Bone	Thyroid	NMSC	Other
Leukemia															
CNS															
HL															
NHL															
Wilms															
NBL															
STS															
Osteosarcoma															
Other Bone															
Total															

Table 3: Observed and Expected and SIRs of Subsequent Neoplasms by Primary Childhood Cancer Diagnosis

	Second Malignant Neoplasms						**NMSCs**		**Meningiomas**	
Primary Diagnosis	Number at risk	Cases observed	Cases expected	SIR (95% CI)	EAR/1000py (95% CI)	CI (%) (95% CI)	Cases observed	CI (%) (95% CI)	Cases observed	CI (%) (95% CI)
All Diagnoses										
Leukemia										
CNS										
HL										
NHL										
Wilms										
NBL										
STS										
Osteosarcoma										
Other Bone										

Table 4: Observed and Expected Numbers and SIRs of Subsequent Neoplasms after age 40 years by Demographic and Treatment-Related Factors

Characteristics	Cases expected	Cases observed	SIR (95% CI)	p-value
Overall				

Sex				
Male				
Female				
Attained age				
40-45				
45-50				
50-55				
>55				
Age at first cancer				
<5				
5-9				
10-14				
≥15				
Type of first cancer				
Leukemia				
HL				
CNS				
STS				
Renal				
Osteosarcoma				
Other Bone				
NHL				
NBL				
Type of subsequent neoplasm				
Breast				
Thyroid				
STS				
Osteosarcoma				
Other Bone				
CNS				
Lymphoma				
Melanoma				
Leukemia				
Lung				
GU				
Head and neck				
Renal				
Treatment exposure				
Radiation				
Alkylating agent				
Anthracycline				
Epipodophyllotoxin				
Platinum				
Radiation alone				
Chemotherapy alone				
Radiation + Chemotherapy				

Table 5: Multivariable table

	Any SN	Malignant cancers	Meningioma	NMSC

Variable	HR (95 % CI)	P-value	RR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex								
Male								
Female								
Age at diagnosis of first cancer								
0-4								
5-9								
10-14								
≥ 15								
Attained age								
40-45								
45-50								
50-55								
>55								
Radiation therapy								
yes								
no								
Splenectomy								
yes								
no								
Type of first cancer								
Leukemia								
HL								
CNS								
STS								
Renal								
Osteosarcoma								
Other Bone								
NHL								
NBL								
Alkylator score								
1								
2								
3								
Anthracycline exposure								
None								
1-100mg/m2								
101-300mg/m2								
≥301								
Epipodophyllotoxin exposure								
None								
1-1000mg/m2								
1001-4000mg/m2								
≥4001mg/m2								
Platinum exposure								
None								
1-400mg/m2								
401-750mg/m2								
≥751mg/m2								
Development of SN < age 40								
No								
Yes								

Figure 2: Cumulative incidence of second neoplasms over time (3 charts, possibly others depending on results of Cox regression)

A. Overall group
B. Radiation and Non-radiation exposed curves
C. Second neoplasm < 40 years and no second neoplasm < 40 year

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