CHILDHOOD CANCER SURVIVOR STUDY- Analysis Concept Proposal

1. TITLE: Psychosocial Concerns Among Siblings of Childhood Cancer Survivors

2. WORKING GROUP INVESTIGATORS: This proposed study will be within the Psychology Working Group.

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3. BACKGROUND AND RATIONALE:

Approximately 80% of childhood cancer patients will achieve five-year survival with the majority being cured of their cancer [1]. Thus, it is estimated that there are now over 420,000 childhood cancer survivors in the United States (US) [2]. The National Cancer Institute, Office of Cancer Survivorship defines "family members, friends, and caregivers" as part of the survivorship experience [3]. Given the increasing survival rate for childhood cancers and the fact that the average US family has two children, [4] there is a large and growing population of siblings of childhood cancer survivors.

Research with siblings of children on active therapy for cancer demonstrates impaired psychosocial health and a myriad of concerns including those related to health and cancer risk [5-8]. Unfortunately, little is known about these siblings when they reach adulthood and the child with cancer becomes a long-term survivor [9]. Siblings of childhood cancer survivors remain at risk for psychological distress, post-traumatic stress symptoms, and risky alcohol practices, [10-13] findings that suggest that some siblings demonstrate long-term impairment in psychosocial health. Siblings are also at risk for impairment in specific domains of health-related quality of life (HRQOL) despite overall positive HRQOL outcomes when the group is compared to normative data [14]. Despite our understanding that psychosocial distress may persist in some siblings of childhood cancer survivors, in-depth characterization of ongoing concerns including those related to future health and cancer risk is missing in the extant literature. Prevalence of survivor concerns related to future health and cancer risk were recently described and compared to siblings [15]. Although survivors endorsed greater concerns with respect to future health, survivor concerns with respect to cancer risk were not different from siblings. The importance of these findings is underscored by the fact that adult siblings of childhood cancer survivors are a group at high risk for the development of cancer [16-17]. Moreover, siblings may play a critical role in shaping survivor motivation to pursue positive health behaviors.

Recent data from the Childhood Cancer Survivor Study has characterized unique risk factors for psychosocial distress among adult siblings of childhood cancer survivors [10]. These risk factors have included sociodemographic (e.g., siblings younger than the survivor, siblings of male survivors), as well as cancer- and treatment-related variables (e.g., diagnosis of sarcoma, adverse survivor physical and psychological health). Factors related to physical health and cancer risk remain unknown; however, sociodemographic and cancer and treatment-related factors may again be associated. The adult cancer literature suggests age (e.g., younger siblings at the time of

diagnosis) and marital status (e.g., unmarried) are associated with greater concerns among sibling [18]. The specific cancer diagnosis and treatment type or intensity may also be associated with greater sibling concerns. Having a brother or sister who survived cancer and now has disfigurement, or is experiencing poor health, mentally and/or physically, may serve as a constant reminder of the cancer experience and potential risk among siblings [10, 19].

Previous studies focusing on siblings of childhood cancer survivors have largely employed cross-sectional study designs limiting the ability to understand the impact of survivorship on siblings over time. Further longitudinal information, drawn from large, diagnostically diverse samples, is needed to best identify risk factors as well as protective factors for sibling psychological concerns and adjustment in adulthood. The aim of this study is to use the CCSS data [20-21] to identify demographic, health, and cancer-related factors that may shape the trajectory of sibling psychosocial concerns over time.

4. SPECIFIC AIMS:

Aim 1: Using baseline data from the original and expansion cohorts we will describe psychosocial concerns (e.g., concerns regarding future health, cancer risk) among siblings of childhood cancer survivors by era of the survivor's diagnosis (1970-1979, 1980-1989, and 1990-1999; respectively).

Aim 2: Using baseline data as well as follow-up data from the original (baseline, follow-up 4, follow-up 5) and expansion cohorts (baseline, follow-up 5) we will describe sibling psychosocial concerns (e.g., concerns regarding future health, cancer risk) by the amount of time elapsed since diagnosis (5-10 years, 10-15 years, 15-20 years, etc.).

Aim 3: Using baseline data as well as the most recent follow-up data from the original (baseline, follow-up 4, follow-up 5) and expansion cohorts (baseline, follow-up 5) we will describe longitudinal patterns of psychosocial concerns (e.g., a decrease or increase in concerns regarding future health, cancer risk) as well as risk and protective factors which shape these patterns of psychosocial concerns among siblings of survivors.

Hypothesis*: We hypothesize that sibling factors including older age at baseline, female gender, low educational status at baseline, unemployment at baseline, unmarried at baseline, fair or poor health status, presence of chronic health conditions, greater psychological distress) will be associated with the presence of increased psychosocial concerns (future health, cancer risk) among siblings of survivors.*

We hypothesize that the matched survivors' diagnosis (e.g. brain tumor, bone tumor, sarcoma), treatment intensity, survivors' health status at baseline (e.g. fair or poor health status), presence of chronic health conditions, death, presence of second malignant neoplasms, and survivors' mental health status at baseline (e.g. greater psychological distress) will be associated with the presence of increased psychosocial concerns (future health, cancer risk) among siblings of survivors.

5. ANALYSIS FRAMEWORK:

5.1 Sample:

The proposed analyses will utilize data collected in the Original Cohort (Baseline, Follow-up 4, Follow-up 5) and Expanded Cohort (Baseline & Follow-up 5) from adult siblings (greater than or equal to 18 years of age) and their sibling survivors. Siblings whose survivor

siblings have died since study entry will be included to avoid potential bias which would be introduced by excluding bereaved siblings as they may have greater psychosocial concerns. Aims 1 and 2 will include all subjects who respond to a baseline survey while 3 will require baseline as well as at least one follow-up survey.

5.2 Outcomes of Interest and Predictor Variables:

Aim 1: Outcomes of interest (baseline data from the original and expansion cohorts)

A. Sibling concerns regarding future health
B. Sibling concerns regarding cancer risk

* Each outcome uses a 5-point Likert response scale: very concerned / somewhat concerned / concerned / not very concerned / not at all concerned. This will be dichotomized by very concerned / somewhat concerned / concerned vs. not very concerned / not at all concerned.

Main Effect Variable:

A. None – descriptive by era of survivor's cancer diagnosis (1970-1979, 1980-1989, 1990-1999)

Aim 2: Outcomes of interest (baseline, at least one follow-up survey - follow-up 4, and follow-up 5 data from the original cohort or baseline and at least one follow-up - follow-up 5 data from the expansion cohort)

A. Sibling concerns regarding future health
B. Sibling concerns regarding cancer risk

* Each outcome uses of 5-point Likert response scale: very concerned / somewhat concerned / concerned / not very concerned / not at all concerned. This will be dichotomized by very concerned / somewhat concerned / concerned vs. not very concerned / not at all concerned.

Main Effect Variable:

A. Amount of time elapsed since diagnosis (5-10 years, 10-15 years, 15-20 years, etc.).

B. Sibling Demographic Characteristics
   a. Age current
   b. Gender
   c. Educational attainment
   d. Marital status
   e. Employment

C. Sibling Health Characteristics at Baseline
   a. Health status (fair/poor vs. good/very good/excellent)
   b. Chronic health conditions at baseline- none vs. grade 1/2 vs. grade 3/4
   c. Psychological distress (BSI-18, GSI T<63 vs. T ≥ 63)

D. Survivor Diagnostic, Treatment, Health Characteristics at Baseline
   a. Diagnosis
   b. Treatment Intensity (composite variable of surgery/chemotherapy/radiation therapy exposures, Stuber ML, et al. Pediatrics 2010; 125:e1124-34).
   c. Survivor health status at baseline (fair/poor vs. good/very good/excellent
   d. Survivor chronic health conditions at baseline - none vs. Grade 1/2, Grade 3/4
   e. Survivor psychological health at baseline (BSI-18, GSI T<63 vs. T ≥ 63)
   f. Relapse/2nd cancer after study entry, but before survivor sibling survey response (yes vs. no)
   g. Death after study entry, but before survivor sibling survey response (yes vs. no)

Aim 3: Outcomes of interest (baseline and at least one follow-up survey - follow-up 5 data from the original cohort or baseline and at least one follow-up survey – follow-up 5 data from the expansion cohort)

A. Class membership: sibling concerns regarding future health
B. Class membership: sibling concerns regarding cancer risk

* Longitudinal latent profile analysis will use longitudinal measurements of sibling psychosocial concerns to derive classes which will represent classes of future health concerns and cancer risk concerns. For example, we may find that one group of siblings will have persistent psychosocial concerns such that they endorse future health concerns at baseline measurement and each subsequent measurement.

Main Effect Variable:

B. Sibling Demographic Characteristics
   a. Age current
   b. Gender
   c. Educational attainment
   d. Marital status
   e. Employment

C. Sibling Health Characteristics at Baseline
   a. Health status (fair/poor vs. good/very good/excellent)
   b. Chronic health conditions at baseline- none vs. grade 1/2 vs. grade 3/4
   c. Psychological distress (BSI-18, GSI T<63 vs. T ≥ 63)

C. Survivor Diagnostic, Treatment, Health Characteristics at Baseline
   a. Diagnosis
   b. Treatment Intensity (composite variable of surgery/chemotherapy/radiation therapy exposures, Stuber ML, et al. Pediatrics 2010; 125:e1124-34).
   c. Survivor health status at baseline (fair/poor vs. good/very good/excellent
   d. Survivor chronic health conditions at baseline - none vs. Grade 1/2, Grade 3/4
   e. Survivor psychological health at baseline (BSI-18, GSI T<63 vs. T $\geq$ 63)
   f. Relapse/2nd cancer after study entry, but before survivor sibling survey response (yes vs. no)
   g. Death after study entry, but before survivor sibling survey response (yes vs. no)

5.3 Statistical analysis plan:

Table 1 will provide descriptive statistics of the sibling population including demographic characteristics, such as, age of the sample, sex, race/ethnicity, household income, and educational attainment. Selected characteristics of matched survivors will also be provided including diagnosis, treatment intensity, and time since diagnosis. Data will be reported in this table by cohort using baseline data from the original and expansion cohorts only. This will help us understand the comparability of the individual cohorts.

Aim 1:

For the purposes of Aim 1, responses to the questions regarding sibling future health concerns, and cancer risk concerns will be analyzed utilizing the outcome as a 5-point Likert response scale dichotomized as: very concerned /somewhat concerned / concerned vs. not very concerned / not at all concerned. Table 2 will report descriptive statistics including frequency counts and proportions describing the endorsement of psychosocial concerns among siblings of childhood cancer survivors by era of the survivor's diagnosis (1970-1979, 1980-1989, and 1990-1999; respectively). Logistic regression models for the impact of calendar era of cancer diagnosis, adjusted for potential confounding variable listed above as Sibling Demographic Characteristics will also be fit to ensure difference across time aren't due to other factors.

Aim 2:

For the purposes of Aim 2, responses to the questions regarding sibling future health concerns, and cancer risk concerns will be analyzed utilizing the outcome as a 5-point Likert response scale dichotomized as: very concerned /somewhat concerned / concerned vs. not very concerned / not at all concerned similar to a recent analysis in Gibson et al (Cancer, 2018). Table 3A will report descriptive statistics including frequency counts and proportions describing the endorsement of psychosocial concerns among siblings of childhood cancer survivors by the amount of time elapsed between diagnosis of their siblings' cancer and the survey response (5-10 years, 10-15 years, 15-20 years, etc.). This aim will utilize any of baseline follow-up 4 (not available for expansion cohort) and/or follow-up 5 survey responses. Thus each sibling may contribute multiple records to the analysis, each of which will be categorized into the time period relevant to the time since their survivor sibling's cancer diagnosis. If one subject has two responses that fall within the same time interval, we will only use the first survey response data.

Using multivariable GEE logistic regression (to account for correlated responses) we will construct multivariable models as depicted in Table 3B in which we will assess the aforementioned dichotomized scheme of sibling future health concerns, and cancer risk concerns with the main effect variable as time elapsed since diagnosis of their siblings' cancer (5-10 years, 10-15 years, 15-20 years, etc.) controlling for sibling sociodemographic characteristics, sibling health characteristics at baseline, and survivor diagnostic, treatment, and health characteristics at baseline. Adjusted odds ratios with 95% confidence will be reported, with adjustment for sibling demographic and health characteristics and their survivor sibling's health and treatment characteristics. In order to ensure representativeness of the sample, we will compare sibling sociodemographic and health characteristics at baseline, and survivor diagnostic, treatment, and health characteristics at baseline among those siblings with baseline and at least one follow-up survey with those that only have a baseline survey to determine whether there are biases with regard to types of participants who continue to fill out follow-up surveys. Similarly, characteristics of siblings with response data available within each time interval will be compared to determine possible biases. If interesting, we may construct curves illustrating the predicted proportion of siblings with health concerns across time intervals. Analyses will be carried out using the SAS statistical software (SAS Institute, Cary, NC).

Aim 3:

For Aim 3, only subjects who have at least two surveys with response data regarding health concerns available will be utilized (see Aim 2 for analyses to be carried out to evaluate potential biases due to this restriction). Longitudinal latent profile analysis will use longitudinal measurements of sibling psychosocial concerns to derive classes which will represent patterns of trajectories of health concerns, and cancer risk concerns. Various statistical indicators will be utilized to ensure adequate model fit, including Bayesian information criterion (BIC) and the sample size–adjusted BIC (ABIC), Vuong-Lo-Mendell-Rubin likelihood ratio (VLMR) test and sample size–adjusted VLMR *P* values, entropy, and minimum class membership size. An optimal model will be chosen based on model fit statistics and meaningfulness of the classes. Once class membership is assigned we will provide a graphical depiction of longitudinal classes of sibling psychosocial concerns across baseline and follow-up time points. Table 4 will provide an evaluation of class membership by proportion of siblings endorsing psychosocial concerns at baseline and follow-up time points. Tables 5-8 will provide univariable logistic regression models of predictors of class membership by siblings' demographic factors (e.g., age, gender, marital status, employment status), and health-related factors (e.g., general health status, chronic health conditions, psychological health). We will also provide univariable models of predictors of class membership by siblings' matched survivor diagnosis, treatment-related, and health-related factors.

Table 9 will present the result of final multivariable logistic regression models which will evaluate sibling and survivor risk factors as well as protective factors for class membership relating to longitudinal changes in sibling psychosocial concerns (future health, cancer risk concerns) among siblings of survivors. Individual sibling and survivor characteristics will each be evaluated in separate models adjusted by all other relevant sibling sociodemographic characteristics including (e.g., calendar year (era) of diagnosis, time elapsed since diagnosis). Those sibling factors that are statistically significantly associated with sibling psychosocial concerns at the $p < 0.10$ level will be included in the final multivariable model in Table 9. We will start with a full model and reduce the model by eliminating those factors that are not statistically significant at the $p < 0.05$ level. The construction of this model will include those factors that are felt to be important predictors of psychosocial health in the general population including the sibling sociodemographic characteristics such as current age, sex, etc. which will be forced into

the model. Other factors will be included if they are significant or if their inclusion markedly modifies the effects of another variable. Adjusted odds ratios with 95% confidence will be reported. As noted above, in order to ensure representativeness of the sample, we will compare sibling sociodemographic characteristics, sibling health characteristics at baseline, and survivor diagnostic, treatment, and health characteristics at baseline among those siblings with baseline and at least one follow-up survey with those that only have a baseline survey. Analysis will be carried out using the SAS statistical software (SAS Institute, Cary, NC).

APPENDIX A

TABLE 1: Characteristics of the Sibling Population and their Matched Survivors

Variable	Siblings Original N = (%)	Expanded N = (%)	Total N = (%)	Survivors N = (%)
Age 18-20 20-29 30-39 40+				
Gender Male Female				
Race/ethnicity White Non-white				
Household Income <$9,999 $10,000-19,999 $20,000-39,000 $40,000-59,999 Over $60,000				
Education High school graduate or less More than high school graduate				
Diagnosis Brain tumor Leukemia Hodgkin Lymphoma Non-Hodgkin Lymphoma Kidney tumor Bone tumor Sarcoma Neuroblastoma				
Treatment Intense Yes No				

TABLE 2: Sibling Psychosocial Concerns by period of survivor's diagnosis.

Variable	**Future Health** **N (%)**	**Cancer Risk** **N (%)**
Time Period of Diagnosis 1970-1979 1980-1989 1990-1999		

TABLE 3A: Sibling Psychosocial Concerns by the Amount of Time Elapsed Since Diagnosis (5-10 years, 10-15 years, 15-20 years, etc.).

Variable	**Future Health** **N (%)**	**Cancer Risk** **N (%)**
Time Elapsed Since Diagnosis 5-10 years 10-15 years 15-20 years 20+		

TABLE 3B: Sibling Psychosocial Concerns: Multivariable GEE Logistic Regression Models Predicting Future Health Concerns and Future Cancer Risk Concerns by the Amount of Time Elapsed Since Diagnosis (5-10 years, 10-15 years, 15-20 years, etc.) Controlling For Sibling Sociodemographic, Sibling Health Characteristics, as well as Survivor Diagnostic, Treatment, and Health Characteristics at Baseline.

Variable	Future Health Concerns OR_{adj}	95% CI	P	Future Cancer Risk Concerns OR_{adj}	95% CI	P
Time Elapsed Since Diagnosis 5-10 years 10-15 years 15-20 years 20+						
Sibling Age 18-30 30-40 40+						
Sibling Gender Female .						
Education Greater than HS Less than HS						
Marital Status Married Unmarried						
Employment Status Employed Unemployed						
Sibling Health Status Fair/Poor Good/Very good/Excellent						
Sibling Chronic Health Condition None Mild/Moderate Severe/Life Threatening						
Sibling Psychological Health GSI T≥63 GSI T<63						
Survivor Health Status Fair/Poor Good/Very good/Excellent						
Survivor Chronic Health Condition vs. None Mild/Moderate Severe/Life Threatening						
Survivor Psychological Health GSI T≥63 GSI T<63						

Relapse/2nd Cancer Yes No						
Death After Study Entry Yes No						
Survivor Diagnosis vs. Leukemia Brain Tumor Bone Tumor / Sarcoma						
Survivor Treatment Intense Yes No						

TABLE 4: Proportion of Siblings Endorsing Psychosocial Concerns by Class Membership at Baseline and Follow-up Time Points

Variable	**Baseline** **N (%)**	**Follow-up 4** **N (%)**	**Follow-up 5** **N (%)**
Future Health Class 1 Class 2 …			
Cancer Risk Class 1 Class 2 ……			

TABLE 5A: Future Health Concerns: Univariate Models Predicting Class Membership – Sibling Demographic Characteristics

Variable	**Class 2 vs. Referent Class** **OR (95% CI)**	**Class 3 vs. Referent Class** **OR (95% CI)**
Sibling Age 18-30 30-40 40+		
Sibling Gender Female		
Education Greater than High School Less than High School		
Marital Status Unmarried Married		
Employment Employed Unemployed		

TABLE 5B: Future Cancer Risk Concerns: Univariate Models Predicting Class Membership – Sibling Demographic Characteristics

Variable	**Class 2 vs. Referent Class** **OR (95% CI)**	**Class 3 vs. Referent Class** **OR (95% CI)**
Sibling Age 18-30 30-40 40+		
Sibling Gender Female		
Education Greater than High School Less than High School		
Marital Status Unmarried Married		
Employment Employed Unemployed		

TABLE 6A: Future Health Concerns: Univariate Models Predicting Class Membership – Sibling Health Characteristics

Variable	**Class 2 vs. Referent Class** **OR (95% CI)**	**Class 3 vs. Referent Class** **OR (95% CI)**
Sibling Health Status Fair/Poor Good/Very good/Excellent		
Sibling Chronic Health Condition None Mild/Moderate Severe/Life Threatening		
Sibling Psychological Health GSI T≥63 GSI T<63		

TABLE 6B: Future Cancer Risk Concerns: Univariate Models Predicting Class Membership – Sibling Health Characteristics

Variable	**Class 2 vs. Referent Class** **OR (95% CI)**	**Class 3 vs. Referent Class** **OR (95% CI)**
Sibling Health Status Fair/Poor Good/Very good/Excellent		
Sibling Chronic Health Condition None Mild/Moderate Severe/Life Threatening		
Sibling Psychological Health GSI T≥63 GSI T<63		

TABLE 7A: Future Health Concerns: Univariate Models Predicting Class Membership – Survivor Health Characteristics

Variable	**Class 2 vs. Referent Class** OR (95% CI)	**Class 3 vs. Referent Class** OR (95% CI)
Survivor Health Status Fair/Poor Good/Very good/Excellent		
Survivor Chronic Health Condition None Mild/Moderate Severe/Life Threatening		
Survivor Psychological Health GSI T≥63 GSI T<63		
Relapse/2nd Cancer Yes No		
Death After Study Entry Yes No		

TABLE 7B: Future Cancer Risk Concerns: Univariate Models Predicting Class Membership – Survivor Health Characteristics

Variable	**Class 2 vs. Referent Class** OR (95% CI)	**Class 3 vs. Referent Class** OR (95% CI)
Survivor Health Status Fair/Poor Good/Very good/Excellent		
Survivor Chronic Health Condition None Mild/Moderate Severe/Life Threatening		
Survivor Psychological Health GSI T≥63 GSI T<63		
Relapse/2nd Cancer Yes No		
Death After Study Entry Yes No		

TABLE 8A: Future Health Concerns: Univariate Models Predicting Class Membership – Survivor Diagnosis and Treatment Characteristics

Variable	**Class 2 vs. Referent Class** OR (95% CI)	**Class 3 vs. Referent Class** OR (95% CI)
Survivor Diagnosis Leukemia Brain Tumor Bone Tumor / Sarcoma		
Survivor Treatment Intense Yes No		

TABLE 8B: Future Cancer Risk Concerns: Univariate Models Predicting Class Membership – Survivor Diagnosis and Treatment Characteristics

Variable	**Class 2 vs. Referent Class** OR (95% CI)	**Class 3 vs. Referent Class** OR (95% CI)
Survivor Diagnosis Leukemia Brain Tumor Bone Tumor / Sarcoma		
Survivor Treatment Intense Yes No		

TABLE 9A: Future Health Concerns: Multivariable Models Predicting Class Membership Pertaining to Longitudinal Changes in Sibling Psychosocial Concerns

Variable	**Class 2 vs. Referent Class** **OR_{adj}**	**95% CI**	**P**	**Class 3 vs. Referent Class** **OR_{adj}**	**95% CI**	**P**
Sibling Age 18-30 30-40 40+						
Sibling Gender Female .						
Education Greater than HS Less than HS						
Marital Status Married Unmarried						
Employment Status Employed Unemployed						
Sibling Health Status Fair/Poor Good/Very good/Excellent						
Sibling Chronic Health Condition None Mild/Moderate Severe/Life Threatening						
Sibling Psychological Health GSI T≥63 GSI T<63						
Survivor Health Status Fair/Poor Good/Very good/Excellent						
Survivor Chronic Health Condition vs. None Mild/Moderate Severe/Life Threatening						
Survivor Psychological Health GSI T≥63 GSI T<63						
Relapse/2nd Cancer Yes No						
Death After Study Entry Yes No						

Survivor Diagnosis vs. Leukemia Brain Tumor Bone Tumor / Sarcoma						
Survivor Treatment Intense Yes No						

TABLE 9B: Future Cancer Risk Concerns: Multivariable Models Predicting Class Membership Pertaining to Longitudinal Changes in Sibling Psychosocial Concerns

Variable	Class 2 vs. Referent Class OR_{adj}	95% CI	P	Class 3 vs. Referent Class OR_{adj}	95% CI	P
Sibling Age 18-30 30-40 40+						
Sibling Gender Female .						
Education Greater than HS Less than HS						
Marital Status Married Unmarried						
Employment Status Employed Unemployed						
Sibling Health Status Fair/Poor Good/Very good/Excellent						
Sibling Chronic Health Condition None Mild/Moderate Severe/Life Threatening						
Sibling Psychological Health GSI T≥63 GSI T<63						
Survivor Health Status Fair/Poor Good/Very good/Excellent						
Survivor Chronic Health Condition vs. None Mild/Moderate Severe/Life Threatening						
Survivor Psychological Health GSI T≥63 GSI T<63						
Relapse/2nd Cancer Yes No						
Death After Study Entry Yes No						

Survivor Diagnosis vs. Leukemia Brain Tumor Bone Tumor / Sarcoma						
Survivor Treatment Intense Yes No						

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