Analysis Concept Proposal

Study Title: Racial/Ethnic Differences in Neurocognitive, Psychological and Quality of Life Outcomes in Adult Survivors of Childhood Cancers

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1. Background and Rationale

Childhood cancer survivors are known to be at increased risk of neurocognitive impairment when compared to siblings, with up to 20-40% of survivors showing deficits [1, 2]. Additionally, certain populations of survivors have been found to be at increased risk for poor emotional and health-related quality of life (HRQOL) outcomes. Many risk factors for these impairments have been identified by prior studies; however, there is limited literature on the moderating effects of race and ethnicity on these outcomes.

While prior studies in the field of pediatric oncology evaluating race and ethnicity primarily focused on differential survival rates after primary cancer, two early studies within the CCSS cohort examined differences in long-term outcomes among these groups. Castellino *et al.* studied differences in health status (including mental health, general health, functional impairment, limitations of activity, pain as a result of cancer and anxiety/fear related to cancer), late mortality, health care utilization, and health behaviors [3]. This was performed using the original cohort with participants at mean ages ranging from 25.7-27.1 years across racial/ethnic groups. The study found that when adjusted for socioeconomic status, black survivors were less likely to report mental health problems than white survivors. However, a later study by Zeltzer *et al.* found black survivors to be at increased risk for mental health problems as well as global emotional distress [4]. However, neither of these studies evaluated neurocognitive function.

Risk factors for poor neurocognitive, emotional or quality of life outcomes are reasonably well established. Neurocognitive impairment is associated with exposure to CNS directed radiation or chemotherapy, corticosteroids, high dose systemic antimetabolites, female sex and younger age at treatment [4-9]. Both emotional distress and sociodemographic outcomes, including unmarried status and lower educational attainment, are associated with poor neurocognitive function in non-CNS cancer

survivors [6]. Global psychological distress is associated with a CNS tumor diagnosis, more intensive treatment, female sex, diagnosis during adolescence, and unmarried status [4-6]. Interestingly, while survivors as a whole have increased global distress compared with siblings, mean scores for the group are below (i.e. better than) those of the general population [4]. HRQOL outcomes mirror those of emotional distress as lower educational attainment, female sex, low household income, unemployment, unmarried status, uninsured status, major medical problems, and treatment with surgery or cranial radiation are associated with survivor report of poor HRQOL [4, 10].

In a more recent CCSS study by Liu *et al.*, non-Hispanic black (NHB) and Hispanic survivors reported lower educational attainment when compared to non-Hispanic white (NHW) survivors. A larger proportion of minority survivors did not complete or attain education beyond high school, had annual household incomes <\$20,000 or were uninsured. This study found that while there were differences in mortality and cardiovascular events for populations based on race/ethnicity, these differences were no longer observed when adjusting for socioeconomic status and/or cardiovascular risk factors. This suggested that the observed differences by race/ethnicity were driven by racial/ethnic differences in SES and traditional cardiovascular risk factors [11].This study did not include neurocognitive, emotional or HRQOL outcomes.

With the expansion of the CCSS cohort, new investigations into associations between race/ethnicity and neurocognitive, emotional and HRQOL outcomes are possible. There is an increase in available survivor and sibling data from racial and ethnic minority groups including a total of 1536 non-Hispanic black survivors and 151 siblings, and 1806 Hispanic survivors and 214 siblings. This is more than twice the number of both non-Hispanic black and Hispanic survivors included in the original cohort. Additionally, the CCSS-NCQ, BSI-18 and SF-36 used to evaluate neurocognitive, emotional and HRQOL domains respectively are now available from this cohort using follow-up 5 at a similar time from diagnosis and treatment as those surveys from follow-up 2 in the original cohort. Given the complex interplay of socioeconomic, educational attainment, health insurance and demographic factors on neurocognitive and emotional outcomes, our primary comparison for this analysis of the impact of race/ethnicity will be between survivors and siblings of the same race/ethnicity group, which will allow for a comparison of differences between survivors and siblings across three race/ethnicity populations.

Given the historically demonstrated influence of CNS-directed therapy on neurocognitive, emotional and HRQOL outcomes, and to determine whether there are treatment-specific associations between race/ethnicity and these outcomes, we will specifically look at differences in outcomes stratified by CNS radiation exposure. We will include methotrexate exposure, both systemic and intrathecal, in our analysis given the previously observed negative effects on neurocognitive and emotional outcomes in patients receiving this chemotherapy as part of their treatment regimen [2, 4-6, 12]. We will also include corticosteroid exposure in our analysis, differentiating between patients who received dexamethasone and those who did not, given previously observed negative effects on neurocognitive and emotional outcomes in patients received corticosteroids who did not receive CNS radiation therapy [6-9].

2. Specific Aims

- 2.1. Evaluate differences in neurocognitive outcomes between survivors and siblings stratified by racial and ethnic group, overall and by cranial radiation exposure (yes/no), using the NCQ.
- 2.2. Evaluate differences in emotional outcomes between survivors and siblings stratified by racial and ethnic group, overall and by cranial radiation exposure (yes/no), using the BSI-18.
- 2.3. Evaluate differences in health related quality of life (HRQOL) between survivors and siblings stratified by racial and ethnic group, overall and by cranial radiation exposure (yes/no), using the SF-36.

3. Hypotheses

- 3.1. While we hypothesize we will observe differences in neurocognitive outcomes between survivors and siblings within each racial/ethnic group, we expect no difference (i.e., test the difference but expect not rejecting the null hypothesis of no difference) when the magnitudes of the survivor-sibling differences are compared across racial/ethnic groups overall and among populations who received cranial RT. We hypothesize that NHB and Hispanic survivors will display a similar difference in neurocognitive outcome when compared to NHB and Hispanic siblings as that of NHW survivors with their siblings overall and among populations who received cranial RT.
- 3.2. While we hypothesize we will observe differences in emotional distress between survivors and siblings within each racial/ethnic group, we expect no difference when the magnitudes of the survivor-sibling differences are compared across racial/ethnic groups overall and among populations who received cranial RT. We hypothesize that NHB and Hispanic survivors will have a similar difference in emotional distress when compared to NHB and Hispanic siblings as that of NHW survivors with their siblings overall and among populations who received cranial RT.
- 3.3. While we hypothesize we will observe differences in HRQOL outcomes between survivors and siblings within each racial/ethnic group, we expect no difference when the magnitudes of the survivor-sibling differences are compared across racial/ethnic groups overall and among populations who received cranial RT. We hypothesize that NHB and Hispanic survivors will have a similar difference in HRQOL outcomes when compared to NHB and Hispanic siblings as that of NHW survivors with their siblings overall and among populations who received cranial RT.

4. Methods

- 4.1. Study Population: The study population will include survivors and siblings in both the original and expansion CCSS cohorts who had complete information for race/ethnicity in the baseline questionnaire. We will use neurocognitive, emotional and HRQOL data from follow-up 2 for participants from the original cohort and follow-up 5 for participants from the expansion cohort. Analyses regarding treatment variables will be restricted to survivors who have signed medical record releases and have treatment exposure data abstracted by CCSS institutions.
- 4.2. Outcome Variables
 - 4.2.1. CCSS-NCQ (J1-25 on FU2 and Q1-33 on FU5): Neurocognitive impairment in survivors will be assessed using the self-reported CCSS-NCQ which was developed for use and validated within the CCSS cohort using 4 factors; Task Efficiency, Emotional Regulation, Organization, and Memory. Scores will be reported as a continuous variable for the primary analysis.
 - 4.2.2. BSI-18 (G1-18 on FU2 and L1-18 on FU5): Emotional distress will be assessed using the self-reported Brief Symptom Inventory-18 (BSI-18) which has been validated in cancer patients and with the CCSS cohort [13, 14]. The BSI-18 includes the global distress index as

well as 3 subscales for anxiety, depression and somatization assessed based on symptoms within the past 7 days. Scores will be reported as a continuous variable.

- 4.2.3. SF-36 (E1-22 & F1-14 on FU2 and O1-8 & P1-3 on FU5): Health Related Quality of Life (HRQOL) will be assessed using the self-reported Medical Outcomes Short Form-36 (SF-36) which includes questions regarding general health, well-being, and quality of life over the previous 4 weeks. This tool has been used in population studies and survivor samples, including within the CCSS [10, 15, 16]. The SF-36 includes eight subscales of various aspects of well-being where higher scores represent "better" quality of life. Scores will be reported as a continuous variable.
- 4.3. Covariates:
 - 4.3.1. Sex
 - 4.3.2. Age at diagnosis
 - 4.3.3. Age at follow-up
 - 4.3.4. Chemotherapy (CNS exposure including systemic MTX (none, <4.3 g/m², ≥4.3 g/m²), IT MTX (none, <230 mg/m², ≥230 mg/m²), Corticosteroids (none, dexamethasone, non-dexamethasone)) [7, 8, 17].
 - 4.3.5. CNS radiation exposure (None, >0 and <20 Gy, \geq 20 Gy and <30 Gy, \geq 30 Gy to <50 Gy, \geq 50 Gy)[6, 12]
 - 4.3.6. Major Medical Condition
- 4.4. Statistical Analysis Framework:

Rationale: We initially intended to follow the model utilized in the most recent CCSS Race/Ethnicity paper by Liu *et al.* where outcomes were analyzed adjusting for clinical/demographic variables, then with the incremental addition of treatment and finally SES into the model [11]. However, socioeconomic status is likely a result of neurocognitive function (i.e. education, employment and income, as currently collected by CCSS surveys, are all downstream to neurocognitive outcome in the causal pathway). Additionally, CCSS does not have parental education status at the time of diagnosis or treatment which would be ideal for adjustment. For these reasons, we are proposing a comparison of each survivor group to their racial/ethnically specific sibling group, leveraging the assumption that siblings shared a similar SES environment to survivors.

- 4.4.1. Frequency distributions will be used to categorize relevant covariates according to reasonable groupings consistent with prior CCSS manuscripts. (Table 1) Descriptive statistics including means and standard deviations will be calculated for the primary outcome of interest (NCQ, BSI-18 and SF-36). (Tables 2-4)
- 4.4.2. Comparisons of the primary outcome variables (CCSS-NCQ, BSI-18 and SF-36) will be made between racial/ethnic groups and their siblings using general linear models (Tables 2-4) with a modification by Generalized Estimating Equations to account for possible withinfamily correlation between survivors and siblings from the same family. Outcomes will be reported as means, differences in means and associated standard deviations based on a continuous variable from the raw scores. For each outcome, we will initially compare sibling and survivor outcomes within race/ethnic groups and will then examine the role of clinical/demographic factors such as diagnosis, sex, age and treatment that may explain survivor-sibling differences. Further analyses will compare the intra racial/ethnic survivor-sibling differences across racial/ethnic stratum. For example, we will test whether the

difference between NHB survivors and siblings is different from the difference between NHW survivors and siblings.

4.4.3. We will then modify the model to assess survivor-sibling differences in each racial/ethnic group stratified by CNS radiation exposures. This will be accomplished by adding an interaction between the CNS radiation indicator and the survivor/sibling status indicator (this will stratify survivors by CRT but not siblings), but adjusting for the same covariates as in 4.4.2. Within the structure of that model, we will assess the differences between CRT treated survivors and non-CRT treated survivors and siblings within each racial/ethnic group and compare those differences with one another. Further analyses will compare within CRT stratum survivor-sibling differences across racial/ethnic groups.

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		Surv	ivors		Siblings					
	White, NH Black, NH Hispanic				White, NH Black, NH Hispanic					
	(n=)	(n=)	(n=)	Р	(n=)	(n=)	(n=)	Р		
Sex, n (%)										
Male										
Female										
Age at diagnosis, n (%)										
0-4										
5-9										
10-14										
15-20										
Year of diagnosis, n (%)										
1970-79										
1980-89										
1990-99										
Age at follow-up, n (%)										
<25 yrs.										
25-34 yrs.										
35-44 yrs.										
45-54 yrs.										
≥55 yrs.										
Diagnosis, n (%)										
Acute lymphoblastic leukemia										
Acute myeloid leukemia										
Other leukemia										
Astrocytoma										
Medulloblastoma, PNET										
Other CNS tumors										
Hodgkin lymphoma										
Non-Hodgkin lymphoma										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										
Other bone tumors										
CNS Radiation therapy										
received, n (%)										
None										
>0* to <20 Gy										
20 to <30 Gy										
30 to <50 Gy										
≥50 Gy										
Chemotherapy, n (%)										
Systemic Methotrexate dose										
None										
<4.3 g/m ²										
≥4.3 g/m ²										
IT Methotrexate										
None										
<230 mg/m ²										
≥230 mg/m ²										
Systemic Corticosteroid, n (%)										
None										
Dexamethasone										
Non-Dexamethasone										
Socioeconomic status, n (%)										
Health Insurance status										
Yes										
No										
Household Income (\$**)										
<20,000										
20-39,999										
40-59,999										
60-79999										

80-99999	
≥100,000	
Educational attainment	
< HS graduate or GED	
High school graduate	
Any college or post-HS training	
College graduate or post-	
graduate degree	
Social/Financial Independence,	
n (%)	
Marital Status	
Never married	
Ever married	
Lives independently	
Yes	
No	
Employment	
Unable to work	
Unemployed	
Employed/Student	
Medications, n (%)	
Antidepressants	
Yes	
No	
Anxiolytics	
Yes	
No	
Major Medical Condition, n (%)	
Yes	
No *Only direct CNS radiation doses were included this does not include low doses fro	

*Only direct CNS radiation doses were included, this does not include low doses from body site scatter.

**Income values adjusted to 2016 dollar values.

	Task Efficiency												
	NHW			NHB	NHB				Hispanic				
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		
č	Emotional Regulation												
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling			-	Í		-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
0	Organizatio	on											
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling			-		-	-	-		-	-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			_			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-	1		-	0.xx			-	0.xx		
	Working N	lemory			ı								
	NHW	•		NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling			-	T T		-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-	1		-	0.xx	1		-	0.xx		

P= p-value for comparison to siblings of same race/ethnicity group

P*= p-value for comparison of the difference between survivor and sibling, referenced to NHW survivor and sibling difference.







	Depression												
	NHW			NHB	NHB				Hispanic				
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	Р*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		
	Anxiety												
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	Ρ*	Mean	SD	Р	P*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
	Somatizati	on											
	NHW	011		NHB	NHB				Hispanic				
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling	Wiedi	50	-	Wicdii	50	-	-	wican	50	-	-		
Survivor			0.xx			0.xx	-			0.xx	_		
Difference from sibling			-			0.77	0.xx			0.00	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			0.22			0.77	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		
	Global Stat	us Index					0.00				0.00		
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling	wicun	50	-	Wican	50	-	-	wicun	50	-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			0.77			0.77	- 0.xx			-	- 0.xx		
Survivor with CRT			- 0.xx			- 0.xx	-			- 0.xx	-		
Difference from Sibling			-			-	- 0.xx			-	- 0.xx		

P= p-value for comparison to siblings of same race/ethnicity group

P*= p-value for comparison of the difference between survivor and sibling, referenced to NHW survivor and sibling difference.

	Role Emotional												
	NHW			NHB	NHB				Hispanic				
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	Ρ*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		
	Social Fund	ction											
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	Р*	Mean	SD	Р	Р*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling						0.77					0.00		
Difference from sibling		1.1	-			-	0.xx			-	0.xx		
	Mental Health							10 sector					
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	Ρ*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		
		omponent Sum	imary										
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	Ρ*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		
		mponent Sum	mary										
	NHW			NHB				Hispanic					
	Mean	SD	Р	Mean	SD	Р	P*	Mean	SD	Р	P*		
Sibling			-			-	-			-	-		
Survivor			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor no CRT			0.xx			0.xx	-			0.xx	-		
Difference from sibling			-			-	0.xx			-	0.xx		
Survivor with CRT			0.xx			0.xx	-			0.xx	-		
Difference from Sibling			-			-	0.xx			-	0.xx		

P= p-value for comparison to siblings of same race/ethnicity group

P*= p-value for comparison of the difference between survivor and sibling, referenced to NHW survivor and sibling difference.