Study Title: Self-Reported Neuropsychological Outcomes in Adult Survivors of Neuroblastoma

Working Group: This report will be written within the Psychology Working Group with secondary oversight by the Chronic Disease Working Group.

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1. Background

There has been significant improvement in survival in patients with high-risk neuroblastoma over the past few decades, and five year survival is now around 50%.[1,2] Over the past 20 years treatment has been tailored to risk groups based on the biologic features of the tumor, and we have seen improvements in survival in all these groups, leading to growing populations of long-term survivors.[3] Risk stratification has allowed decreases in treatment intensity among low and intermediate risk groups without a decrease in survival.[4] The treatment for high-risk disease has increased and intensified.[5,6] Despite multi-agent induction chemotherapy followed by consolidation with high-dose chemotherapy with autologous stem cell rescue and radiation[6], 50% of patients would relapse. To better treat minimal residual disease the differentiating agent isotretinonin was introduced with improvement in event free survival.[7] The addition of immunotherapy with anti ganglioside 2 chimeric antibody and cytokines has improved event free and overall 5-year survival for high-risk patients.[8] However, a recent CCSS analysis of late mortality by Armstrong et al., which examined neuroblastoma survivors in aggregate (not delineated by stage or risk group), showed an increased risk of late mortality in more recent treatment eras.[9] This is presumed to be due to increased therapeutic intensity of treatment that resulted in increased 5-year survival but also an increased risk of late effects. Thus, we are at a critical juncture to better understand the detailed late effects of long-term survivors of neuroblastoma. Neuropsychological outcomes are of particular importance in neuroblastoma survivors, given the young age at which patients were treated, the therapies used to treat the disease, as well as the long-term impact of cognitive deficits on attainment of milestones during adulthood and quality of life.[10] To date, there are few large studies describing these outcomes in neuroblastoma survivors.

The neurocognitive domains that are most affected in survivors of childhood cancers are attention, memory, visuospatial abilities, executive functioning, and cognitive processing speed.[11] Studies have found that up to 40% of childhood cancer survivors can experience impairment in one or more of these domains.[12,13,14] Most prior work examining neuropsychological outcomes in childhood cancer survivors focused on survivors of acute lymphoblastic leukemia and central nervous system tumors.[15,16,17,18,19,20] These studies suggested that patients treated for neuroblastoma

may be particularly vulnerable to neurocognitive late effects given their young age at diagnosis and the specific therapies they receive.[21,22] For example, Kadan-Lottick et al examined adult survivors of non-CNS cancers and found that diagnosis age younger than 6 years, having received cranial radiation therapy and hearing impairment were associated with neurocognitive impairment.[23] Childhood cancer survivors treated with platinum based therapy are at high risk of hearing loss, which occurs in 23%-31% of these survivors.[24,25] The cornerstones of treatment for neuroblastoma include platinum based therapy for induction chemotherapy and radiation for local control as well as for myeloablation. Importantly, there is a lack of studies looking specifically at the impact of these therapies on the neuropsychological outcomes of neuroblastoma survivors. The CCSS provides a unique opportunity to evaluate the neuropsychological outcomes of this group across treatment eras. The detailed exposure data will allow examination of relationships between specific exposures and neuropsychological outcomes.

Direct neuropsychological testing is the gold standard for assessing neurocognitive functioning,[26,27] however it is not feasible for many due to cost, access, and time required. The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) was created as a way to identify survivors at high risk for neurocognitive dysfunction.[14] It is a self reported questionnaire that evaluates cognitive domains that are commonly affected in cancer survivors. It contains four domains; emotional regulation, organization, task efficiency and memory. The first two address executive functioning while the latter two address processing speed/attention and working/long term memory, respectively. It has been validated and used in numerous studies.[28,29,30] Zheng is currently undertaking a study looking at cognitive and behavioral outcomes in survivors of neuroblastoma using the CCSS. That study is using the Behavior Problem Index (BPI) to examine behavioral outcomes based on parental reports of patients younger than 18 years old at the time of their survey response. Our proposed project will be restricted to survivors over age 18 at the time of the CCSS-NCQ survey, which will allow us to utilize their self-reported CCSS-NCQ to evaluate neurocognitive outcomes.

The current proposal seeks to assess the neuropsychological outcomes of survivors of neuroblastoma over the age of 18 years treated between 1970-1999 (N=1853) in relation to changing trends in treatment.

2. Specific aims

1. To characterize the prevalence of neuropsychological impairments in long-term survivors of neuroblastoma as determined through the CCSS NCQ Instrument.
2. To examine changing proportions of neuropsychological impairments across treatment eras from 1970-1999.
3. To identify treatment related risk factors associated with development of neuropsychological impairment identified in the CCSS NCQ.
4. To examine the impact of chronic health conditions on neuropsychological outcomes in survivors of neuroblastoma.
5. To examine the impact of impaired neuropsychological functioning on education attainment, employment and ability to live independently.

3. Hypotheses

1. Neuroblastoma survivors will report worse neuropsychological impairment in comparison to siblings, adjusted for age and sex.
2. More recently treated patients will have worsening neuropsychological outcomes compared to those from earlier treatment periods.
3. Survivors with more chronic health conditions as well as more severe chronic health conditions will have more neuropsychological impairment.
4. Survivors with neuropsychological impairment will have lower school attainment, be less likely to be employed and less likely to be living independently.

4. Analysis framework

A. Study population

All 5-year survivors of neuroblastoma participating in the CCSS original and expansion cohort (diagnosed between 1970-1999) along with sibling controls, who completed the CCSS Neurocognitive Questionnaire as part of follow-up number 2 and 5 respectfully. (CCSS-NCQ; Survivor N=836, Sibling N=728).

B. Outcomes of interest

The primary outcome will be neurocognitive dysfunction as assessed by the CCSS-NCQ: a questionnaire used to assess cognitive and emotional function in areas commonly affected by cancer treatment. The questionnaire uses a Likert scale ranging from 1 ("never a problem") to 3 ("often a problem"). The tool examines 4 domains of task efficiency, emotional regulation, organization and memory. A higher score indicates worse impairment. This tool has been previously validated in a CCSS sample. CCSS-NCQ corresponds to questions J.1 –J.25 on Follow- up 2 survey in 2003. As has been done previously we will examine continuous scores and frequency of impairment in each domain. We will define impairment as falling $\leq 10^{th}$ percentile based on values obtained in the sibling cohort. To account for age at time of response, FU2 questionnaire will be used for the original cohort (and their siblings) and FU5 questionnaire for the expanded cohort (and their siblings). Both groups will be analyzed using the original CCSS-NCQ.

C. Predictor variables to be analyzed:

A: Sex

B: Race or ethnic group

C: Treatment era (diagnosis years 1970-1979; 1980-1989; 1990-1999)

D: Age at primary cancer diagnosis (in years)

E: Age at time of assessment (in years)

F: Treatment exposures

-Surgery (yes/no)

-Chemotherapy (yes/no)

-Alkylating agents (cyclophosphamide equivalent dose (CED) mg/m2)[31] grouped as:

- none
- >0-<4,000
- >=4,000-<8,000
- >=8,000-<12,000
- >=12,000-<16,000
- >=16,000-<20,000
- >= 20,000

-Anthracycline dose (mg/m2) grouped as:

- none
- >0-<150
- >=150 < 300
- >= 300

-Platinum agents cumulative dose (mg/$m^{2;}$ continuous variable)

-Vinca alkaloids cumulative (mg/m^2)

-Retinoic acid (mg/m^2)

-Radiation (yes/no)

-type and dose (Gy; maximum prescribed dose to be examined in 10 Gy increments)

- Cranial
- Thoracic
- Pelvic

G: Highest education level achieved by the time of assessment

- 1- 8 years (grade school)

- 9-12 years high school but did not graduate
- Completed high school
- Training after high school other than college
- Some college
- College graduate
- Post graduate level

H: Employment status at the time of the assessment

- Full time
- Part time
- Unemployed
- Unable to work due disability or illness
- Student
- Other

I: Marital status at the time of assessment

- Single
- Married
- Widow
- Divorced
- Separated

J: Independent living at the time of assessment (yes, no)
I: Hearing loss prior to assessment (grade 2-4)
K: Chronic health conditions at time of assessment (grade 2-4)

- Cardiac
- Respiratory
- Endocrine
- Neurologic

D. Analysis

We will calculate descriptive statistics for demographic and treatment variables for cancer survivors in both the original cohort and the expanded cohort, as well as for their siblings. Demographic characteristics will be compared between survivors and siblings using generalized estimating equation (GEE) models (linear, log-binomial) with robust variances to account for intra-family correlations. CCSS-NCQ scores will be summarized for survivors and siblings. Results for the four factors of the CCSS-NCQ (i.e., task efficiency, organization, memory, and emotional regulation) will be reported as 1) means and standard deviations of *T* scores and 2) percentages of individuals with scores in a low functioning range (i.e., with impairment), which was calculated as percentages of patients with *T* score of 63 or higher, approximately corresponding to the lowest 10% range of siblings' scores, as has been used in previous studies.

Neuroblastoma survivors and siblings will be compared on each of the four CCSS-NCQ factor scores by use of multiple linear regression with GEE and robust variances and on each of the four impairment outcomes (binary outcome) by use of multivariable log-binomial regression (for impairment risk) with adjustment for current age, sex, and race (**Aim 1**).

In analyses restricted to survivors, we will examine the impact of calendar year (in decades) using similar models as above, adjusted for age, sex, and race (**Aim 2**). In a separate model (without calendar time included), we will examine associations between treatment factors (described above) and neuropsychological impairments on the 4 NCQ domains and build a multivariable model incorporating key independent risk factors for each domain (**Aim 3**). If calendar year is identified as a significant factor in Aim 2 analyses, we will evaluate whether it remains so when we add it to the treatment model defined in Aim 3. If it is no longer significant, it would indicate that changes in treatment over time may explain the changes we observed over time in neuropsychological impairment.

In separate, but similarly structured models from those with treatment effects (since treatments are risk factors for the chronic conditions), we will evaluate associations of chronic conditions occurring prior to the NCQ survey response with neuropsychological impairment (**Aim 4**). Self-reported health conditions have been graded as per Common Terminology Criteria for Adverse Events (CTCAE) as described previously.[32, 33,34] We will evaluate the occurrence of any grade 2-4 chronic condition, multiple grade 2-4 chronic conditions and if the prevalence is sufficient, we will also examine chronic conditions from specific organ systems that are known to impact neurocognitive functioning; such as cardiac, pulmonary, endocrine, and neurological. The prevalence of hearing loss among neuroblastoma survivors is already known to be high and therefore is already listed as a variable.

Finally, to illustrate the impact that neuropsychological impairment has on the functional life of neuroblastoma survivors, we will evaluate associations between impairment on each of the NCQ domains with each of the following outcomes: employment, educational attainment of some college education, and living independently (**Aim 5**). Models will be *a priori* adjusted for age at evaluation, age at diagnosis, sex and race.

E. Tables/Figures-

a. Groupings within categories may change based on final cell count. Variable type such as categorical versus continuous may also change based on final data
b. ⌘ denotes comparison group

Table 1. Demographic and treatment characteristics of Neuroblastoma Survivors in the CCSS cohort and sibling cohort.

Characteristic	Neuroblastoma survivor	Siblings	
	# (%)	# (%)	P
Sex Female Male			
Race/ethnicity White Black Hispanic Other			
Age at diagnosis (years)	y +/- mean (range)	N/A	
Age at evaluation (years)	y +/- mean (range)	y +/- mean (range)	
Treatment era 1970-1979 1980-1989 1990-1999		N/A	
Highest education achieved 1- 8 years (grade school) 9-12 years high school but did not graduate Completed high school Training after high school other than college Some college College graduate Post graduate level			
Employment status Full time Part-time Unemployed Disabled Retired Student Other			
Marital Status Single Married Divorced Widowed			
Living independently Yes No			

Table 2. Treatment characteristics by era

Treatment	Number total	1970-1979	1980-1989	1990-1999
	N (%)	N (%)	N (%)	N (%)
Surgery only				
Chemotherapy and surgery				
Radiation and surgery				
Chemotherapy, radiation and surgery				
Cranial radiation Yes No				
Cranial radiation None Examine in 10Gy increments				
Thoracic radiation Yes No				
Thoracic radiation None Examine in 10Gy increments				
Pelvic radiation Yes No				
Pelvic radiation None Examine in 10Gy increments				
Alkylating agents Yes No				
Alkylating agent (CED, mg/m2) none >0-<4,000 >=4,000-<8,000 >=8,000-<12,000 >=12,000-<16,000 >=16,000-<20,000 >= 20,000				
Anthracycline Yes No				
Anthracycline cumulative dose (mg/m2) None >0-<150 >=150-<300 >=300				
Vinca alkaloids Yes No				
Vinca alkaloid dose median (range) mg/m^2				
Platinum agent Yes No				
Platinum agent median dose (range) mg/m^2				
Retinoic acid Yes No				
Retinoic acid median (range) mg/m^2				

Table 3: Comparison of neuropsychological outcomes between neuroblastoma survivors and siblings based on CCSS NCQ

a. Univariate Means, prevalences and p-values comparing survivors vs. siblings.

Group	Task Efficiency					Organization					Memory					Emotional Regulation				
	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P
Survivors																				
Siblings																				

b. Adjusted comparisons of Mean scores (β = Differences in mean values)

Group	Task Efficiency			Organization			Memory			Emotional Regulation		
	β*	95% CI	P	β*	95% CI	P	β*	95% CI	P	β*	95% CI	P
Survivors												
Siblings	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-

*Adjusted for age, sex, race

c. Adjusted comparisons of Percent Impaired (RR)

Group	Task Efficiency			Organization			Memory			Emotional Regulation		
	RR*	95% CI	P	RR*	95% CI	P	RR*	95% CI	P	RR*	95% CI	P
Survivors												
Siblings	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-

*Adjusted for age, sex, race

Table 4: Comparison of neuropsychological outcomes by era based on CCSS NCQ

a. Univariate means, prevalence and p values compared by era

Era	Task Efficiency					Organization					Memory					Emotional Regulation				
	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P
1999-1990																				
1980-1989																				
1970-1979⌘																				

b. Adjusted comparisons of Mean scores (β = Differences in mean values)

Group	Task Efficiency			Organization			Memory			Emotional Regulation		
	β*	95% CI	P	β*	95% CI	P	β*	95% CI	P	β*	95% CI	P
1990-1999												
1980-1989												
1970-1979	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-

*adjusted for age, sex and race

c. Adjusted comparison for %impaired

Group	Task Efficiency			Organization			Memory			Emotional Regulation		
	RR*	95% CI	P	RR*	95% CI	P	RR*	95% CI	P	RR*	95% CI	P
1990-1999												
1980-1989												
1970-1979	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-

*adjusted for age, sex and race

Table 5: Patient and treatment factors that were associated with impaired neurocognitive functioning outcomes among neuroblastoma survivors

a. Univariate means, % impaired and p values compared by treatment factors

Patient or treatment factor	Task Efficiency					Organization					Memory					Emotional Regulation				
	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P	N	Mean (SD)	P	% impaired	P
Sex Male⌘ Female																				
Ethnicity White⌘ Other																				
Age at diagnosis 0-4.99⌘ 5-9.99 10-14.99 15-18																				
Chemotherapy No⌘ Yes																				
Alkylating agents No⌘ Yes																				
Alkylating agent (CED#, mg/m2) None⌘ >0-<4,000 >=4,000-<8,000 >=8,000-<12,000 >=12,000-<16,000 >=16,000-<20,000 >= 20,000																				
Anthracycline No⌘ Yes																				
Anthracycline cumulative dose (mg/m2) None⌘ >0-<150 >=150-<300 >=300																				
Vinca alkaloids No⌘ Yes																				
Vinca alkaloid dose ranges (range) mg/m^2																				
Platinum agent No⌘ Yes																				
Platinum agent median dose (range) mg/m^2																				
Radiation No⌘ Yes																				

Radiation None⌘ Cranial Thoracic Pelvic																				
Radiation dose (Gy) -Will examine above sites in 10Gy increments																				
Retinoic acid No⌘ Yes																				
Retinoic acid median (range) mg/m^2																				

b. Adjusted comparisons of Mean scores (β = Differences in mean RR values)

Patient or treatment factor	Task Efficiency			Organization			Memory			Emotional Regulation		
	β*	95% CI	P	β*	95% CI	P	β*	95% CI	P	β*	95% CI	P

** only factors found to be significant in the univariate model plus the a priori variables (age, sex and race) will be included in the multivariable model

Table 6**:** Burden of Chronic health conditions among survivors and siblings

Health Condition	Neuroblastoma survivor	Siblings	P value
	# (%)	# (%)	
None or grade 1 conditions			
Any grade 2 -4 conditions			
Multiple grade 2-4 conditions			
Grade 2-4 cardiac conditions			
Grade 2-4 pulmonary conditions			
Grade 2-4 endocrine conditions			
Grade 2-4 neurologic conditions			
None or grade 1 hearing loss			
Grade 2-4 hearing loss			

Table 7**:** Chronic health conditions burden and neuropsychological outcomes of survivors based on CCSS NCQ

Chronic Health Condition	Task Efficiency				Organization				Memory				Emotional regulation			
	%impaired	RR	CL	P	%impaired	RR	CL	P	%impaired	RR	CL	P	%impaired	RR	CL	P
None or grade 1 conditions⌘																
Any grade 2-4 conditions																
Multiple grade 2-4conditions																
None or grade 1 cardiac conditions⌘																
Grade 2-4 cardiac conditions																
None or grade 1 pulmonary conditions⌘																
Grade 2-4 pulmonary conditions																
None or grade 1 endocrine conditions⌘																
Grade 2-4 endocrine conditions																
None or grade 1 neurologic conditions⌘																
Grade 2-4 neurologic conditions																
None or grade 1 hearing loss⌘																
Grade 3 or 4 hearing loss																

*adjusted for age, sex and race

Table 8**:** Relative risk of educational attainment, employment and living independently in neuroblastoma survivors based on impairment in neurocognitive functioning among survivors

Neurocognitive Domain	Educational attainment of some college or more			Currently employed (part time or full time)			Living independently		
	N(%)	RR	p	N(%)	RR	p	N(%)	RR	p
Task Efficiency Impairment No impairment									
Organization Impairment No impairment									
Memory Impairment No impairment									
Emotional Regulation Impairment No impairment									

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