

## **Childhood Cancer Survivor Study – Analysis Concept Proposal**

**1. TITLE:** Impact of neurocognitive impairment on financial hardship in adult survivors of childhood cancer

### **2. INVESTIGATORS:**

The proposed study will be shared between two co-primary working groups: Cancer Control and Psychology.

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### **3. BACKGROUND AND RATIONALE:**

Financial hardship is an evolving construct that encompasses the burden from the financial strain of cancer-directed therapy in three distinct domains: material (out of pocket expenses as well as decreased productivity from job interruptions), psychological (distress over cost of care), and behavioral (maladaptive financial coping behaviors including decreased medical care).<sup>1</sup> This hardship is increasingly recognized as a critical patient-centered outcome and now demonstrated to be highly prevalent in adult survivors of childhood cancer after prior work had focused more on survivors of adult cancers.<sup>2-5</sup> Specifically, Nathan et al found that among a large cohort of >3500 childhood cancer survivors enrolled in the CCSS, more than 60% reported financial hardship in at least one domain. Compared to siblings, survivors were statistically significantly more likely to report being sent to debt collection, foregoing needed medical care, and not having enough money to buy nutritious meals. Clearer understanding of the drivers of financial hardship in childhood cancer survivors is critical to inform optimal screening and the design of future interventions to mitigate its impact in this patient population.

A study from the St. Jude Life Cohort examined the impact of chronic health conditions as a potential determinant of financial hardship and found increased risk of hardship in survivors who had experienced a myocardial infarction, peripheral neuropathy, subsequent neoplasm, seizure, stroke, reproductive disorder, amputation, upper gastrointestinal disease, or hearing loss.<sup>6</sup>

However, this study did not include examination of neurocognitive impairment as a potential risk factor. Extensive work has shown that childhood cancer survivors of a wide range of diagnoses are at increased risk of neurocognitive impairment in attention, working memory, processing speed, executive function, and emotional regulation.<sup>7,8</sup> Several studies have linked neurocognitive impairment with lower educational attainment and unemployment in this patient population.<sup>9-11</sup>

While there is a logical relationship between neurocognitive impairment and financial hardship due to this association with lower educational attainment and unemployment, this has not been previously studied or reported in childhood cancer survivors. There are also reasons to believe that neurocognitive impairment has additional impact on financial hardship beyond educational and employment outcomes, as cognitive functioning is important for the management of one's finances. Work in older adult patients with dementia and other cognitive impairments has demonstrated that patients with mild cognitive impairment have significant decline in financial skills over time, self-report greater difficulty in managing their finances, and needed more time and were significantly more likely to make an error when given a multistep financial task.<sup>12-15</sup> These difficulties in financial management would likely have downstream implications for overall financial hardship.

Globally, the substantial risk of developing severe chronic health conditions has been well described in multiple studies of childhood cancer survivors with the 20-year cumulative incidence of at least one grade 3-5 chronic condition in the CCSS ranging from 27-34%.<sup>16-18</sup> Severe chronic health burden has direct impact on financial outcomes as has been demonstrated in both cancer survivor populations as well as general populations.<sup>19,20</sup> A systematic review of the impact of chronic conditions on the economic burden of cancer survivorship in adults concluded that cancer survivors with comorbidities incurred significantly more in total medical costs and out-of-pocket costs.<sup>21</sup> It is plausible that survivors with both neurocognitive impairment and severe chronic health burden could face even greater financial hardship due to compounded challenges in managing their health and health-related expenses. Further exploration of a potential interaction is critical.

Lastly, prior literature has also demonstrated an association between lower socioeconomic status and worse neurocognitive functioning.<sup>22,23</sup> Impoverished environments are posited to contribute to poorer cognitive development and functioning through chronic stress and decreased cognitive stimulation.<sup>24</sup> Examining neurocognitive functioning as an exposure for financial hardship highlights the potential cyclical and bi-directional nature of this problem. We propose the first analysis of neurocognitive outcomes and their relationship with financial hardship outcomes in childhood cancer survivors. Better understanding of how neurocognitive status relates to financial hardship is critical for optimizing screening practices and the design of interventions for childhood cancer survivors as these tools may need to be multi-modal to best support this patient population.

#### **4. SPECIFIC AIMS:**

**Aim 1:** Assess the association between neurocognitive impairment and financial hardship outcomes.

**Hypothesis:** *We hypothesize that survivors with worse overall neurocognitive impairment will demonstrate greater financial hardship compared to survivors without neurocognitive impairment and siblings.*

**Aim 2a:** Assess whether there is a synergistic effect (interaction) between neurocognitive impairment and lower educational attainment on financial hardship outcomes.

**Hypothesis:** *We hypothesize that survivors with worse neurocognitive impairment and lower educational attainment (doubly exposed) will demonstrate worse financial hardship outcomes compared to survivors with other combinations of neurocognitive functioning and educational attainment.*

**Aim 2b:** Assess whether there is a synergistic effect (interaction) between neurocognitive impairment and unemployment on financial hardship outcomes.

**Hypothesis:** *We hypothesize that survivors with worse neurocognitive impairment and unemployment (doubly exposed) will demonstrate worse financial hardship outcomes compared to survivors with other combinations of neurocognitive functioning and employment status.*

**Aim 3:** Assess whether there is a synergistic effect (interaction) between neurocognitive impairment and chronic health burden on financial hardship outcomes.

**Hypothesis:** *We hypothesize that survivors with worse neurocognitive impairment and worse chronic health burden (doubly exposed) will demonstrate worse financial hardship outcomes compared to survivors with other combinations of neurocognitive functioning and chronic health burden.*

## **5. ANALYSIS FRAMEWORK:**

### **5.1 Sample**

The proposed analyses will include data from the subset of adult survivors in the Childhood Cancer Survivor Study (CCSS) who have completed both the revised CCSS Neurocognitive Questionnaire (NCQ) in the Follow Up 5 (FU5) Survey and the financial hardship questionnaire in the Follow Up 6 (FU6) Survey – medium version. As previously reported, these survivors are  $\geq 5$ -year survivors of cancer diagnosed before 21 years of age between 1970-1999. Consistent with the original financial hardship CCSS publication, we will restrict analysis to individuals  $\geq 26$  years old at time of survey as individuals are allowed to remain on parents' insurance up to this age as a result of the Affordable Care Act.<sup>2</sup>

### **5.2 Outcomes of Interest and Covariates**

#### Outcomes

The primary outcome for Aims 1 and 2 will be financial hardship outcomes from the FU6 survey. As previously reported and operationalized in Nathan *et al.*, we will plan on analyzing financial hardship outcomes by mapped domains of behavioral hardship, material hardship/financial sacrifices, and psychological hardships in addition to two items (sent to debt collection and ever filed for bankruptcy) that do not map onto any specific domain and are considered separately. Appendix A details the specific questionnaire items and their corresponding domains. For each domain, we will employ a similar strategy of two scoring methods: (1) binary scoring for any affirmative response in the domain and (2) standardized domain scores calculated using unweighted summation of affirmative responses in each domain and subsequently dividing by the standard deviation among survivors.

### Covariates

The main exposure of interest is neurocognitive impairment as measured by the revised NCQ administered as part of the FU5 survey. The NCQ has items related to the specific domains of task efficiency, memory, organization, and emotional regulation. Consistent with prior analyses, we will define impairment on a domain as a Z score  $> 1.28$  which corresponds to the worst 10<sup>th</sup> percentile of scores based on healthy control age-adjusted normative values.<sup>25, 26</sup>

For specific Aim 2, we will use the educational attainment and employment status data from the FU5 survey. For consistency, the use of these covariates will be similar to the original CCSS publication on financial hardship which restricted the population to age  $\geq 26$  years as detailed above.<sup>2</sup> We will categorize educational attainment as some college or higher vs. less than college. We will categorize employment status as full time or part time employment vs. not working. Students will be excluded from the employment analysis.

For specific Aim 3, we will use chronic health conditions as compiled in the CCSS chronic condition matrix based on cumulative report across baseline and follow up surveys and graded by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.<sup>27, 28</sup> We will use previously published methodology to assign a severity/burden category for chronic health conditions.<sup>29, 30</sup> Categories are defined as "none/low" being grade 1 conditions only; "medium" being  $\geq 1$  grade 2 and/or 1 grade 3 condition; "high" being  $\geq 2$  grade 3, or 1 grade 4 and 1 grade 3 conditions; and "very high" being  $\geq 2$  grade 4 or  $\geq 2$  grade 3 and 1 grade 4 condition.

Additional covariates for all three aims will include descriptive statistics from FU5. These are detailed in Table 1. With regards to analysis for adjusted models, we will adjust for a priori selected covariates including sex, race/ethnicity, age at survey completion, number of household members, marital status, cancer diagnosis, cumulative anthracycline exposure, cumulative alkylating agent exposure, stem cell transplant, and radiation therapy.<sup>2</sup> We will perform sensitivity analyses looking specifically at the covariate of dependent living as this is likely to be strongly correlated with severe neurocognitive impairment, but may also distinctly influence the degree of reported/experienced financial hardship if a parent or sibling is instead primarily managing the finances. We will also explore how to handle income and insurance, as these covariates may lay in the causal pathway between neurocognitive impairment and financial

hardship. Education, employment, and chronic health burden will not be adjusted for a priori and instead explored as detailed in Specific Aims 2 and 3.

### ***5.3 Statistical Analysis Plan***

#### **Aim 1: Identify the association between neurocognitive impairment and worse financial hardship outcomes.**

Descriptive demographic statistics and disease/treatment characteristics of survivors will be tabulated and reported overall and by number of NCQ domains impaired, as well as by specific domain (Tables 1 and 2). We will compare proportions reporting financial hardship for each item (Supplementary Table 1) as well as overall any affirmative response in each domain (Figure 1) using chi-square tests. For each domain of financial hardship, we will conduct a log binomial regression analysis comparing the prevalence ratio of each financial hardship domain among survivors by the number of domains with neurocognitive impairment in addition to a priori selected covariates specified above (Table 3).<sup>2</sup> The two individual items of debt and bankruptcy that were not included in the three domains of financial hardship will be analyzed similarly using multivariable log binomial regression. These same analyses will also be repeated modeling the standardized domain scoring method with linear regression as a sensitivity analysis. Additional sensitivity analyses exploring exclusion of brain tumor patients and/or proxy respondents will be performed to interrogate the possibility that survivors with severe cognitive impairment may have difficulty accurately reporting their financial hardship issues.

#### **Aim 2a: Assess whether there is a synergistic effect (interaction) between lower educational attainment and neurocognitive impairment on financial hardship outcomes.**

Multivariable log binomial regression models will be constructed (unadjusted and adjusted) for each domain of financial hardship using the binary scoring method, as well as the two individual items of debt and bankruptcy. The independent and joint effects of neurocognitive impairment and educational attainment will be examined (Table 4) using a reference group of the survivors who have no/less neurocognitive impairment and high educational attainment (i.e., college or higher). To determine the exact reference group of “less neurocognitive impairment,” we will perform exploratory analyses examining the distribution and association of severity (by score and number of domains impacted) of neurocognitive impairment and educational attainment and adapt accordingly. The adjusted models will include the same covariates as detailed in Aim 1, with the exception of education as it is an exposure of interest in this analysis. To quantify the interaction on the multiplicative scale, we will calculate the ratio of the prevalence ratio. These same analyses will also be repeated modeling the standardized domain scoring method with linear regression as a sensitivity analysis.

#### **Aim 2b: Assess whether there is a synergistic effect (interaction) between unemployment and neurocognitive impairment on financial hardship outcomes.**

Multivariable log binomial regression models will be constructed (unadjusted and adjusted) for each domain of financial hardship using the binary scoring method, as well as the two individual items of debt and bankruptcy. The independent and joint effects of neurocognitive impairment

and employment will be examined (Table 5) using a reference group of the survivors who have no/less neurocognitive impairment and high employment status (full time or part time employment). To determine the exact reference group of “less neurocognitive impairment,” we will perform exploratory analyses examining the distribution and association of severity (by score and number of domains impacted) of neurocognitive impairment and employment and adapt accordingly. The adjusted models will include the same covariates as detailed in Aim 1, with the exception of employment as it is an exposure of interest in this analysis. To quantify the interaction on the multiplicative scale, we will calculate the ratio of the prevalence ratio. These same analyses will also be repeated modeling the standardized domain scoring method as a sensitivity analysis.

**Aim 3: Assess whether there is a synergistic effect (interaction) between neurocognitive impairment and chronic health burden on financial hardship outcomes.**

Multivariable log binomial regression models will be constructed (unadjusted and adjusted) for each domain of financial hardship using the binary scoring method, as well as the two individual items of debt and bankruptcy. The independent and joint effects of neurocognitive impairment and chronic health burden will be examined (Table 6) using a reference group of the survivors who have no/less neurocognitive impairment and lower chronic health burden. To determine the exact reference group of “less neurocognitive impairment,” we will perform exploratory analyses examining the distribution and association of severity (by score and number of domains impacted) of neurocognitive impairment and chronic health burden and adapt accordingly. Similar exploratory analyses to determine “lower chronic health burden” will be performed. The adjusted models will include the same covariates as detailed in Aim 1. To quantify the interaction on the multiplicative scale, we will calculate the ratio of the prevalence ratio. These same analyses will also be repeated modeling the standardized domain scoring method as a sensitivity analysis.







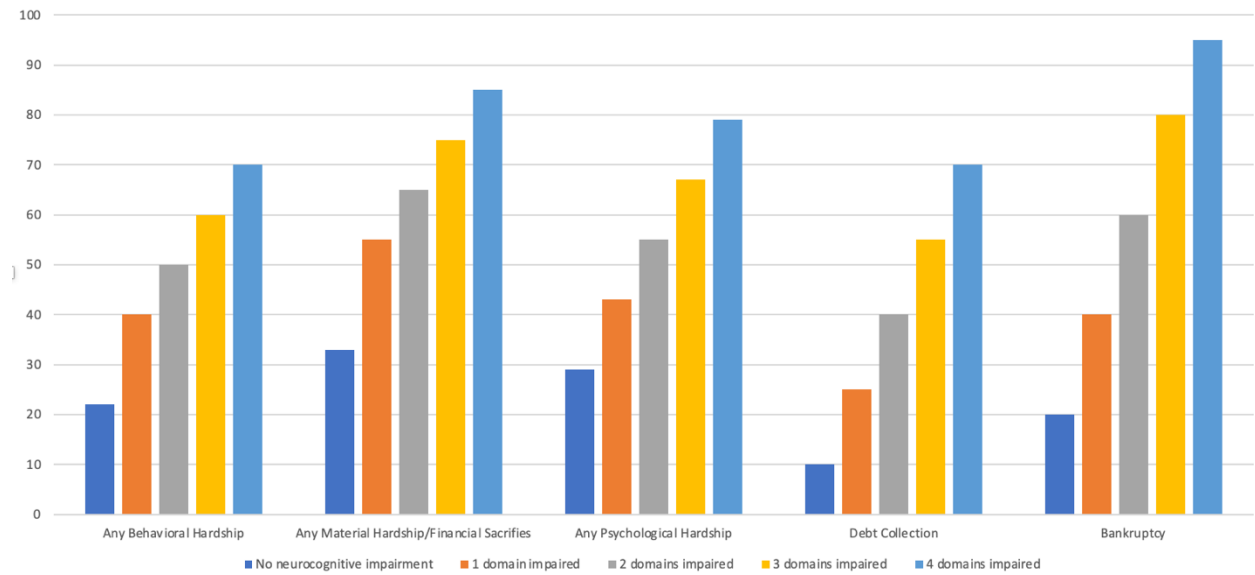


CNS	***	***	***	***	***	***	
Hodgkin lymphoma	***	***	***	***	***	***	
Non-Hodgkin lymphoma	***	***	***	***	***	***	
Wilms' tumor	***	***	***	***	***	***	
Neuroblastoma	***	***	***	***	***	***	
Soft-tissue sarcoma	***	***	***	***	***	***	
Bone cancer	***	***	***	***	***	***	
Anthracycline (mg/m <sup>2</sup> in doxorubicin equivalent dose)							***
None	***	***	***	***	***	***	
>0 to <250	***	***	***	***	***	***	
≥250	***	***	***	***	***	***	
Alkylating agent (mg/m <sup>2</sup> in cyclophosphamide equivalent dose)							***
None	***	***	***	***	***	***	
>0 to <4,000	***	***	***	***	***	***	
4,000 to <8,000	***	***	***	***	***	***	
≥8,000	***	***	***	***	***	***	
Stem-cell transplant							***
Yes	***	***	***	***	***	***	
No	***	***	***	***	***	***	
Radiation therapy							***
None	***	***	***	***	***	***	
TBI only	***	***	***	***	***	***	
Cranial RT, no TBI	***	***	***	***	***	***	
Chest RT without cranial or TBI	***	***	***	***	***	***	
Other RT	***	***	***	***	***	***	
Chronic health burden							***
None/low	***	***	***	***	***	***	
Medium	***	***	***	***	***	***	
High	***	***	***	***	***	***	
Very high	***	***	***	***	***	***	

**Supplementary Table 1. Financial hardship among survivors by number of domains of neurocognitive impairment**

Hardship Domain	Survey Question	Number of domains of neurocognitive impairment					P
		0	1	2	3	4	
Behavioral	Within the last 12 months have you forgone...						
	... any needed medical care?	***	***	**	**	**	***
	... specialist visit?	***	***	**	**	**	***
	... annual primary care visit?	***	***	**	**	**	***
	... prescription medicine?	***	***	**	**	**	***
	... dental care?	***	***	**	**	**	***
	... follow up care?	***	***	**	**	**	***
	... eyeglasses?	***	***	**	**	**	***
	... mental health care/counseling?	***	***	**	**	**	***
Material/ financial sacrifices	Within the past 2 years, have you...						
	... reduced spending on vacation or leisure?	***	***	**	**	**	***
	... delayed or reduced spending on home improvement?	***	***	**	**	**	***
	... reduced spending for large purchases?	***	***	**	**	**	***
	... used savings set aside for other purposes?	***	***	**	**	**	***
	... reduced spending on basics?	***	***	**	**	**	***
	... made a change to living situation?	***	***	**	**	**	***
	Currently do you ...	***	***	**	**	**	***
	... have problems paying medical bills?	***	***	**	**	**	***
	... pay off medical bills over time?	***	***	**	**	**	***
Psychological	Within the last 12 months, do you worry/stress about having enough money to ...						
	... pay household utilities?	***	***	**	**	**	***
	... pay rent or mortgage?	***	***	**	**	**	***
	... buy nutritious meals?	***	***	**	**	**	***
Individual questions not mapped to a specific domain	Have you ever been sent to debt collection?	***	***	**	**	**	***
	Have you ever filed for bankruptcy protection?	***	***	**	**	**	***

**Figure 1. Proportion reporting any financial hardship in each domain by neurocognitive status**



**Table 3. Adjusted prevalence ratios of financial hardship domains in survivors by number and type of neurocognitive domain impaired**

	Psychological Hardship		Material Hardship / Financial Sacrifices		Behavioral Hardship		Debt Collection		Bankruptcy	
	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*
<b>By number of domains impaired</b>										
No neurocognitive impairment	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
1 domain impaired	***	***	***	***	***	***	***	***	***	***
2 domains impaired	***	***	***	***	***	***	***	***	***	***
3 domains impaired	***	***	***	***	***	***	***	***	***	***
4 domains impaired	***	***	***	***	***	***	***	***	***	***
<b>Specific domain impaired</b>										
Memory	***	***	***	***	***	***	***	***	***	***
Task Efficiency	***	***	***	***	***	***	***	***	***	***
Organization	***	***	***	***	***	***	***	***	***	***
Emotional Regulation	***	***	***	***	***	***	***	***	***	***

\*Adjusted for sex, race/ethnicity, age at survey completion, number of household members, health insurance coverage, marital status, cancer diagnosis, cumulative anthracycline exposure, cumulative alkylating agent exposure, stem cell transplant, radiation therapy, and chronic health burden

**Table 4. Adjusted prevalence ratios of financial hardship domains in survivors by level of neurocognitive impairment and educational attainment**

	Psychological Hardship		Material Hardship / Financial Sacrifices		Behavioral Hardship		Debt Collection		Bankruptcy	
	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*	Unadjusted PR	Adjusted PR*
No/less neurocognitive impairment, high educational attainment	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
No/less neurocognitive impairment, low educational attainment	***	***	***	***	***	***	***	***	***	***
Worse neurocognitive impairment, high educational attainment	***	***	***	***	***	***	***	***	***	***
Worse neurocognitive impairment, low educational attainment	***	***	***	***	***	***	***	***	***	***

\*Adjusted for sex, race/ethnicity, age at survey completion, number of household members, health insurance coverage, marital status, cancer diagnosis, cumulative anthracycline exposure, cumulative alkylating agent exposure, stem cell transplant, radiation therapy, and chronic health burden







## APPENDIX A.

<b>Hardship Domain</b>	<b>Survey Question</b>
Behavioral	Within the last 12 months have you forgone...
	... any needed medical care?
	... specialist visit?
	... annual primary care visit?
	... prescription medicine?
	... dental care?
	... follow up care?
	... eyeglasses?
	... mental health care/counseling?
Material/financial sacrifices	Within the past 2 years, have you...
	... reduced spending on vacation or leisure?
	... delayed or reduced spending on home improvement?
	... reduced spending for large purchases?
	... used savings set aside for other purposes?
	... reduced spending on basics?
	... made a change to living situation?
	Currently do you ...
	... have problems paying medical bills?
	... pay off medical bills over time?
Psychological	Within the last 12 months, do you worry/stress about having enough money to ...
	... pay household utilities?
	... pay rent or mortgage?
	... buy nutritious meals?
Individual questions not mapped to a specific domain	Have you ever been sent to debt collection?
	Have you ever filed for bankruptcy protection?

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