1. Study Title: Psychological and Neurocognitive outcomes in survivors diagnosed with cancer as adolescent and young adults

2. Working Group: Psychology

2.1 Investigators:

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* I am a new investigator and appreciate the opportunity to work with the CCSS data. I am a new pediatric hematology/ oncology faculty member at LSU Children's Hospital in New Orleans. I have had the opportunity to start a late effects clinic in Louisiana though I have been interested in late effects and clincal research incorporating late effects for many years. I trained at Vanderbilt University and completed a MPH while looking at data from the Bone Marrow Transplant group. With my clinical practice, I have had the opportunity to observe diverse neurocognitive and psychological outcomes of patients that are concerning to families. It was through this experience that I decided to write the current proposal.

3. Background/Rationale:

Currently there are estimated to be over 300,000 survivors of childhood and young adult cancer in the U.S[1, 2]. However, survival is associated with a cost. Two-thirds of those who survive face at least one chronic health condition [3, 4]. As multi-modality therapies increase the success of curing childhood and young adult cancer, there are a growing number of adolescent and young adult survivors that have medical and psychological sequelae from their treatment. There are many studies that have examined survivors of childhood cancer, but few that have focused on survivors who were diagnosed with cancer during their adolescence or young adulthood.

Adolescence and young adulthood is a period of advanced neurocognitive and brain maturation, a time when functional patterns are established and engrained [5]. The brain continues to develop throughout adolescence and into young adulthood, with accelerated development of higher order skills such as executive functions and social cognition [5, 6]. The full extent of executive dysfunction may only become evident in late childhood and adolescence, when children are required to act more independently and utilize planning and reasoning abilities[7]. Literature from traumatic brain injury patients demonstrates that mild injury during early adolescence can impact executive function that is not seen in mild injury during younger childhood or when compared to typically developing early adolescents [8]. Studies using magnetic resonance imaging of the adolescent brain have shown periods of rapid development in temporal gray matter, areas related to memory and emotional functions, and also the dorsal lateral prefrontal cortex, important for abstract reasoning and problem solving, during early adolescence (i.e. 11-15 years of age).[9] Thus, within the adolescent age range, the period of time between 11-15 years of age may be more sensitive to disrupted function compared to the phase of older adolescence (i.e. 16-21 years of age) or even pre-adolescence (i.e. 6-10 years of age). Neurocognitive

dysfunction has been demonstrated in up to 40% of childhood cancer survivors, with relatively higher rates of problems in processing speed, attention or memory [10, 11]. Difficulties in higher order executive functions have been examined less frequently. Since children diagnosed during adolescence are usually collapsed into a larger range of patient diagnostic ages, neurocognitive deficits, particularly executive dysfunction, have not been well studied in survivors diagnosed during adolescence.

In addition to important neurocognitive developments, adolescents and young adults also experience a number of socioemotional changes, including the formation of critical peer relations, development of career, religious, and political identities, and knowledge about responsibilities and activities required for independent living [12]. Adolescent age at diagnosis, length of survivorship, current age and life transitions may all affect emotional adjustment of adolescent and young adult cancer survivors [13, 14]. Treatment of AYAs can be longer and more challenging than that of younger children due to unique developmental and psychosocial aspects of adolescence [13]. Current studies have shown that childhood cancer survivors transitioning out of adolescence may be at greater risk for psychological issues such as post traumatic stress disorder when compared to their younger peers[15-17].A recent study by Kazak et al examined psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancers and compared them to age matched controls. They found survivors diagnosed during adolescence (over the age of 13 years) to be more likely to report symptoms of post-traumatic stress disorder and re-experience symptoms than those diagnosed between the ages of 6 and 12 years. Survivors had lower psychosocial health related quality of life, and significantly lower health perceptions and cognitive competence than those diagnosed earlier [18]. Survivors with the highest level of treatment intensity had greater anxiety and fewer positive health beliefs. Stuber et al found that survivors of childhood cancers were four times more likely to experience symptoms of post-traumatic stress disorder when compared to their siblings [19]. Treatment intensity and older age at diagnosis were significant predictors of post-traumatic stress symptoms. [20, 21]The aim of this study is to characterize emotional and neurocognitive function in long-term survivors of childhood cancer diagnosed during the time of adolescence, and to identify risk factors within this group that may guide the development of targeted interventions to reduce adverse behavioral and social outcomes.

4. Specific Aims:

4.1 Primary Aim:

4.1.1 To describe neurocognitive and emotional functioning among long-term survivors of cancer diagnosed during adolescence and young adulthood, defined as 11 to 21 years of age

4.2 Secondary aims:

4.2.1. To identify periods of relative sensitivity within the adolescent range for emotional and neurocognitive outcomes.

Rationale for primary and secondary aims: To provide a characterization of psychological outcomes in survivors who were diagnosed with cancer during adolescence. There are very few publications that report on outcomes for those diagnosed with cancer during the AYA age ranges. Previous CCSS studies examining psychological and neurocognitive outcomes have used a variety of age at diagnosis contrasts (e.g. Zebrack 2002, <10 vs. > 10; Zebrack 2004, 0-4 vs. 5-11 vs. ≥12; Zeltzer 2008, 03 vs.

4-9 vs. 10-14 vs. 15-20; Kadan-Lottick 2010, 0-5 vs. ≥6), with none clearly focused on adolescent phases.

4.3 Hypothesis:

4.3.1 Survivors of cancer diagnosed during adolescence and young adulthood will be at increased risk for emotional distress compared to siblings and survivors diagnosed at a younger age.

4.3.2 Compared to siblings, survivors diagnosed during adolescence and young adulthood will exhibit higher rates of executive dysfunction.

4.3.3 Survivors diagnosed during early adolescence (i.e. 11-15 years of age) will be at increased risk for neurocognitive impairment compared to survivors diagnosed during late adolescence (i.e. 16-21 years).

Rationale for hypotheses: Various studies have shown that early adolescence to young adulthood is a phase when emotional and behavioral patterns become engrained. Executive functions that are important for problem solving and emotional stability undergo rapid development in adolescence. We are aware that children diagnosed before the age of six years are at highest risk for poor neurocognitive outcomes but there are still other phases of development that occur during adolescence that have not been well studied. From the traumatic brain injury literature, adolescents are at high risk for executive function deficits. We believe that it is important to compare this group to the pre-adolescents (6-10 years) and the post adolescent (16-21) ranges for reference.

5. Methods:

5.1 ***Population***: Cancer survivors and siblings who completed the Follow-up 2003 survey and completed both the BSI-18 and the CCSS-NCQ.

5.2 ***Feasibility***: Preliminary analyses show 2492 survivors diagnosed during adolescence, between 11-21 years, completed both NCQ and BSI at Follow-up 2003, radiation dosimetry is available for 2275 of these participants.

5.3 ***Outcomes of interest***: The primary outcomes of interest are emotional functions, as assessed with BSI scales of somatization, depression and anxiety, and neurocognitive functions, as assessed by the NCQ domains of task efficiency, emotional regulation, organization and memory.

5.4 ***Predictors:***

- Age at time of diagnosis: <6 yrs of age, 6-10 yrs of age, 11-15 yrs of age, 16-21 yrs of age

5.5 ***Covariates:***

- Age at Questionnaire (Baseline A2)
- Length of Follow-up
- Gender (Baseline A2)
- Race/Ethnicity (Baseline A4, 4a)

- Education (FU 2003, Q1)
- Employment (FU 2003, Q4)
- Marital Status (FU 2003, Q2, Q3)
- Chemotherapy
    - Antimetabolites (Categorize variable for IV and IT Methotrexate)
    - Corticosteroids (yes/no)
- Cranial Radiation (none, ≤18Gy, >18-24Gy, >24Gy)
- Surgery(yes/no)
- Health Insurance Status (FU 2003 Section M)
- Household Income (Baseline Q8)
- Anti-depressant and anti-anxiety medications (FU 2003, Section Q)

5.7 Statistical Modeling:

5.7.1. Frequency distributions will be used to categorize relevant outcome variables, predictors and covariates according to reasonable groupings consistent with previous CCSS manuscripts.(table I)

5.7.2 Descriptive statistics including means, medians, standard deviations, ranges, frequencies and percents will be calculated for the primary outcome of interest (BSI and NCQ) (table II and III)

5.7.3 Comparisons of the primary outcome variables (BSI and NCQ) will be made between the different ages at time of diagnosis using logistic regression (table IV). Outcomes will be classified as impaired based on performance falling below 10%ile of reference norms.

5.7.4 A multivariate model adjusted for chemotherapy, CNS treatment and radiation will be developed and odds ratios (OR) and 95% confidence intervals will be reported for the comparison between groups of survivors defined by age of diagnosis (<6, 6-10, 11-15, 16-21, but may be combined if outcome data is sparse). Separate models will be constructed for each primary outcome. All factors listed above will be evaluated and included in a final model if they are significant at $p<0.05$, or if they modify the effect of age at diagnosis on the outcome of interest (more than 10% change in OR). Interactions between age at diagnosis and treatment variables will be evaluated, though likely it will be necessary to combine ages 11-21 into a single group for this.

6. Examples of Tables:

Table 1:

Descriptive Statistics at Baseline

	Survivor		Sibling	
	No.	%	No.	%
Current Age				
< 15 yrs				
15-19 yrs				
20-24 yrs				
25-29 yrs				
30-34 yrs				
≥ 35 yrs				
Length of follow-up			N/A	
Sex				
Female				
Male				
Age at Diagnosis			N/A	
<6 yrs				
6-10 yrs				
11-15 yrs				
16-21 yrs				
Diagnosis			N/A	
Leukemia				
CNS				
HD				
NHL				

Wilms'	
Neuroblastoma	
Soft tissue sarcoma	
Osteosarcoma	
Overall treatment	N/A
Surgery Only	
Chemotherapy	
Radiation	
Chemotherapy and Radiation	
No surgery, chemotherapy or radiation	
Unknown	
Chemotherapy	N/A
Antimetabolites	
Corticosteroids	
CNS Radiation	N/A
None	
<18 Gy	
>18 – 24 Gy	
> 24 Gy	
Second Malignancy or Recurrence	N/A
Education	
< 8 yrs	
9-12 yrs	
High school grad	
Post HS Training	
College	
Post Grad	
Employment	
Unable to work	

Unemployed

Student

Working PT

Working FT

Income

<20,000

20,000-39,999

40,000-59,999

60,000-79,999

80,000-99,999

>100,000

Marital Status

Single

Married

Living as married

Divorced/Separated

Health Insurance Status

Yes

No

Medications

Anti-depressants

Anxiolytics

Table II

Survivor Descriptive Statistics for BSI-18

	Somatization	Depression	Anxiety
Age at Time of Diagnosis			
<6 yrs			
N%			
Mean			
SD			
Median			
% impaired at ≥ 90th%ile			
6- 10 yrs			
N%			
Mean			
SD			
Median			
% impaired at ≥ 90th%ile			
11-15 yrs			
N%			
Mean			
SD			
Median			
% impaired at ≥ 90th%ile			
16-21 yrs			
N%			

Mean

SD

Median

% impaired at ≥ 90th%ile

Table III

Survivor Descriptive Statistics for NCQ

	Task Efficiency	Emotional Regulation	Organization	Memory
Age at Time of Diagnosis				
<6 yrs				
N%				
Mean				
SD				
Median				
% impaired at ≥ 90th%ile				
6-10 yrs				
N%				
Mean				
SD				
Median				
% impaired at ≥ 90th%ile				
11-15 yrs				
N%				
Mean				
SD				
Median				
% impaired at ≥ 90th%ile				
16-21 yrs				

N%	
Mean	
SD	
Median	
% impaired at≥ 90th%ile	

Table IV

Multivariate model for the prediction of psychological function and neurocognitive outcomes by age at diagnosis with adjustment for all listed variables

[We understand that the variables shown will vary depending on different risk factors for the multivariate model].

	Somatization	Depression	Anxiety
	OR, 95% CI, p	OR, 95% CI, p	OR, 95% CI, p
Age at diagnosis			
<6 yrs			
6-10 yrs			
11-15 yrs			
16-18 yrs			
16-21 yrs			
Current Age*			
Chemotherapy			
Antimetabolites			
Corticosteroids			
Cranial Radiation			
No radiation			
Cranial radiation ≤ 18 Gy			
Cranial radiation > 18-24 Gy			

Cranial radiation >24 Gy

Second Malignancy

No

Yes

Table V

Multivariate model for the prediction of psychological function and neurocognitive outcomes by age at diagnosis with adjustment for all listed variables

[We understand that the variables shown will vary depending on different risk factors for the multivariate model].

	Task Efficiency	Memory	Emotional Regulation	Organization
	OR, 95% CI, p	OR, 95% CI, p	OR, 95% CI, p	OR, 95% CI, p
Age at diagnosis				
<6 yrs				
6-10 yrs				
11-15 yrs				
16-18 yrs				
16-21 yrs				
Current Age*				
Chemotherapy				
Antimetabolites				
Corticosteroids				
Cranial Radiation				
No radiation				
Cranial radiation ≤ 18 Gy				
Cranial radiation > 18-24 Gy				
Cranial radiation >24 Gy				
Second Malignancy				

No

Yes

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