CCSS Analysis Concept Proposal

Study Title: Neurocognitive Outcomes in Survivors of Early Adolescent and Young Adult Hematologic Cancers

Working Group and Investigators: This project is developed through the Psychology Working Group with secondary oversight by the Chronic Disease Working Group.

Amy Wang	Amy.Wang@uchospitals.edu	The University of Chicago
Tara Henderson	thenderson@peds.bsd.uchicago.edu	The University of Chicago
Wendy Stock	Wstock@medicine.bsd.uchicago.edu	The University of Chicago
Kevin Krull	Kevin.Krull@stjude.org	St Jude Children's Research Hospital
Yutaka Yasui	Yutaka.Yasui@stjude.org	St Jude Children's Research Hospital
Wendy Leisenring	wleisenr@fhcrc.org	Fred Hutchinson Cancer Research Center
Greg Armstrong	Greg.Armstrong@stjude.org	St Jude Children's Research Hospital
Kevin Oeffinger	Kevin.Oeffinger@duke.edu	Duke University
Eric Chow	ericchow@uw.edu	University of Washington

Background and Rationale:

Advancements in cancer diagnosis and management over the past several decades have improved 5-year overall survival rates across all age groups.[1] With more than 80% of pediatric and young adult patients now achieving long-term survivorship, an understanding of the late health effects of cancer treatments is critical, as survivors are at high risk for developing treatment-related co-morbidities.[1–3]

The adolescent and young adult (AYA) cancer survivors represent one such group where treatment-related health effects are of paramount importance. The AYA cohort consists of patients diagnosed with cancer between the ages of 15-39, making up approximately 78,000 or 6% of new diagnoses annually in the United States.[4] Due to their life stage at diagnosis, AYAs with cancer face significant life disruptions that give rise to unique psychosocial challenges not typically seen in other age cohorts.[5] Some challenges include interruptions in educational and career pursuits, social isolation from disrupted peer relationships, threatened fertility potential, financial toxicities of treatment, and body image issues.[6] Altogether, these experiences can alter their sense of self and lead to psychological distress.[6] There is evidence to suggest that neurocognitive function plays an important role in an adolescent or early young adult cancer survivor's ability to overcome these life challenges after cancer.[7,8] However, much of the literature on neurocognitive outcomes have focused on survivors of childhood cancers.[9–15] Due to the high intensity nature of treatments most leukemias and lymphomas, a better understanding of the neurocognitive outcomes in adult survivors of early AYA hematologic cancers is urgently needed.

Cancer-related neurocognitive impairment occurs as a result of chemotherapy, neurosurgery, or radiation treatment.[16] More than 40% of childhood cancer survivors report having neurocognitive problems, and these impairments may contribute to emotional distress, lower health-related quality of life (HRQOL), and reduced education attainment and employment.[9,15,17] Objective neuropsychological testing in survivors of non-central nervous system (CNS) cancers demonstrated impairments across multiple domains involving concentration, memory, processing speed, and executive function.[9–13,18]

Corresponding structural changes on brain imaging have also been reported in survivors.[18,19] Factors associated with worse neurocognitive outcomes included treatment less than 6 years of age, female sex, cranial radiation therapy, hearing impairment, and intrathecal chemotherapy.[9–12,15,20] Furthermore, there is evidence for evolving neurocognitive impairments over time, according to Liu et al, who reported worse executive function but improved sustained attention in survivors at long-term (> 5 year) follow up when compared with the end of therapy.[10] In recognition of these poor outcomes, the treatment of pediatric cancers, in particular acute lymphoblastic leukemia (ALL), has evolved to minimize CNS directed therapies, which have reduced but not yet mitigated the risk for neurocognitive impairment.[11,12] In addition, the landscape of pediatric cancer treatments has evolved towards risk-adapted or response-adapted approaches to treatment, guided by tumor biology, individual genetics, and imaging.[21] It is similarly important to understand the effects on neurocognition from these shifts in therapeutic approaches and intensity on the early AYA hematologic cancer survivor population.

With respect to the AYA cohort, the adolescent period is a time of significant morphological and physiological changes in the human brain, and maturation of the prefrontal cortex is typically not complete until approximately 25 years of age.[22] This suggests that the AYA brain may be susceptible to the effects of cancer treatment. A report from the Childhood Cancer Survivor Study (CCSS) by Prasad et al found that survivors of early AYA cancer (primary cancer diagnosis at age 11-21 years) reported more problems with task efficiency, emotional regulation, memory, as well as depression and anxiety when compared with sibling controls.[7] Moreover, impaired task efficiency increased risk for unemployment, not being college educated, and not living independently.[7] This study has laid the groundwork for conducting further research in neurocognitive outcomes in the AYA cancer survivor cohort.

Since the publication of the 2015 report by Prasad et al, additional neurocognitive data are now available through the CCSS expansion cohort, which provided additional participants plus longitudinal follow-up. The data would reflect neurocognitive outcomes as a result of even longer-term follow up as well as the advancements in therapeutics across multiple decades. Neurocognitive function was assessed by the CCSS – Neurocognitive Questionnaire (CCSS-NCQ), which is a self-reported instrument consisting of 4 subscales of task efficiency, emotional regulation, planning/organization, and working memory.[20] This instrument was validated in both pediatric and early AYA cancer survivor cohorts.[7,15,20,23] The current proposal seeks to conduct a focused study of neurocognitive outcomes in adult survivors of early AYA hematologic cancers (age 15-21 at diagnosis) with the aim to describe changes in neurocognitive impairment across treatment groups that reflect shifts in therapeutic approaches, as well as evolution of impairments with advancing time (and age) after diagnosis.

Specific Aims:

1. To characterize the prevalence of neurocognitive impairments in long-term survivors of early AYA (eAYA) hematologic cancers stratified across treatment groups in comparison to survivors who were diagnosed at age <15 years, as well as a sibling control group
2. To characterize the evolution of neurocognitive impairments over time after cancer diagnosis in long-term survivors of eAYA hematologic cancers.
3. To identify treatment-related factors associated with development of neurocognitive impairment in survivors of eAYA hematologic cancers.

4. To examine the impact of neurocognitive impairment on health status, health behaviors, healthcare utilization, and social functioning in survivors of eAYA hematologic cancers.

Research Hypotheses:

1. The prevalence of neurocognitive impairments in survivors of eAYA hematologic cancers will be higher than their sibling controls but lower than survivors of childhood cancers, adjusted for age and sex, but the prevalence will vary by treatment groups that reflect shifts in treatment approaches.
2. The longitudinal trajectory of neurocognitive impairment will vary across each of the 4 domains – emotional regulation, organization, task efficiency, and memory – and impairments in executive function (e.g. emotional regulation and organization) will worsen over time.
3. Survivors who received cranial radiation therapy and higher cumulative doses of methotrexate will report worse neurocognitive impairment.
4. Survivors with neurocognitive impairment will report lower health status (e.g. chronic medical conditions), worse health behaviors (e.g. tobacco, alcohol, physical activity), health care utilization, and social functioning (e.g. education attainment, employment status, ability to live independently).

Analysis Framework:

1. Study Population

The population of interest is all survivors (≥ 5 years from diagnosis) of ALL, acute myeloid leukemia (AML), or Hodgkin lymphoma who were diagnosed at age ≥ 15 years between 1970 – 1999, who participated in the CCSS original (1970 – 1986) and expansion (1987 – 1999) cohorts, and who completed the CCSS-NCQ as part of 2003 follow-up #2 (FU2) and/or 2014 follow up #5 (FU5) and/or 2017 follow up #6 (FU6). This group will subsequently be referred to as the "eAYA survivor" group. To provide a basis for comparison, a cohort of younger survivors diagnosed at age <15 years, subsequently referred to as the "childhood survivor" group, along with a sibling cohort, will serve as the controls.

To focus the analysis, we chose to exclude survivors of other leukemias (e.g. chronic myeloid leukemia) and non-Hodgkin lymphoma due to low subject numbers and the heterogeneity of treatment.

DIAGNOSIS	Frequency of eAYA survivors	Percent
Leukemia	401	30.9
ALL	315	24.3
AML	86	6.6
Hodgkin Lymphoma	896	69.1
Total	1,297	100.0

The "initial assessment" as referenced below refers to FU2 (2003) for the original cohort and FU5 (2014) for the expansion cohort. This means that FU2 was the initial assessment for survivors from the 1980-1986 cohort, and those from 1987-1989 took their first assessment in FU5. Follow up assessments for the original cohort include FU5 and FU6; follow up assessment for the expansion cohort includes FU6 only.

2. Outcomes of interest

The primary outcome will be neurocognitive function as assessed by the CCSS-NCQ (FU2, J1-25; FU5, Q1-33; FU6, G1-33), which is a self-reported survey of cognitive and emotional function consisting of 4 subscales of task efficiency, emotional regulation, planning/organization, and working memory. Participants from follow up #2 received the original 25-item NCQ, and follow up #5 and #6 (long) received the revised NCQ, which is a 33-item measure on a 3-point Likert scale. This revised version includes 19 items from the original NCQ plus an additional 14 items to increase sensitivity,[20] and this overlap allows for adequate comparison of results in a longitudinal manner. This instrument has been validated in pediatric and AYA cancer survivor cohorts.[7,15,20,23] The NCQ is scored for each survivor by calculating a total raw score for each scale. Impairment is defined as falling $\leq 10^{th}$ percentile based on values obtained in the sibling cohort.

3. Co-variates to be analyzed

Predictor Variables:

a. Sex (Baseline original, A2; baseline expansion, A2)
b. Race/ethnicity (Baseline, A4, A4a; baseline expansion A5, A5a)
c. Age at time of assessment (in years)
    i. Age at FU2
    ii. Age at FU5
    iii. Age at FU6
d. Diagnosis
    i. Acute lymphoblastic leukemia (ALL)
    ii. Acute myeloid leukemia (AML)
    iii. Hodgkin disease (HD)
e. Treatment groups (**We plan to aggregate into fewer groups for the analysis. For the purposes of this proposal, these groups for the time being will be represented by a default "ALL 1-3", "AML +/-SCT", and "HD 1-3"*)
    i. ALL survivors (Dixon's tx categories)
        1. Relapse/Transplant
        2. 1970s-like
        3. 1980s SR-like
        4. 1980s HR-like
        5. 1990s SR/Essig
        6. 1990s HR-like
        7. Unknown
        8. Other
    ii. AML survivors
        1. Chemotherapy
        2. Chemotherapy + stem cell transplant (SCT)
    iii. Hodgkin lymphoma survivors (Oeffinger's tx categories)
        1. High risk relapse or transplant
        2. High risk RT only
        3. High risk combined modality
        4. High risk chest RT only

5. Intermediate combined (15-34.9 Gy + anthracycline AND alkylator)
6. Intermediate combined (15-34.9 Gy + anthracycline OR alkylator)
7. Low risk
8. Unknown RT or chemo
9. Other

f. Education level achieved (FU2, #1; FU5, A4) (limit to >25yr olds)
   i. < 12 years
   ii. High school graduate
   iii. College graduate
   iv. Postgraduate level
g. Employment (FU2, #4; FU5, A5) (limit to >25yr olds)
   i. Unable to work (includes "retired")
   ii. Unemployed (includes "caring for home or family")
   iii. Student
   iv. Working part time
   v. Working full time
h. Marital Status (FU2, #2; FU5, M2) (limit to >25yr olds)
   i. Single
   ii. Married/living as married
   iii. Divorced/separated
   iv. Widowed
i. Household income (FU2, S1; FU5, A7)
   i. < $20,000
   ii. $20,000 - $39,999
   iii. $40,000 - $59,999
   iv. ≥ $60,000
j. Health insurance status (yes/no) (FU2, M1; FU5, A10)
   i. Yes / Canadian resident
   ii. No
k. Live independently[24] (yes/no) (FU2, #3; FU5, M1) (limit to >25yr olds)
   i. Yes (live with spouse, live alone, roommate, or other non-dependent living situation)
   ii. No (live with parent, brother/sister, other relatives, or specified nursing/caregiver support)
l. Chronic health conditions (Grade ≥2, based on CTCAE grading criteria)
   i. Cardiac
   ii. Respiratory
   iii. Endocrine
   iv. Neurologic
m. Treatment characteristics
   i. Surgery (yes/no)
   ii. Chemotherapy (yes/no)
      1. Antimetabolites (methotrexate cumulative dose for IV and IT)
         a. None

b. Any antimetabolite
c. Methotrexate (MTX) – IV/PO/IM
d. Methotrexate – IT/Ommaya

2. Corticosteroids
    a. Dexamethasone (Dex)
    b. Prednisone (Pred)
    c. Hydrocortisone (HC)
3. Anthracycline, cumulative dose (mg/m2)
    a. None
    b. >0 - <250
    c. 250 - <400
    d. ≥ 400
4. Alkylating agent (CED, mg/m2)
    a. None
    b. >0 - <4,000
    c. 4,000 - <8,000
    d. 8,000 - <12,000
    e. 12,000 - <16,000
    f. 16,000 - <20,000
    g. ≥ 20,000
5. Vinca alkaloid cumulative dose (mg/m2)
6. Platinum cumulative dose (mg/m2)
7. L-asparaginase (yes/no)

iii. Any radiation
1. CNS radiation (should include contribution of TBI)
    a. None and indirect
    b. Direct <20 Gy
    c. Direct ≥20 Gy
2. Chest radiation (yes/no)
3. Other sites (yes/no)

Outcome variables to be analyzed

a. Education level achieved (limit to >25yr olds)
    i. College graduate
    ii. < College graduate
b. Employment (limit to >25yr olds)
    i. Employed
    ii. Unemployed
c. Marital Status (limit to >25yr olds)
    i. Ever married
    ii. Never married
d. Household income
    i. ≥ $60,000
    ii. < $60,000

e. Health insurance status (yes/no)
f. Live independently (limit to >25yr olds) (yes/no)
g. General health status (FU2, E1; FU5, O1; FU6, E1)
    a. Poor ("poor" or "fair")
    b. Not poor
h. Tobacco[25] (FU2, L1-5; FU5, N7-12)
    a. Ever smoked (defined as exposures to at least 100 cigarettes and no longer smoking)
    b. Current smoker (defined as exposure to at least 100 cigarettes and smoking on a regular basis)
    c. Never smoker (defined as exposure to less than 100 cigarettes in one's lifetime)
i. Alcohol[25,26] (FU5, N1-6)
    a. Heavy drinking (defined as ≥5 drinks/day for women and ≥6 drinks/day for men at least once a month in the past year)
    b. Risky drinking (defined as >3 drinks/day or 7 drinks/week for women, and >4 drinks/day or 14 drinks/week for men)
    c. Current drinker (defined as one or more drinks in the past year)
    d. No alcohol use (defined as <2 drinks in one's lifetime)
j. Physical activity, in MET-hours per week[27] (FU2, D1-7, E3-12; FU5, N15-21, N29, O3a-j; FU6, D1-7, E3a-j)
    a. 0
    b. 3-6
    c. 9-12
    d. 15-21
k. Health care utilization (in preceding 2 years, responses not mutually exclusive)[26] (FU2, A1, A2, A4, A6, A8; FU5, B1, B4, B4a, B4b, B4c, B4d; FU6, B1, B4, B4a, B4b, B4c, B4d)
    a. No medical care
    b. General medical care (medical visit unrelated to their prior cancer)
    c. General survivor-focused care (medical visit related to their prior cancer)
    d. Risk-based survivor-focused care (medical visit related to their prior cancer in which screening tests were discussed or ordered or the survivor was counseled on how to reduce his/her specific risks)

4. Analysis

Aim 1: Descriptive statistics will be calculated for demographic and treatment variables for the eAYA survivors, childhood survivors, and their sibling controls. Differences between survivors and siblings will be evaluated using logistic regression with a generalized estimating equation (GEE) robust variances to account for intra-family correlations. If the prevalence of impaired neurocognition does not exceed 10%, we will use generalized linear models with a log-link function and Poisson error with robust variances to directly estimate prevalence ratios for all models, but for ease of presentation we refer to logistic regression throughout the proposal plan. CCSS-NCQ T scores will be summarized for survivors and siblings. Results of the subscales within 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 the impaired range,

which corresponds to ≤10% range of siblings' scores or approximately T scores of 63 or higher, as defined in previous studies.

The prevalence of neurocognitive impairment between survivors and siblings across different treatment groups will be compared on each of the four subscales of the CCSS-NCQ by use of logistic regression with GEE robust variances to account for intra-family correlations, adjusting for age and sex. The subgroups listed in the tables below may be aggregated for sample size/power considerations based on expoloratory data analysis (EDA).

Hodgkin Disease (HD) treatment groups in eAYA survivors (N=896)			
HD paper definition	**Treatment group description**	**Frequency**	**Percent**
High risk relapse or transplant	Within 5 years of diagnosis	83	9.26
High risk RT only	Chest, abdomen, and pelvis directly radiation dose>=3500cGy	244	27.23
High risk combined modality	Chest radiation dose>=3500 and (has anthracycline or has alkylating)	82	9.15
High risk chest RT only	Chest radiation dose>=3500 and (without anthracycline and alkylating)	72	8.04
Intermediate combined (15-34.9 Gy +anth AND CED)	1500<=Chest radiation dose<3500 and (has anthracycline and has alkylating)	110	12.28
Intermediate combined (15-34.9 Gy +anth OR CED)	1500<=Chest radiation dose<3500 and (has anthracycline or alkylating)	73	8.15
Low risk	Without chest radiation and has anthracycline and has alkylating)	53	5.92
Unknown RT or chemo	One of Chest radiation, anthracycline or alkylating information is missing	132	14.73
Other	1500<=Chest radiation dose<3500 and (without anthracycline or alkylating) or others	47	5.25

ALL treatment groups in eAYA survivors (N=315)			
ALL paper definition	**Treatment group description**	**Frequency**	**Percent ***
Relapse/Transplant	Within 5 years of diagnosis	42	13.21
1970s-like	CRT>20Gy and Cytarabine IT in original cohort and no Cytarabine in expanded cohort and no Dexamethasone	28	8.07
1980s SR-like	0<CRT<=20Gy and no Dexamethasone and 0<Anthracycline<=120mg/m2	38	11.43
1980s HR-like	CRT>0 and and Cytarabine IV/IM, SUB-Q in original cohort and with any Cytarabine in the expanded cohort and no Dexamethasone and Anthracycline>120mg/m2	28	8.75

1990s SR/Essig	CRT=0 and 0<Anthracycline<=120mg/m2 and 0<Cyclophosphamide<=1000mg/m2	24	8.08
1990s HR-like	With Dexamethasone and Anthracycline>120mg/m2 and Cyclophosphamide>1000mg/m2	42	14.22
Unknown	Any treatment information missing in the other groups	31	9.61
other	other	82	26.63

*percent considered the sample weight of ALL

Aim 2: Next, for all hematologic cancer survivors and siblings who have multiple data points, the impairments in each subscale will be analyzed in a longitudinal fashion stratified by either diagnosis or treatment group, using the same GEE models as Aim 1 to account for intra-subject correlations across multiple time points, adjusted for age and sex. Further sub-group analysis will be performed to track the trajectories of the survivors who were impaired at the initial assessment as well as those who were not impaired.

Aim 3: In a separate model of the same longitudinal GEE analysis, associations between treatment characteristics and neurocognitive impairment across the 4 subscales will be analyzed in the eAYA and childhood survivor population to identify independent treatment-related risk factors for neurocognitive impairment using all available assessments including survivors with a single assessment (singletons). Dose-response relationships of specific chemotherapy agents on neurocognition will be evaluated. We are specifically interested in the effect of high-dose and intrathecal methotrexate, but we recognize that that the dose and routes can be difficult to summarize and that cumulative methotrexate dosing only reflects the intravenous and intrathecal routes of administration, and not oral administrations. Hence, we plan to conduct thorough EDA of grouping of methotrexate routes and doses before regression analysis.

Aim 4: Lastly, we will evaluate associations between neurocognitive impairment with health status (i.e., general health status, health insurance), health behaviors (i.e., tobacco, alcohol, physical activity, health screening), healthcare utilization (i.e., seeking appropriate medical care), and social functioning (i.e., living independently, education, employment, and financial status), again using multivariable modeling (linear and logistic) to identify prognostic factors. These outcomes will be obtained from a subsequent follow up survey and evaluated against the initial neurocognitive assessment from a prior survey (i.e., longitudinal evaluation) in order to strengthen causality inference (instead of the weaker cross-sectional evaluation).

5. Tables & figures

Table 1: Demographics and characteristics of survivors and siblings of eAYA vs childhood cancers at each follow up cohort (FU2, FU5, FU6), plus survivors and siblings with multiple follow up time points (FU2+5, FU5+6, FU2+6, FU2+5+6)

	eAYA Survivors (n =) # (%)							**Childhood Survivors (n =) # (%)**							**Siblings (n =) # (%)**						
Characteristics	**FU2**	**FU5**	**FU6**	**FU2+5**	**FU5+6**	**FU2+6**	**FU2+5+6**	**FU2**	**FU5**	**FU6**	**FU2+5**	**FU5+6**	**FU2+6**	**FU2+5+6**	**FU2**	**FU5**	**FU6**	**FU2+5**	**FU5+6**	**FU2+6**	**FU2+5+6**
Sex Female Male																					
Race/ethnicity White Black Hispanic Other																					
Current age, years 20-29 30-39 40-49 50-59 ≥ 60																					
Diagnosis ALL AML HD															NA	NA	NA	NA	NA	NA	NA
Treatment groups ALL 1 2 3 AML SCT+ SCT- HD 1 2 3															NA	NA	NA	NA	NA	NA	NA
Education < 12 years High school College Postgraduate level																					
Employment Unable to work Unemployed Student Working part time Working full time																					
Marital Status Single Married																					

Divorced Widowed																				
Household income < $20,000 $20,000 - $39,999 $40,000 - $59,999 ≥ $60,000																				
Health insurance status Yes No																				
Live independently Yes No																				
Chronic health conditions Cardiac Respiratory Endocrine Neurologic																				
General health status Poor Not poor																				
Tobacco use Never smoked Ever smoked Current smoker																				
Alcohol use None Heavy drinking Risky drinking Current drinking																				
Physical Activity† 0 3-6 9-12 15-21																				
Healthcare utilization No medical care General medical care General survivor-focused care Risk-based survivor-focused care																				

†MET-hours/week. 20min vigorous exercise per week is equivalent to 3 MET-hours/week

Table 2: Treatment characteristics of eAYA and childhood survivors by treatment groups and diagnosis

	eAYA survivors									**Childhood survivors**								
Characteristic	ALL 1 # (%)	ALL 2 # (%)	ALL 3 # (%)	AML SCT+ # (%)	AML SCT- # (%)	HD 1 # (%)	HD 2 # (%)	HD 3 # (%)	P	ALL 1 # (%)	ALL 2 # (%)	ALL 3 # (%)	AML SCT+ # (%)	AML SCT- # (%)	HD 1 # (%)	HD 2 # (%)	HD 3 # (%)	P
Overall treatment Surgery only Chemotherapy Radiotherapy Chemotherapy and radiotherapy																		
Antimetabolite None Any MTX IV/PO/IM MTX IT/Ommaya Cumulative dose (range), mg (IV, IT only)																		
Corticosteroids Dex Pred HC																		
Anthracycline cumulative dose (mg/m2) None >0 - <250 250 - <400 ≥ 400																		
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																		
Vinca alkaloid Yes No Cumulative dose (range) mg/m2																		
Platinum agent Yes No Cumulative dose (range) mg/m2																		
L-asparaginase Yes No																		
CNS irradiation None and indirect Direct <20 Gy Direct ≥20 Gy Chest radiation Other sites of radiation																		

Table 3: Neurocognitive outcomes between eAYA survivors by era of diagnosis and their siblings based on all follow up assessments **(AIM #1)**

a. Univariate means, prevalences, and p-values comparing survivors and 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
Siblings																				
eAYA survivors																				
Total leukemia																				
ALL1																				
ALL2																				
ALL3																				
AML SCT+																				
AML SCT-																				
Total HD																				
HD1																				
HD2																				
HD3																				
Childhood survivors																				
Total leukemia																				
ALL1																				
ALL2																				
ALL3																				
AML SCT+																				
AML SCT-																				
Total HD																				
HD1																				
HD2																				
HD3																				

The initial assessment indicates FU2 (2003) for the original cohort and FU5 (2014) for the expansion cohort. This means that FU2 was the initial assessment for survivors from the 1980-1986, and those from 1987-1989 took their first assessment in FU5.

b. Neurocognitive outcomes by era of diagnosis based on the all follow up assessments, stratified by diagnoses, adjusted for age and sex

Group	Task Efficiency			Organization			Memory			Emotional Regulation		
	No. Impaired	% Impaired	OR (95% CI)	No. Impaired	% Impaired	OR (95% CI)	No. Impaired	% Impaired	OR (95% CI)	No. Impaired	% Impaired	OR (95% CI)
Siblings			Ref			Ref			Ref			Ref
eAYA survivors												
Total leukemia												
ALL1												
ALL2												
ALL3												
AML SCT+												
AML SCT-												

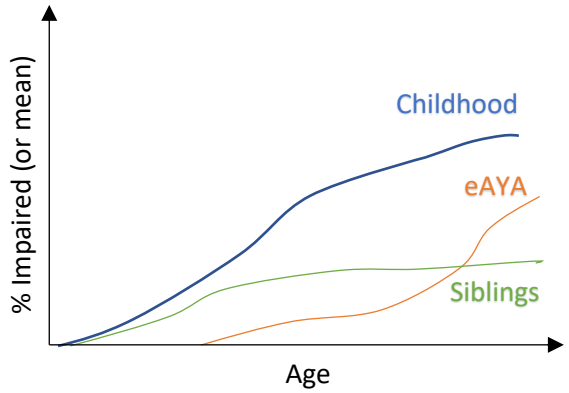
Total HD												
HD1												
HD2												
HD3												
Childhood survivors												
Total leukemia												
ALL1												
ALL2												
ALL3												
AML SCT+												
AML SCT-												
Total HD												
HD1												
HD2												
HD3												

c. Extent of Neurocognitive Impairments

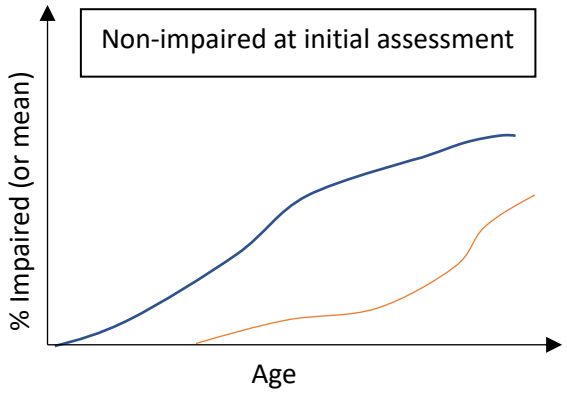
	Impaired Domains # (%)					
	0	1	2	3	4	Impairment in ≥1 domain
eAYA survivors						
Total leukemia						
ALL1						
ALL2						
ALL3						
AML SCT+						
AML SCT-						
Total HD						
HD1						
HD2						
HD3						
Childhood survivors						
Total leukemia						
ALL1						
ALL2						
ALL3						
AML SCT+						
AML SCT-						
Total HD						
HD1						
HD2						
HD3						

Figure 1: Longitudinal trajectory of neurocognitive impairment in eAYA and childhood survivors by treatment groups **(AIM #2)**

Examples of potential figures:



Graph as scatter plot with best fit line. Separate graphs can be constructed for aggregate data, then by diagnosis, and then by whether impairment was present on initial assessment.



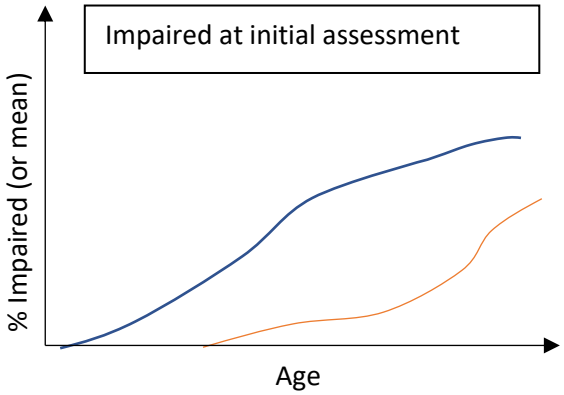


Table 4b: Trajectory of Demographics and Characteristics in the Survivors from 2003 to 2014 from the original cohort (initial assessment in FU2)

	eAYA survivors			Childhood survivors			Siblings		
Characteristics	FU2	FU5	FU6	FU2	FU5	FU6	FU2	FU5	FU6
	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)	# (%)
Total									
Education* < 12 years High school graduate College graduate Postgraduate level			NA			NA			NA
Employment* Unable to work Unemployed Student Working part time Working full time			NA			NA			NA
Marital Status* Single Married			NA			NA			NA

Divorced Widowed									
Household income < $20,000 $20,000 - $39,999 $40,000 - $59,999 ≥ $60,000			NA			NA			NA
Health insurance status Yes No			NA			NA			NA
Live independently* Yes No			NA			NA			NA
Chronic health conditions Cardiac Respiratory Endocrine Neurologic			NA			NA			NA
General health status Poor Not poor									
Tobacco use Never smoked Ever smoked Current smoker			NA			NA			NA
Physical Activity 0 3-6 9-12 15-21			_____			_____			_____
Healthcare utilization No medical care General medical care General survivor-focused care Risk-based survivor-focused care									

*Limited to age >25 years old

Table 5: Association of treatment characteristics with neurocognitive impairments in eAYA survivors **(AIM #3)**

	eAYA Survivors											
Characteristic	Task Efficiency			Organization			Memory			Emotional Regulation		
	Impaired	Not Impaired	OR (95% CI)	Impaired	Not Impaired	OR (95% CI)	Impaired	Not Impaired	OR (95% CI)	Impaired	Not Impaired	OR (95% CI)

Sex Female Male												
Current age, years 20-29 30-39 40-49 50-59 ≥ 60												
Overall treatment Surgery Chemo Radiation ChemoRT												
Antimetabolite None Any MTX IV/PO/IM MTX IT/Ommaya												
Corticosteroids Dex Pred HC												
Anthracycline cumulative dose (mg/m2) None >0 - <250 ≥ 250												
Alkylating agent (CED, mg/m2) None >0 - <4,000 8,000 - <12,000 12,000 - <16,000 16,000 - <20,000 ≥ 20,000												
Vinca alkaloid Yes No Cumulative dose												
Platinum agent Yes No Cumulative dose												
L-asparaginase Yes No												
CNS irradiation None and indirect Direct <20 Gy Direct ≥20 Gy Chest radiation Other sites of radiation												

(Further analysis is to stratify by diagnosis of leukemia or HD)

Table 6a: Association of neurocognitive impairment with health status and social functioning in eAYA survivors. **(AIM #4)**

Neurocognitive Function	OR (95% CI)

	< College Graduate*	Unemployed*	Never married*	Income <$60,000	Uninsured	Living dependently	Poor health status
Task Efficiency Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Organization Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Memory Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Emotional regulation Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Sex Male Female	1.0	1.0	1.0	1.0	1.0	1.0	1.0

*Limited to age >25 years old

Table 6b: Association of neurocognitive impairment with health behaviors and health care utilization in eAYA survivors. **(AIM #4)**

Neurocognitive Function	OR (95% CI)														
	Tobacco use			Alcohol use				Physical Activity†				Healthcare utilization			
	Never smoked	Ever smoked	Current smoker	None	Heavy	Risky	Current	0	3-6	9-12	15-21	No medical care	General medical care	General survivor-focused care	Risk-based survivor-focused care
Task Efficiency Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Organization Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Memory Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Emotional regulation Impaired Not impaired	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Sex Male Female	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

†MET-hours/week. 20min vigorous exercise per week is equivalent to 3 MET-hours/week

Special Consideration: None

References:

1. Keegan THM, Ries LAG, Barr RD, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer*. 2016;122(7):1009-1016. doi:10.1002/cncr.29869

2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. *N Engl J Med*. 2006;355(15):1572-1582. doi:10.1056/NEJMsa060185

3. Baker K, Syrjala K. Long-term complications in adolescent and young adult leukemia survivors. *Hematol Am Soc Hematol Edu Progr*. 2018;2018:146-153.

4. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. www.cdc.gov/cancer/dataviz. Published 2019. Accessed September 25, 2019.

5. Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and Addressing the Needs of Adolescents and Young Adults With Cancer: Summary of an Institute of Medicine Workshop. *Oncologist*. 2015;20(2):186-195. doi:10.1634/theoncologist.2014-0265

6. Husson O, Huijgens PC, van der Graaf WTA. Psychosocial challenges and health-related quality of life of adolescents and young adults with hematologic malignancies. *Blood*. 2018;132(4):385-392. doi:10.1182/blood-2017-11-778555

7. Prasad PK, Hardy KK, Zhang N, et al. Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. 2015;33(23):2545-2552. doi:10.1200/JCO.2014.57.7528

8. Jim HSL, Jennewein SL, Quinn GP, Reed DR, Small BJ. Cognition in Adolescent and Young Adults Diagnosed With Cancer: An Understudied Problem. *J Clin Oncol*. 2018;36(27):2752-2754. doi:10.1200/JCO.2018.78.0627

9. Krull KR, Brinkman TM, Li C, et al. Neurocognitive Outcomes Decades After Treatment for Childhood Acute Lymphoblastic Leukemia: A Report From the St Jude Lifetime Cohort Study. *J Clin Oncol*. 2013;31(35):4407-4415. doi:10.1200/JCO.2012.48.2315

10. Liu W, Cheung YT, Conklin HM, et al. Evolution of neurocognitive function in long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *J Cancer Surviv*. 2018;12(3):398-406. doi:10.1007/s11764-018-0679-7

11. Jacola LM, Krull KR, Pui CH, et al. Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. *J Clin Oncol*. 2016;34(11):1239-1247. doi:10.1200/JCO.2015.64.3205

12. Mulrooney DA, Hyun G, Ness KK, et al. The changing burden of long-term health outcomes in survivors of childhood acute lymphoblastic leukaemia: a retrospective analysis of the St Jude Lifetime Cohort Study. *Lancet Haematol*. 2019;6(6):e306-e316. doi:10.1016/S2352-3026(19)30050-X

13. Kanellopoulos A, Andersson S, Zeller B, et al. Neurocognitive Outcome in Very Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia After Treatment with Chemotherapy Only. *Pediatr Blood Cancer*. 2016;63(1):133-138. doi:10.1002/pbc.25690

14. Park JL, Brandelli Y, Russell KB, et al. Unmet Needs of Adult Survivors of Childhood Cancers:

Associations with Developmental Stage at Diagnosis, Cognitive Impairment, and Time from Diagnosis. *J Adolesc Young Adult Oncol*. 2018;7(1):61-71. doi:10.1089/jayao.2017.0023

15. Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive Functioning in Adult Survivors of Childhood Non-Central Nervous System Cancers. *JNCI J Natl Cancer Inst*. 2010;102(12):881-893. doi:10.1093/jnci/djq156

16. Lange M, Joly F, Vardy J, et al. Cancer-Related Cognitive Impairment: An update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol*. 2019;30(12):1925-1940. doi:10.1093/annonc/mdz410

17. Tonning Olsson I, Brinkman TM, Wang M, et al. Neurocognitive and psychosocial outcomes in adult survivors of childhood soft-tissue sarcoma: A report from the St. Jude Lifetime Cohort. *Cancer*. January 2020:cncr.32694. doi:10.1002/cncr.32694

18. Krull KR, Sabin ND, Reddick WE, et al. Neurocognitive function and CNS integrity in adult survivors of childhood Hodgkin lymphoma. *J Clin Oncol*. 2012;30(29):3618-3624. doi:10.1200/JCO.2012.42.6841

19. Zając-Spychała O, Pawlak M, Karmelita-Katulska K, et al. Anti-leukemic treatment-induced neurotoxicity in long-term survivors of childhood acute lymphoblastic leukemia: impact of reduced central nervous system radiotherapy and intermediate- to high-dose methotrexate. *Leuk Lymphoma*. 2018;59(10):2342-2351. doi:10.1080/10428194.2018.1434879

20. Kenzik KM, Huang I-C, Brinkman TM, et al. The Childhood Cancer Survivor Study–Neurocognitive Questionnaire (CCSS-NCQ) Revised: Item response analysis and concurrent validity. *Neuropsychology*. 2015;29(1):31-44. doi:10.1037/neu0000095

21. Saletta F, Seng M, Lau L. Advances in paediatric cancer treatment. *Transl Pediatr*. 2014;3(2):156–182. doi:10.3978/j.issn.2224-4336.2014.02.01

22. Arain M, Haque M, Johal L, et al. Maturation of the adolescent brain. *Neuropsychiatr Dis Treat*. 2013;9:449-461. doi:10.2147/NDT.S39776

23. Krull KR, Gioia G, Ness KK, et al. Reliability and validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. *Cancer*. 2008;113(8):2188-2197. doi:10.1002/cncr.23809

24. Kunin-Batson A, Kadan-Lottick N, Zhu L, et al. Predictors of independent living status in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer*. 2011;57(7):1197-1203. doi:10.1002/pbc.22982

25. Lown EA, Hijiya N, Zhang N, et al. Patterns and predictors of clustered risky health behaviors among adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. 2016;122(17):2747-2756. doi:10.1002/cncr.30106

26. Nathan PC, Ford JS, Henderson TO, et al. Health behaviors, medical care, and interventions to promote healthy living in the Childhood Cancer Survivor Study cohort. *J Clin Oncol*. 2009;27(14):2363-2373. doi:10.1200/JCO.2008.21.1441

27. Tonorezos ES, Ford JS, Wang L, et al. Impact of exercise on psychological burden in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. 2019;125(17):3059-3067. doi:10.1002/cncr.32173

CCSS Analysis Concept Proposal