

CCSS Analysis Concept Proposal

1. Study title: Associations between special education services, educational attainment, and chronic health conditions among long-term childhood cancer survivors

2. Working groups: Psychology (Primary) and Chronic Disease (Secondary)

Investigators:

Lisa Bashore	lisa.bashore@cookchildrens.org
Paul Bowman	paul.bowman@unthsc.edu
Tyler Hamby	tyler.hamby@cookchildrens.org
Zahra Merchant	zahra.merchant@my.unthsc.edu
Aaron McDonald	aaron.mcdonald@stjude.org
TBN Analyst	
Wendy Leisenring	wleisenr@fhcrc.org
Philip Lupo	philip.lupo@bcm.edu
Allison King	king_a@wustl.edu
Rebecca Howell	rhowell@mdanderson.org
Kevin Oeffinger	kevin.oeffinger@duke.edu
Todd Gibson	todd.gibson@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Kevin Krull	kevin.krull@stjude.org

3. Background and rationale:

Survival rates for childhood cancer have improved steadily over the past two decades,¹ due to advances in treatment, including the administration of multimodal therapy using both chemotherapy and radiation. Treatment-related late-effects impact educational attainment and use of special education services in survivors of childhood cancer, particularly those who have central nervous system (CNS) directed therapy.²⁻⁶ While age at diagnosis and sex have been shown to moderate the treatment impact on educational attainment,^{3,7} these factors do not fully explain the variability in this important outcome.

Survivors of childhood cancer more often report repeating a grade and report more school absences than their sibling controls, though they also report similar plans to attend college and interest in

occupational outcomes compared to siblings.⁸ However, a comprehensive characterization of the extent and pattern of special education utilization and educational attainment has not yet been examined in a large diagnostically diverse cohort, including those treated on contemporary therapeutic protocols. Several factors, including cancer diagnosis, cancer therapies, neurocognitive impairment, and chronic health conditions may all influence the use of special education and educational attainment. Studies suggest survivors of childhood acute lymphoblastic leukemia (ALL) and CNS tumors have a higher risk for use of special education services and lower educational attainment compared to those with other cancer diagnoses.^{2,6} It is hypothesized that this increased risk is driven by exposure to cranial radiation and/or administration of intrathecal or high dose intravenous methotrexate.²⁻⁴ Additionally, survivors with neurocognitive impairments, which often accompany the need for special education services, have lower educational attainment compared to survivors without neurocognitive impairment, regardless of age and sex.^{2,4}

Chronic health conditions may also impact educational outcomes. Survivors of CNS and non-CNS solid tumors with either severe hearing loss,⁴ or who develop seizures⁵ are at risk for low educational attainment. Survivors of CNS tumors in the Childhood Cancer Survivor Study (CCSS) have been reported to have high frequency of hearing loss, paralysis, and cerebrovascular events.⁹⁻¹¹ In addition, these survivors reported difficulties with memory and task efficiency, which were associated with low educational attainment.¹² There remains limited data on the impact of other chronic health conditions like cardiac, pulmonary or endocrine morbidity, and limitations in mobility on educational outcomes in a diverse group of childhood cancer survivors.

With the recent expansion of the CCSS cohort, further understanding of special education services and educational attainment in childhood cancer survivors and siblings is possible, particularly for survivors treated on more modern protocols. The current study proposes to examine special education usage and educational attainment in survivors and their siblings across the past three decades of the survivors' diagnoses (1970-79, 1980-89, 1990-1999). We will compare outcomes to siblings, also dividing them by the decade of their survivor sibling's diagnosis and examine the impact of disease and treatment factors influencing these outcomes, as well as the impact of chronic medical conditions.

4. Specific Aims and Primary Hypotheses

Aim 1: Describe the use of special education services and educational attainment in survivors compared to siblings (educational attainment will be examined in survivors and siblings >25 years of age at time of completion of most recent questionnaire).

Hypothesis 1.1: Special education use will be higher and education attainment (college graduate) will be lower among survivors compared to siblings. See Table 2.

Aim 2: Evaluate temporal trends in special education services and education attainment by decade of diagnosis (i.e. 1970-79, 1980-89, 1990-99) in long-term survivors of childhood cancer AND their siblings.

Hypothesis 2.1: The difference in special education use and education attainment between survivors and siblings of similar age/sex will be smaller for more recent decades (1980-89; 1990-99) compared to most remote decade (1970-79). See Tables 3, 4.

Aim 3: Determine disease- and treatment-related factors associated with the use of special education services and educational attainment in long-term survivors of childhood cancer.

Hypothesis 3.1: Survivors of ALL, non-Hodgkin lymphoma, and CNS tumors will have higher special education use compared to survivors of solid tumors, controlling for sex and age at diagnosis. See Table 5.

Hypothesis 3.2: Having received higher dose of CNS radiation, intravenous methotrexate and/or intrathecal methotrexate will be associated with higher risk of special education use and lower educational attainment compared to survivors without those exposures. See Table 6.

Aim 4: Examine associations between use of special education services (Yes or No) and educational attainment (college graduate) with chronic health conditions in long-term survivors of childhood cancer.

Hypothesis 4.1: Survivors with more severe chronic health conditions (i.e. CTCAE grades 3/4) will be more likely to report lower educational attainment (no college degree) and greater use of special education services compared to survivors with no or less severe conditions (CTCAE grades 1/2), controlling for sex and age at diagnosis. See Table 7.

5. Analysis Framework:

5.1 Study Population: All Survivors and siblings enrolled in both the original and expansion CCSS cohorts.

- **Overall Cohort:** Baseline data from all survivors and siblings (≥ 18 years) and parent survey for survivors and siblings (< 18 years). For analyses of educational attainment, we will only include this outcome from survivors and siblings who were ≥ 25 years of age at the most recent survey.
- Exclusion criteria: any genetic condition associated with cognitive impairment (e.g. Down syndrome, Klinefelter's syndrome, Turner's syndrome).

5.2 Variables of Interest

Aims 1, 2 and hypotheses 1.1, 2.1

- Outcomes: use of special education services (Baseline O3-O4: Expansion R3-R4) and educational attainment (collected from most recent survey completed by survivor and sibling at ≥ 25 years of age)
 - School History:
 - Survivors: Special education usage: Special Education (Original Baseline O3, Expansion R3); Categories of Special Education (Original Baseline O4, Expansion R4); Educational attainment: College graduate (cumulative summary across surveys).
 - Siblings: Special education usage: Special Education (Original Baseline O3, Expansion R3); Grades of Special Education (Original Baseline O4, Expansion R3); Educational attainment: College graduate (cumulative summary across surveys)
- Predictors/Covariates: Demographics
 - Demographics: Original Baseline age (A1), sex (A2), race/ethnicity (4,4a); Original Baseline Sibling age (A1), sex (A2), race/ethnicity (4,4a); Expansion Baseline age (A1), sex (A2), race/ethnicity (A5,5a), Age at most recent FU survey (for Educational Attainment).

We will assess the history of special education usage at baseline and cumulative educational attainment (college degree) in both survivors and siblings in both the original and expansion cohorts. We will then assess whether the decade of diagnosis of survivors predicted their use of special education and educational attainment compared to their siblings, also classified by decade of their survivor sibling's decade of diagnosis. For educational attainment, we will limit analyses to survivors ≥ 25 years of age at follow-up; similarly, only siblings of similar age will be included in the analysis

Aim 3, and hypotheses 3.1, 3.2

- Outcomes: use of special education services (Baseline O3-O4: Expansion R3-R4) and educational attainment (most recent survey completed) by diagnosis and treatment.
- Predictors/Covariates: Demographics, Clinical data
 - Demographic information: Original Baseline age (A1), sex (A2), race/ethnicity (4,4a); Expanded Baseline age (A1), sex (A2), race/ethnicity (4,4a)
 - School History:
 - Survivors: Special education usage: Special Education (Original Baseline O3, Expansion R3); Grades of Special Education (Original Baseline O4, Expansion R4); Educational attainment: College graduate (cumulative across surveys)

- Clinical Data: Medical abstraction for all survivors; all ages in original/expansion cohorts
 - Age at time of diagnosis: continuous and categorical
 - Chemotherapy: IT and IV methotrexate {cumulative dose}; cisplatin [cumulative doses]
 - Radiation: NONE; Cranial < 20 Gy, ≥ 20Gy
 - Maximum radiation dose to the brain and maximum dose to each of 4-segments of the brain.

Aim 4 and hypothesis 4.1

Outcomes: use of special education services (Baseline O3-O4; Expansion R3-R4) and educational attainment (Baseline O1-O2; Follow up 5 A3; Expansion R1-R2) by reported chronic health conditions as of 25 years of age (based on CTCAE grading).

- Predictors/Covariates:
 - Demographic information: Original Baseline age (A1), sex (A2), race/ethnicity (4,4a); Expanded Baseline age (A1), sex (A2), race/ethnicity (4,4a)
 - School History:

Survivors: Special education usage: Special Education (Original Baseline O3, Expansion R3); Grades of Special Education (Original Baseline O4, Expansion R4); Educational attainment: College Graduate
 - Chronic Health Conditions:

CTCAE grading for hearing loss, blindness, stammering/other speech problems, endocrine conditions, respiratory conditions, cardiovascular conditions, GI conditions, renal conditions, musculoskeletal conditions, neurologic conditions (paralysis of any kind, epilepsy, problems with balance, tremors, sensory neuropathy).; Only conditions that are present prior to 25 years of age will be considered (this limit is applied as educational attainment ≥ 25 years of age will be used as outcome).

5.3 Summary of Proposed Analyses

Aims 1 and 2: Descriptive statistics will be calculated to compare survivors to siblings by frequency of special education use and educational attainment. Adjusted logistic regression (or similar log-binomial) models will be used to make these comparisons overall for (Aim 1) and by decade of diagnosis (Aim 2).

Adjustment factors will include sex, age at relevant survey. For comparison by decade of diagnosis, siblings will be classified into decades based on the date that their sibling survivor was diagnosed. Indicator variables for decade will be included along with survivor vs. sibling variables and the interactions between decade and survivor/sibling status will be tested to evaluate whether educational outcome rate ratios between survivors and siblings change across decades. The magnitude of the rate ratios and associated 95% confidence interval between survivors and siblings will be summarized for each decade. (Tables 1-4).

Aim 3: Among survivors, we will use multivariable logistic (or log-binomial) regression models to examine associations between chemotherapy and cranial radiation variables and special education use and educational attainment outcomes. Models will be adjusted for sex and age at diagnosis (Table 5). Similar models will be conducted replacing treatment exposures with diagnosis (Table 6).

Aim 4: We will examine the associations between chronic health conditions that occur prior to 25 years of age and educational attainment and special education use with multivariable logistic regression analyses. We will begin by exploring associations with univariate analyses. Those predictors associated with an outcome at $p < .20$ at univariate models will be included in multivariable models. Age at diagnosis, current age and sex will be included as covariates *a priori* (Table 7). If significant associations are identified between educational outcomes and treatment exposures, as well as educational outcomes and chronic health conditions, mediation analyses will be considered to determine whether chronic health conditions mediate the impact of treatment exposures on educational outcomes.

References

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Table 1. Survivor and sibling factors

Variable	Survivors	Siblings	P-Value
Diagnosis age	No. (%)		
0-4	X (X%)	-	-
5-9	X (X%)	-	-
10-18	X (X%)	-	-
Diagnosis	No. (%)		
Leukemia	X (X%)	-	-
CNS Tumors	X (X%)	-	-
Hodgkin Lymphoma	X (X%)	-	-
NonHodgkin Lymphoma	X (X%)	-	-
Solid Tumors	X (X%)	-	-
Treatment	No. (%)		
Corticosteroids	X (X%)	-	-
Platinum Agents	X (X%)	-	-
Anthracyclines	X (X%)	-	-
Antimetabolites	X (X%)	-	-
Surgery (CNS)	X (X%)	-	-
Radiation to the CNS	X (X%)	-	-
Decade of Diagnosis	No. (%)		
1970-1979	X (X%)	-	-
1980-1989	X (X%)	-	-
1990-1999	X (X%)	-	-
Age at survey completion	No. (%)		.XX
< 18	X (X%)	X (X%)	
≥ 18	X (X%)	X (X%)	
Sex	No. (%)	No. (%)	.XX
Female	X (X%)	X (X%)	
Male	X (X%)	X (X%)	
Special education use	No. (%)	No. (%)	.XX
Yes	X (X%)	X (X%)	
No	X (X%)	X (X%)	
Special education use	No. (%)	No. (%)	.XX
K-2nd	X (X%)	X (X%)	
3rd-5th	X (X%)	X (X%)	
6th-8th	X (X%)	X (X%)	
9th-12th	X (X%)	X (X%)	
Reasons for special education	No. (%)	No. (%)	.XX
Missed school	X (X%)	X (X%)	
Low test scores	X (X%)	X (X%)	
Problems learning or concentrating	X (X%)	X (X%)	
Emotional/behavioral problems	X (X%)	X (X%)	
College graduate*	No. (%)	No. (%)	.XX
Yes	X (X%)	X (X%)	
No	X (X%)	X (X%)	

*Only those participants and siblings who are 25 years of age or greater at time of survey completion will be included in this analysis

Table 2. Multivariable analysis of educational attainment and special education use

Variable	College Graduate*		Special Education Use	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Participant		.XX		.XX
Sibling (referent)	1.0		1.0	
Survivor	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Sex		.XX		.XX
Female (referent)	1.0		1.0	
Male	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Age at Survey (per year)	X.XX (X.XX to X.XX)	.XX	X.XX (X.XX to X.XX)	.XX

*Only those participants and siblings who are 25 years of age or greater at time of survey completion will be included in this analysis

Table 3. Survivor and sibling special education use by decade of survivor diagnosis

Variable	Survivors			Siblings*			P-Values**		
	1970-1979	1980-1989	1990-1999	1970-1979	1980-1989	1990-1999	P1	P2	P3
	(n=?)	(n=?)	(n=?)	(n=?)	(n=?)	(n=?)			
Special education use	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	.XX	.XX	.XX
Yes	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
No	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
Special education use							.XX	.XX	.XX
K-2nd	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
3rd-5th	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
6th-8th	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
9th-12th	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
Reason for special education							.XX	.XX	.XX
Missed school	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
Low test scores	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
Problems learning or concentrating	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
Emotional/behavioral problems	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
College graduate							.XX	.XX	.XX
Yes	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			
No	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)			

*Decades for Siblings established by the decade of diagnosis for the survivor of the sibling.

**P-values for survivors/siblings by decade 1970-79 (P1); 1980-89 (P2); 1990-99 (P3)

Table 4. Multivariable analysis of educational attainment and special education use

Variable	College Graduate*		Special Education Use	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Decade of diagnosis		.XX		.XX
1970's (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
1980's	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
1990's	1.0		1.0	
Participant		.XX		.XX
Sibling (referent)	1.0		1.0	
Survivor	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Sex		.XX		.XX
Female (referent)	1.0		1.0	
Male	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Age at Survey (per year)	X.XX (X.XX to X.XX)	.XX	X.XX (X.XX to X.XX)	.XX

*Only those participants and siblings who are 25 years of age or greater at time of survey completion will be included in this analysis

Table 5. Multivariable analysis of diagnosis and outcomes of educational attainment and special education use among survivors

Variable	College Graduate*		Special Education Use	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Diagnosis		.XX		.XX
Solid Tumors (referent)	1.0		1.0	
Leukemia(s)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Hodgkin's Lymphomas	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Non-Hodgkin's Lymphomas	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Sarcomas	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
CNS Tumors	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Sex	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Female (referent)				.XX
Male	1.0		1.0	
Diagnosis age	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
0-4 (referent)		.XX		.XX
5-9	1.0		1.0	
10-18	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	

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Table 6. Chemotoxic therapy associated with outcomes of educational attainment and predictors of special education use among survivors

Variable	College Graduate*		Special Education Use	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
If brain radiation received		.XX		.XX
1-19.9 Gy	1.0		1.0	
20-29.9 Gy	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
30-49.9 Gy	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
> 50 Gy (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Heavy Metals		.XX		.XX
Yes (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
No	1.0		1.0	
IV Methotrexate		.XX		.XX
Yes (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
No	1.0		1.0	
IT Methotrexate		.XX		.XX
Yes (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
No	1.0		1.0	
Corticosteroids		.XX		.XX
Yes (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
No	1.0		1.0	
Sex		.XX		.XX
Female (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Male	1.0		1.0	
Diagnosis Age		.XX		.XX
0-4 (referent)	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
5-9	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
10-18	1.0		1.0	

*Only those participants who are 25 years of age or greater at time of survey completion will be included in this analysis

Table 7. Multivariable analysis of chronic conditions/grading on outcomes of educational attainment and special education use

	College Graduate*		Special Education Use	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Onset of Chronic Condition (per Year)	X.XX (X.XX to X.XX)	.XX	X.XX (X.XX to X.XX)	.XX
Hearing		.XX		.XX
< Grade 3 (referent)	1.0		1.0	
≥Grade 3	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Vision		.XX		.XX
< Grade 3 (referent)	1.0		1.0	
≥Grade 3	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Speech		.XX		.XX
< Grade 3 (referent)	1.0		1.0	
≥Grade 3	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Neurological		.XX		.XX
< Grade 3 (referent)	1.0		1.0	
≥Grade 3	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Renal/GI		.XX		.XX
< Grade 3 (referent)	1.0		1.0	
≥Grade 3	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Musculoskeletal		.XX		.XX
< Grade 3 (referent)	1.0		1.0	
≥Grade 3	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Sex		.XX		.XX
Female (referent)	1.0		1.0	
Male	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
Diagnosis age		.XX		.XX
0-4 (referent)	1.0		1.0	
5-9	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	
10-18	X.XX (X.XX to X.XX)		X.XX (X.XX to X.XX)	

*Only those participants and siblings who are 25 years of age or greater at time of survey completion will be included in this analysis

Figure 1. Potential Mediation Analyses

