1. **STUDY TITLE:** Social and behavioral phenotypes of adolescent survivors of childhood cancer

2. **WORKING GROUP AND INVESTIGATORS**

2.1. Working Group: Psychology

2.2. Investigators:

Tara M. Brinkman, PhD	tara.brinkman@stjude.org
Jordan Gilleland, PhD	jordan.gilleland@choa.org
Jin-Shei Lai, PhD, OTR/L	js-lai@northwestern.edu
Kathryn A. Vannatta, PhD	kathryn.vannatta@nationwidechildrens.org
Cara Kimberg, PhD	cara.kimberg@stjude.org
Pinki K. Prasad, MD, MPH	pprasa@lsuhsc.edu
Chongzhi Di, PhD	cdi@fhcrc.org
Wendy M. Leisenring, ScD	wleisenr@fhcrc.org
Leslie L. Robison, PhD	les.robison@stjude.org
Gregory T. Armstrong, MD, MSCE	greg.armstrong@stjude.org
Kevin R. Krull, PhD	kevin.krull@stjude.org

3. **BACKGROUND AND RATIONALE**

Approximately one in every four children has a mental health disorder. Epidemiological studies of child and adolescent mental health disorders consistently find high co-morbidity[1,2]. Recent lifetime prevalence data from the National Comorbidity Survey Replication Adolescent Supplement indicated that nearly half of adolescents 13 to 18 years of age were affected by at least one class of mental health disorder (22% exclusive of substance use disorders)[3]. Approximately 40% of all affected adolescents also met criteria for a second mental health disorder. Importantly, comorbidity in adolescence is associated with increased risk for severe mental health problems in adulthood[4], substance abuse[5], and poor physical health[6].

Adolescent survivors of childhood cancer are at-risk for treatment related physical and cognitive late effects, which may increase vulnerability to psychological and behavioral difficulties, particularly during a period of development marked by transition and increasing expectations of independence. Studies have reported increased risk for attention, learning, and social difficulties as well as internalizing problems such as anxiety, depression, and withdrawal[7] in adolescent survivors of childhood cancer. In the largest study to date, a report from the Childhood Cancer Survivor Study (CCSS) baseline cohort indicated that adolescent survivors of childhood cancer were 1.5 times more likely to have symptoms of depression/anxiety and 1.7 times more likely to have antisocial behaviors compared to siblings[8]. Survivors of CNS tumors and leukemia also demonstrated elevated scores in the domain of attention deficit as well as reduced social competence scores compared to siblings. treatment with cranial radiation and/or intrathecal methotrexate were specific risk factors. However, this analysis did not look at the presence or patterns of comorbidity, but rather examined each individual symptom independently.

In non-cancer populations a number of factors have been associated with adolescent social functioning and psychological adjustment. Adolescent females are at increased risk for internalizing disorders (e.g., anxiety, depression) while males are more likely to develop externalizing disorders (e.g. conduct disorder). Children who experience physical disfigurement report persistent symptoms of depression and anxiety.[9] Children and adolescent with hearing loss and speech deficits are at risk for social isolation.[10] Attention deficits, conduct disorder, and depressive symptoms are more common in obese than non-obese children.[11] Symptoms such as headaches and chronic pain have been associated with internalizing mental health symptoms.[12]

No study has examined comorbidity of behavioral and emotional symptoms in adolescent survivors of childhood cancer. Understanding comorbidities has implications for screening and intervention efforts

as well as future research examining the contribution of adolescent mental health complications to adult outcomes. For example, although treatment with stimulant medication is recommended for adolescents with attention problems, if those attention problems co-occur with anxiety stimulants are contra-indicated and treatment of the anxiety is recommended prior to treatment of the attention problems.[13]

As treatment exposures have been associated with behavioral outcomes in adolescent survivors, a comparison of behavioral comorbidities in adolescents enrolled in CCSS cohort and treated across eras from 1970 to 1999 may provide insight toward understanding the impact of contemporary treatment approaches on psychological health in survivors.

4. SPECIFIC AIMS AND RESEARCH HYPOTHESES

4.1. **Aim 1:** To identify social and behavioral phenotypes through examination of symptom patterns and comorbidities (i.e. classes of co-occurring symptoms).

4.1.1. **Hypothesis 1:** Several patterns of co-occurring internalizing (e.g. anxiety/depression) and externalizing (e.g. hyperactivity, conduct problems) symptoms will be identified (e.g., high externalizing – high internalizing; high externalizing – low internalizing; low externalizing – high internalizing; low externalizing – low internalizing).

4.2. **Aim 2**: To examine adolescent social and behavioral symptoms and phenotypes in survivors by treatment era (i.e. 1970-1979; 1980-1989; 1990-1999).

4.2.1. **Hypothesis 2a:** The prevalence of symptoms (6 domains) and phenotypes (latent class symptom patterns) will differ by treatment era.

4.3. **Aim 3**: To examine treatment predictors of social and behavioral phenotypes in survivors.

4.3.1. **Hypothesis 3:** Treatment exposures will be associated with the phenotypes identified in Aim 1 (e.g. cranial radiation; surgery only).

4.4. **Aim 4:** To investigate the association between treatment-related late effects (e.g., scarring/disfigurement, sensory impairment, pain, health status) and adolescent social and behavioral phenotypes in survivors.

4.4.1. **Hypothesis 4:** The presence of late effects will be associated with the phenotypes identified in Aim 1.

5. ANALYSIS FRAMEWORK

5.1. **Population:** Survivors who were 12-17 years of age at completion of the baseline survey. See Table 1 for an estimated number of available adolescent survivors by decade of diagnosis. We will exclude survivors and siblings with genetic conditions known to be associated with developmental delays (Down's syndrome, Tuner's syndrome, Klinefelters syndrome, Fragile X syndrome).

5.2. **Outcomes of Interest:** The primary outcome of interest is social and behavioral functioning as measured by the Behavior Problem Index (BPI; Q K1-K6). The BPI is a subset of 27 questions from the Child Behavior Checklist and provides scores for six symptom domains: depression/anxiety, headstrong, attention deficit, peer conflict/social withdrawal, antisocial, and social competence. Each question is scored on a scale of 1 to 3, where 1 indicates no observation of the behavior and 3 frequent observation of a specific behavior. Schultz et al. examined construct validity of the BPI in CCSS and reported internal consistency of 0.87 for depression/anxiety, 0.89 for headstrong, 0.86 for peer conflict/social withdrawal, 0.80 for attention deficit, and 0.87 for antisocial. The social competence domain was determined by

summing the scores to the six questions about friendship and social interactions [Q K1-K3]. Total scores for the six domains will be modeled as continuous outcomes.

5.3. **Aim 1: Statistical analysis**

5.3.1. Descriptive statistics including means, standard deviations, medians, and ranges will be calculated for the six symptom domains of interest. We will use latent profile analysis (model-based clustering procedure using continuous observed variables and categorical latent variables) to identify classes of survivors based on six symptom domains reported on the BPI. LPA fit indices will include the Bayesian Information Criterion (BIC) and a likelihood difference test (VLMR) with *p* values reported to indicate which model provides the best fit. We will place more emphasis on the BIC values when selecting the number of classes. We expect that several classes will be identified but **will not pre-specify a set number of classes** (e.g. high internalizing-low externalizing; high externalizing-low internalizing). A cross-validation of the identified classes will be conducted. Specifically, the repeated random sub-sampling validation approach will be used. Sub-sampling will be completed 10 times, with each sub-sample representing the number of identified classes multiplied by the minimum number of participants required per class. Split-half reliability will also be calculated. To assure adequate power for subsequent analyses we will require that each latent class include no less than 5% of survivors (see Table 3).

5.4. **Aim 2: Statistical analysis**

5.4.1. To address the second aim, frequencies of latent class membership identified in Aim 1 will be compared across treatment eras using Chi-Square analyses (Table 4). Descriptive statistics including means, standard deviations, medians, and ranges will also be calculated for the six symptom domains of interest. We will compare means and standard deviations for each domain by treatment eras. This analysis will be completed using independent-sample t-tests and/or analysis of variance procedures with Bonferonni correction for multiple comparisons.

5.5. **Aim 3: Predictors and statistical analysis**

- 5.5.1.1. Sex [Q A2]
- 5.5.1.2. Age at survey (years)
  - 5.5.1.2.1. 12-14 years vs. 15-17 years
- 5.5.1.3. Race/ethnicity [QA5]
  - 5.5.1.3.1. White, Black, Hispanic, Other
- 5.5.1.4. Age at diagnosis (years)
- 5.5.1.5. Treatment (separate model from diagnosis)
  - 5.5.1.5.1. Surgery only (yes/no)
  - 5.5.1.5.2. Chemotherapy
    - 5.5.1.5.2.1.1. Corticosteroids
      - 5.5.1.5.2.1.1.1. Dexamethasone & Prednisone
      - 5.5.1.5.2.1.1.2. Prednisone alone
      - 5.5.1.5.2.1.1.3. None
    - 5.5.1.5.2.1.2. Methotrexate
      - 5.5.1.5.2.1.2.1. High dose (yes/no)
    - 5.5.1.5.2.1.3. Cytarabine
      - 5.5.1.5.2.1.3.1. High dose (yes/no)
    - 5.5.1.5.2.1.4. Anthracyclines (tertiles)
      - 5.5.1.5.2.1.4.1. Low ($\leq$100 mg/m^2)
      - 5.5.1.5.2.1.4.2. Moderate (101-40 0mg/m^2)
      - 5.5.1.5.2.1.4.3. High (>400 mg/m^2)
      - 5.5.1.5.2.1.4.4. None
    - 5.5.1.5.2.1.5. Cyclophosphamide (tertiles)
      - 5.5.1.5.2.1.5.1. Low ($\leq$4480 mg/m^2)
      - 5.5.1.5.2.1.5.2. Moderate (4481-9750 mg/m^2)
      - 5.5.1.5.2.1.5.3. High (>9751 mg/m^2)

5.5.1.5.2.1.5.4. None
5.5.1.5.2.1.6. Intrathecal
5.5.1.5.2.1.6.1. None
5.5.1.5.2.1.6.2. Intrathecal (IT)
5.5.1.5.2.1.6.3. Triple intrathecal therapy (TIT)
5.5.1.5.3. Non-cranial radiation (yes/no)
5.5.1.5.4. Cranial radiation
5.5.1.5.4.1.1. Max dose to the head (if available)
5.5.1.6. Cancer Diagnosis (separate model from treatment)
5.5.1.6.1. Leukemia
5.5.1.6.2. CNS tumors
5.5.1.6.3. Hodgkin
5.5.1.6.4. Non-Hodgkin
5.5.1.6.5. Neuroblastoma
5.5.1.6.6. Wilms
5.5.1.6.7. Soft tissue sarcoma
5.5.1.6.8. Osteosarcoma

5.5.2. For the third aim, we will utilize multivariable logistic regression procedures to identify treatment-related predictors of the specific phenotypes/classes identified in Aim 1. Models will be adjusted for sex, current age, and race/ethnicity. Separate models will examine diagnosis and treatment related predictors (see Tables 5a and 5b). We note that this approach may underestimate associations between covariates and classes. Therefore, we will consider the use of a maximum likelihood based correction method.[14] For Aims 3 and 4, once the number of phenotypes/classes and numbers of subjects included in each are identified in Aim 1, an assessment of the complexity of analyses possible will be carried out and appropriate adjustments made to this analysis.

5.6. **Aim 4: Predictors and statistical analysis**
5.6.1.1. Sex [Q A2]
5.6.1.2. Age at survey (years)
5.6.1.2.1. 12-14 years vs. 15-17 years
5.6.1.3. Race/ethnicity [QA5]
5.6.1.3.1. White, Black, Hispanic, Other
5.6.1.4. Household income [Q T11]
5.6.1.5. Scarring/disfigurement [Q B7]
5.6.1.5.1. Amputation of arm, leg, foot [Q I1]
5.6.1.5.1.1. Yes vs. no
5.6.1.6. Sensory impairment
5.6.1.6.1. Hearing impairment [Q C1-C6]
5.6.1.6.1.1. No, no longer present vs. condition still present
5.6.1.7. Speech deficits [Q C19-20]
5.6.1.7.1.1. No, no longer present vs. condition still present
5.6.1.8. Body mass index
5.6.1.8.1. Height [Q A3]
5.6.1.8.2. Weight [Q A4]
5.6.1.9. Growth hormone
5.6.1.9.1. Deficiency of growth hormone [Q E8]
5.6.1.9.2. Injections of growth hormone [Q E9]
5.6.1.9.2.1. No, no longer present vs. condition still present
5.6.1.10. Physical health status [Q O7]
5.6.1.10.1. Excellent, very good, good vs. fair, poor
5.6.1.11. Pain
5.6.1.11.1. Bodily pain [Q K9]
5.6.1.11.1.1. None, very mild, mild vs. moderate, severe very severe
5.6.1.11.2. Headaches [Q J3; J4]

5.6.1.11.2.1. No, no longer present vs. condition still present

5.6.2. To address the final aim, we will again utilize multivariable logistic regression procedures to identify associations among treatment late effects and the phenotypes/classes identified in Aim 1. We will examine collinearity among all predictors and select variables to be included based on reasonable groupings (e.g. adequate cell size). Models will be adjusted for sex, current age, race/ethnicity, and household income (see Table 6).

Table 1. Diagnosis by treatment era (original and expansion cohorts combined)

	Decade of diagnosis		
	1970-1979	**1980-1989**	**1990-1999**
Leukemia	125 (34.92)	1367 (46.26)	392 (26.81)
CNS	55 (15.36)	397 (13.43)	342 (23.39)
HD	6 (1.68)	44 (1.49)	11 (0.75)
NHL	16 (4.47)	130 (4.40)	51 (3.49)
Kidney (Wilms)	39 (10.89)	450 (15.23)	220 (15.05)
Neuroblastoma	78 (21.79)	327 (11.07)	339 (23.19)
Soft tissue sarcoma	22 (6.15)	200 (6.77)	74 (5.06)
Bone cancer	17 (4.75)	40 (1.35)	33 (2.26)
Total	358	2955	1462

Table 2. Characteristics of Survivors by Treatment Era

	1970-1979		1980-1989		1990-1999	
	M	SD	M	SD	M	SD
Age at diagnosis						
Time since diagnosis						
Age at survey completion						
	N	%	N	%	N	%
Sex						
Female						
Male						
Race/Ethnicity						
White, non-Hispanic						
Black						
Hispanic						
Other						
Household Income						
<20,000						
≥20,000						
Treatment						
Surgery only						
Chemotherapy						
Corticosteroids						
Methotrexate						
Cytarabine						
Anthracyclines						
Cyclophosphamide						
Intrathecal						
Cranial Radiation						
Max dose to head						
Non-cranial radiation						
Diagnosis						
Leukemia						
CNS tumor						
Hodgkin Disease						
Non-Hodgkin						
Neuroblastoma						
Wilms Tumor						
Osteosarcoma						
Soft tissue sarcoma						

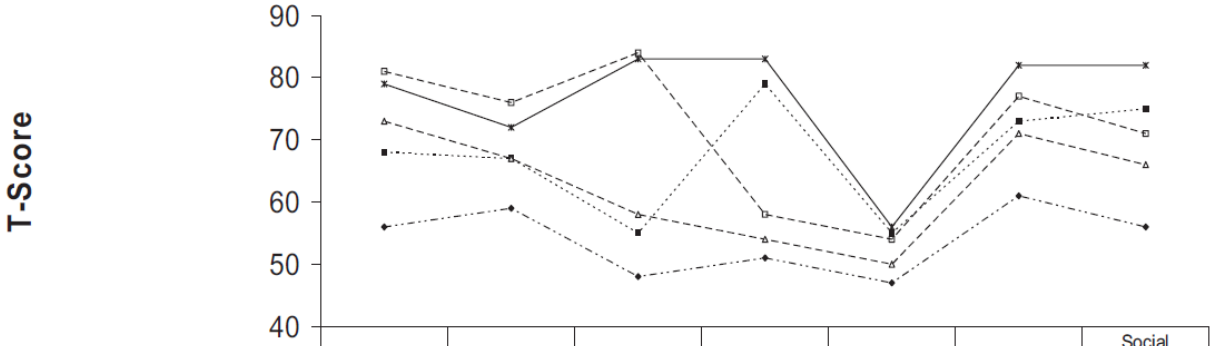
Table 3. Model fit indices for 1 to X class solutions for survivor BPI scores

Model	BIC	Adjusted BIC	VLMR*p*	Adjusted VLMR*p*	Entropy	Minimum Posterior Probability	Smallest Class %
1-class							
2-class							
3-class							
4-class							
5-class							

Table 4. Proportion of survivors with each phenotype by treatment era

	Total N(%)	1970-1979	1980-1989	1990-1999
Class 1				
Class 2				
Class 3				
Class 4				
Class 5				

Figure 1. Clinical characteristics of latent classes for survivors (Example from Herman et al., 2007[15])



	Oppositional	Inattention	Hyperactive	Anxious/Shy	Perfectionism	Psychosomatic	Social Problems
Depressed Only (20%)	56	59	48	51	47	61	56
Anxious (19%)	68	67	55	79	55	73	75
Oppositional (32%)	73	67	58	54	50	71	66
Severely Disruptive (19%)	81	76	84	58	54	77	71
Anxious-Severely Disruptive (10%)	79	72	83	83	56	82	82

Figure 1. Clinical characteristics of classes.

Table 5a. Treatment predictors of behavioral phenotypes (latent class membership)

	Latent Class 1	Latent Class 2	Latent Class 3	Latent Class 4	Latent Class 5
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age at diagnosis					
Time since diagnosis					
Age at survey completion					
Sex					
Male	Ref	Ref	Ref	Ref	Ref
Female					
Race/Ethnicity					
White, non-Hispanic	Ref	Ref	Ref	Ref	Ref
Black					
Hispanic					
Other					
Treatment					
Surgery					
None	Ref	Ref	Ref	Ref	Ref
Yes					
Corticosteroids					
None	Ref	Ref	Ref	Ref	Ref
Dex & Pred					
Prednisone alone					
High dose methotrexate					
No	Ref	Ref	Ref	Ref	Ref
Yes					
Anthracyclines					
None	Ref	Ref	Ref	Ref	Ref
Low					
Moderate					
High					
Cyclophosphamide					
None	Ref	Ref	Ref	Ref	Ref
Low					
Moderate					
High					
Intrathecal					
None	Ref	Ref	Ref	Ref	Ref
Intrathecal					
Triple Intrathecal					

Table 5b. Diagnosis and behavioral phenotypes (latent class membership)

	Latent Class 1	Latent Class 2	Latent Class 3	Latent Class 4	Latent Class 5
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age at diagnosis					
Time since diagnosis					
Age at survey completion					
Sex					
Female					
Male	Ref	Ref	Ref	Ref	Ref
Race/Ethnicity					
White, non-Hispanic	Ref	Ref	Ref	Ref	Ref
Black					
Hispanic					
Other					
Diagnosis					
Leukemia	Ref	Ref	Ref	Ref	Ref
CNS tumor					
Hodgkin Disease					
Non-Hodgkin					
Neuroblastoma					
Wilms Tumor					
Osteosarcoma					
Soft tissue sarcoma					

Table 6. Late effects and behavioral phenotypes in survivors

	Latent Class 1	Latent Class 2	Latent Class 3	Latent Class 4	Latent Class 5
Age at survey					
Sex					
Female					
Male	Ref	Ref	Ref	Ref	Ref
Household Income					
<20,000					
≥20,000	Ref	Ref	Ref	Ref	Ref
Race/Ethnicity					
White, non-Hispanic	Ref	Ref	Ref	Ref	Ref
Black					
Hispanic					
Other					
Yes					
No	Ref	Ref	Ref	Ref	Ref
Sensory Impairment					
Yes					
No	Ref	Ref	Ref	Ref	Ref
Speech Impairment					
Yes					
No	Ref	Ref	Ref	Ref	Ref
Body Mass Index					
≥25					
<25	Ref	Ref	Ref	Ref	Ref
Growth hormone deficiency					
Yes					
No	Ref	Ref	Ref	Ref	Ref
Physical health status					
Fair, poor					
≥Good	Ref	Ref	Ref	Ref	Ref
Bodily Pain					
None, mild					
≥Moderate	Ref	Ref	Ref	Ref	Ref
Headaches					
Yes					
No	Ref	Ref	Ref	Ref	Ref

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