Analysis Concept Proposal

1. **Study Title**: Neurocognitive Functioning, Emotional Status and Quality of Life among Asian/Pacific Islander Childhood Cancer Survivors

2. **Primary working group**: Psychology
   Secondary working groups: Epidemiology and Biostatistics; Chronic Conditions

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4. Background and Rationale

Contemporary treatment strategies have contributed to an observed decline in late mortality among 5-year survivors of childhood cancer.[1] However, survivorship comes at a cost of developing a myriad of treatment-related health conditions such as cardiovascular, endocrine and pulmonary complications.[2,3] Additionally, long-term survivors of childhood cancer are at risk for neurocognitive deficits in domains of attention, executive functions, processing speed, and memory.[4-9] These deficits have a negative impact on employment and occupational outcomes.[10-12] A recent report from the Childhood Cancer Survivors Study (CCSS) revealed that in a cohort of 5507 adult survivors of childhood cancer (mean age of 31.8 years; 23.1 years from cancer diagnosis), 22.8% of survivors reported problems with task efficiency, 12.4% with memory, 12.7% with organization, and 12.3% with emotional regulation.[5] Risk factors for poor neurocognitive function, emotional status and quality of life in survivors of childhood cancer are reasonably well established in the literature. Neurocognitive impairment is associated with exposure to central nervous system (CNS) directed therapies such as radiation and neurosurgery, and neurotoxic chemotherapy (intrathecal methotrexate,

corticosteroids, high dose systemic methotrexate or cytarabine). Other clinical factors associated with increased risk for poor outcomes include female sex and younger age at treatment.[4,9,13,14]

Even within the United States, differences in cultural values and family relationships between the Western and Asian cultures may determine divergent psychosocial development.[26] Cross-cultural research in the field of neuropsychology has demonstrated that one's personal experience, including the culture in which one is raised, could influence attention and thought processes.[24] Cultural differences can influence episodic memory and cognitive correlations across ethnic groups.[25] For example, one study reported that Caucasian families seem to emphasize more emotional care than Chinese families of children with cancer in the United States.[27] This highlights the need to conduct neurocognitive and psychosocial research that is unique to the Asian population of childhood cancer survivors in the United States.

In addition to intrinsic differences in drug responses and susceptibility to developing adverse chronic toxicities associated with the cancer treatment, a recent position paper by CCSS discussed other potential contributors to racial/ethnic differences in morbidity and mortality experienced by survivors of childhood cancer. They include socioeconomic characteristics (ie. disparity in annual household income, education and insurance status), risky health behaviors, patterns of healthcare utilization, and surveillance for long-term toxicities and presence of comorbidities. These characteristics may affect neurocognitive and psychological outcomes[22,23], leading to differences across ethnic groups.

The majority of the cognitive studies in the literature are focused on survivors of childhood cancer from western heritage in the United States and Europe. There is a paucity of robust studies that evaluate neurocognitive, emotional and psychosocial outcomes in native Asian survivors within the continent of Asia. Li et al. noted comments of "memory loss", "shortened attention span" and having to "take extra efforts in order to catch up with studies" during structured interviews by Chinese survivors in Hong Kong.[16] Interestingly, one Japanese study revealed that there was no significant difference in depression and anxiety between survivors (n=185) and their siblings (n=72). But survivors had higher post-traumatic stress symptoms and post-traumatic growth, as compared to non-cancer controls.[18] At a mean of 6.6 years post-diagnosis, Korean survivors of acute lymphoblastic leukemia (n=42) demonstrated lower scores than age-matched healthy controls (n=42) on full scale, perceptual and verbal IQ, though none of these comparisons were statistically significant.[20] Interpretation of the studies described above is limited by modest sample sizes. We acknowledge that outcomes evaluated in Asian American survivors cannot be extrapolated to survivors in the Asia continent due to differences in treatment regimens, healthcare systems and lifestyle factors. However, it is hoped that findings from Asian Americans may justify the need for such outcomes research in Asia, which is projected to be facing an emerging population of childhood cancer survivors in the next decades.

With these research gaps in mind, we propose to describe neurocognitive function, emotional status,

HRQoL and social attainment among Asian/Pacific Islander survivors of childhood cancer in the CCSS. With the expansion of the CCSS cohort, new investigations into associations between race/ethnicity and long-term health and psychosocial outcomes are possible. As of February 2017, there was an increase in available survivor and sibling data from the minority groups, including 371 Asian / Pacific Islander survivors and 52 siblings. We will first compare differences between survivors of Asian / Pacific Islander descent and their siblings to those for survivors of Caucasian descent and their siblings. We will also identify sociodemographic, treatment and clinical predictors to evaluate neurocognitive function, emotional status, health-related quality of life (HRQoL) and social attainment in cancer survivors of Asian/Pacific islander descent.

Note: *We realize the sample size proposed for the current analysis is relatively small compared to most other CCSS proposals, though it is substantially larger than most other published reports on this topic. We see this study as laying a foundation for future research in this growing population of Asian survivors. Drs. Sato, Cheung, Li and Zhang are planning to develop a follow-up project to expand upon the results obtained in this study by collecting new data in their home countries of mainland China, Hong Kong and Japan.*

5. Specific Aims and Primary Hypotheses

Aim 1: To describe neurocognitive function, emotional status, HRQoL and social attainment in childhood cancer survivors and non-cancer siblings of Asian/Pacific islander descent.

Aim 2: To compare differences in neurocognitive function, emotional status, HRQoL and social attainment between childhood cancer survivors of Asian/Pacific islander descent to differences seen in survivors of Caucasian descent and their siblings.

> Hypothesis 2.1: The size of the differences in neurocognitive function, emotional status, HRQoL and social attainment between survivors of Asian/Pacific islander descent and their siblings will be comparable to the size of the differences between survivors of Caucasian descent and their siblings.

Aim 3: To identify treatment and clinical predictors of neurocognitive function, emotional status, HRQoL and social attainment in cancer survivors of Asian/Pacific islander descent.

> Hypothesis 3.1: Treatment factors (cranial radiation, methotrexate exposure [intrathecal or/and intravenous], corticosteroids, neurosurgery etc.) will be associated with neurocognitive function, emotional status, HRQoL and social attainment in survivors of Asian/Pacific islander descent
> Hypothesis 3.2: Clinical factors (CNS tumor, age at diagnosis, time since diagnosis, chronic conditions etc.) are associated with neurocognitive function, emotional status, HRQoL and social attainment in survivors of Asian/Pacific islander descent

6. Methods

6.1 **Study Population:** The study population will include survivors and siblings in both the original and expansion CCSS cohorts. We will use neurocognitive, emotional, HRQoL and social attainment data from follow-up 2 for participants from the original cohort and follow up 5 for participants from the expansion cohort.

"Asian/ Pacific Islander" refers to survivors who answered "Asian" or "Pacific Islander" [original baseline survey A4; expansion baseline survey A5]

"Caucasian" refers to survivors who answered "White" [original baseline survey A4; expansion baseline survey A5]

6.2 **Outcome Variables**

6.2.1 **Neurocognitive function** will be assessed using the CCSS-NCQ which was developed for use and validated within the CCSS cohort using four factors; Task Efficiency, Emotional Regulation, Organization and Memory. Scores will be reported as a continuous variable for the primary analysis. Consistent with previous CCSS studies, impaired performance was defined as a score falling ≥90th percentile based on values obtained in the sibling cohort. [original FUP2 J1 to J25; expansion FUP5 Q1 to Q33]

6.2.2 **Emotional distress** will be assessed using the self-reported Brief Symptom Inventory-18 (BSI-18) which has been validated in cancer patients and within the CCSS cohort. The BSI-18 includes the global severity index as well as subscales for anxiety depression and somatization assessed based on symptoms within the past seven days. Scores will be reported as a continuous variable for the primary analysis. Consistent with previous CCSS studies, distress will be defined as T-scores ≥ 63 (90th percentile) for each subscale. [original FUP2 G1 to G18; expansion FUP5 L1 to L18]

6.2.3 **Health-related quality of life** will be assessed using the Medical Outcomes Short Form-36 which includes questions regarding general health, well-being, and quality of life over the previous four weeks. This tool has been used in population studies and survivor samples, including within the CCSS. The SF-36 includes eight subscales of various aspects of well-being (Performance Function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health) where higher scores represent "better" quality of life. Scores will be reported as a continuous variable for the primary analysis. Impairment is defined as scores falling below a T-score of 40 (1 standard deviation below the mean). [original FUP2 E1 to E22, F1 to F14; expansion FUP5 O1 to O8; P1 to P3]

6.2.4 **Social attainment** will be assessed by:

- Highest education attainment [original FUP2 1; expansion FUP5 A4]
    - Below college graduate vs College graduate and above

- Employment status [original FUP2 4; expansion FUP5 A5]
    - Employed Fulltime vs less than Fulltime
- Marital status [original FUP2 2; expansion FUP5 M2]
    - Ever married vs never married
- Living arrangement [original FUP2 3; expansion FUP5 M1]
    - Living dependently (with parents, siblings, other relatives) vs. independently
- Income [original FUP2 S1 to S3; expansion FUP5 A7 to A9]
    - Dichotomy to be determined based on data distribution

6.3 Predictors for Aim 3 (and potential covariates for Aims 1 and 2):

6.3.1 Age at follow-up (years, continuous) [original baseline A1; expansion baseline A1]

6.3.2 Sex (male vs female) [original baseline A2; expansion baseline A2]

6.3.3 Diagnosis: Type of cancer (categories including leukemia, CNS tumor, Wilms' tumor, neuroblastoma, soft tissue sarcoma)

- Leukemia vs. CNS tumor vs. others
- Age at diagnosis (years, continuous)

6.3.1 Radiation variable (dose effects will be modeled per 10 Gy given relatively small sample size)

- Chest radiation (continuous per 10 Gy)
- Abdomen radiation (continuous per 10 Gy)
- Pelvic radiation (continuous per 10 Gy)
- Cranial radiation (continuous per 10 Gy)

6.3.2 Chemotherapy variables

- IV Methotrexate (cumulative dose)
- IT Methotrexate (cumulative dose)
- Corticosteroids (yes/no)

6.3.3 Neurosurgery (yes/no)

6.3.4 Chronic health conditions (CHC)

- Presence of cardiovascular, pulmonary, endocrine systems and neurologic CHCs is pre-defined as having a Grade 2 and above condition (i.e. moderate, severe and life-threatening conditions).
- For this study, the health conditions of interest were limited to cardiovascular, pulmonary, endocrine and neurologic systems, given their association with neurocognitive function and psychological distress in the general population, as well as in previous CCSS papers.
- ***Note:*** *Depending on the proportion of survivors who reported CHCs, a skewed distribution may require categories to be dichotomized differently, or CHCs may be omitted from subsequent analyses. Within this relatively small sample, the frequency of chronic health may be too small to include in formal analytic models. If this is the case,*

such conditions will only be included descriptively and used to power future studies to examine this impact.

6.4 Statistical analysis

Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percentages will be calculated for the primary outcomes, predictors and covariates. Presentation of descriptive data will be done according to reasonable groupings and consistent with previous CCSS manuscripts (Table 1).

For Aim 1, among survivors and siblings of Asian/ Pacific Islander descent, descriptive statistics will be generated for the outcomes (NCQ, BSI and SF-36 scores - continuous). Means, standard deviations, ranges and impairment percentages will be displayed in tabular and/or graphical form. For categorical variables (e.g. social attainment), frequencies and percentages within each category will be generated.

For Aim 2, comparisons of the outcomes (NCQ, BSI and SF-26 scores - continuous) will be conducted between survivors of Asian/ Pacific Islander descent and survivors of Caucasian descent using GLM, adjusting for potential covariates (adjusted for sex and age at evaluation first, then include treatment variables within the same model). Standardized estimates and standard errors will be reported. Comparisons of the social attainment outcomes (employment, marital status, education attainment etc.) will be conducted using logistic regression, adjusting for potential covariates (adjusted for sex and age at evaluation first, then include treatment variables within the same model). The analyses above will also be conducted with and without the adjustment for CHCs as the CHCs may mediate the group differences. Odds Ratios (OR) and 95% confidence (CI) intervals will be reported.

Exploratory analysis to account for socioeconomic status:

A methodology to account for the effect of socioeconomic status on self-reported outcomes was developed by Dixon et al in her recent CCSS concept proposal. We will compare each survivor group to their racial/ethnically specific sibling group, leveraging on the assumption that siblings shared a similar socioeconomic environment to survivors. We will conduct further analyses to compare the intra racial/ethnic survivor sibling differences across racial/ethnic stratum i.e. we will compare difference in outcomes between survivors and siblings of Asian Asian/Pacific islander descent versus the difference between Caucasian survivors and siblings.

For Aim 3, within survivors of Asian/ Pacific Islander descent, GLM will be conducted to examine the association between predictors listed in Section 6.3 and the NCQ scores, including covariates as appropriate, both for the overall cohort (Table 4). The same analytical approach will be applied for BSI (Table 5) and SF-36

(Table 6). Standardized estimates and standard errors will be reported. Logistic regression will be used to examine association between predictors listed in Section 6.3 and social attainment outcomes, including covariates as appropriate (Table 7). Adjusted OR and 95% CI will be reported. Separate models will be run for each outcome.

References

1. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, Stovall M, Oeffinger KC, Bhatia S, Krull KR, Nathan PC, Neglia JP, Green DM, Hudson MM, Robison LL. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med*. 2016;374(9):833-842. http://dx.doi.org/10.1056/NEJMoa1510795. doi: 10.1056/NEJMoa1510795.

2. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK, Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309(22):2371-2381.

3. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, Chemaitilly W, Ehrhardt MJ, Bass J, Bishop MW, Shelton K, Lu L, Huang S, Li Z, Caron E, Lanctot J, Howell C, Folse T, Joshi V, Green DM, Mulrooney DA, Armstrong GT, Krull KR, Brinkman TM, Khan RB, Srivastava DK, Hudson MM, Yasui Y, Robison LL. The cumulative burden of surviving childhood cancer: An initial report from the st jude lifetime cohort study (SJLIFE). *The Lancet*. ;390(10112):2569-2582. http://dx.doi.org/10.1016/S0140-6736(17)31610-0. doi: 10.1016/S0140-6736(17)31610-0.

4. Krull KR, Cheung YT, Liu W, Fellah S, Reddick WE, Brinkman TM, Kimberg C, Ogg R, Srivastava D, Pui CH, Robison LL, Hudson MM. Chemotherapy pharmacodynamics and neuroimaging and neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2016;34(22):2644-2653.

5. Cheung YT, Brinkman TM, Li C, Mzayek Y, Srivastava D, Ness KK, Patel SK, Howell RM, Oeffinger KC, Robison LL, Armstrong GT, Krull KR. Chronic health conditions and neurocognitive function in aging survivors of childhood cancer: A report from the childhood cancer survivor study. *Journal of National Cancer Institute*. ;In Press.

6. Cheung YT, Brinkman TM, Mulrooney DA, Mzayek Y, Liu W, Banerjee P, Panoskaltsis-Mortari A, Srivastava D, Pui CH, Robison LL, Hudson MM, Krull KR. Impact of sleep, fatigue, and systemic inflammation on neurocognitive and behavioral outcomes in long-term survivors of childhood acute lymphoblastic leukemia. *Cancer*. 2017;123(17):3410-3419.

7. Cheung YT, Sabin ND, Reddick WE, Bhojwani D, Liu W, Brinkman TM, Glass JO, Hwang SN, Srivastava D, Pui CH, Robison LL, Hudson MM, Krull KR. Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: A longitudinal analysis. *Lancet Haematol*. 2016;3(10):e466.

8. Edelmann MN, Daryani VM, Bishop MW, Liu W, Brinkman TM, Stewart CF, Mulrooney DA, Kimberg C, Ness KK, Cheung YT, Srivastava DK, Robison LL, Hudson MM, Krull KR. Neurocognitive and patient-reported outcomes in adult survivors of childhood osteosarcoma. *JAMA Oncol*. 2016;2(2):201-208.

9. Cheung YT, Krull KR. Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. *Neurosci Biobehav Rev*. 2015;53:108-120.

10. Huang I, Brinkman TM, Cheung YT, Pui C, Hudson MM, Krull KR. Functional consequence of cognitive impairment in survivors of childhood acute lymphoblastic leukemia (ALL): The role of cancer symptoms as mediators. *JCO*. 2016;34(3):235.

11. Mohrmann C, Henry J, Hauff M, Hayashi RJ. Neurocognitive outcomes and school performance in solid tumor cancer survivors lacking therapy to the central nervous system. *J Pers Med*. 2015;5(2):83-90. doi: 10.3390/jpm5020083 [doi].

12. Kirchhoff AC, Krull KR, Ness KK, Armstrong GT, Park ER, Stovall M, Robison LL, Leisenring W. Physical, mental, and neurocognitive status and employment outcomes in the childhood cancer survivor study cohort. *Cancer Epidemiol Biomarkers Prev*. 2011;20(9):1838-1849. doi: 10.1158/1055-9965.EPI-11-0239 [doi].

13. Krull KR, Sabin ND, Reddick WE, Zhu L, Armstrong GT, Green DM, Arevalo AR, Krasin MJ, Srivastava DK, Robison LL, Hudson MM. 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 [doi].

14. Krull KR, Brinkman TM, Li C, Armstrong GT, Ness KK, Srivastava DK, Gurney JG, Kimberg C, Krasin MJ, Pui C, Robison LL, Hudson MM. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the st jude lifetime cohort study. *Journal of Clinical Oncology*. 2013;31(35):4407-4415. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3842908/. doi: 10.1200/JCO.2012.48.2315.

15. Vuotto SC, Krull KR, Li C, Oeffinger KC, Green DM, Patel SK, Srivastava D, Stovall M, Ness KK, Armstrong GT, Robison LL, Brinkman TM. Impact of chronic disease on emotional distress in adult survivors of childhood cancer: A report from the childhood cancer survivor study. *Cancer*. 2017;123(3):521-528.

16. Li HC, Lopez V, Joyce Chung OK, Ho KY, Chiu SY. The impact of cancer on the physical, psychological and social well-being of childhood cancer survivors. *Eur J Oncol Nurs*. 2013;17(2):214-219.

17. Chou L, Hunter A. Factors affecting quality of life in taiwanese survivors of childhood cancer. *J Adv Nurs*. 2009;65(10):2131-2141. http://dx.doi.org/10.1111/j.1365-2648.2009.05078.x. doi: 10.1111/j.1365-2648.2009.05078.x.

18. Kamibeppu K, Sato I, Honda M, Ozono S, Sakamoto N, Iwai T, Okamura J, Asami K, Maeda N, Inada H, Kakee N, Horibe K, Ishida Y. Mental health among young adult survivors of childhood cancer and their siblings including posttraumatic growth. *J Cancer Surviv*. 2010;4(4):303-312. doi: 10.1007/s11764-010-0124-z [doi].

19. Ishida Y, Honda M, Kamibeppu K, Ozono S, Okamura J, Asami K, Maeda N, Sakamoto N, Inada H, Iwai T, Kakee N, Horibe K. Social outcomes and quality of life of childhood cancer survivors in japan: A cross-sectional study on marriage, education, employment and health-related QOL (SF-36). *Int J Hematol*. 2011;93(5):633-644. https://doi.org/10.1007/s12185-011-0843-6. doi: 10.1007/s12185-011-0843-6.

20. Kim SJ, Park MH, Lee JW, Chung NG, Cho B, Lee IG, Chung SY. Neurocognitive outcome in survivors of childhood acute lymphoblastic leukemia: Experience at a tertiary care hospital in korea. *J Korean Med Sci*. 2014;30(4):463-469. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4366968/. doi: 10.3346/jkms.2015.30.4.463.

21. Ng DL, Leong YC, Gan GG. Quality of life amongst lymphoma survivors in a developing country. *Support Care Cancer*. 2016;24(12):5015-5023. doi: 10.1007/s00520-016-3364-2 [doi].

22. Syn NL, Yong WP, Lee SC, Goh BC. Genetic factors affecting drug disposition in asian cancer patients. *Expert Opin Drug Metab Toxicol*. 2015;11(12):1879-1892.

23. Cheung Y. Cancer pharmacoethnicity: Ascertaining chronic health outcomes in survivors of childhood cancer in asia. *Glob J Pharmaceu Sci.* 2017;4(4):555634.

24. Choudhury S. Culturing the adolescent brain: What can neuroscience learn from anthropology? *Social Cognitive and Affective Neuroscience*. 2009;5(2-3):159-167. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2894667/. doi: 10.1093/scan/nsp030.

25. Park DC, Huang C. Culture wires the brain: A cognitive neuroscience perspective. *Perspectives on psychological science : a journal of the Association for Psychological Science*. 2010;5(4):391-400. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409833/. doi: 10.1177/1745691610374591.

26. Ho C, Bluestein DN, Jenkins JM. Cultural differences in the relationship between parenting and children's behavior. *Dev Psychol*. 2008;44(2):507-522.

27. Martinson IM, Leavitt M, Liu CY, Armstrong V, Hornberger L, Zhang JQ, Han XP. Comparison of chinese and caucasian families caregiving to children with cancer at home: Part I. *J Pediatr Nurs*. 1999;14(2):99-109. doi: S0882-5963(99)80044-X [pii].

Table 1: Demographic and Clinical Characteristics (Baseline)

	Asian/ Pacific Islander descent		Caucasian descent	
	Survivors (N=)	Siblings (N=)	Survivors (N=)	Siblings (N=)
	n (%)	n (%)	n (%)	n (%)
Sex				
Male				
Female				
Age at assessment* (years)				
Health Insurance				
Yes				
No				
Not specified				
Household Income				
< $20000				
≥$20,000				
Not specified				
Diagnosis				
Leukemia				
CNS tumor				
Others				
Age at Diagnosis* (years)				
Chemotherapy				
Anthracycline				
Alkylating Agent				
IV Methotrexate* (cumulative)				
IT Methotrexate* (cumulative)				
Anti-tumor Antibiotic				
Corticosteroids				
Enzymes				
Epipodophyllotoxins				
Heavy Metals				
Plant Alkaloids				
Radiation				
Chest radiation (Gy)				

Abdomen radiation (Gy)				
Pelvic radiation (Gy)				
Cranial radiation (Gy)				
Surgery				
Neurosurgery				
Chronic Health Conditions				
Cardiovascular				
None or Mild (0/1)				
Moderate or Severe/life-threatening (2/3/4)				
Pulmonary				
None or Mild (0/1)				
Moderate or Severe/life-threatening (2/3/4)				
Endocrine				
None or Mild (0/1)				
Moderate or Severe/life-threatening (2/3/4)				
Neurologic				
None or Mild (0/1)				
Moderate or Severe/life-threatening (2/3/4)				

*Presented as a continuous variable: mean (standard deviation)

Table 2: Comparison of Neurocognitive Function, Emotional Status, Heath-related Quality of Life and Social Attainment in Survivors and Siblings of Asian/ Pacific Islander Descent

	Survivors		**Siblings**		***Comparison***		
	Mean (SD)	% impaired	Mean (SD)	% impaired	**Est.**	**SE**	***P***
Neurocognitive function[1]							
Task Efficiency							
Emotional Regulation							
Organization							
Memory							
Emotional status[2]							
Anxiety							
Depression							
Somatization							
Health-related quality of life[3]							
Performance Function							
Role Physical							
Bodily Pain							
General Health							
Vitality							
Social Functioning							
Role Emotional							
Mental Health							
Social attainment[4]							
	n	**%**	**n**	**%**	**OR**	**95% CI**	***P***

Education level:							
Below college graduate							
College graduate and above							
Personal income							
< 20,000							
≥ 20,000							
Employment status							
Unemployed							
Employed/ Student							
Current marital status							
Ever married							
Never married							
Independent living							
Yes							
No							

[1] Neurocognitive function refers to scores on the Neurocognitive Questionnaire (NCQ). A higher score indicates more cognitive problems. Impaired performance is defined as a score falling ≥90th percentile based on values obtained in the sibling cohort.

[2] Emotional status refers to scores on the Brief Symptom Inventory (BSI-18). A higher score indicates more symptoms. Significant distress will be defined as T-scores ≥ 63 (90th percentile) for each subscale.

[3] Health-related quality of life refers to scores on the Short-form 36 (SF-36). A higher score indicates better quality of life. Impairment is defined as scores falling below a T-score of 40 (1 standard deviation below the mean).

[4] Categorization of the social attainment variables may change depending on the frequency distribution.

P: Adjusted comparisons of the outcomes scores on the NCQ, BSI-18 and SF-36 will be conducted using general linear modeling (GLM), adjusting for potential covariates (sex, age at evaluation). Standardized estimates and standard errors will be reported. Comparisons of the social attainment outcomes (employment, marital status, education attainment etc.) will be made using logistic regression, adjusting for potential covariates (sex, age at evaluation).

Siblings will be assigned as the referent group. Odds Ratios (OR) and 95% confidence (CI) intervals will be reported.

Table 3: Comparison of Neurocognitive Function, Emotional Status, Heath-related Quality of Life and Social Attainment in Survivors of Asian/ Pacific Islander Descent and of Caucasian Descent

	Asian/ Pacific Islander descent		**Caucasian descent**		***Comparison***		
	Mean (SD)	% impaired	Mean (SD)	% impaired	**Est.**	**SE**	***P***
Neurocognitive function[1]							
Task Efficiency							
Emotional Regulation							
Organization							
Memory							
Emotional status[2]							
Anxiety							
Depression							
Somatization							
Health-related quality of life[3]							
Performance Function							
Role Physical							
Bodily Pain							
General Health							
Vitality							
Social Functioning							
Role Emotional							
Mental Health							
Social attainment[4]							
	n	**%**	**n**	**%**	**OR**	**95% CI**	***P***

Education level:							
Below college graduate							
College graduate and above							
Personal income							
< 20,000							
≥ 20,000							
Employment status							
Unemployed							
Employed/ Student							
Current marital status							
Ever married							
Never married							
Independent living							
Yes							
No							

[1] Neurocognitive function refers to scores on the Neurocognitive Questionnaire (NCQ). A higher score indicates more cognitive problems. Impaired performance is defined as a score falling ≥90th percentile based on values obtained in the sibling cohort.

[2] Emotional status refers to scores on the Brief Symptom Inventory (BSI-18). A higher score indicates more symptoms. Significant distress will be defined as T-scores ≥ 63 (90th percentile) for each subscale.

[3] Health-related quality of life refers to scores on the Short-form 36 (SF-36). A higher score indicates better quality of life. Impairment is defined as scores falling below a T-score of 40 (1 standard deviation below the mean).

[4] Categorization of the social attainment variables may change depending on the frequency distribution.

P: Adjusted comparisons of the outcomes scores on the NCQ, BSI-18 and SF-36 will be conducted using general linear modeling (GLM), adjusted for sex and age at evaluation first, then include treatment variables within the same model. Comparisons of the social attainment outcomes will be conducted using

logistic regression, adjusting for sex and age at evaluation first, then include treatment variables within the same model. The analyses above will also be conducted with and without the adjustment for CHCs as the CHCs may mediate the group differences.

Table 4: Association of Factors with Neurocognitive Function in Survivors of Asian/ Pacific Islander Descent (All)

	Neurocognitive Function							
	Task Efficiency		**Memory**		**Organization**		**Emotional Regulation**	
	Est. (SE)	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*
Clinical characteristics								
Sex								
Male (referent)	--	--	--	--	--	--	--	--
Female								
Age at baseline (years)								
Age at diagnosis (years)								
Cancer diagnosis								
Others (referent)	--	--	--	--	--	--	--	--
Leukemia								
CNS tumor								
Neurosurgery								
No (referent)	--	--	--	--	--	--	--	--
Yes								
Chemotherapy								
IV Methotrexate (cumulative doses)								
IT Methotrexate (cumulative doses)								
Corticosteroids								
No (referent)	--	--	--	--	--	--	--	--
Yes								
Radiation								
Chest (continuous per 10 Gy)	--	--	--	--	--	--	--	--

Abdomen (continuous per 10 Gy)								
Pelvic (continuous per 10 Gy)								
Cranial (continuous per 10 Gy)								

Neurocognitive function refers to scores on the Neurocognitive Questionnaire (NCQ). A higher score indicates more cognitive problems. A positive estimate indicates that the group with the variable of interest reported more problems than the referent group.

Table 5: Factors Associated with Emotional Status in Survivors of Asian/ Pacific Islander Descent

	Emotional Status					
	Depression		**Anxiety**		**Somatization**	
	Est. (SE)	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*
Clinical characteristics						
Sex						
Male (referent)	--	--	--	--	--	--
Female						
Age at baseline (years)						
Age at diagnosis (years)						
Cancer diagnosis						
Others (referent)	--	--	--	--	--	--
Leukemia						
CNS tumor						
Neurosurgery						
No (referent)	--	--	--	--	--	--
Yes						
Chemotherapy						
IV Methotrexate (cumulative doses)						
IT Methotrexate (cumulative doses)						
Corticosteroids						
No (referent)						
Yes						
Radiation						
Chest (continuous per 10 Gy)						

Abdomen (continuous per 10 Gy)						
Pelvic (continuous per 10 Gy)						
Cranial (continuous per 10 Gy)						

Emotional status refers to scores on the Brief Symptom Inventory (BSI-18). A higher score indicates more emotional problems. A positive estimate indicates that the group with the variable of interest reported more problems than the referent group.

Table 6: Association of Factors with Health-related Quality of Life in Survivors of Asian/ Pacific Islander Descent (All)

	Health-related Quality of Life															
	Performance Function		**Role Physical**		**Bodily Pain**		**General Health**		**Vitality**		**Social Functioning**		**Role Emotional**		**Mental Health**	
	Est. (SE)	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*	*Est. (SE)*	*P*
Clinical characteristics																
Sex																
Male (referent)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Female																
Age at baseline (years)																
Age at diagnosis (years)																
Cancer diagnosis																
Others (referent)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Leukemia																
CNS tumor																
Neurosurgery																
No (referent)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Yes																
Chemotherapy																
IV Methotrexate (cumulative doses)																
IT Methotrexate (cumulative doses)																
Corticosteroids																
No (referent)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Yes																
Radiation																

Chest (continuous per 10 Gy)																		
Abdomen (continuous per 10 Gy)																		
Pelvic (continuous per 10 Gy)																		
Cranial (continuous per 10 Gy)																		

Health-related quality of life refers to scores on the Short-form (SF-36). A higher score indicates better quality of life. A positive estimate indicates that the group with the variable of interest reported better quality of life than the referent group.

Table 7: Association of Factors with Social Attainment in Survivors of Asian/ Pacific Islander Descent (All)

	Social Attainment									
	Education		**Employment**		**Marital status**		**Independent living**		**Personal income**	
	Less than high school		Unemployed		Single, never married		No		< 20,000	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Clinical characteristics										
Sex										
Male (referent)	--	--	--	--	--	--	--	--	--	--
Female										
Age at baseline (years)										
Age at diagnosis (years)										
Cancer diagnosis										
Others (referent)	--	--	--	--	--	--	--	--	--	--
Leukemia										
CNS tumor										
Neurosurgery										
No (referent)	--	--	--	--	--	--	--	--	--	--
Yes										
Chemotherapy										
IV Methotrexate (cumulative doses)										
IT Methotrexate (cumulative doses)										
Corticosteroids										
No (referent)	--	--	--	--	--	--	--	--	--	--
Yes										
Radiation										

Chest (continuous per 10 Gy)										
Abdomen (continuous per 10 Gy)										
Pelvic (continuous per 10 Gy)										
Cranial (continuous per 10 Gy)										