

**SF 424 R&R and PHS-398 Specific  
Table of Contents**

SF 424 Cover Page ..... 2

Research & Related Other Project Information..... 3

Project Summary/Abstract..... 4

Relevance Statement..... 5

Facilities and Other Resources ..... 6

PHS 398 Cover Page Supplement.....10

PHS 398 Research Plan .....11

Specific Aims .....12

Research Strategy .....14

Protection of Human Subjects.....22

Inclusion of Women and Minorities.....26

Planned Enrollment Report .....27

Inclusion of Children .....28

Resource Sharing Plan .....29

<b>PI: Huang, I-Chan</b>	Title: Symptom progress and adverse health outcomes in adult childhood cancer survivors	
	FOA: PAR13-146	
	FOA Title: NCI EXPLORATORY/DEVELOPMENTAL RESEARCH GRANT PROGRAM (NCI OMNIBUS R21)	
	Organization: ST. JUDE CHILDREN'S RESEARCH HOSPITAL	
<i>Senior/Key Personnel:</i>	<i>Organization:</i>	<i>Role Category:</i>
I-Chan Huang	St. Jude Childrens Research Hospital	PD/PI

## RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?  Yes  No
- 1.a If YES to Human Subjects
- Is the Project Exempt from Federal regulations?  Yes  No
- If NO, is the IRB review pending?  Yes  No
2. Are Vertebrate Animals Used?  Yes  No
3. Is proprietary/privileged information included in the application?  Yes  No
- 4a. Does this project have an actual or potential impact on the environment?  Yes  No
5. Is the research performance site designated, or eligible to be designated, as a historic place?  Yes  No
6. Does this project involve activities outside of the United States or partnerships with international collaborators?  Yes  No

## PROJECT SUMMARY/ABSTRACT

Childhood cancer survivors are vulnerable to treatment-related late effects, which include physical and psychosocial morbidity, subsequent malignancies, and premature death. Symptoms representing one's perceptive abnormal physical, emotional, or psychosomatic state are common late effects in childhood cancer survivors. Survivors often experience multiple, concurrent symptoms, known as a symptom cluster. Although the association between symptom presence and poor quality of life in childhood cancer survivors has been reported, it is uncertain whether individual symptom domains and clusters change over time, and whether the change in individual symptom domains and clusters are associated with adverse health outcomes, including chronic conditions and premature mortality. In addition, very few studies have examined if specific cancer therapeutic exposures (e.g., cranial irradiation, anthracyclines, and alkylating agents) contribute to the change in individual symptoms and symptom clusters over time.

Our long-term goal of cancer survivorship care is to identify important symptoms for early indication of adverse health events (e.g., cardiac arrest and premature mortality), and to design interventions targeting at symptoms for promotion of healthy aging in cancer survivors. To achieve this goal, the current study proposes two specific aims: 1) to investigate the presence of individual symptom domains (sensation abnormality, motor/movement problems, cardiac symptoms, pulmonary symptom, pain, anxiety, depression, and somatization) and symptom clusters across multiple time points spanning 25 years in adult survivors of childhood cancers, and investigate the transition of symptom clusters over time, and 2) to investigate the prognostic value of individual symptom domains and symptom clusters for the development of chronic conditions and premature mortality in adult survivors of childhood cancers.

The proposed study will overcome the limitations of previous research by utilizing repeated symptom data collected from participants in the Childhood Cancer Survivor Study to elucidate the extent to which symptom progress is associated with mortality and with chronic conditions identified during risk-based comprehensive medical assessment in the St. Jude Lifetime Cohort Study (N>700) at St. Jude Children's Research Hospital. We will group chronic conditions by eight organ systems: cardiovascular, endocrine/reproductive, hepatic, neurocognitive, neurosensory, skeletal, pulmonary, and urinary categories. In addition, we will develop a classification methodology to identify symptom clusters based on eight individual symptom domains, and use a transition analytic method to capture the change in symptom cluster over time. Our team includes renowned researchers with expertise in patient-reported outcomes, symptom measurement, psychology, pediatric/adult survivorship care, and translational science research.

**RELEVANCE STATEMENT**

We propose to address a significant knowledge gap in the linkage of symptom presence with adverse health outcomes including chronic conditions and premature mortality using 25-year longitudinal data. This study will help identify specific interventions to address symptoms and, potentially, manage and/or prevent adverse health outcomes for long-term adult survivors of childhood cancer.

## FACILITIES AND OTHER RESOURCES

### **Clinical:**

**St. Jude Children's Research Hospital (SJCRH)** is a National Cancer Institute (NCI) designated Comprehensive Cancer Center and the largest pediatric oncology center in North America, specializing in the development of new protocols for the treatment of cancer and other catastrophic diseases of childhood. The institution's 67 faculty-level clinical investigators and 34 clinical fellows collaborate extensively with basic science investigators. The campus has 2.5 million square feet of research, clinical and administrative space. The 200,000-square-foot patient care building houses 78 inpatient beds, a surgical suite, an intensive care unit, and five outpatient clinics that accommodate more than 40,000 visits annually. St. Jude provides clinical care to thousands of patients each year (approximately 500 new patients yearly), irrespective of ability to pay. Essentially all patients are treated on active clinical research protocols, many of which incorporate translational research findings. All staff members are experienced in the conduct of clinical trials.

**The After Completion of Therapy (ACT) Clinic** occupies over 1,400 square feet in the ambulatory care unit at SJCRH. This space includes five exam rooms, five consultation rooms, three neuropsychology evaluation rooms, one staff room for discussions and medical record review, one administrative area, and two general supply areas. The ACT Clinic was established in 1984 to specifically address the medical and psychosocial needs of childhood cancer survivors treated at St. Jude. Patients who are in remission five years after diagnosis and at least two years following completion of anti-neoplastic therapy are transferred to the SJCRH ACT Clinic for late effects monitoring. The multidisciplinary clinic provides annual medical evaluations of longterm survivors who were treated at SJCRH. Compliance with long-term follow-up is excellent, in part, due to the fact that the institution supports travel and domiciliary care costs of survivors returning for annual evaluations after completion of therapy, and underwrites the costs of evaluations not covered by third party payers. Currently, staffing includes four part-time pediatric oncologists (one is also an internist) who maintain active oncology practices, two full-time staff physicians (family practice), six nurse practitioners, ten technical research and two administrative staff members. Survivors are evaluated annually by the clinic staff until they are 18 years of age or ten years post-diagnosis, whichever occurs later. Currently over 5,100 five-year survivors are monitored by the staff of the ACT Clinic; 1350 of these are still in an active period of follow-up and return annually for clinical evaluations. The remaining five-year alumni survivors who have been discharged to the care of the community physicians are monitored by the SJCRH Tumor Registry and through the St. Jude Lifetime Cohort Study. Over 4,000 5-year survivors are now being invited to return to the ACT clinic as participants in the St. Jude Lifetime Cohort Study. It is important to emphasize that institutional funds have been committed to cover all costs associated with participation in the St. Jude Lifetime Cohort Study (i.e., travel, housing, meals, medical screening). The unique combination of both research and clinical care expertise, in addition to the large population of cancer survivor alumni at St. Jude provides the ideal platform for this evaluation of survivors of pediatric cancer.

**The Kmart St. Jude Life Center** provides an outpatient site for Phase I, II, and III clinical trials of novel therapeutic or prophylactic agents. The unit works with basic science investigators to guide translational trial design and facilitate regulatory approval for on-site trials or cooperative efforts. It also assists in the conduct and analysis of on-site Phase I and II studies. The unit has 18 clinic rooms and an adjacent laboratory that processes, stores, distributes, and ships clinical research specimens. The unit allows the conduct of 10 to 20 additional Phase I protocols per year and the simultaneous conduct of two Phase II trials. Because the Kmart St. Jude Life Center is a core facility, it manages multiple, concurrent, scientifically diverse trials. The unit is

currently investigating a Para influenza virus vaccine and a pneumococcal vaccine trial is pending. It also houses HIV Programs, and infectious diseases. The ACT clinics are contained within the Kmart St. Jude Life Center.

**The Department of Radiological Sciences** is dedicated to clinical investigation and patient care in the diagnosis and treatment of childhood cancer and related diseases. The divisions of Radiation Oncology, Diagnostic Imaging, Nuclear Medicine/Molecular Imaging, and Translational Imaging Research focus on applying novel, sophisticated technologies to study optimizing radiation therapy for children with cancer, diagnostic techniques (including X-ray, ultrasound, MRI, and CT) and interventional radiology in children with catastrophic diseases, diagnostic and therapeutic applications of radiopharmaceuticals (nuclear scans) and development of new ways to image molecular (subcellular) targets, and means to optimize imaging capabilities (including improved diagnostic techniques in brain and body MR imaging), respectively. Specifically, the Department of Radiological Sciences hosts a fully equipped diagnostic imaging, nuclear imaging and interventional radiology divisions. The Department also includes Radiation Dosimetry lab, which provides detailed radiation exposure data for current patients and long-term survivors treated at St. Jude.

#### **Laboratory:**

**The Human Performance Laboratory** occupies 753 square feet in the Kmart St. Jude Life Center within the clinical research space utilized by the Department of Epidemiology and Cancer Control. It is equipped with a Biodex System III Isokinetic Strength Testing System, a Smart Equitest with ten foot dual force plates and surface EMG monitoring capability. Other major equipment includes Treadmill and Cycle Ergometers, a MedGraphics Ultima Cardio2 metabolic cart, a V02000 portable metabolic cart and a MedGraphics Cardioperfect ECG System. Hand held dynamometry, myometry, range of motion, flexibility, and sensory testing equipment, and gait analysis equipment are also available. Peripheral vascular testing equipment was added in 2011 and early 2012. Testing capabilities include anthropomorphic evaluation, vital sign monitoring, ECG monitoring, cardiopulmonary stress testing, portable blood pressure monitoring, determination of peripheral vascular resistance, autonomic stress testing, balance and muscle strength evaluations, electromyography, determination of sensory capabilities, gait evaluation, coordination assessment and fitness field testing. Lab personnel also perform standard gross and fine motor developmental evaluations and assessments of capabilities in activities of daily living. The lab staff includes one faculty member (Director), three full time Masters Level exercise specialists, and two physical therapists.

#### **Office and Other:**

**The Department of Epidemiology and Cancer Control** is the home department of the MPIs (Drs. Huang and Krull), and includes 12 faculty members, plus an additional 93 full-time equivalent FTEs of research and support staff, and is the cornerstone of the Cancer Prevention and Control Program for the SJCRH Cancer Center. The Department is internationally recognized for work in childhood cancer survivorship research, and is the coordinating center for the NCI-funded Childhood Cancer Survivor Study (CCSS), a retrospective cohort study designed to characterize health outcomes among 35,000 childhood cancer survivors treated between 1970 and 1999 at 27 institutions across North America. It also houses the support for the St. Jude Lifetime Cohort Study, an institutionally supported initiative designed to characterize health and health outcomes in over 4,000 aging childhood cancer survivors. The department houses a large Survey Research Center, a Database and Informatics Support Group, and the Human Performance Laboratory to provide support to researchers whose primary goals include reducing morbidity and mortality among children with cancer and other hematological disease.

- **Office Space** for The Department of Epidemiology and Cancer Control is located within the Barry Building on the north side of the St. Jude campus. Departmental faculty and staff occupy 21,750 square feet of contiguous office space located on floors 4, 5, and 6. In addition, 3,150 square feet of clinical space is located in the Kmart St. Jude Life Center, which is adjacent to the Barry Building.
- **The Survey Research and Data Center** provides a wide range of support to departmental research including: participant recruitment/retention/tracking, questionnaire design, distribution of surveys, conduction of telephone interviews, data collection and editing, collection of biological specimens, validation of key adverse events, data coding and cleaning, National Death Index searches, and tracing of study subjects. The volume of work conducted by the Survey Research and Data Center is substantial and carried out in coordination with other key units within the Department.
- **The Database and Informatics Support Group** provides support for departmental research by developing data collection instruments in scanable, direct-entry and web-based formats, and designing back-end database warehousing. In addition, Database and Informatics Support Group staff supports the design and maintenance of study-specific tracking databases with complex automation to maximize staff productivity and for monitoring recruitment and participation status of study subjects. Currently they maintain over one hundred active multi-format surveys and roughly fifty tracking and survey databases. The Database and Informatics Support Group also conducts post-collection data cleaning and, where applicable, integrates built-in real time data checking mechanisms for data entry quality control. The Group also coordinates the direct downloading of data from laboratory and diagnostic imaging facilities on campus, programming various mechanisms to automate the conversion of the raw data into analyzable formats. The group is also responsible for managing the various network and data security configurations for the Department's research labs and staff, as well as creation and maintenance of project intranet and internet websites. They also provide front-line interaction with the SJCRH Information Sciences.

**The Department of Biostatistics** provides statistical support to investigators in the SJCRH Cancer Center for peer-reviewed, funded grants, and statistical design for institutional clinical and pre-clinical studies as well as for basic science projects. The primary objectives of the Biostatistics Shared Resource are to provide Cancer Center investigators access to uniformly high quality, innovative statistical science; a centralized randomization system; access to statistical software; technical support for a web-based distributed data management system; and advice on data management issues. Two faculty members (including Dr. Srivastava) and six additional Doctoral and Master prepared biostatisticians specifically provide support to the faculty in the Department of Epidemiology and Cancer Control. Dr. Srivastava will serve as the statistical Co-Investigator for this proposed study. His involvement spans the design, conduct, analysis and reporting for this study.

**The Central Protocol and Data Monitoring Office (CPDMO)** provides centralized services that support the design and conduct of clinical trials. The office assists clinical investigators in the development of high-quality protocols, provides a centralized registration system for clinical trials, designs and develops case report forms, and monitors clinical trials. The CPDMO's clinical protocol development services ensure that protocols, amendments, and revisions are complete and in compliance with all requirements. The office works closely with PIs, research team members, and research analysts during protocol development to define data collection requirements and to design case report forms for each protocol. The office works with PIs to

create and maintain computerized "roadmaps" that allow patient- and date-specific central documentation of treatment, treatment modifications, and patient-related notes. The Office coordinates the development of preprinted, standardized order sets for therapeutic protocols to ensure that patient care and the conduct of the protocol research are of the highest quality. The office also provides centralized patient protocol entry to facilitate the correct application of entry criteria. The CPDMO monitors protocol data collection and key study information to ensure that studies are performed in accord with the protocols, that the rights and safety of patients are protected, and that the data generated are of the highest quality and integrity.

**The Information Sciences (IS)** Department is responsible for most information technology operations on campus. It includes three divisions: Enterprise Informatics with responsibilities for administrative support, networking and telecom, intra/internet development, and data center management; Clinical Informatics with responsibility for the electronic medical record and all ancillary applications; and Research Informatics with responsibility for all basic and clinical research application and database development, high performance computing, and bioinformatics support activities.

**Computer** support is provided by Information Technology Services (ITS) for approximately 3600 PCs, desktop user support and training, telecommunications and network infrastructure, centralized computing and storage, and disaster recovery services. ITS also evaluates and implements new applications and technologies and supports integrated and timely solutions for financial and administrative information needs. The PIs, Co-Investigators and staff on the project have state-of-the-art computers, monitors, and desk-top printers. Fax, duplication, and other printed material services are readily available to the project staff based at SJCRH. The faculty investigators and research support staff are each equipped with a personal and/or laptop computer for word processing, data analysis and communication. They also have access to the internet and intranet for retrieving information. Current software capabilities include Windows XP, Microsoft Office XP Professional (Word, Access, Excel, PowerPoint, Publisher, and Outlook), SAS, STATA, SPSS, R, and Mplus. Present hardware includes Dell GX520 desktops with 3.2 GHz processor and 1 GB RAM, Dell D620 Latitude laptops with 1.66 GHz processor and 1 GB RAM and docking station, and Hewlett-Packard LaserJet 2420 printers.

**The Tri Delta House** is located on the SJCRH campus adjacent to the ACT Clinic and provides comfortable housing for patients, and their families, who are undergoing short-term treatment or who are participating in follow-up care at the hospital. Combined with the mid- and long-term housing provided at the Ronald McDonald House of Memphis and the Target House, St. Jude is able to ensure that out-of-town patients and their families do not need to be housed in hotels during treatment. The Tri Delta House can accommodate up to 100 families at a time, with 64 hotel-style rooms and 36 suites. Among the amenities for guests are recreation and family areas, as well as rooms specifically designed for use by adults and children. This service is provided to all patients at no expense to them.

**The Office of Technology Licensing (OTL)** oversees the patenting and licensing of technologies developed by the faculty and staff of St. Jude in order to promote development of drugs, diagnostic assays and other products of benefit to the public. In addition, the OTL negotiates agreements for collaborative research projects and exchanging materials and information with other academic institutions and companies, and fulfills St. Jude's obligations for reporting inventions made with federal funding. These activities allow St. Jude to share inventions and discoveries with researchers and clinicians all over the world, thus benefiting the maximum number of patients.

# PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:

First Name: I-Chan

Middle Name:

Last Name: Huang

Suffix:

## 2. Human Subjects

Clinical Trial?  No  Yes

Agency-Defined Phase III Clinical Trial?  No  Yes

## 5. Human Embryonic Stem Cells

\* Does the proposed project involve human embryonic stem cells?  No  Yes

## PHS 398 Research Plan

OMB Number: 0925-0001

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	Specific_Aims.pdf
3. Research Strategy*	Research_Strategy.pdf
4. Progress Report Publication List	
<b>Human Subjects Sections</b>	
5. Protection of Human Subjects	Human_Subjects.pdf
6. Inclusion of Women and Minorities	Inclusion_of_Women_and_Minorities.pdf
7. Inclusion of Children	Inclusion_of_Children.pdf
<b>Other Research Plan Sections</b>	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	Multiple_PI_Leadership.pdf
11. Consortium/Contractual Agreements	
12. Letters of Support	LOS_Huang.pdf
13. Resource Sharing Plan(s)	Data_Resource_Sharing_Plan.pdf
<b>Appendix (if applicable)</b>	
14. Appendix	REV_COMPLETE_APP__2__Revised.pdf

## SPECIFIC AIMS

Although advances in treatment and follow-up care have markedly improved the 5-year survival rate of childhood cancers,<sup>1</sup> survivors are vulnerable to late effects, including a variety of symptoms, chronic conditions, and premature death.<sup>2</sup> Using systematic medical assessments, the St. Jude Lifetime Cohort Study (SJLIFE) of adult survivors of childhood cancer found that by age 45 years, 95% developed >1 chronic condition and 80% had a severe or life-threatening condition.<sup>3</sup> Using self-reported outcomes, the Childhood Cancer Survivor Study (CCSS) found that the cumulative incidence of a severe, life-threatening, or fatal condition was greater among survivors than siblings (53.6% vs 19.8%) by age 50 years.<sup>4</sup> Our recent report from the SJLIFE cohort found a longer time since diagnosis was associated with higher cumulative prevalence in 12 symptom domains. The most frequent symptoms included pain involving sites other than head, neck and back (59%), followed by disfigurement (56%), pain in back/neck (49%), and pain in head (36%).<sup>5</sup> Symptoms play a unique role in the cancer survivorship trajectory because they are proximal to cancer diagnosis and treatment exposure, and are predictive of deteriorated health outcomes.<sup>6</sup> Although cancer survivors often report multiple, concurrent symptoms (i.e., symptom clusters),<sup>7</sup> it is unclear to what extent symptom clusters affect long-term adverse health outcomes including the occurrence of chronic conditions and mortality.<sup>8,9</sup>

Previous symptom studies are largely based on a cross-sectional design that denotes a snapshot of symptom experience. Indeed, individual symptoms experienced by cancer patients can be dynamic and change over a short period of time (<12 months); the presence of one symptom also tends to increase the risk of another symptom in the future.<sup>10</sup> Although some studies have reported the association between symptom presence and the change in quality of life,<sup>11</sup> no studies have investigated the change in individual symptom domains/clusters over time, and whether the change of individual symptom domains/clusters are associated with adverse health outcomes including chronic conditions and premature mortality. In addition, very few studies have examined if specific cancer therapeutic exposures (e.g., cranial irradiation, anthracyclines, alkylating agents) contribute to the change of individual symptom domains/clusters over time.<sup>12,13</sup> Identification of the dynamic nature and prognostic value of individual symptoms/clusters related to chronic conditions, mortality, and other adverse outcomes is critical for planning medical assessment and interventions to promote healthy aging in long-term cancer survivors. Success in this line of research relies upon the availability of large survivor cohorts, longitudinal symptom data, and rigorous medical assessment.

The longitudinal and repeated symptom data collected over 15 years from the CCSS participants who also receive risk-based comprehensive medical assessment from SJLIFE (N>700) at St. Jude Children Research Hospital offer a unique opportunity to elucidate the extent to which symptom progress is associated with morbidity and mortality in adult survivors of childhood cancers. In this study, we propose to examine data collected from survivors who are jointly enrolled in CCSS and SJLIFE studies to address two specific aims: Aim 1: To investigate the presence of individual symptom domains (sensation abnormality, motor/movement problems, cardiac symptoms, pulmonary symptom, pain, anxiety, depression, and somatization) and symptom clusters in multiple time points spanning 25 years among adult survivors of childhood cancers, and to investigate the survivors' change of symptom clusters over time related to treatment intensity.

Hypothesis 1a: Survivors who have received more intensive treatment (e.g., radiotherapy with or without chemotherapy) will present with more individual symptom domains and more severe symptom clusters than those who have received less intensive treatment (chemotherapy or surgery alone). The associations between specific treatments (e.g., anthracyclines, alkylating agents) and the occurrence of specific symptoms (e.g., cardiac, anxiety, pain) will also be explored.

Hypothesis 1b: Prevalence of individual symptom domains and severity of clusters will increase with time since treatment completion, and the rate of increase will be associated with treatment intensity.

Aim 2: To investigate the prognostic value of individual symptom domains and symptom clusters for the development of chronic conditions and all-cause mortality in adult survivors of childhood cancers. The analyses for all-cause mortality will be considered exploratory.

Hypothesis 2a: Greater persistence in individual symptom domains and severe symptom clusters over time will relate to higher risk of diagnosed chronic conditions and all-cause mortality.

Hypothesis 2b: Persistence of symptom clusters will have a greater prognostic value for diagnosed chronic conditions and all-cause mortality than the persistence of individual symptom domains.

This study will provide an important foundation toward improving quality and efficacy of medical interventions for childhood cancer survivors. Our results will help clinicians determine appropriate sentinel symptoms that may lead to early screening for adverse medical events (e.g., unexplained cardiac arrest),<sup>14</sup> and promote early symptom interventions to reduce the likelihood of future morbidity and mortality.

## RESEARCH STRATEGY

### A. SIGNIFICANCE

#### A1. Importance

While the 5-year survival rate of childhood cancers has improved from <20% in the 1960s to >80% today,<sup>1</sup> more than 420,000 childhood cancer survivors in the US are vulnerable to late effects.<sup>2</sup> Common late effects include physical sequelae (e.g., cardiac, pulmonary, endocrine, musculoskeletal), psychological sequelae (e.g., cognition, depression), symptoms (e.g., pain, fatigue), subsequent neoplasms, and premature death. A SJLIFE study using systematic medical assessments estimated a 95% cumulative prevalence of >1 chronic condition among childhood cancer survivors by age 45 years, and 80% for a severe or life-threatening condition.<sup>3</sup> In contrast to non-cancer controls, survivors have more impaired functional status and quality of life,<sup>15,16</sup> and live 4–18 fewer years.<sup>17</sup>

Symptoms that represent one's perception of abnormal physical, emotional, cognitive, or psychosomatic state are common late effects experienced by cancer survivors. Conceptually, symptoms are proximal to treatment exposure and disease progression, and are the most important factors associated with deteriorated health outcomes.<sup>6</sup> Overall, 19-30% of adult survivors of childhood cancers have fatigue;<sup>18,19</sup> 12- 21% have pain;<sup>20</sup> 8-13% have psychological distress;<sup>15,16</sup> and 17% have insomnia.<sup>18,19</sup> The prevalence may be underestimated because these studies have largely used a single item to measure a specific symptom. Our SJLIFE study detailing the presence of 12 symptom domains found that pain involving sites other than head, neck and back, and disfigurement were most prevalent, 59% and 56%, respectively, followed by pain in back/neck, and pain in head, 49% and 36%, respectively.<sup>5</sup> Further, evidence indicates fatigue, pain, and anxiety are related to radiotherapy exposure to brain and/or chest, alkylating agents, and anthracyclines.<sup>15,21</sup>

Longitudinal studies have reported that greater baseline depressive, anxiety, somatization, and pain symptoms predict future all-cause mortality in adult cancer and general populations.<sup>22-26</sup> Importantly, cancer survivors often experience two or more concurrent symptoms, known as symptom clusters that may share a common etiology.<sup>7</sup> Cancer patients with the presence of symptom clusters (e.g., fatigue/pain,<sup>27</sup> reflux/cough,<sup>27</sup> anxiety/depression/dyspnea/fatigue,<sup>28</sup> fatigue/cough/dyspnea<sup>29</sup>) have shown a greater risk of death than those without symptom clusters. In addition to mortality, researchers have only recently begun to investigate the association of symptoms with the occurrence of chronic conditions, and hope to identify the prognostic value of symptoms for the multiple adverse chronic outcomes. A previous study noted that psychological and somatic symptoms predict fatal and non-fatal coronary heart disease over a 7-year follow-up period with non-cancer patients.<sup>30</sup> **As the growing population of childhood cancer survivors have been exposed to toxic therapies,<sup>2</sup> it is critical to investigate whether these therapies are related to the increase and transition of different symptoms over the survival trajectory, and to explore whether the temporal change of symptoms can signal subsequent chronic conditions and premature death.**

#### A2. Barriers to Progress

Significant barriers remain that limit our utilization of symptom information for clinical decision-making. First, symptom data are often collected through cross-sectional or short-term follow-up design (<12 months) that merely denotes a snapshot of symptom experience. With this approach, we cannot ascertain whether symptoms are predictors or consequences of a chronic condition. Indeed, symptoms experienced by cancer survivors are likely to change over time, and the presence of one symptom may induce another symptom.<sup>10,31</sup> Without collecting repeated symptom data (≥3 time points) over extended follow-up, we neither understand the changing characteristics of symptoms over time nor identify the temporal relations between symptom presence and adverse health outcomes. Second, methodologies to determine the

persistence/transition of symptom clusters over time and to test the association between temporal change of symptom clusters and adverse health outcomes have not been employed. An emerging hypothesis argues that the aggregates of concurrent symptoms may have a stronger prognostic value for adverse outcomes than that of a single symptom.<sup>27</sup> Investigating the construct of symptom clusters and the change of symptom clusters over time requires the use of complex psychometric methodology and large sample size (N>500). Third, chronic conditions of cancer survivors are frequently evaluated through surveys. Although survey is a feasible and cost-saving approach for collecting data, chronic conditions self-reported from surveys have been demonstrated to underestimate prevalence when compared to data collected from comprehensive medical assessment.<sup>3</sup> Fourth, for childhood cancer survivors who have elevated risk of chronic conditions and mortality, it is critical to explore the persistence/transition in the type and severity of symptom clusters across the life trajectory, and to evaluate the prognostic value of symptom clusters for morbidity and mortality. Unfortunately, investigating the impact of symptom phenotype on the outcomes of childhood cancer survivors is still sparse.<sup>18,32,33</sup> **We plan to address these barriers by testing the associations between longitudinal symptom progress and multiple chronic conditions and mortality using a cohort of long-term adult survivors of childhood cancer.**

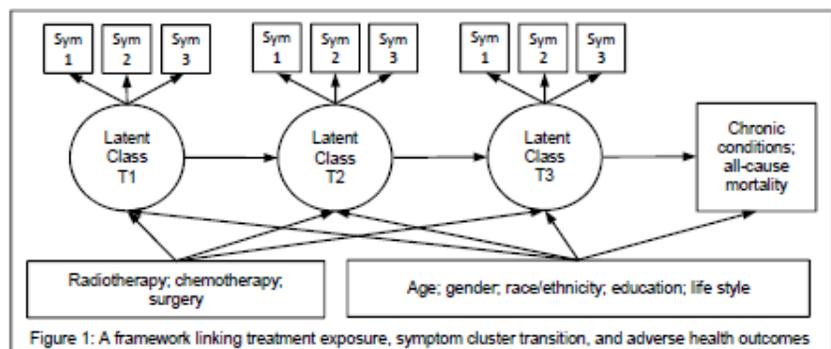
### A3. Approach to Improve Knowledge

People who overlook the significance of symptoms may delay early diagnosis and disease prevention strategies, and may be more likely to develop adverse outcomes (e.g., 3.3 times for colorectal cancer<sup>34</sup>). A longitudinal study examining the change in fatigue between breast cancer survivors and controls over a 24-month follow-up has shown that fatigue in survivors increased 5 months prior to relapse.<sup>35</sup> The most important step toward increasing symptom information for clinical application is to characterize the patterns of various symptoms that are clinically meaningful to survivors, and investigate the effect of symptom persistence and transition on adverse health outcomes. This proposed study plans to use longitudinal, repeated symptom data collected from CCSS participants between 1992 and 2007, who also participated in SJLIFE between 2007 and 2016 for comprehensive risk-based medical assessment to identify type and severity of chronic conditions. **This is a unique opportunity to link symptom presence, persistence, and transition over 15 years to the occurrence of chronic conditions and mortality over the next 10 years. This study will improve our knowledge in symptom research through development of a longitudinal analytic framework to quantify the temporal change of symptom clusters in childhood cancer survivors.**

## B. INNOVATION

### B1. Novel Conceptual Framework

The novelty of the proposed research is centered in establishing the associations between treatment exposures, symptoms, and adverse health outcomes for adult survivors of childhood cancers (Figure 1) using cutting-edge methodologies and research resources. Based on our previous study,<sup>5</sup> we will use eight symptom domains (cardiac, pulmonary, motor/movement problems, pain, sensation abnormality, anxiety, depression, and somatization) to link cancer treatment exposures with different adverse health outcomes. We will focus not only on the presence of individual symptom domains but also the



number and severity of symptom clusters. Data collected from survivors at three time points spanning 25 years will be used to quantify the changing pattern of individual domains and clusters. Characterizing the symptom phenotypes helps test if cancer treatments lead to 1) development of specific symptom domains and clusters at each time point, and 2) the change in symptom domains and clusters over time (Aim 1). This novel framework will also test if change in symptom domains and clusters predict the occurrence of future chronic conditions and mortality (Aim 2).

### B2. Novel Resources/Data for Studying Childhood Cancer Survivor Population

Although several childhood cancer survivor cohorts (e.g., CCSS, British CCSS, Adult Life after Childhood Cancer in Scandinavia) have been established, these cohorts largely use survey-based methods to collect cancer recurrence and chronic condition data. In fact, chronic conditions reported by survivors tend to be underestimated compared with clinical-based assessment.<sup>3</sup> **To correct this bias, we will utilize novel resources to identify survivors who take part in both CCSS and SJLIFE studies for accessing self-reported symptom and medically assessed chronic condition data.** CCSS is a National Cancer Institute-funded retrospective cohort study of children and adolescents who were diagnosed with cancer between 1970 and 1986 when <21 years of age, and treated at 26 medical centers in the US and Canada.<sup>36,37</sup> A total of 14,370 survivors were enrolled in the CCSS cohort. SJLIFE is a newly established childhood cancer survivor research cohort with the goal of characterizing the pathophysiology and trajectory of cancer-related injury to facilitate earlier interventions.<sup>38,39</sup> Participants are individuals diagnosed and treated with a malignancy during childhood at St. Jude Children's Research Hospital who are now  $\geq 10$  years from diagnosis and >18 years of age. The SJLIFE protocol was opened for enrollment in late 2007, and continuously recruits participants who return to the St. Jude campus to undergo a 3-4 day outpatient comprehensive medical assessment consistent with the Children's Oncology Group Long-term Follow-Up Guidelines<sup>40</sup> augmented with a core battery of physical, psychological, and laboratory-based assessments. Health conditions are ascertained by parameters collected from biologic specimens, metabolic, cognitive, and neuromuscular function exams, and screening of organ dysfunction. **Approximately 700 CCSS participants who completed multiple surveys have enrolled in the SJLIFE study, which provides a unique opportunity for testing temporal relations of multiple symptoms with adverse health outcomes (e.g., chronic conditions and mortality).**

### B3. Novel Methods to Measure Temporal Changes of Symptom Phenotypes

Exploratory factor analysis and hierarchical cluster analysis have been widely used to generate symptom clusters for cancer survivors/patients,<sup>41</sup> though these approaches are not able to examine the change of symptom clusters from one time point to another. In this proposed study, we will use latent class analysis (LCA) to classify survivors' membership in symptom clusters based on eight individual symptom domains, and jointly use latent transition analysis (LTA) to directly model the change of symptom cluster over time.<sup>42</sup> LCA assumes that an underlying categorical latent variable will be sufficient to represent an individual's group membership (i.e., latent class). LTA estimates the persistence/transition for the latent membership of symptom clusters over time using an autoregressive model in which group membership at each time point is estimated by a LCA. For individual survivors, the probabilities of being with each latent class of symptom clusters at each time point and the transition probabilities denoting the likelihood of class membership at time  $t$ , conditional on the state at time  $t-1$ , will be estimated. **The joint model of LCA and LTA has not been used to test the temporal change of symptom clusters in cancer populations.**

#### B4. Innovative Implications for Future Applications

This study can have substantial impact on future innovative research to improve outcomes of childhood cancer survivors. If the relationship between treatment exposures and symptom clusters is established, the common etiology dominating the mechanisms from treatment exposure to symptom clusters can be examined in a future prospective study. The mechanism may include autonomic nervous system activation, systemic inflammation, alteration of hypothalamic-pituitary-adrenal axis, and endothelial dysfunction.<sup>43</sup> If the temporal relationship between symptom clusters and occurrence of chronic conditions and mortality is confirmed, symptom clusters can serve as surrogates of adverse health outcomes. Establishing this linkage helps identify sentinel symptoms for early diagnosis of adverse events (e.g., unexplained cardiac arrest<sup>14</sup>). For monitoring purposes, future applications can design/apply innovative technology (e.g., mHealth/eHealth) to collect symptom data efficiently.<sup>44-46</sup> Although survivorship guidelines have noted the importance of screening fatigue, depression, and anxiety as an avenue for ascertaining chronic problems,<sup>47,48</sup> screening for symptom clusters has not been pinpointed. Interventions on early symptoms may improve adverse events.<sup>49</sup> Various cognitive-behavioral,<sup>50</sup> psycho-educational,<sup>51,52</sup> exercise,<sup>53</sup> and pharmacological<sup>54</sup> strategies are effective in improving individual symptoms (e.g., depression,<sup>50,52,55</sup> anxiety,<sup>50,52,56</sup> pain,<sup>57,58</sup> fatigue,<sup>59,60</sup>), though their efficacy in improving symptom clusters for preventing future chronic conditions has not been established.<sup>61</sup> **Understanding the relationships between individual symptom domains/clusters will provide the knowledge-base for development and testing of future clinical interventions.**

#### C. APPROACH

##### C1a. Preliminary Study 1

We evaluated symptom prevalence in 1,667 adult survivors of children cancers enrolled in the SJLIFE study.<sup>5</sup> Twelve symptom domains were examined: cardiac, pulmonary, motor/movement, pain in head, pain in back/neck, pain in sites other than head, neck and back, sensation abnormalities, disfigurement, learning/memory, anxiety, depression, and somatization. Two symptom domains were reported by >50% of survivors: pain involving sites other than head, neck and back (59%), and disfigurement (56%); three domains were noted by 30-50% of the survivors: pain in back/neck (49%), pain in head (36%), and sensation abnormalities (34%). Approximately 60% of survivors reported 2-5 symptom domains, and 20% reported >5 symptom domains. Prevalence of all symptoms increased from 10 to 30 years post-diagnosis (Figure 2). Symptoms alone accounted for roughly 60% of the variance in quality of life scores. **High prevalence and clusters of symptoms observed in this pilot study lead to testing the change of symptom phenotypes over time in the proposed study.**

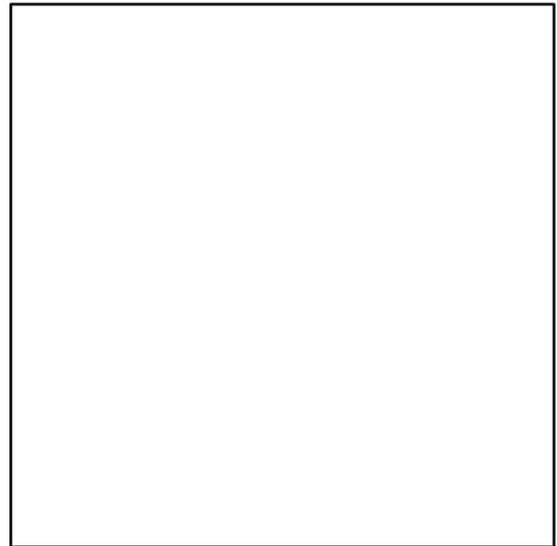


Figure 2. Cumulative prevalence of individual symptoms

##### C1b. Preliminary Study 2

We compared symptom prevalence in 604 adult cancer survivors and 6,166 non-cancer controls who participated in the 2010 US National Health Interview Survey.<sup>62</sup> Six symptoms were examined: sensation abnormality, pain, fatigue, cognition, depression, and anxiety. Survivors had greater sensation, pain, fatigue, and cognition abnormalities than the controls: ORs=2.4, 2.1, 1.4, and 1.8 (P's<0.01), respectively, after adjusting for covariates (e.g., age,

gender, race/ethnicity, education). The association of symptoms with quality of life by the NIH PROMIS scales revealed that participants with respective symptoms had poorer physical quality of life regardless of cancer experience: pain ( $\beta=-8.8$ ), cognition ( $\beta=-8.4$ ), fatigue ( $\beta=-7.8$ ), depression ( $\beta=-7.1$ ), sensation ( $\beta=-6.1$ ), and anxiety ( $\beta=-5.9$ ) ( $P$ 's $<0.001$ ). Similar results were found for mental quality of life. Survivors with all six symptoms had the lowest physical and mental quality of life ( $\beta=-15.5$ ,  $-14.7$ ), followed by controls with six symptoms ( $\beta=-14.6$ ,  $-14.4$ ), and controls without symptoms ( $\beta=-0.85$ ,  $-0.30$ ). **The robust association between symptoms and quality of life provides strong support for investigating the causal links of changing symptom phenotypes to chronic conditions and mortality in the proposed study.**

## C2. Research Design/Study Cohort

The study sample includes adult survivors of childhood cancer who have participated in the CCSS 1992 baseline survey (T1), CCSS 2007 follow-up survey (T2), SJLIFE survey (T3), and risk-based medical assessment after the surveys. Although CCSS and SJLIFE have conducted several surveys, we will focus on the surveys at these time points because they use the same items to measure symptoms. CCSS and SJLIFE data are housed in the Survey Research and Data Center of the MPIs' Department (see Letters of Support).

## C3. Enrollment on Study

Our inclusion criteria are:  $\geq 10$  years from initial diagnosis of pediatric cancer/malignancy;  $\geq 18$  years old; enrolled in the CCSS and SJLIFE studies; and participated in the CCSS 1992 baseline (T1), CCSS 2007 follow-up survey (T2), and SJLIFE (T3). Exclusion criteria are: known severe neurocognitive impairment, which requires proxies/parents to complete the symptom survey; and residing outside the U.S., which limits access of on-site risk-based medical assessment for chronic conditions.

A total of 1,357 survivors enrolled in both CCSS and SJLIFE are eligible for this study; among these eligible participants, 578 have completed symptoms survey at T1, T2 and T3, and SJLIFE risk-based medical assessment. SJLIFE will recruit  $>130$  additional survivors for on-campus visits in 2015, providing at least 700 survivors available for statistical analyses. Currently, 607 SJLIFE participants have completed one or more subsequent on-campus visits, and data collected from the most recent visit will be used in the present study.

## C4. Symptom Assessment, Symptom Domains, and Clusters

This study will use symptom information from the CCSS and SJLIFE surveys, which has been individually analyzed and reported in numerous separate publications.<sup>5,37,38</sup> Eight symptom domains will be constructed: five domains related to physical symptoms and three domains related to psychological symptoms. In the CCSS and SJLIFE surveys, 23 items measuring human organ impairment will be used to categorize five physical symptom domains: cardiac (3 items); pulmonary (3 items); motor/movement problems (5 items); pain (2 items); sensation abnormalities (10 items). For each item, three response categories ("yes, the condition is still present," "yes, but the condition is no longer present," and "no") will be used. Presence of a symptom domain is denoted if one endorsed "yes, the condition is still present" for any item measuring that particular symptom. The Brief Symptoms Inventory-18<sup>63</sup> will be used to measure three psychological symptoms: anxiety (6 items), depression (6 items), and somatization (6 items). For each item, a five-point Likert scale (from "not at all" to "extremely") will be used to explore the level of symptom bothersome. A summated item score of a particular domain will be calculated and converted to a T-score (mean= 50; SD=10), and a cutoff ( $\geq 63$ ) will be used to denote the presence of a symptom domain.

For each survivor, symptom clusters will be determined by LCA (see Section C8). At each time point, we hypothesize that three clusters of subjects will emerge to represent the severity of multiple symptom domains: high (high physical/high psychological domains),

intermediate (high physical/low psychological domains or low physical/high psychological domains), and low (low physical/low psychological domains) clusters. We will classify the persistence of symptom clusters based on the change of clusters over time. Individuals remaining in high and low severity clusters across all time points will be classified as persistently symptomatic and persistently asymptomatic status, respectively. Individuals will be classified as intermediate persistence if they are not with the persistently symptomatic and persistently asymptomatic status.

#### C5. Risk-Based Medical Assessment, Treatment Intensity, and Chronic Conditions

A unique advantage of using this CCSS/SJLIFE joint cohort is the accessibility of complete treatment exposure records and all chronic and late-occurring medical conditions that are ascertained by the SJLIFE study. Medical record abstractions have already been conducted to obtain information of chemotherapy including cumulative doses for 32 specific agents, radiotherapy including fields and doses, surgical procedures, hematopoietic cell transplantation, and acute life-threatening organ toxicity. Treatment will be categorized on a continuum of increasing intensity, from surgery only (low intensity), chemotherapy only with/without surgery (moderate intensity), to radiotherapy with/without chemotherapy or surgery (high intensity).<sup>38</sup> Associations of symptom presence with chemotherapy agents/doses and with radiation fields/doses will also be explored.

All SJLIFE participants undergo a core battery of medical examination comprised of neurologic exam, resting heart rate, blood pressure, 1- and 2-lead electrocardiography; laboratory tests such as complete blood cell count, comprehensive metabolic panel, fasting lipid profile, insulin and hemoglobin A1c, thyroid and gonadal function, urinalysis; and neurocognitive testing such as memory, processing speed. Participants also receive comprehensive risk-based medical assessment, including echocardiography, pulmonary function testing, audiological testing, ophthalmologic evaluation, and bone mineral density testing.<sup>3</sup> Information collected from these assessments will be used to classify specific chronic conditions for each survivor. We will group these conditions by eight organ systems: cardiovascular, endocrine/reproductive, hepatic, neurocognitive, neurosensory, skeletal, pulmonary, and urinary categories (Table 1). For each survivor, severity of each chronic condition will be assigned as none (grade 0), mild (grade 1), moderate (grade 2), serious/disabling (grade 3), and life-threatening (grade 4) based on the Common Terminology Criteria for Adverse Event (CTCAE) version 4.0. Presence of the chronic conditions related to symptoms will be analyzed by individual organ systems and individual conditions under each organ system if the sample size is >30.

Table 1: Categorization of chronic conditions by organ systems, and numbers of survivors by CTCAE Grades (G1, G2, G3, G4)\*

Organ system	Specific chronic conditions	G1	G2	G3	G4
Cardiovascular	Cardiomyopathy, left ventricular systolic dysfunction, heart valve disorder, arrhythmia, conduction disorder, cardiac ischemia, hypertension, dyslipidemia	683	177	17	20
Endocrine/reproductive	Growth hormone deficiency, adrenocorticotropic hormone deficiency, luteinizing hormone/ follicle-stimulating hormone deficiency, central/primary hypothyroidism, diabetes mellitus, ovarian failure, oligospermia, azoospermia, Leydig cell failure	417	332	324	29
Hepatic	Hepatopathy	10	40	21	0
Neurocognitive	Neurocognitive impairment	23	27	129	0
Neurosensory	Cataract, glaucoma, retinopathy, reduced visual acuity, hearing loss, neuropathy	209	56	36	10
Skeletal	Osteoporosis, osteopenia	177	35	0	0
Pulmonary	Abnormal pulmonary function	50	35	17	9
Urinary	Chronic kidney disease, hemorrhagic cystitis, incontinence, dysfunctional voiding	35	18	5	1

\* Numbers of survivors who were diagnosed with any chronic condition in a specific organ system

## C6. All-Cause Mortality Ascertainment

All survivors eligible for participation in CCSS and SJLIFE studies are included in a search for deaths using the National Death Index (NDI) from 1979 to 2014. Maintained by the National Center for Health Statistics, NDI provides underlying and multiple causes of death for deceased individuals using the International Classification of Disease, the 9<sup>th</sup> version. As of February 20<sup>th</sup>, 2015, 35 of the participants are deceased, therefore we will focus on all-cause mortality comprised of a direct consequence of the original cancers (e.g., recurrence, progression of primary cancers), cancer treatment-related causes (e.g., subsequent malignant neoplasm, cardiac, pulmonary toxicity), and non-treatment-related causes (e.g., accidents, suicide).

## C7. Background Variables and Potential Confounders

Age, sex, length of follow-up, race, education, physical activity, and substance use (tobacco, alcohol, smoking) from the CCSS and SJLIFE surveys (see Appendices 1-2) will be used as covariates in the analyses.

## C8. Statistical Analyses

Hypothesis 1a assumes there will be a higher proportion of survivors treated with more intensive treatment in each symptom domain and a higher proportion of survivors classified into the most severe cluster at baseline than those treated with less intensive treatment. Each symptom domain will be categorized as normal vs. abnormal (see Section C4), and logistic regression in SAS PROC LOGISTIC will be used to model the probability of abnormal status as a function of treatment intensity and other covariates (see Section C7). For symptom clusters, LCA in MPlus will be used to obtain the latent class for each survivor. The class number will be decided using Bayesian information criterion, Lo-Mendell-Rubin test, bootstrap likelihood ratio test,<sup>42</sup> and a minimum of  $\geq 5\%$  of the observations in each class. The class number will be validated using survivors engaged in the baseline CCSS but not in this study (N=13,000). Once the classes are decided, the classes can be ordered in a progressive manner (from least to most severe). Multinomial logistic regression will be used to model the probability of being in more vs. least severe class as function of treatment intensity and covariates.

Hypothesis 1b assumes the prevalence of each symptom domain and proportion of the most severe symptom cluster will increase progressively with longer follow-up, and is more pronounced for those receiving intensive treatment vs. those receiving less intensive treatment. For each symptom domain, generalized estimating equation<sup>64</sup> in SAS PROC GENMOD will be used for the correlated binary data over three time points. Treatment intensity and other covariates (see Section C7) will be included in the model. For the symptom clusters, we will first test if the number and structure of clusters are consistent and non-invariant over time. If this is the case, we will model the proportion of survivors in progressively more severe class vs. those in least severe class as a function of time (current age and length of follow-up), treatment intensity, and other covariates using GEE approach<sup>64</sup> for repeated nominal categorical responses and implemented in SAS PROC GENMOD. However, if the number and structure of clusters are inconsistent or invariant, we will obtain the latent classes at baseline, and apply the criteria from baseline to the two latter time points to classify survivors into the classes identified at baseline, and use the approach above to evaluate if the proportion of survivors in the most severe class increases with time in a more pronounced manner in those receiving intensive treatment. Once it is established that the class structure was similar, the transition patterns across the three time points would be estimated using the LCA with likelihood method or Bayesian approach.<sup>65</sup>

Hypothesis 2a assumes persistence of individual symptom domain and cluster over time will have prognostic value in developing chronic disease and mortality. For symptom domain or

cluster, a survivor will be classified as “persistently symptomatic” if he/she presents individual symptom domain or is in the most problematic cluster across three time points, “persistently asymptomatic” if he/she has no presence of specific symptom domains or is in the least severe symptom cluster across three time points, and “intermediate” if he/she is neither persistently symptomatic nor persistently asymptomatic. A logistic regression model will be used to assess the relationship between each of the abnormal (Grade 2 or higher) chronic conditions (see Table 1) as a function of persistence of eight symptom domains (8 independent models) and covariates (see Section C7). Similarly, logistic regression will be used to model the relationship with each chronic condition as a function of symptom cluster persistence and covariates. The relationship with mortality after SJLIFE visit (i.e. define survival time as time from SJLIFE visit to the time of conducting analyses) as a function of persistence of eight symptom domains (8 independent models)/symptom cluster persistence and covariates (see Section C7) will be tested using Cox’s proportional hazards model and implemented in SAS PROC PHREG.

Hypothesis 2b assumes the model for the persistence of symptom clusters over time would be superior to eight models for the persistence of individual symptom domains in predicting chronic conditions and mortality. For chronic conditions, the method of Bloch (1997)<sup>66</sup> will be used to test if the symptom cluster model is superior to individual symptom models in predicting each chronic condition. The method of Kang (2015)<sup>67</sup> will be used to test if the symptom cluster model is superior to individual symptom models in predicting survival.

**C9. Limitations**

The main study limitation is the death toll (5-8%) captured by the study sample. We will not be able to test the association of symptoms with condition-specific mortality. A second potential limitation is generalizability of the findings to other survivor samples. Because we focus on dual enrollment in CCSS and SJLIFE studies, the association of symptoms with adverse health outcomes may be limited to patient treated at St. Jude. Future studies should replicate our findings with a broader cohort over a longer follow-up period.

**C10. Timeline: The study timeline is described in Table 2.**

Table 2: Timeline for implementing this proposed study

Project activities	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Complete risk-based medical assessment (N=130)	X	X	X	X				
Link symptom data to chronic condition and NDI				X				
Conduct statistical analysis for Aim 1 (N=700)					X	X		
Conduct statistical analysis for Aim 2 (N=700)						X	X	
Draft manuscript/submit conference abstract							X	X

## **PROTECTION OF HUMAN SUBJECTS**

St. Jude Children's Research Hospital accepts all patients eligible for protocols regardless of sex, race/ethnicity, origin, religion, or financial status. All data generated by clinical trials within St. Jude are reviewed at least annually by the Central Protocol and Data Monitoring Office. Key personnel are required to receive training and certification in human subject research by taking on-line course and examinations. The relevant study and consent forms will be reviewed and monitored by the St. Jude's Trials Scientific Review Committee (CT-SRC) and Institutional Review Board (IRB).

IRB approval has been obtained and is currently active for the SJLIFE study participants. The infrastructure at St. Jude is Health Insurance Portability and Accountability Act (HIPAA) compliant and thus maintains the confidentiality of the study participant's records in accordance with all regulations. All participant data are identified by a code to assure confidentiality. Data from studies may be published; however, the participant will not be identified by protected health information such as name and contact information, etc. The confidentiality of the data is maintained within legal limits.

### **Study Population**

Study enrollment criteria include those who are  $\geq 10$  years from initial diagnosis of pediatric cancer/malignancy;  $\geq 18$  years old; enrolled in CCSS and SJLIFE studies; and participated in CCSS 1992 baseline (T1), CCSS 2007 follow-up survey (T2), and SJLIFE (T3). There are no age, sex or ethnic restrictions. Data sources of the proposed study include the existing symptom and chronic condition data that were already collected from survivors who have enrolled in CCSS and SJLIFE studies, and the new data that will be collected from survivors who have completed symptom surveys at T1, T2, and T3, yet the comprehensive medical assessment for diagnosed chronic conditions. Specifically, a total of 1,357 survivors enrolled in both CCSS and SJLIFE are eligible for this proposed research; among these eligible participants, 578 have completed symptoms survey at T1, T2, and T3 and risk-based medical assessment. The SJLIFE protocol continuously recruits participants for outpatient visit on the St. Jude campus to collect self-reported health outcomes data (including symptoms) and to receive comprehensive risk-based medical assessment consistent with the Children's Oncology Group Long-term Follow-Up Guidelines.<sup>40</sup> SJLIFE study will recruit approximately 130 eligible survivors for campus visits in 2015, leaving at least 700 survivors available for statistical analyses (see Appendices 3-4 for recruitment materials).

### **Adequacy of Protection against Risks**

For recruiting survivors who are eligible for SJLIFE study participation, a Lead Clinical Research Associate (also the Project Coordinator in this application) will fully explain the purpose and nature of the research and informed consent. This individual will review the study in detail with each participant, go over the study protocol, and inform the participant that he/she can refuse to participate at any time. Informed consent is in writing, and participants will be instructed to keep a copy of the consent with the MPIs' (Dr. Huang and Krull) contact information in case they have questions before, during, or after the completion of the study. We will also inform the participants that their data are protected at every level, and results will only be reported in aggregate. Data used for statistical analyses will be de-identified and stored in secured servers at St. Jude (see Section of Data Protection below).

### **Recruitment and Consent**

The Lead Clinical Research Associate will review the SJLIFE chart abstractions to confirm inclusion and exclusion criteria, and eligible patients will be mailed a letter and then contacted by phone. Following verbal consent, new history provided during the consent process will be used to confirm eligibility. A registered nurse will enter the necessary orders, consistent

with the SJLIFE standard of care and the additional measures for this proposal. The patient will be scheduled for a visit and travel arrangements will be made by the St. Jude's travel office. All participants will be scheduled for 3-4 day visit in order to provide time to coordinate the various studies. Potentially eligible participants will be sent a letter describing the study, and informing them an interviewer will be contacting them within two weeks to discuss the study and to inquire about their participation. A second letter and a second telephone call will be attempted two to four weeks after the original letter if no initial response is received. The Lead Clinical Research Associate will inform the participants of the study and ask them to sign an informed consent. The consent form fulfills the requirements set out by the CTSRC and IRB. Consent forms will be HIPAA compliant. Consent will be obtained to mail questionnaires. The participants will be given the opportunity to refuse to participate at any point in the study. They will be told that their participation will in no way affect their standard clinical treatment at St. Jude.

### **Data Sources**

For the survivors returning for an on-campus medical assessment, the SJLIFE Survivorship Care Team will schedule their clinical assessment. Clinical information regarding cancer diagnosis, treatment, and medical events will be abstracted from the medical records for all eligible survivors.

### **Potential Risks**

This study will not place participants in a situation where the probability and magnitude of harm or discomfort anticipated in the research is greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations. This study will involve assessment using standard clinical approaches as recommended by the Children's Oncology Group Screening Guidelines. Participants can ask to stop and withdraw from any uncomfortable tests or activities at any time.

### **Data Protection**

Risks to confidentiality are minimized by maintaining a single list linking study participants by a study identification number to the data collected. The information is kept in a locked file of a locked office for security. The data are coded and analyzed without characteristics that would identify individual study participants. The computer storage of this data is password protected and access limited to authorized individuals.

### **Potential Benefits of the Proposed Research to the Subjects and Others (Risk-Benefit Ratio)**

All participants are provided feedback concerning the results of their SJLIFE evaluations. Recommendations for follow-up are provided as needed. Standard operating procedures have been established for the follow-up of participants identified with conditions requiring medical follow-up. The SJLIFE Survivorship Care Team, including dedicated social workers, work closely with study participants to facilitate access to medical care by local health care providers. Therefore, we believe the potential benefits from participation in this study outweigh potential harm.

### **Importance of Knowledge Gained**

The knowledge gained from this study will improve our understanding of late effects in survivors of childhood cancer. Establishing the linkages of symptoms and occurrence of chronic conditions and mortality helps identify sentinel symptoms for early diagnosis of adverse health events. Information obtained from the SJLIFE cohort will directly impact future recommendations for care of the growing population of childhood cancer survivors, and form a

foundation for future modifications to the *Childhood Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*.<sup>40</sup>

### **Data Collection, Monitoring and Confidentiality**

Data from the comprehensive medical assessment and the survey are recorded by study personnel by participant identification number on optical recognition forms and downloaded daily on to a computer server with restricted access to the research team. The medical records are abstracted and the data are recorded using an established database. All files are password protected. Identifying information is stored separately and the files linked by identification number. Any paper forms are stored in a locked file cabinet. Biological samples are labeled with only the participant identification number and sample number. Data are evaluated without identifiers for safety monitoring, process evaluation and outcomes analysis, and linked to the identifying information only if necessary for participant safety.

Source document verification of eligibility for all SJLIFE cases is performed within two weeks of completion of enrollment. This includes verification of appropriate documentation of consent. Monitoring of timeliness of adverse and serious adverse event reporting will be done as events are reported. Monitoring of modified NCI Clinical Data Update System elements, adverse event reporting, and compliance with the conduct of the protocol will be conducted according to recommended schedule for this study.

Confidentiality will be maintained. Data forms are kept in locked file cabinets of locked office space, accessed only by study staff on an “as needed” hierarchical basis. Data files are de-identified, linked by a participant identification number to a separate secure database. Data files downloaded for statistical analyses do not contain personal identifiers.

### **Advantages and Limitations to Proposed Research**

Access to a large and well-characterized study population: St. Jude Children’s Research Hospital is one of the largest facilities for treatment of childhood cancer in North America, and first began treating patients in 1962. St. Jude is one of few institutions capable of identifying and characterizing a population of sufficient size and age to identify long-term outcomes in adult survivors of childhood cancer. Results from this study will inform evidence-based development of future screening guidelines.

Cost-sharing with ongoing SJLIFE Cohort: The feasibility of this study, from both a logistical and financial perspective, is significantly enhanced by the commitment of St. Jude to establish the SJLIFE Cohort Study. As described in the application, St. Jude Children’s Research Hospital will cost share many components of this research project by bearing the complete cost of medical assessment, patient transportation, lodging, food, and daily compensation of \$150. In addition, the costs of chart abstraction, medical examination, and routine laboratory assessment are fully funded by St. Jude. The SJLIFE study is an ongoing project that is intended to continue well into the future. As such, we will be able to follow the patients enrolled into the proposed project for many years to come, and identify new onset morbidity and mortality in the future.

Representativeness of study population: In spite of the fact that many long-term cancer survivors have demonstrated a commitment to participation in previous studies at St. Jude (participation rates in survivorship research have typically been greater than 80%), this study is still subject to incomplete ascertainment of the study population and to participation bias. Non-participants may include potentially eligible survivors who are lost to follow-up and those who decline to participate. It is also possible that childhood cancer survivors who are severely disabled will be reluctant to return or will be cognitively unable to participate in this proposed study even if the evaluation is provided free of charge and includes transportation and housing during their stay at St. Jude. We anticipate that this population’s previous tie to St. Jude facilitates recruitment and reduces the possible impact of participation bias. In addition, we have

available treatment records for patients who are eligible for participation in this study. We conduct regular abstraction from the National Death Index, and will be able to ascertain participation bias. This will allow us to further characterize the non-participants.

**INCLUSION OF WOMEN AND MINORITIES**

Study subjects will not be excluded based on gender and race/ethnicity. Our eligible cohort includes 51% female. Because of the racial distribution of patients treated at St. Jude Children's Research Hospital and the survival rates among specific racial/ethnic groups, the survivors eligible for the proposed study include 8% minorities. We will, however, attempt to recruit all available minorities. In addition, we will compare symptom profiles of the 700 study samples to symptom profiles of Hispanic and other minority samples in the larger CCSS cohort for those who are not enrolled in SJLIFE study. Specific sex and ethnicity information is already known and presented in the Targeted/Planned Enrollment Table.

**Planned Enrollment Report****Study Title:** Symptom progress and adverse health outcomes in adult survivors of childhood cancer**Domestic/Foreign:** Domestic**Comments:**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	3	0	0	<b>3</b>
Asian	2	2	0	0	<b>4</b>
Native Hawaiian or Other Pacific Islander	0	0	0	0	<b>0</b>
Black or African American	30	18	0	0	<b>48</b>
White	317	318	5	1	<b>641</b>
More than One Race	0	1	1	2	<b>4</b>
<b>Total</b>	<b>349</b>	<b>342</b>	<b>6</b>	<b>3</b>	<b>700</b>

Study 1 of 1

**INCLUSION OF CHILDREN**

The proposed study will focus on adult survivors of childhood cancer with  $\geq 18$  years old when they enrolled in CCSS and SJLIFE cohort studies. Children will be excluded from this study.

## **RESOURCE SHARING PLAN**

Data collected in the proposed study will be made available to other researchers in compliance with the NIH Data Sharing Policy. The investigative team's approach is to ensure that the study makes an impact on enhancing the research base relative to long-term outcomes of cancer patients diagnosed and treated during childhood and adolescence. To achieve this goal, we will ensure that data are shared in compliance with the NIH Data and Resource Sharing Policy.

We will develop a data and resource sharing agreement with the legal advice from the St. Jude's Compliance Office. We will require that researchers enter into a data- and resource-sharing agreement before the data are shared with them. This agreement will ensure: 1) the commitment to use the data only for research purposes and not identify any individual participant; 2) commitment to secure data using appropriate computer technology; and 3) commitment to destroy or return data after analyses are completed. Potential risks to human subjects include disclosure of sensitive health data (symptoms, chronic conditions, cause of death, and other variables) and we will take all steps to ensure that this does not happen when data are shared. Accordingly, when data are shared, all identifying information related to the individual participants will be removed, and a new ID number selected at random will be used to replace our study ID number. Furthermore, we will strongly recommend that all recipient groups ensure that every member of the staff sign a Confidentiality Agreement.

With regards to the current proposal, in each of the data sharing efforts, the outside investigator will work closely with the proposal's investigative team, who will serve as a liaison, in providing the necessary data and assisting with the analysis. De-identified data sets will be prepared by the statistical Co-Investigator (Dr. Srivastava), with oversight by MPIs Drs. Huang and Krull. Dr. Srivastava will work closely with the SJLIFE Databases & Informatics Support Group to provide detailed documentation on the variables created, and suggested approaches to the analysis using SAS and Mplus. All requests for data sharing will be reviewed and approved by the investigative team lead by Drs. Huang and Krull.