Analysis Concept Proposal

1. Study Title
Congenital Anomalies and Chronic Health Conditions among Childhood Cancer Survivors

2. Working Group
Primary: Chronic Disease Working Group
Secondary: Second Malignancy Working Group
Secondary: Genetics Working Group

Investigators

Amanda Janitz, PhD, MPH	Amanda-Janitz@ouhsc.edu
Philip Lupo, PhD, MPH	Philip.Lupo@bcm.edu
Jeremy Schraw, PhD	schraw@bcm.edu
Sogol Mostoufi-Moab, MD, MSCE	moab@email.chop.edu
Lindsay Morton, PhD	mortonli@mail.nih.gov
Lisa Mirabello, PhD	mirabellol@mail.nih.gov
Douglas Stewart, MD	drstewart@mail.nih.gov
Kevin Oeffinger, MD	kevin.oeffinger@duke.edu
Joseph Neglia, MD, MPH	jneglia@umn.edu
Lucie Turcotte, MD, MPH	turc0023@umn.edu
Smita Bhatia, MD, MPH	sbhatia@peds.uab.edu
Wendy Leisenring, ScD	wleisenr@fredhutch.org
Gregory Armstrong, MD, MSCE	Greg.Armstrong@stjude.org

3. Background and Rationale
Congenital anomalies, defined here as 1) genetic conditions or 2) health conditions present at birth, are strong risk factors for developing childhood cancer. In our previous work, we identified that the risk of childhood cancer was 12 times higher among children with chromosomal anomalies and 2.5 times higher among those with non-chromosomal anomalies compared to unaffected children.[1, 2] We also identified that the prevalence of congenital anomalies was 11%-14% among children with cancer compared to 3-5% in the general population. Several of these associations are due to known cancer predisposition syndromes that include congenital anomalies (e.g., Beckwith-Wiedemann syndrome, Down syndrome, and Fanconi anemia). However, there may also be a subset of these children with other unrecognized cancer predisposition syndromes. The clinical impact of congenital anomalies in childhood cancer survivors is compounded by a critical knowledge gap around health outcomes in this population. Addressing this gap will allow development of future strategies to better detect and treat these outcomes. Ultimately, our goal is to decrease excess premature mortality related to serious health outcomes and improve quality of life in this at-risk population.

There are approximately 500,000 survivors of childhood cancer in the US.[3] The majority of children diagnosed with a malignancy now achieve 5-year survival, but these individuals have substantial risk of morbidity and mortality later in life due to the late effects of cancer and its treatment.[3] In the first report of chronic health conditions from the Childhood Cancer Survivor Study (CCSS), survivors had a three times greater risk of any chronic health condition compared to siblings without a history of cancer (Hazard Ratio [HR]: 3.3, 95% confidence interval [CI]: 3.0, 3.5).[4] The estimated cumulative incidence of survivors developing any chronic condition is estimated at 73% by 30 years after their childhood cancer diagnosis.[4] In a more recent analysis, childhood cancer survivors were at higher risk for developing subsequent malignant neoplasms compared to the general population (Standardized Incidence Ratio [SIR]: 5.4, 95% CI: 5.1, 5.7).[5] Higher risks of subsequent malignant neoplasms are present among females, and those with exposure to radiation treatment (any dose), history of splenectomy, exposure to cyclophosphamide equivalent dose (≥4000 mg/m^2), and exposure to platinum agents (≥401 mg/m^2) during treatment for their initial cancer compared to survivors without these exposures.[5]

Few studies from the CCSS have evaluated health outcomes among children with congenital anomalies; these focused on Down syndrome[6] and neurofibromatosis 1 (NF1).[7, 8] Regarding Down syndrome, Goldsby et al.[6] observed that the risks of severe chronic conditions (defined as Common Terminology Criteria for Adverse Events [CTCAE] grades 3-5) (HR: 1.7, 95% CI: 1.1, 2.6) and developing three or more chronic conditions

(CTCAE grades 1-5) (HR: 1.7, 95% CI: 1.2, 2.4) were higher among leukemia survivors with Down syndrome compared to survivors without Down syndrome. The estimated cumulative incidence of any chronic condition over 25 years among leukemia survivors was 83% for those with Down syndrome and 69% for those without Down syndrome. The authors also identified significantly increased risks of known health problems associated with Down syndrome, including hearing loss, cataracts, endocrine effects, and hypothyroidism compared to survivors without Down syndrome. Children with Down syndrome had a lower risk of subsequent malignant neoplasms (HR: 0.1, 95% CI: 0.0, 0.9).[6] Regarding NF1, de Blank et al.[8] observed a higher risk of developing any chronic health condition (CTCAE grade 3-5) among survivors with NF1 compared to survivors without NF1 (RR: 1.5, 95% CI: 1.1, 2.1). Furthermore, Bhatia et al.[7] observed that CCSS participants with NF1 had a higher risk of developing subsequent malignant neoplasms compared to survivors without NF1 (HR: 3.5, 95% CI: 1.7, 6.5). However, little is known about the long-term health complications for cancer survivors with other types of congenital anomalies. Furthermore, less is known about risk of subsequent malignant neoplasms in survivors with non-syndromic defects and it is unclear whether any such risk is attributable to the underlying anomaly or treatment-related exposures.

4. Specific Aims and Research Hypotheses

The long-term goal of this research is to reduce the risk of adverse health outcomes among childhood cancer survivors, particularly among those with congenital anomalies. As a first step towards achieving this goal, we need to understand the epidemiology of poor health outcomes among children with congenital anomalies and cancer. The research objective is to leverage the CCSS to determine whether adverse health outcomes, including chronic health conditions, mortality, and subsequent malignant neoplasms, differ for cancer survivors with and without congenital anomalies. Congenital anomalies were self-reported by participants or their proxy, defined as genetic conditions (e.g., Beckwith-Wiedemann syndrome, Down syndrome) and conditions present at birth (e.g., cleft lip/palate, clubfoot). We hypothesize that childhood cancer survivors with congenital anomalies have a higher burden (including number and severity) of chronic health conditions, mortality, and subsequent malignant neoplasms compared to survivors without congenital anomalies. We propose the following aims:

Specific Aim 1. Determine whether childhood cancer survivors with congenital anomalies have a higher risk of chronic health conditions compared to survivors without congenital anomalies. *Hypothesis: Survivors with congenital anomalies have a higher risk of non-malignant chronic health conditions compared to survivors without congenital anomalies.* We will evaluate differences in the relationship between congenital anomalies and chronic health conditions stratified by sex, type of congenital anomaly (genetic conditions v. conditions present at birth), cancer diagnosis, treatment exposure, and chronic condition (including number and severity as defined by CTCAE).

Specific Aim 2. Estimate all-cause mortality and cause-specific mortality for chronic health conditions among survivors with congenital anomalies compared to survivors without congenital anomalies. *Hypothesis: Survivors with congenital anomalies will have higher all-cause and cause-specific mortality compared to survivors without congenital anomalies.* We will estimate mortality rates per person-time at risk among survivors with and without congenital anomalies. We will compare mortality rates with the expected mortality rate in the US population by calculating standardized mortality ratios adjusted for age, sex, and calendar year.

Specific Aim 3. Explore whether childhood cancer survivors with congenital anomalies have a higher risk of subsequent malignant neoplasms compared to survivors without congenital anomalies, excluding survivors with genetic conditions. *Hypothesis: Survivors with congenital anomalies have a higher risk of subsequent malignant neoplasms compared to survivors without congenital anomalies, though this may vary by type of congenital anomaly, cancer, and treatment.* We will explore differences in the relationship between congenital anomalies and subsequent malignant neoplasms by sex, original cancer diagnosis, and treatment. We plan to exclude children with genetic conditions (self-reported and identified through whole exome sequencing data) in this aim, as the association between these syndromes and subsequent malignant neoplasms is well described.

5. Analysis Framework

Study Population. We will include survivors from the original and expansion cohorts (see Table 1). In an initial review of CCSS data, 4,062 survivors reported at least one congenital anomaly from the original cohort (reported on Follow-Up 1 or Follow-Up 5) and the expansion cohort baseline survey. We will include all survivors with (n=4,062) and without (n=18,185) reported congenital anomalies, including those reported by proxy. All participants in the CCSS have provided informed consent. Medical record abstraction occurred at local institutions to verify cancer treatment history. Vital status and cause of death were obtained through the National Death Index and death certificates (US participants).

Table 1. Timeline of included CCSS surveys.

Variable	Original Baseline (1992-2005)	Follow-Up 1 (2000)	Follow-Up 2 (2003)	Follow-Up 3 (2005)	Follow-Up 4 (2007)	Follow-Up 5 (2014)	Expansion Baseline (2008-2018)
Congenital Anomalies							
Chronic Medical Conditions							
Secondary Malignant Neoplasms							

Data Sources for Independent Variables. For congenital anomalies, we will include data from the original and expansion cohorts (Table 2). Questions about congenital anomalies were asked during the baseline surveys and selected follow-up surveys of survivors. In the original baseline survey, there was a question to describe any anomalies occurring in the participant from a list in the questionnaire. Participants were instructed to complete the question if they had any of the listed conditions (Table 2). Information collected includes name of participant, date of birth, specific type of birth defect or hereditary condition (listing of all known anomalies), and age of onset. More detailed questions about individual types of congenital anomalies were asked in the first and fifth follow-up surveys for all original cohort participants and in the expansion cohort baseline survey. This included an option for the participants to select “Yes”, “No”, or “Not sure” for each type of genetic condition and condition present at birth that the participant’s physician told them that they were born with or had. The expansion and follow-up surveys also included an option to report the specific types of ‘other congenital heart defect’ and any other disorders not included in the provided lists of genetic conditions and conditions present at birth. We will work with the CCSS statisticians to determine the optimal classification of reported congenital anomalies from baseline and follow-up surveys. We plan to analyze conditions reported on any survey, with primary analysis focused on 1) congenital anomalies overall and 2) stratified by genetic conditions and conditions present at birth as classified by the CCSS surveys. For anomalies identified on the original baseline cohort survey, we will use the anomalies reported on the Follow Up 1 and Follow Up 5 surveys for those who responded. For participants who reported congenital anomalies at baseline, but did not complete follow up surveys, we will review the baseline data and classify anomalies into the categories included in the later surveys. We acknowledge that this may require manual review of the anomalies reported in the baseline cohort to identify inconsistencies in reporting and may not be feasible. We will conduct sensitivity analyses excluding the original baseline survey data and stratifying results by original and expanded cohorts. Chronic health conditions reported within five years of the initial cancer diagnosis will be considered as prevalent events at 5 years, but will not be utilized in prospective, post-five-year analyses (such as Cox models). Subsequent events that occur after five years may be included for these individuals. For Specific Aim 3 we will restrict analyses to participants without a genetic condition listed in Table 2. We acknowledge the need to work closely with the CCSS statisticians and to allow adequate time to identify children with congenital anomalies in the CCSS surveys.

Table 2. Reported congenital anomalies in the CCSS.

Genetic Conditions	Conditions Present at Birth
Ataxia telangiectasia	Cleft lip or palate
Beckwith-Wiedemann syndrome	Club foot
Bilateral acoustic neurofibromatosis (Neurofibromatosis Type 2)	Large or multiple birthmarks
Bloom's syndrome	Deafness or impaired hearing at birth
Down syndrome	Blindness or difficulty seeing at birth
Klinefelter's syndrome	Eyes different colors or missing an iris
Fanconi's anemia	Hydrocephalus
Multiple exostoses	Spina bifida or other neural tube defect
Familial adenomatous polyposis (FAP or Gardner syndrome)	Microcephaly
Neurofibromatosis (Type 1)	Hemihypertrophy
Nevoid basal cell carcinoma syndrome	Extra fingers, deformed chest, shortened limbs or any other skeletal abnormality
Turner's syndrome	Hole in the heart or other congenital heart defect
Von Hippel-Lindau syndrome	Any congenital abnormality of the pancreas, liver, or digestive tract
Wiskott-Aldrich syndrome	Any kidney, bladder, or genital abnormalities
Xeroderma pigmentosum	Undescended testes
Any other genetic disorder	Any other birth defects

Because some congenital anomalies, particularly genetic syndromes, may increase the risk of chronic health conditions regardless of a child’s cancer treatment history, we plan to evaluate this potential problem by

conducting post-hoc analyses based on the associations identified in our sample. For example, if we identify relationships between congenital anomalies and specific chronic health conditions (as proposed in Example Table 3), the study team will review the literature and use subject matter expertise of the co-investigators to determine whether any reported anomalies are also causally related to the specific health outcome. We will then conduct analyses using a "leave one out" approach where we will exclude the children with a specific anomaly from the analyses to determine if results change. We expect the number of these anomaly/chronic health condition relationships to be low in the CCSS sample.

To evaluate the overlap between self-reported genetic conditions/conditions present at birth and genetic syndromes identified in sequencing analyses, we will evaluate exome data in a subset of CCSS participants (n=5,451).[9] The included participants were 48% male and 94% European ancestry. Kim and Gianferante et al.[9] analyzed 237 candidate cancer-susceptibility genes. We are proposing to leverage their findings to identify individuals who have pathogenic or likely pathogenic variants in cancer susceptibility genes, without further analysis of raw sequencing data. The use of these calls will enable us to better classify individuals with conditions present at birth that may be attributable to genetic syndromes in our study (see methods below in Analytic Approach). Twenty-two percent (22%, n=4,062) of survivors self-reported the presence of a congenital anomaly in the CCSS on either the first or fifth follow-up survey of the baseline cohort or the baseline survey for the expansion cohort. Thus, we expect to include approximately 1,200 participants with self-reported congenital anomalies and 4,251 participants without a reported anomaly with exome data in this descriptive analysis.

Data Sources for Outcome Variables.

Aim 1. Chronic Health Conditions: To classify patient-reported chronic health conditions, we will use the Common Terminology Criteria for Adverse Events (CTCAE v. 4.03) with scores ranging from 1 (mild) to 5 (fatal). These scores will be identified through the most recent follow-up surveys based on age first reported and highest score, as done in previous analyses.[4, 6] Chronic conditions identified at least five years after the initial cancer diagnosis will be identified from baseline and follow-up surveys of the original and expansion cohort data. Chronic conditions were self-reported, with approximately 140 individual questions across eight body systems/procedures. Chronic conditions occurring within five years of the initial cancer diagnosis will not be included in the analysis, though they may be shown as prevalent events on cumulative incidence curves. We will exclude malignant conditions from this analysis.

Aim 2. All-Cause and Cause-Specific Mortality: Deaths among participants were identified through the National Death Index (NDI) and deaths as of December 31, 2017. Death certificates were requested from the state of death.[10] If a death certificate was not available, cause of death codes form the NDI were requested. Death certificates were only obtained for US residents; thus, we will exclude Canadian residents from cause-specific mortality rate estimates, but include these participants in all-cause mortality rate estimates. Cause of death was classified by International Classification of Disease (ICD) 9 and 10 codes as: 1) directly related to original cancer diagnosis (e.g., disease progression or recurrence; acute toxicity of treatment), 2) subsequent neoplasms (includes malignant, benign, in situ, and uncertain/unspecified behavior) (ICD-9: 140-239; ICD-10: C00-C97 and D10-D36), 3) cardiac-related deaths (ICD-9: 390-398, 402, 404, 410-429; ICD-10: I00-I02, I05-I09, I11, I13, I14, I20-I28, I130-I52), 4) pulmonary-related deaths (ICD-9: 460-519; ICD-10: J00-J99), 5) deaths not related to original cancer or cancer treatment (e.g., suicide, motor vehicle accident) (ICD-9: 800-999; ICD-10: V00-V99, Y00-Y89, X00-X99, W00-W99), and 6) all other causes of death (all other ICD codes).[10, 11] We will obtain age-, sex-, and calendar year-specific mortality rates for the general US population from the National Center for Health Statistics to estimate the expected number of deaths.

Aim 3. Subsequent Malignant Neoplasms: All baseline and follow-up surveys include questions about additional cancers for survivors, which includes cancer, leukemia, tumor, or other similar illness, or a recurrence/relapse of the original cancer. Participants or proxies provided the name of the condition, facility where it was diagnosed, physician's name, and date of diagnosis/recurrence. Self-reported secondary cancers were confirmed with pathology report review by a CCSS pathologist and oncologist. When pathology reports were unavailable, other medical records or death certificates were used for confirmation. We will include subsequent malignant neoplasms that were diagnosed at least five years after the original cancer diagnosis and will exclude cancers that were a recurrence of the original cancer. We will also exclude non-melanoma skin cancers and benign meningioma. We will include covariates of age at diagnosis of the second cancer and time from initial cancer diagnosis to the second cancer diagnosis.

In this exploratory aim, we will exclude participants reporting genetic conditions and participants reporting a condition present at birth that may indicate an underlying cancer predisposition syndrome (approximately 14% of survivors reporting any congenital anomaly). Conditions present at birth that will be excluded are hemihypertrophy and large/multiple birthmarks. However, we will also evaluate cross-tabulations between the congenital anomaly categories of genetic conditions and conditions present at birth and additionally exclude participants who report both a genetic condition and condition present at birth if that overlap includes a cancer predisposition syndrome.

Covariates. Demographic characteristics will be obtained from baseline and follow-up questionnaires as detailed in Table 3. We will evaluate socioeconomic status based on the participant's education, household income, and health insurance. In addition, we will include information on the original cancer diagnosis, including treatments received.

Table 3. Planned demographic and treatment characteristics from the CCSS.

Participant Demographics	Initial Treatment Characteristics
Age at last follow-up	Initial cancer diagnosis (site, histology)
Years of follow-up since diagnosis	Age at initial cancer diagnosis
Sex	Year of primary cancer diagnosis
Race/ethnicity	Chemotherapy (yes, no)
Education	Type of chemotherapy and cumulative dose (alkylating agents, anthracycline, epipodophyllotoxins, platinum agents)
Household income	Radiation (yes/no) and maximum dose by body region (Total body irradiation, craniospinal/testicular [no TBI], other location [no TBI])
Health insurance	Surgery (yes/no) and type (biopsy/resection, amputation, limb sparing procedure, splenectomy, nephrectomy)
Vital status	
Proxy for survey reporting	

Analytic Approach.

Descriptive Statistics: We will calculate frequencies and percentages for categorical variables and means and standard deviations for continuous variables for survivors with and without congenital anomalies. To evaluate overlap between the congenital anomaly categories of genetic conditions and conditions present at birth, we will analyze cross-tabulations between the categories (Example Table 1). We will plot cumulative incidence of chronic conditions (Aim 1), death (Aim 2), and diagnosis of subsequent malignant neoplasms (Aim 3), as done previously (Example Figure 1).[6, 12]

We will evaluate cross-tabulations of the presence/absence of genetic syndromes previously identified using the existing exome data described in Kim and Gianferante et al.[9] (Example Table 2). We will use the Kappa statistic to determine agreement between the sequencing data and self-reported data. We will also calculate sensitivity and specificity of anomaly classification using these data. This will allow us to validate the self-reported data and conduct sensitivity analyses to adjust for the misclassification of exposure, particularly to improve classification of unreported genetic conditions.

Specific Aim 1. Determine whether childhood cancer survivors with congenital anomalies have a higher risk of chronic health conditions compared to survivors without congenital anomalies.

We will estimate cumulative incidence of chronic health conditions (overall and specific types) for survivors with and without congenital anomalies. Curves will be plotted by years since the initial cancer diagnosis, beginning at five years after the initial diagnosis, and will account for competing risks.[13] To compare cumulative incidence between groups at 20 years after diagnosis, we will use the Wald test.[14] We will evaluate the incidence of any chronic condition (CTCAE grade 1-5), severe chronic conditions (CTCAE grade 3-5), and number of chronic conditions (≥2 and ≥3 conditions) (Example Figure 2). We will also compare cumulative incidence by congenital anomaly type.

To estimate HRs and 95% CIs, we will use the Cox Proportional Hazards Model with age as the time scale. We will account for competing events of deaths due to conditions other than those under study.[15] We will account for undersampling of acute lymphoblastic leukemia in the expansion cohort (1987-1999) with a weight of 1.21

for survivors diagnosed at age 0 or 11-20 years and a weight of 3.63 for survivors diagnosed from ages 1-10 years.[6] We will conduct a bivariate analysis of survival time examining the congenital anomaly variable along with each potential confounding variable to identify important confounding variables for inclusion in the model. We will evaluate the proportional hazards assumption by 1) assessing the relationship between the Schoenfeld residuals and the log of survival time and 2) including an interaction term with the log of survival time and the variable of interest. Based on a preliminary directed acyclic graph, we plan to include sex, race/ethnicity, and socioeconomic status (measured through education, household income, and health insurance) as potential confounders. We will evaluate covariates, including treatment type and sex, as effect modifiers of the association between congenital anomalies and chronic medical conditions. As sample size allows, we will evaluate separate models for genetic conditions and conditions present at birth and evaluate models by type of cancer, treatment, and health outcome. To assess effect modification, we will include an interaction term in the model, with $p<0.05$ indicating a statistically significant interaction (Example Table 3).

Specific Aim 2. Estimate all-cause mortality and cause-specific mortality for chronic health conditions among survivors with congenital anomalies compared to survivors without congenital anomalies.

We will plot the cumulative all-cause and cause-specific mortality by years since original cancer diagnosis among CCSS survivors with anomalies, survivors without anomalies, and the US general population for comparison (Example Figure 3). We will estimate yearly mortality rates and compare mortality rates of survivors with and without anomalies with the expected mortality rate in the US population per person-year by calculating standardized mortality ratios (SMR) for all-cause mortality and cause-specific mortality for 1) survivors with anomalies and 2) survivors without anomalies compared to the expected mortality in the US.[11, 12] In models of cause-specific mortality, we will treat all other causes of death as competing risks. We will use Poisson regression to estimate SMRs and 95% CIs adjusted for age, sex, and calendar time, with the US population expected deaths as the offset. Since there is no expected population comparison for deaths directly related to the initial cancer diagnosis and treatment, we will only report mortality rates for these survivors. In addition, we will stratify models by original cancer diagnosis and type of congenital anomaly (conditions present at birth and genetic conditions) for all-cause and cause-specific SMRs (Example Table 4).

Specific Aim 3. Explore whether childhood cancer survivors with congenital anomalies have a higher risk of subsequent malignant neoplasms compared to survivors without congenital anomalies, excluding survivors with genetic conditions.

We will estimate cumulative incidence of subsequent malignant neoplasms for survivors with and without congenital anomalies (Example Figure 4). We will primarily focus on the risk of any subsequent malignant neoplasm and will explore specific neoplasm types (e.g., breast, thyroid, etc.) as sample size allows. Curves will be plotted by years since the initial cancer diagnosis, beginning at five years after the initial diagnosis, and will account for competing risks.[13] To compare cumulative incidence between groups at 20 years after diagnosis, we will use the Wald test.[14]

To estimate HRs and 95% CIs, we will use the Cox Proportional Hazards Model with age as the time scale. We will account for competing events of deaths due to conditions other than those under study.[15] We will account for undersampling of acute lymphoblastic leukemia in the expansion cohort as noted in Specific Aim 1. We will also similarly conduct a bivariate analysis of survival time for each candidate confounding variable. We will evaluate the proportional hazards assumption by 1) assessing the relationship between the Schoenfeld residuals and the log of survival time and 2) including an interaction term with the log of survival time and the variable of interest. Based on a preliminary directed acyclic graph, we plan to include sex and race/ethnicity as potential confounders. We will evaluate covariates, including treatment type and sex, as effect modifiers of the association between congenital anomalies and subsequent malignant neoplasms. As sample size allows, we will evaluate models by type of cancer, treatment, and subsequent malignant neoplasm type. To assess effect modification, we will include an interaction term in the model, with $p<0.05$ indicating a statistically significant interaction (Example Table 5).

In addition, we will compare incidence rates of subsequent malignant neoplasms of survivors with and without conditions present at birth with the expected cancer incidence rate in the US population. To estimate the expected cancers, we will use age-, sex-, and calendar year-specific Surveillance, Epidemiology, and End

Results (SEER) incidence rates per person-year and calculate standardized incidence ratios (SIR).[5] We will use Poisson regression to estimate SIRs and 95% CIs adjusted for attained age (10 year intervals), treatment dose, and 5-year treatment era, with the expected incidence as the offset.[5] We will also stratify models by original cancer diagnosis (Example Table 6). We will also estimate the excess absolute risk (EAR) of subsequent malignant neoplasms by subtracting the expected number of cancers from the observed number of cancers, divided by the person-years at risk, and presented per 10,000 person-years at risk with 95% CIs.[16]

Potential Problems and Alternative Solutions. One limitation is that congenital anomalies and chronic medical conditions are self-reported, which may result in misclassification. When comparing survivors with and without congenital anomalies, we expect potential misclassification to be non-differential since cancer survivors will have received thorough medical exams during their initial cancer treatment. To evaluate the potential for participation bias, we will stratify by the severity of the congenital anomaly. We will compare the percentage of children with specific types of anomalies that are minor in terms of morbidity (e.g., cleft lip/palate) with major anomalies that may result in more severe morbidity (e.g., spina bifida). If we observe differences in CCSS compared to the general population from published reports of congenital anomalies, this may indicate participation bias. Furthermore, we will include proxy reports for deceased participants, which will reduce the risk of survival bias and allow us to evaluate this bias by comparing differences in associations through stratification by reporting source.

Future Directions. This project will provide preliminary data to support a future NIH R01 application to develop interventions to reduce poor health outcomes among cancer survivors with congenital anomalies. For example, survivors with Down syndrome and acute lymphoblastic leukemia (ALL) have increased risk of severe chronic health conditions, and future studies can evaluate modifications to initial cancer treatment and/or enhanced surveillance during survivorship to reduce the risk of these outcomes.[6] Although individual congenital anomalies are rare, we will identify overlapping, targetable health outcomes for investigation in future studies. By understanding whether childhood cancer survivors with congenital anomalies have increased risk of poor health outcomes following cancer treatment, we can intervene along the cancer care continuum to improve health outcomes among this uniquely vulnerable population.

Example Tables and Figures.

Tables.

Table 1. Demographic, treatment, and first primary cancer characteristics of survivors with and without birth defects.

Characteristic	Survivors	
	Congenital Anomalies Present n (%)	Congenital Anomalies Absent n (%)
Total number of participants		
Age at last follow-up (years)		
<10		
10-19		
20-29		
30-39		
40-49		
≥50		
Sex		
Male		
Female		
Years of follow-up or death since diagnosis		
5-14		
15-19		
20-24		
25-29		
30-34		
≥30		
Race		
American Indian/Alaska Native		
Asian/Pacific Islander		

Black		
Other		
Unknown		
White		
Ethnicity		
Hispanic		
Non-Hispanic		
Education		
<High school (did not graduate)		
Completed high school/GED		
Training after high school/some college		
College graduate		
Post graduate level		
Household income		
<$9,999		
$10,000-<$20,000		
$20,000-<$40,000		
$40,000-<$60,000		
≥$60,000		
Current health insurance		
Yes or Canadian resident		
No		
Vital status		
Alive		
Deceased		
Proxy		
Yes		
No		
Diagnosis		
Acute lymphoblastic leukemia		
Acute myeloid leukemia		
Other leukemia		
Astrocytomas		
Medulloblastoma, PNET		
Other CNS tumors		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Wilms tumor		
Neuroblastoma		
Soft-tissue sarcoma		
Ewing sarcoma		
Osteosarcoma		
Other bone tumors		
Age at primary cancer diagnosis (years)		
<1		
1-4		
5-16		
≥17		
Year of primary cancer diagnosis		
1970-1973		
1974-1977		
1978-1981		
1982-1986		
1987-1990		
1991-1994		
1995-1999		
Radiation therapy		
None		
Any site		
Chest		
Brain or spine		
Abdomen		
Pelvis		
Cyclophosphamide equivalent dose; mg/m^2		
None		
Any		

1-<4,000		
4,000-<8,000		
8,000-<12,000		
12,000-<16,000		
16,000-<20,000		
≥20,000		
Anthracyclines dose; mg/m^2		
None		
Any		
1-<100		
100-<250		
250-<400		
≥400		
Epipodophyllotoxins dose; mg/m^2		
None		
Any		
1-<100		
≥100		
Platinum compounds dose; mg/m^2		
None		
Any		
1-<300		
≥300		
Surgery		
None		
Biopsy/Resection of primary tumor		
Amputation (if bone tumor or soft tissue sarcoma)		
Limb sparing procedure (if bone tumor or soft tissue sarcoma		
Splenectomy (if Hodgkin lymphoma)		
Chronic Conditions		
None		
Hearing/vision/speech		
Urinary		
Hormonal/endocrine		
Heart/circulatory		
Respiratory		
Digestive		
Brain systems		
Surgical procedures		
CTCAE Score		
No condition		
Grade 1 (mild)		
Grade 2 (moderate)		
Grade 3 (severe)		
Grade 4 (life-threatening or disabling)		
Grade 5 (fatal)		
Multiple conditions		
≥2		
≥3		
Subsequent malignant neoplasms		
None		
Yes		
Type of subsequent malignant neoplasm		
None		
Any		
Leukemia		
ALL		
AML		
Other leukemia		
Lymphoma		
CNS tumors		
Glial tumor		
Medulloblastoma/PNET		
Breast cancer		
Bone cancer		
Soft-tissue sarcoma		

Thyroid cancer		
Melanoma		
All other cancers		
Cause of Death		
All cause		
Directly related to original cancer diagnosis		
Subsequent malignant neoplasms		
Cardiac-related deaths		
Pulmonary-related deaths		
Deaths not related to original cancer or cancer treatment		
Time from childhood cancer diagnosis to development of first severe (Grade 3 or higher) chronic health condition		
Time from childhood cancer diagnosis to death (median, years)		
Age at diagnosis of subsequent malignant neoplasms (median, years)		
Time from childhood cancer diagnosis to diagnosis of second primary neoplasm (median, years)		

Table 2. Cross-tabulations of self-reported congenital anomalies (genetic conditions and conditions present at birth) by identified pathogenic variants from whole exome/genome sequencing.

Congenital Anomalies (Self-Reported)	**Identified Pathogenic Variants (across columns), N (%)**
No Reported Congenital Anomalies	
Self-Reported Genetic Conditions	
None	
Ataxia telangiectasia	
Beckwith-Wiedemann syndrome	
Bilateral acoustic neurofibromatosis (Neurofibromatosis Type 2)	
Bloom syndrome	
Down syndrome	
Klinefelter syndrome	
Fanconi anemia	
Multiple exostoses	
Familial adenomatous polyposis (FAP or Gardner syndrome)	
Neurofibromatosis (Type 1)	
Nevoid basal cell carcinoma syndrome	
Turner syndrome	
Von Hippel-Lindau syndrome	
Wiskott-Aldrich syndrome	
Xeroderma pigmentosum	
Any other genetic disorder	
Self-Reported Conditions Present at Birth (excluding survivors reporting genetic conditions)	
None	
Cleft lip or palate	
Club foot	
Large or multiple birthmarks	
Deafness or impaired hearing at birth	
Blindness or difficulty seeing at birth	
Eyes different colors or missing an iris	
Hydrocephalus	
Spina bifida or other neural tube defect	
Microcephaly	
Hemihypertrophy	
Extra fingers, deformed chest, shortened limbs or any other skeletal abnormality	
Hole in the heart or other congenital heart defect	
Any congenital abnormality of the pancreas, liver, or digestive tract	
Any kidney, bladder, or genital abnormalities	
Undescended testes	
Any other birth defects	

Table 3. Analysis of chronic health conditions among survivors with and without congenital anomalies.

		Any Congenital Anomaly (v. none)			Genetic Condition (v. none)			Condition Present at Birth (v. none)		
Chronic health condition	None n (%)	n (%)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	n (%)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	n (%)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Any condition										
Grades 1-5										
Grades 3-5										
Multiple conditions										
≥2										
≥3										
Specific conditions										
Hearing/vision/speech										
Urinary										
Hormonal/endocrine										
Heart/circulatory										
Respiratory										
Digestive										
Brain systems										
Surgical procedures										
Any Condition										
Any condition, Grades 1-5										
Sex										
Male										
Female										
Cancer type										
Acute lymphoblastic leukemia										
Acute myeloid leukemia										
Other leukemia										
Astrocytomas										
Medulloblastoma, PNET										
Other CNS tumors										
Hodgkin lymphoma										
Non-Hodgkin lymphoma										
Wilms tumor										
Neuroblastoma										
Soft-tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										
Other bone tumors										
No chemotherapy or radiation										
Chemotherapy										
Any chemotherapy										
Alkylating agent (dose categories)										
Anthracyclines (dose categories)										
Epipodophyllotoxins (dose categories)										
Platinum agents (dose categories)										
Radiation therapy										

Any irradiation										
Total body radiation (dose categories)										
Craniospinal/testicular (dose categories)										
Other location (dose categories)										
Surgery										
No surgery										
Biopsy/resection										
Amputation										
Limb sparing procedure										
Splenectomy										
Nephrectomy										

*Adjusted for sex, race/ethnicity, and socioeconomic status

Table 4. Yearly mortality rates and standardized mortality ratio (SMR)* by cause of death for survivors with and without congenital anomalies.

	All cause		Subsequent malignant neoplasms		Cardiac-related deaths		Pulmonary-related deaths		External Causes (not related to original cancer)		Other causes		Directly related to original cancer diagnosis**
	Mortality Rate (%)	SMR (95% CI)	Mortality Rate (%)	SMR (95% CI)	Mortality Rate (%)	SMR (95% CI)	Mortality Rate (%)	SMR (95% CI)	Mortality Rate (%)	SMR (95% CI)	Mortality Rate (%)	Mortality Rate (%)	Mortality Rate (%)
Presence of Congenital anomalies													
Original Cancer Diagnosis													
Acute lymphoblastic leukemia													
Acute myeloid leukemia													
Other leukemia													
Astrocytomas													
Medulloblastoma, PNET													
Other CNS tumors													
Hodgkin lymphoma													
Non-Hodgkin lymphoma													
Wilms tumor													
Neuroblastoma													
Soft-tissue sarcoma													
Ewing sarcoma													
Osteosarcoma													
Other bone tumors													
Congenital anomaly type													
Conditions present at birth													
Genetic conditions													
Absence of Congenital anomalies													
Original Cancer Diagnosis													
Acute lymphoblastic leukemia													
Acute myeloid leukemia													
Other leukemia													
Astrocytomas													
Medulloblastoma, PNET													

Other CNS tumors													
Hodgkin lymphoma													
Non-Hodgkin lymphoma													
Wilms tumor													
Neuroblastoma													
Soft-tissue sarcoma													
Ewing sarcoma													
Osteosarcoma													
Other bone tumors													

*SMR adjusted for age, sex, and calendar year

**SMR not calculated for deaths directly related to original cancer diagnosis due to lack of a comparison group in the US general population

Table 5. Analysis of subsequent malignant neoplasms among survivors with and without congenital anomalies (excluding genetic conditions).

		Presence of Congenital Anomalies (v. none)		
	None n (%)	Any n (%)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Subsequent malignant neoplasms				
Any cancer				
Leukemia				
ALL				
AML				
Other leukemia				
Lymphoma				
CNS tumors				
Glial tumor				
Medulloblastoma/PNET				
Breast cancer				
Bone cancer				
Soft-tissue sarcoma				
Thyroid cancer				
Melanoma				
All other cancers				
Any subsequent malignant neoplasm				
Sex				
Male				
Female				
Cancer type				
Acute lymphoblastic leukemia				
Acute myeloid leukemia				
Other leukemia				
Astrocytomas				
Medulloblastoma, PNET				
Other CNS tumors				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
Wilms tumor				
Neuroblastoma				
Soft-tissue sarcoma				
Ewing sarcoma				
Osteosarcoma				
Other bone tumors				
Treatment				
No chemotherapy or radiation				
Chemotherapy				
Any chemotherapy				
Alkylating agent (dose categories)				
Anthracyclines (dose categories)				
Epipodophyllotoxins (dose categories)				
Platinum agents (dose categories)				
Radiation therapy				
Any irradiation				
Total body radiation (dose categories)				
Craniospinal/testicular (dose categories)				
Other location (dose categories)				
Surgery				
No surgery				
Biopsy/resection				
Amputation				
Limb sparing procedure				
Splenectomy				
Nephrectomy				

*Adjusted for sex and race/ethnicity

Table 6. Observed and expected cancers, standardized incidence ratio (SIR)*, and Excess Absolute Risk for secondary malignant neoplasm for survivors with and without congenital anomalies.

	Observed Cancers	Expected Cancers	SIR (95% CI)	Excess Absolute Risk (95% CI)
Presence of Congenital anomalies				
Original Cancer Diagnosis				
Acute lymphoblastic leukemia				
Acute myeloid leukemia				
Other leukemia				
Astrocytomas				
Medulloblastoma, PNET				
Other CNS tumors				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
Wilms tumor				
Neuroblastoma				
Soft-tissue sarcoma				
Ewing sarcoma				
Osteosarcoma				
Other bone tumors				
Congenital anomaly type				
Conditions present at birth				
Genetic conditions				
Absence of Congenital anomalies				
Original Cancer Diagnosis				
Acute lymphoblastic leukemia				
Acute myeloid leukemia				
Other leukemia				
Astrocytomas				
Medulloblastoma, PNET				
Other CNS tumors				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
Wilms tumor				
Neuroblastoma				
Soft-tissue sarcoma				
Ewing sarcoma				
Osteosarcoma				
Other bone tumors				

*SIR adjusted for attained age, treatment dose, and 5-year treatment era

Figures.

Figure 1. Cumulative incidence of chronic conditions (Aim 1), death (observed and expected) (Aim 2), and subsequent malignant neoplasms (Aim 3).

Chronic Condition Figures (Aim 1):

Figure 2. Cumulative incidence of chronic conditions (any type and grade) among 1) survivors with congenital anomalies and 2) survivors without congenital anomalies (overall and by chronic condition type).

a) Any condition (grade 1-5)
    a. Any congenital anomaly
    b. Genetic conditions
    c. Conditions present at birth
b) Severe conditions (grade 3-5)
c) Multiple conditions (≥2 and ≥3)
d) Hearing/vision/speech
e) Urinary
f) Hormonal/endocrine
g) Heart/circulatory
h) Respiratory
i) Digestive
j) Brain systems
k) Surgical procedures

Mortality Figures (Aim 2):

Figure 3. Cumulative mortality with years since original cancer diagnosis on the x-axis. Within these plots, we will include observed mortality for survivors with anomalies, survivors without anomalies, and the expected mortality in the US population.

a) All-causes
    a. Any congenital anomaly
    b. Genetic conditions
    c. Conditions present at birth
b) Directly related to original cancer diagnosis
c) Subsequent malignant neoplasms
d) Cardiac-related deaths
e) Pulmonary-related deaths
f) External causes of death
g) Deaths not related to original cancer or cancer treatment

Subsequent Malignant Neoplasms Figures (Aim 3):

Figure 4. Cumulative incidence of subsequent malignant neoplasms among 1) survivors with congenital anomalies and 2) survivors without congenital anomalies (overall and by secondary malignant neoplasm type)

a) Overall
b) Leukemia
c) ALL
d) AML
e) Other leukemia
f) Lymphoma
g) CNS tumors
h) Glial tumor
i) Medulloblastoma/PNET

j) Breast cancer
k) Bone cancer
l) Soft-tissue sarcoma
m) Thyroid cancer
n) Melanoma
o) All other cancers

6. <u>Special consideration</u>: Because the original baseline surveys asked about congenital anomalies in a more open-ended manner, the data abstraction may require more intense manual review than in later surveys of both the original and expanded baseline cohorts.

References:

1. Janitz AE, Neas BR, Campbell JE, et al. Childhood cancer in children with congenital anomalies in Oklahoma, 1997 to 2009. *Birth Defects Research Part A: Clinical and Molecular Teratology*. 2016;106(7):633-42. doi:10.1002/bdra.23494
2. Lupo PJ, Schraw JM, Desrosiers TA, et al. Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births. *JAMA Oncology*. 2019;5(8):1150-1158. doi:10.1001/jamaoncol.2019.1215
3. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. Jan 2014;14(1):61-70. doi:10.1038/nrc3634
4. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. Oct 12 2006;355(15):1572-82. doi:10.1056/NEJMsa060185
5. Turcotte LM, Liu Q, Yasui Y, et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. *JAMA*. 2017;317(8):814-824. doi:10.1001/jama.2017.0693
6. Goldsby RE, Stratton KL, Raber S, et al. Long-term sequelae in survivors of childhood leukemia with Down syndrome: A childhood cancer survivor study report. *Cancer*. 2018;124(3):617-625. doi:10.1002/cncr.31065
7. Bhatia S, Chen Y, Wong FL, et al. Subsequent Neoplasms After a Primary Tumor in Individuals With Neurofibromatosis Type 1. *J Clin Oncol*. Nov 10 2019;37(32):3050-3058. doi:10.1200/jco.19.00114
8. de Blank P, Li N, Fisher MJ, et al. Late morbidity and mortality in adult survivors of childhood glioma with neurofibromatosis type 1: report from the Childhood Cancer Survivor Study. *Genetics in medicine : official journal of the American College of Medical Genetics*. Nov 2020;22(11):1794-1802. doi:10.1038/s41436-020-0873-7
9. Kim J, Gianferante M, Karyadi DM, et al. Frequency of pathogenic germline variants in cancer-susceptibility genes in the Childhood Cancer Survivor Study. *JNCI Cancer Spectrum*. 2021;doi:10.1093/jncics/pkab007
10. Mueller S, Kline CN, Buerki RA, et al. Stroke impact on mortality and psychologic morbidity within the Childhood Cancer Survivor Study. *Cancer*. 2020;126(5):1051-1059. doi:10.1002/cncr.32612
11. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute*. Oct 1 2008;100(19):1368-79.
12. Suh E, Stratton KL, Leisenring WM, et al. Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. *The Lancet Oncology*. Mar 2020;21(3):421-435. doi:10.1016/s1470-2045(19)30800-9
13. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. Mar 30 1999;18(6):695-706. doi:10.1002/(sici)1097-0258(19990330)18:6<695::aid-sim60>3.0.co;2-o
14. Gibson TM, Mostoufi-Moab S, Stratton KL, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970-99: a report from the Childhood Cancer Survivor Study cohort. *The Lancet Oncology*. Dec 2018;19(12):1590-1601. doi:10.1016/s1470-2045(18)30537-0
15. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999/06/01 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
16. Ahmed F, Goodman MT, Kosary C, et al. Excess risk of subsequent primary cancers among colorectal carcinoma survivors, 1975-2001. *Cancer*. Sep 1 2006;107(5 Suppl):1162-71. doi:10.1002/cncr.22013