Outline of Proposed Study

Study title: Using the Cumulative Illness Rating Scale to characterize the burden of chronic conditions among childhood cancer survivors.

Working groups: Chronic Disease, Cancer Control, Epidemiology/Biostatistics

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1. Background and Rationale:

Survivors of childhood cancer are at risk for a number of long-term complications as a result of their treatment.[1,2] These include impairment in function of cardiovascular, sensory, respiratory, digestive, neurological, musculoskeletal, and endocrine systems.[1-3] These comorbidities are often additive or even multiplicative in their risk for causing mortality, decreased health status and future hospitalization.[2,4,5] Methodologies for systematic classification of comorbidities is essential to establish incidence and prevalence, and to design preventive interventions. The cumulative illness rating scale for geriatrics (CIRS-G) was designed to help quantify the burden of chronic disease in geriatric patients. It originated from the Cumulative Illness Rating Scale (CIR) which was developed in 1968 as a user friendly way to classify and evaluate common health problems seen in the elderly.[6] It was updated and validated as the CIRS-G in 1991. As such, it now better defines the different morbidities elderly patients commonly manifest[7] (For full description of the measurement see Appendix 1). Recent data has suggested young adult survivors have chronic disease rates similar to older adults.[8] The CIRS-G scale has been applied to cancer patients ages 18-60 years and has been shown to be valid.[9] It has not been applied to survivors of pediatric cancer. The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) was developed by the National Cancer Institute in order to describe adverse events (AE). The grading scale ranges from 1-5 with grade 3 and 4 events being severe, disabling, and life-threatening, and grade 5 being death. An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) The previous version of the CTCAE (3.0) was applied to the CCSS cohort in 2006 by Oeffinger et al. who found 27.5% of cancer survivors had a grade 3 or 4 chronic condition with an adjusted relative risk when compared to siblings of 8.2 for a severe, disabling or life-threatening condition.[10] The CTCAE 3.0 has additionally been applied in a limited manner to survivors still in the pediatric age range.[11-13] Geenen et al. applied it to 1362 five-year survivors of childhood cancer treated in the Netherlands and found that almost 75% of survivors had 1 or more adverse late effects and 24.6% had 5 or more[13]. Wasilewski-Masker et al. applied it to 519 pediatric cancer survivors

and found that 17.4% of the patients had at least one severe (grade 3 or 4) event.[12] van der Pal et al. applied the CTCAE version 3.0 for symptomatic cardiac events to 1362 cancer survivors and found that survivors develop complications at an early age and confirmed anthracyclines and radiotherapy are major risk factors for major cardiac events.[11] More recently, Armstrong et al. utilized the CTCAE version 4.03 and demonstrated that as the CCSS cohort is aging that even more cancer survivors are developing severe conditions with 54.6% of survivors developing at least one by age 50 years compared to only 19.8% of siblings[14]. The CIRS may be an improvement over the CTCAE as it was designed to classify disease burden in an aging childhood cancer survivor population by combining morbidities from multiple organ systems into one cumulative score. It also provides an intensity rating of disease burden across organ systems. This CTCAE does this as well but was not initially designed for this purpose and the CTACE captures the information slightly differently. The proposed project would evaluate not only how the CIRS compares to the CTCAE, but also the utility of the CIRS to predict mortality and future hospitalization. With this in mind we propose the following specific aims.

2. Aims/hypotheses:

Primary Aims:

1) To describe the severity of chronic conditions among childhood cancer survivors using the cumulative illness rating scale (CIRS-G) and compare this score to the CTCAE version 4.03 chronic condition rubric.
2) To describe the association between the maximum CIRS-G scores for each organ system separately, the maximum CTACAE scores for each organ system separately, and overall CIRS severity index from the baseline questionnaire and mortality by the time of the 2007 follow-up questionnaire. In addition, organ systems that show significant association with mortality will be combined into a single model in order to determine the relative contribution of each organ system to predicting mortality and will generate an overall receiver operating curve.
3) To separately describe the association between the maximum CIRS-G scores for each organ system, the maximum CTACAE scores for each organ system, and overall CIRS severity index from the baseline questionnaire with the number of non-obstetric hospitalizations reported between the baseline and the 2007 questionnaire. In addition, organ systems that show significant association with non-obstetric hospitalization will be combined into a single model in order to determine the relative contribution of each organ system in predicting mortality and will generate an overall receiver operating curve.
4) To use National Health and Nutrition Examination Survey (NHANES) 1999-2004 to classify it to the CIRS-G so that the CIRS-G data obtained from the cancer survivor cohort of the CCSS can be directly compared to an age, sex, and race matched cohort and to an elderly cohort.

Hypotheses:

1. The CIRS-G overall risk score as assessed at the baseline questionnaire will strongly correlate with the CTCAE version 4.03 but will provide additional detail that will better capture the patients overall risk of mortality by the 2007 follow-up questionnaire.
2. Subjects with higher maximum CIRS-G scores for each organ system, maximum CTACAE scores for each organ system, and overall CIRS severity index at the baseline questionnaire will have an increased risk of mortality by the 2007 follow-up. A combined model using all significant associated organ systems will be effective in predicting mortality.
3. Subjects with either a higher maximum CIRS-G scores for each organ system separately, a higher maximum CTACAE scores for each organ system separately, and/or an overall higher CIRS severity index at the baseline questionnaire will have an increased risk of having a non-obstetric hospitalizations by the 2007 follow-up questionnaire. A combined model using all significant associated organ systems will be effective in predicting the likelihood of non-obstetric hospitalization.
4. Subjects in the CCSS cohort will have a higher burden of disease as measured by the CIRS-G severity score as compared to an age-matched cohort in NHANES and will be similar to an elderly population (over age 60 years) as obtained from NHANES data.

3. Analysis Framework:

CCSS participants who completed the baseline questionnaire or who were alive at the time of the baseline questionnaire but had a proxy fill out the questionnaire.

Outcome of interest:

Aim 1: Primary outcome will be maximum CIRS-G scores for each organ system separately, the maximum CTCAE scores for each organ system separately, and overall CIRS severity index from the baseline questionnaire and mortality by the time of the 2007 follow-up questionnaire.

Aim 2- Mortality as a time to event by 2007.

Aim 3: Non-obstetric hospitalization as a time to event by 2007.(question B5).

Aim 4: Maximum CIRS-G scores for each organ system separately and overall CIRS severity index as measure from the baseline CCSS cohort and NHANES 1999-2004 for an age, sex, and race matched group as well as an elderly (>age 60) cohort.

Independent variables: For Aims 2 and 3, the primary independent variable will be the CIRS-G severity index which is a ratio of the total CIRS-G risk score and total number of organ systems that were involved. The maximum CIRS-G score and CTCAE scores for each organ system will also be examined. The disease categories for the CIRS-G include Heart, Vascular, Hematopoietic, Respiratory, Eyes/Ears/Nose/Throat/Larynx, Upper GI, Lower GI, Liver, Renal, Genitourinary, Musculoskeletal/Integument, Neurological, Endocrine/Metabolic/Breast, and Psychiatric Illness. As was done for the CTCAE (Appendix 2), a matrix will be created that will specify which question responses from the baseline questionnaire will be used to classify each level of disease severity. For each of the following disease categories from the CIRS-G the following questions from the CCSS baseline questionnaire will be used.

Heart- B.8, F.1-21, I.7-10, I.23, I.31, N.10-11

Vascular- B.8, F.1-20, I.7-10, I.14, I.31

Hematopoietic- B.8, K.1-8, I.26

Respiratory- B.8, G.1-13, I.19-20, I.24, I.31, J.38, K.1-8, N.1

Eyes/Ears/Nose/Throat/Larynx- B.8, B.9, C.1-19, I.28-31

Upper GI- B.8, H.7-11, I.31, J.38, K.1-K8,

Lower GI- B.8, H.12-18, I.11-13, I.31, J.38, K.1-8,

Liver- B.8, H.1-6, I.21, I.27, I.31, J.38, K.1-8, N.3-8

Renal- B.8, D.1-5, I.25, I.31, J.38, K.1-K8

Genitourinary- B.8, D.2-D5, I.31, J.38, K.1-8,

Musculoskeletal/Integument- B.8, B.9, E.10, I.1-6, I.31, K.1-8

Neurological- B.8, F.16, F.20, I.14, I.17, I.31, J.1-15, J.38, N.10-11

Endocrine/Metabolic/Breast-A.10-11, B.8, E.1-18, I.15, I.18, I.31, J.38, K.1-8

Psychiatric Illness- B.8, J.16-35, J.37

As some of the data used in the CIRS-G is not available in the CCSS, careful consideration of how to implement this classification system with the CCSS data will be needed. We will work closely with all the proposed investigators to develop a clear logical system of classification for the final concept prior to the start of the study. An example of how this might work is attached for the Heart organ system (Appendix 3). A matrix was then adapted from this (Appendix 4). This adaptation of the classification system was designed by the PI but was edited by the primary mentors, the biostatistician at St. Jude (Lu Lu) and Dr. Oeffinger. Other independent variables of interest: Age, Gender, Race, history of relapsed disease prior to baseline questionnaire. A similar matrix will be used in order to classify the NHANES data to the CIRS-G.

Statistics:

1) Aim 1: The CIRS-G specific disease severity scores will be calculated for each organ system using the data from the baseline CCSS questionnaire or baseline proxy questionnaire for those who were alive but had a proxy fill it out. There will be a severity score for each of the different organ systems as well a total severity score, severity index (total score/total number of categories endorsed), and a maximum score for each of the organ systems. Quantitative summaries of the differences between the CIRS-G and CTCAE will be evaluated as well as Spearman correlations for each organ system.
2) Aim 2: In order to evaluate the association between mortality and the overall CIRS severity index (baseline), maximum CIRS-G, and maximum CTCAE scores for each organ system, will use Cox Proportional Hazards models with all-cause mortality status as the outcome, censoring data at 2007, the time of the last NDI ascertainment of mortality for the cohort.. Subjects will enter the analysis at the age at which they answered the baseline survey and age will be used as the time scale for analysis. All models will be adjusted for the independent variables described above. We will also secondarily calculate area under the (AUC) receiver operating curves (ROC) to explore which organ system variables have the best predictive power[15]. We will evaluate the comparative prediction capabilities of different organs systems and determine which ones singly and in combination provide the best discriminatory and predictive power for mortality by using a forward and backward selection process for building the model on which AUC will be calculated. Internal cross-validation will be used, resampling from the cohort in order to reduce the likelihood of overfitting the model[16].
3) Aim 3: In order to describe the association between the risk of a non-obstetric hospitalization by the time of the 2007 follow-up and overall CIRS severity index (baseline), maximum CIRS-G, and maximum CTCAE scores for each organ system, we will limit the cohort to those subjects who also responded to the FU2007 survey. We will use logistic regression (or similar log binomial models) to assess associations of each scoring system with the occurrence of a non-obstetric hospitalization by the time of the 2007 follow-up questionnaire. Models will be adjusted for independent variables of interest previously listed. As a secondary analysis, similar to Aim 2, we will also calculate AUCs for ROC curves to determine which organ system variables have the best predictive power and will again determine the optimal prediction model using the organs systems that best independently predict future hospitalization (again similar to methods used for Aim 2).
4) Aim 4: Using the CIRS-G data generated from the CCSS as specified in Aim 1, specific disease severity scores will be calculated for each organ system using the data from the baseline CCSS questionnaire or baseline proxy questionnaire for those who were alive but had a proxy fill it out. There will be a severity score for each of the different organ systems as well a total severity score, severity index (total score/total number of categories endorsed), and a maximum score for each of the organ systems. These will also be obtained from both an age, sex, and race matched and elderly patient group (age >60) that is also matched for sex and race from the 1999-2004 NHANES data. This data is publically available and provides self-reported data very similar to the CCSS and has sufficient information in order apply it to the CIRS-G. Quantitative comparisons of the differences between the CIRS-G and each of the NHANES cohorts will be carried out and statistically compared using the Wilcoxon rank-sum test for continuous variables and Chi-square test for nominal variables.

4. Preliminary Data

In conferring with Dr. Oeffinger and the other collaborators for the project, it was suggested that one disease group be created using the CIRS-G method as a proof of principle to compare to the CTACAE to assess differences and to examine if there is evidence that the CIRS-G may be superior in predicting mortality. This was done for the heart organ system (Appendix 3 and 4). In order to make the CTCAE directly comparable to the CIRS-G, hypertension, cholesterol abnormalities, and stroke were removed from the CTCAE heart classification as the CIRS-G captures these problems under different organ systems. For the CIRS-G, the following heart categories were used: atherosclerotic heart disease, congestive heart disease, arrhythmias, valvular heart disease, and pericardial disease. Using the baseline CCSS questionnaire, the CIRS-G identified 1290 primary cases of heart disease, compared with 1097 identified by the CTCAE classification. From the baseline CCSS questionnaire to the 2007 follow-up questionnaire there were 862 deaths. Cox proportional hazards were done to examine the hazard ratios for death related to each the following three variables: the maximum heart grade as determine by the CIRS-G (model 1), maximum CTCAE grade (model 2), and a CIRS-G severity score (adding up of all the heart problems grades together to get an overall severity score) (model 3), all adjusted for sex and age at baseline.

Analysis of Maximum Likeihood Estimates (Model 1,2,3) all adjusted for sex and age at baseline

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Maximum CIRS-G grade (Model 1)	1	0.36395	0.03648	99.5433	<.0001	1.439
Maximum CTCAE grade (Model 2)	1	0.32286	0.03665	77.5812	<.0001	1.381
CIRS-G severity score (Model 3)	1	0.20311	0.0174	138.8547	<.0001	1.225

In model 1, the maximum CIRS-G score had an adjusted hazard ratio of 1.439, while in model 2 the maximum CTCAE score only had a hazard ratio of 1.381. Finally in model 3, the hazard ratio for the overall CIRS-G severity score was 1.225. Thus, in all three cases more severe heart conditions were significantly associated with increased risk of death. In addition, a higher maximum CIRS-G score confers a greater risk of death than a higher maximum CTCAE score.

References

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Table 1: Diagnosis and treatment-related characteristics of the cancer survivor population

	Number	**%**
Sex		
Male		
Female		
Race/Ethnicity		
Black		
Hispanic		
White		
Other		
Diagnosis		
Leukemia		
Non-CNS Solid Tumor		
CNS Tumor		
Radiation[1]		
None		
Cranial		
Chest		
Abdomen/Pelvis		
Other		
Chemotherapy exposure history		
Yes		
No		
Oncologic Surgery		
Yes (Neurosurgery)		
Yes (Other Oncologic)		
No		
BMT[1]		
Allogenic		
Autologus		
	Median	**25th,75 Quartile**
Age at diagnosis (years)		
Age at time of baseline questionnaire		
Time off cancer therapy at baseline questionnaire (years)		

[1]Categories are not mutually exclusive

Table 2: CIRS-G[1] and CTCAE[2] scores at time of CCSS[3] baseline questionnaire for the cohort and correlation between them

Variable CIRS/CTCAE terminology	CIRS-G[1]	CTCAE[2]	Correlation[4]
Total score[5]		N/A	
Total number of categories endorsed[3]			
Severity index[5]		N/A	
Number of categories with a level 3 or 4 severity[5]			
Sum of maximum grades for each organ system			
Heart/Cardiac Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Vascular/Vascular Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Hematopoietic/Blood and Lymphatic System Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Respiratory/ Respiratory, Thoracic and Mediastinal Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Eyes, Ears, Nose, and Throat and Larynx/Ear and Labyrinth Disorders and Eye Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Upper GI and Lower GI/ Gastrointestinal disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Lower GI/ Gastrointestinal disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Liver/ Hepatobiliary Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Renal/Renal and Urinary Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Genitourinary/Renal and Urinary Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			
≥1 Grade 3 or 4 problem[6]			
Musculoskeletal and Integument/ Musculoskeletal and Connective Tissue Disorders and Skin and Subcutaneous Tissue Disorders			
Maximum grade for organ system			
≥1 Grade 1 or 2 problem[6]			

≥1 Grade 3 or 4 problem[6]	
Neurological/ Nervous System Disorders	
Maximum grade for organ system	
≥1 Grade 1 or 2 problem[6]	
≥1 Grade 3 or 4 problem[6]	
Endocrine, Metabolic and Breast/Endocrine Disorders and Reproductive System and Breast Disorders and Metabolism and Nutrition Disorders	
Maximum grade for organ system	
≥1 Grade 1 or 2 problem[6]	
≥1 Grade 3 or 4 problem[6]	
Psychiatric Illness/ Psychiatric Disorders	
Maximum grade for organ system	
≥1 Grade 1 or 2 problem[6]	
≥1 Grade 3 or 4 problem[6]	

[1]Cumulative Illness rating scale for Geriatrics [2]Common Terminology Criteria for Adverse Events [3]Childhood Cancer Survivor Study [4]Spearman Correlation [5]Median, 25th,75th Quartile [6]N (%)

Table 3 Cox Regression Model for Mortality in Cancer Survivors by 2007

Variable[1]	Hazard Ratio	95% Confidence Interval	P value
CIRS Severity Score			
Age (years)			
Sex (Male)			
Race (Black) vs. White			
Race (Hispanic) vs. White			
Race (Other) vs. White			

[1]All variables assessed at time of Chilhood Cancer Survivor Study baseline questionnaire

Table 4 Logistic Regression Model for Non-obstetric Hospitalization in Cancer Survivors within one year of 2007

Variable[1]	Odds Ratio	95% Confidence Interval	P value
CIRS Severity Score			
Age (years)			
Sex (Male)			
Race (Black) vs. White			
Race (Hispanic) vs. White			
Race (Other) vs. White			

[1]All variables assessed at time of Childhood Cancer Survivor Study baseline questionnaire

Table 5: CIRS-G[1] scores at time of CCSS[2] baseline questionnaire for the cohort and comparison with age-matched and elderly NHANES[3] cohort

Variable **CIRS-G terminology**	CCSS CIRS-G[1]	NHANES age-matched population	p-value[4]	NHANES elderly population	p-value[5]
Total score[6]					
Total number of categories endorsed[6]					
Severity Index[6]					
Number of categories with a level 3 or 4 severity[6]					
Sum of maximum grades for each organ system (Note will likely also include some specific organ systems that show significant differences using format shown in Table 2)					

[1]Cumulative Illness rating scale for Geriatrics [2]Childhood Cancer Survivor Study [3]National Health and Nutrition Examination Survey [4]Comparison between CCSS and age matched NHANES cohort [5]Comparison between CCSS and elderly NHANES cohort [6]Median, 25th,75th Quartile [4]N (%)

Figures:

AUC curves illustrating predictive capabilities of scoring systems and specific organ scores or combinations of organ scores.