I. Study Title: Personalized Risk Prediction to Reduce Cardiovascular Disease in Childhood Cancer Survivors

II. Working Group and Investigators:
This proposed analysis will be within the CCSS Biostatistics/Epidemiology and Chronic Disease Working Groups and the SJLIFE Cardiopulmonary-renal working group. Proposed investigators are:

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III. Background and Rationale:

With overall five-year survival rates exceeding 80%, most children newly diagnosed with a malignancy are expected to become long-term survivors.[1] However, data from our cohorts of adult survivors of childhood cancer (the Childhood Cancer Survivor Study [CCSS][2] and St. Jude Lifetime Cohort Study [SJLIFE][3]), as well as others, report a substantial burden from severe or life-threatening adverse late health conditions contributing to considerable morbidity and premature mortality. Cardiovascular disease (CVD) is recognized as one of the most prominent sequelae and leading causes of death for these survivors.[2,4] We have described a spectrum of CVD among childhood cancer survivors, including cardiomyopathy, coronary artery disease (CAD), heart valve disease, and arrhythmias. Our prior studies demonstrated that CVD risks are largely related to anthracycline chemotherapy and/or chest-directed radiation therapy (RT), and have also defined important heart dose-volume relationships between CVD risk and RT.[5-8]

Previous investigations of RT-related CVD have typically described associations based solely on whole heart dose metrics,[5,7,9,10] overlooking the heterogeneity of the heart and its substructures. Quantitatively, mean whole

heart dose does not adequately describe heterogeneous dose distributions, e.g. the same mean heart dose can be from a uniform dose across the entire heart, a low dose to a large fraction of the heart volume, or a high dose to a small fraction of the heart volume. Additionally, the correlation between mean heart dose and mean cardiac substructure dose weakens with more conformal contemporary RT techniques, which commonly deliver more heterogeneous dose distributions compared to historic RT. [11] Data from survivors of adult cancers demonstrate associations between CVD and RT dose to specific heart substructures and disease outcomes. An analysis of adult lung cancer patients found coronary artery doses were significantly associated with major adverse cardiovascular events and all-cause mortality.[12] Also, two case-control studies of (primarily) adult Hodgkin lymphoma survivors reported significant associations between valvular doses and heart valve disease,[13] and left ventricle dose and heart failure[14]. Recently, we presented novel data from the CCSS cohort, showing that low dose RT (5 – 9.9 Gy) to the coronary arteries and heart valves is associated with increased risk of CAD and heart valve disease, respectively.[15] Our preliminary results were presented at the 2021 annual meetings of the American Society of Clinical Oncology, American Society for Radiation Oncology, American Association of Physicists in Medicine, and the European Society for Radiotherapy and Oncology. Additionally, we recently completed an analysis evaluating associations between radiation and 35-year cumulative incidence and adjusted incidence rate ratios of grades 3-5 CAD and heart valve disease (per the NCI's Common Terminology Criteria for Adverse Events [CTCAE]) among 25,481 five-year cancer survivors participating in the CCSS (manuscript in preparation). Dose-response relationships between coronary artery doses and CAD and between heart valve doses and valve disease were analyzed with piecewise exponential models adjusted for demographic, and treatment-related characteristics including cumulative anthracycline dose. Cumulative incidence curves for CAD associated with mean heart, left anterior descending, and right coronary artery doses are shown in **Fig. 1**. Adjusted incidence rate ratios associated with mean whole heart and respective substructure doses are reported for CAD and valve disease in **Table 1**.

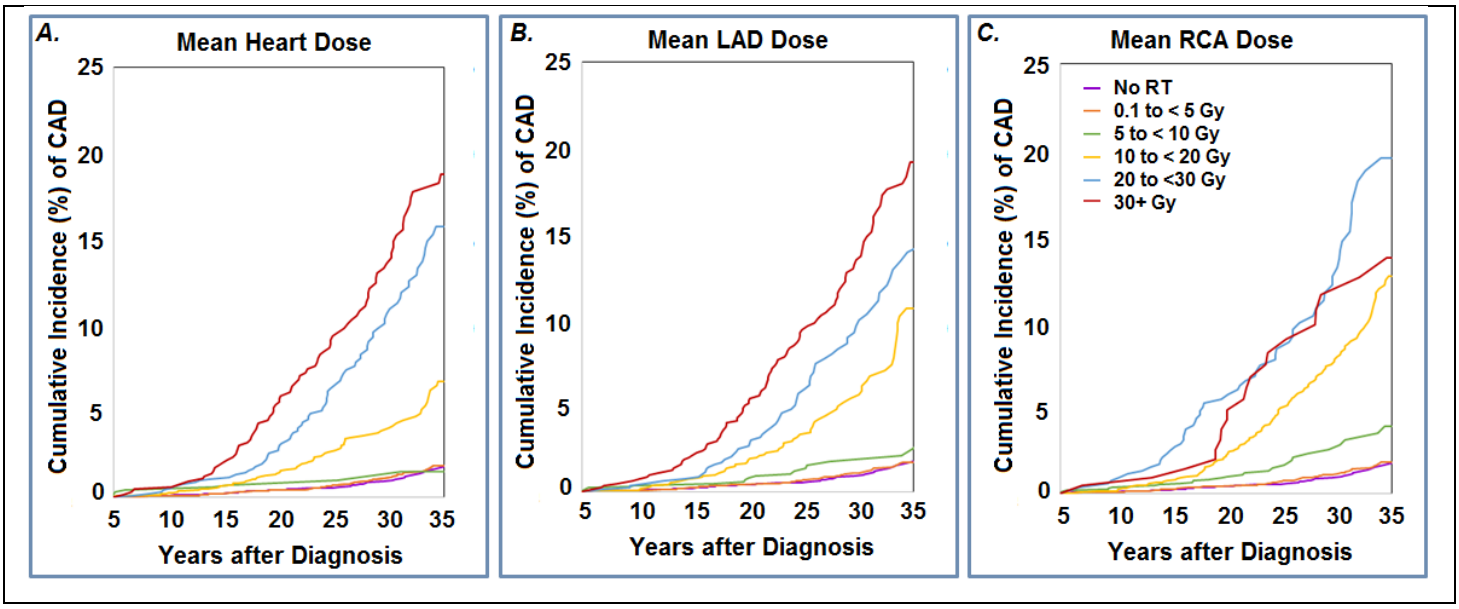

Figure 1. Cumulative incidence of coronary artery disease (CAD) among childhood cancer survivors in the CCSS by mean dose to: **A**. whole heart; **B.** left anterior descending (LAD); and **C.** right coronary artery (RCA). Yellow and green lines (10 to <20 Gy, 5 to<10 Gy) show steeper dose-response curves for LAD and RCA doses than for whole heart dose, suggesting their better risk prediction in the lower dose ranges.

Table 1. Adjusted incidence rate ratios for coronary artery and heart valve diseases by cardiac substructure dose

Coronary Artery Disease				Heart Valve Disease			
Cardiac structure Mean dose (Gy)	**Incidence Rate Ratio**	**95% CI**	**P**	**Cardiac structure Mean dose (Gy)**	**Incidence Rate Ratio**	**95% CI**	**P**
Heart (whole)				**Heart (whole)**			
None	Ref			None			
			0.59	0.1-<5			
			0.44	5-<10			
10-19	**3.7**	**2.6 - 5.2**	**<.001**	**10-19**	**5.0**	**2.5 - 9.8**	**<.001**
20-29	**6.8**	**4.8 - 9.6**	**<.001**	**20-29**	**10.0**	**5.4 - 18.7**	**<.001**
30+	**8.2**	**5.7 - 11.9**	**<.001**	**30+**	**16.1**	**8.8 - 29.6**	**<.001**
Left main				**Aortic valve**			
None	Ref				Ref		
0.1-<5	1.1	0.7 - 1.6			0.5	0.2 - 1.2	0.15
5-<10	1.4	0.4 - 4.4			4.6	1.5 - 14.0	0.008
10-19	**2.5**	**1.6 - 3.9**			**5.8**	**3.0 - 11.2**	**<.001**
20-29	**3.5**	**2.4 - 5.3**			**5.5**	**2.6 - 11.6**	**<.001**
30+	**8.7**	**6.2 - 12.1**			**12.6**	**7.1 - 22.2**	**<.001**
Left anterior				**Mitral valve**			
None	Ref			None			
			0.72	0.1-<5			
5-<10	**1.9**	**1.1 - 3.3**	**0.019**	5-<10			
10-19	**4.7**	**3.3 - 6.7**	**<.001**	**10-19**	**5.0**	**2.5 - 10.0**	**<.001**
20-29	**5.9**	**4.0 - 8.5**	**<.001**	**20-29**	**7.0**	**3.5 - 14.1**	**<.001**
30+	**8.3**	**5.8 - 11.9**	**<.001**	**30+**	**12.2**	**6.9 - 21.5**	**<.001**
				Pulmonary valve			
Left circumflex				None	Ref		
None	Ref			0.1-<5	0.5	0.2 - 1.2	0.15
0.1-<5	1.1	0.7 - 1.5	0.74	5-<10	1.6	0.2 - 13.0	0.64
5-<10	2.0	0.9 - 4.2	0.072	**10-19**	**4.5**	**2.2 - 9.2**	**<.001**
10-19	**4.0**	**2.8 - 5.7**	**<.001**	**20-29**	**6.3**	**2.9 - 13.4**	**<.001**
20-29	**4.0**	**2.6 - 6.0**	**<.001**	**30+**	**14.4**	**8.1 - 25.5**	**<.001**
30+	**7.6**	**5.4 - 10.7**	**<.001**				
Right coronary				**Tricuspid valve**			
None	Ref			None			
			0.48	0.1-<5			
5-<10	**2.6**	**1.6 - 4.1**	**<.001**	**5-<10**	**5.5**	**2.0 - 15.1**	**0.001**
10-19	**5.3**	**3.9 - 7.2**	**<.001**	**10-19**	**4.9**	**2.5 - 9.4**	**<.001**
20-29	**8.5**	**5.9 - 12.2**	**<.001**	**20-29**	**5.7**	**2.6 - 12.8**	**<.001**
30+	**5.1**	**2.9 - 8.9**	**<.001**	**30+**	**12.5**	**7.1 - 22.0**	**<.001**

Our data demonstrate distinct cardiac substructure radio-sensitivities, i.e., some substructures more sensitive to lower doses than other substructures and the whole heart. These fine-tuned analyses are relevant because modern RT techniques can deliver highly conformal dose distributions optimized to minimize dose to specific cardiac substructures. However, routine use of cardiac substructure dose constraints will not become common practice without validated risk prediction models.[16] Such models would facilitate prospective optimization during RT planning to decrease RT dose to cardiac substructures. Additionally, these models could be used to predict CVD risk in current and future childhood cancer survivors.

This proposal will uniquely develop and validate novel personalized CVD risk prediction models that incorporate cardiac substructure doses for pediatric and adolescent cancer patients. The models will be designed for both

prospective and retrospective use. Prospectively, late CVD could be decreased in future survivors by optimizing delivery of chest-directed RT selecting the plan that confers the lowest risk while maintaining optimal clinical target volume coverage. Retrospectively, following treatment, the clinical team could provide evidence-based personalized risk mitigation counseling, based on individualized risks determined from cardiac substructure doses adjusted for chemotherapy exposures and demographics. Furthermore, our prediction models could be used to identify patients at the highest risk for treatment related CVD, knowledge that could be documented in their survivorship care plans and guide risk counseling and a foundation upon which to establish future surveillance guidelines. Our models could also be used to identify patients at low risk for treatment-related CVD; a population for whom "over-surveillance" may increase lifetime costs with limited gains in quality-adjusted life years. The International Late Effects of Childhood Cancer Guideline Harmonization Group recently recommended considering less screening for these survivors.[17]

IV. Specific Aims

SA 1: Develop (in SJLIFE) and independently validate (in CCSS) risk prediction models for cardiomyopathy, CAD, and heart valve disease incorporating cardiac RT substructure doses, adjusting for demographics, comorbidities, and chemotherapy exposures.

Central Hypothesis: Ventricular, coronary artery, and valvular RT doses will be more predictive than whole heart dose for cardiomyopathy, CAD, and heart valve disease, respectively.

1.1 Develop and validate CVD prediction models based on initial cancer treatment exposures (heart RT dose-volume metrics and RT doses to respective cardiac substructures).

1.2 Develop and validate models to predict CVD risk 20 years post-exposure, accounting for age-acquired risk factors, i.e., diabetes, hypertension, obesity, and smoking.

Prediction models for each outcome (SA 1.1 and 1.2) will include chemotherapy exposures, RT doses, and demographic variables, and will be developed for use at two time points (time-of-treatment and 20 years post-treatment) to predict the individual risk of each CVD at age 30, 40, 50, and 60 years. Models will be developed using the SJLIFE cohort as the training dataset and validated with the CCSS cohort (excluding the SJLIFE participants who are also in CCSS). This design will allow us to maximally leverage the strengths of the only two cohorts of long-term survivors of childhood and adolescent cancer for whom CVD outcomes are available and whose RT data were sufficiently detailed to reconstruct dose and dose-volume metrics for the heart and its substructures. Specifically, clinically assessed CVD outcomes in SJLIFE provide the accuracy needed for model training. The large size of the CCSS cohort with similarly collected and graded CVD outcomes with identically detailed RT dosimetry provides an effective validation sample. While self-reported CVD in CCSS is subject to misclassification, it would lead to underestimation (a conservative estimate) of the predictive performance of the models and, thus, it is sensible to use CCSS for validation.

To maximize the application of our study results, models will be developed for two time points, at time-of-treatment and at 20 years post-treatment. Time-of-treatment models will allow us to evaluate the risks related to RT exposure without requiring the knowledge of known risk factors that survivors might develop during survivorship (diabetes, hypertension, obesity, smoking, etc.). Post-treatment models will include not only RT exposure but also these known risk factors for use at 20 years post treatment. We *a priori* selected 20-years post treatment (and will only include survivors who lived at least 20 years post treatment to train the post-treatment models) to allow sufficient time to capture important, often modifiable, risk factors that develop among long-term cancer survivors as they age.

This proposal builds on the work of Chow et al., which reported risk prediction models for ischemic heart disease[18] and heart failure[19]. In those studies, separate models were developed for each outcome with increasing levels of RT data, i.e., with radiation defined as (1) a categorical variable (yes/no), (2) maximum target dose to the chest, and (3) mean whole heart dose. Our models would be characterized as one using more precise radiation data than (3). Specifically, we will develop enhanced whole heart models that include mean whole heart dose and dose-volume metrics (V_5 and V_{20}). We will also develop models that include mean doses to individual

cardiac substructures. In addition to CAD and cardiomyopathy, we will develop prediction models for heart valve disease, an outcome for which there are currently no prediction models reported in the literature.

Prediction Model Development: Prediction models will be developed using SJLIFE data. We will use piecewise-exponential models (a member of generalized linear models that approximate semi-parametric Cox's proportional hazards models), adjusted for attained age during follow-up to examine the relationships between each of the three CVD outcomes and the following potential predictors: sex, age at diagnosis (5-year increments), and doses of anthracycline, alkylating agents, platinum agents (using equivalent dosing for each chemotherapeutic category).[20-22] Effect modifications of the RT related variables by sex and by age at diagnosis will also be examined. Group-regularization by Group Lasso's[23] adaptation, 'Group Elastic Net'[24], will be used to build the base prediction model due to the use of categorical variables and interactions. The core modeling work will be the evaluation of multiple (potentially collinear) whole heart RT dose and dose-volume metrics (V_5 and V20) as additional predictors to the base whole heart mean dose model, modelled by restricted cubic splines. We will initially examine each heart dose and dose-volume metrics for each of the three CVD outcomes, examining the hypothesized associations. The final prediction model for each outcome will be built using Group-regularized Elastic Net[24,25] with cross-validation for selecting tuning parameter values; the set of candidate variables include the base-model variables and heart dose and dose-volume metrics. Since we are primarily interested in prediction, the focus will be on the prediction performance. The same model development procedure will be used for the time-of-treatment models and the post-treatment models, but their start of the at-risk periods will differ: (a) for the time-of-treatment model, the at-risk period will begin at the time of cohort entry (5 years from primary cancer diagnosis for both SJLIFE and CCSS) and (b) for the post-treatment models, the at-risk period will begin at 20 years from primary cancer diagnosis. Additionally, unlike the time-of-treatment models, the post-treatment models will include lifestyle risk factors.[7] Both types of models will go through the identical procedures and evaluations as described below.

Risk Score Creation: Regression coefficients of the final Elastic Net models will be converted to integer risk scores for ease of use for some applications based on previously published methods.[19] This enables the simple sum of the integer risk scores to indicate the overall risk.

Prediction Performance Evaluation: As described in previous work,[18,19,26] we will estimate the area under the curve (AUC) at age K years and the concordance C-statistic through age K years using the time-dependent AUC methods,[27] where K=30, 40, 50, and 60 (the post-treatment models will not use K=30).

Risk Group Creation: We will collapse the risk scores into four risk classification groups, predictive of low, moderate, high risk, and very high risk for each of the CVD outcomes. These classifications will be useful for developing personalized CVD specific risk profiles for individual patients. To determine the most appropriate groupings, individuals' predicted risk scores will be examined based on their absolute risks (cumulative incidence at age 50 years, treating death from other causes as a competing risk).

External validation: External model validation will be carried out using CCSS data. Following the same approach used to estimate time-dependent AUCs and C-statistics for the SJLIFE cohort, we will estimate the time-dependent AUCs and C-statistics for the CCSS cohort using the same models (including coefficients) from the SJLIFE training analyses. Note that CCSS survivors who are also in SJLIFE will be excluded in the validation analysis so that training and validation are fully independent.

SA 2: Integrate CVD risk prediction models into a commercial RT treatment planning system and establish their use for contemporary patients.

Central Hypothesis: CVD risk prediction models that incorporate cardiac substructure RT doses can be successfully integrated into RT treatment planning and used to calculate the risk of CVD for contemporary patients.

We will implement a radiation oncology clinical translation platform that includes CVD risk calculators, which will be executed through easily accessible graphical user interfaces (GUI). These prediction models will be implemented through scripting features available within a commonly used commercial treatment planning system: RayStation (RaySearch Labs, Stockholm, Sweden). Once developed, our radiation oncology clinical

translation platform will be tested through an in-silico treatment planning study. Script development and the in-silico study will be conducted at MD Anderson.

Clinical Implementation of CVD Risk Calculators:

Radiation Oncology: For clinical use in the radiation oncology setting, the time-of treatment CVD risk calculators will be designed and implemented through a scripted GUI within a commercial treatment planning system. A user will first select the treatment plan for risk calculation and execute the script within the treatment planning system. Once executed, the code will populate the heart and substructure doses from the selected plan. The user will then manually enter a patient's age, sex, and chemotherapy exposures and doses; with the option to also set these parameters to unknown. The script will calculate the personalized predicted CVD risks from the patient's actual treatment exposures and demographic variables. The figure below is an illustrative example of a GUI for the CAD risk calculator. The publication related to this research will include the code used to create scripts in RayStation for both the risk calculators which will allow any center to implement our code within their treatment planning systems.

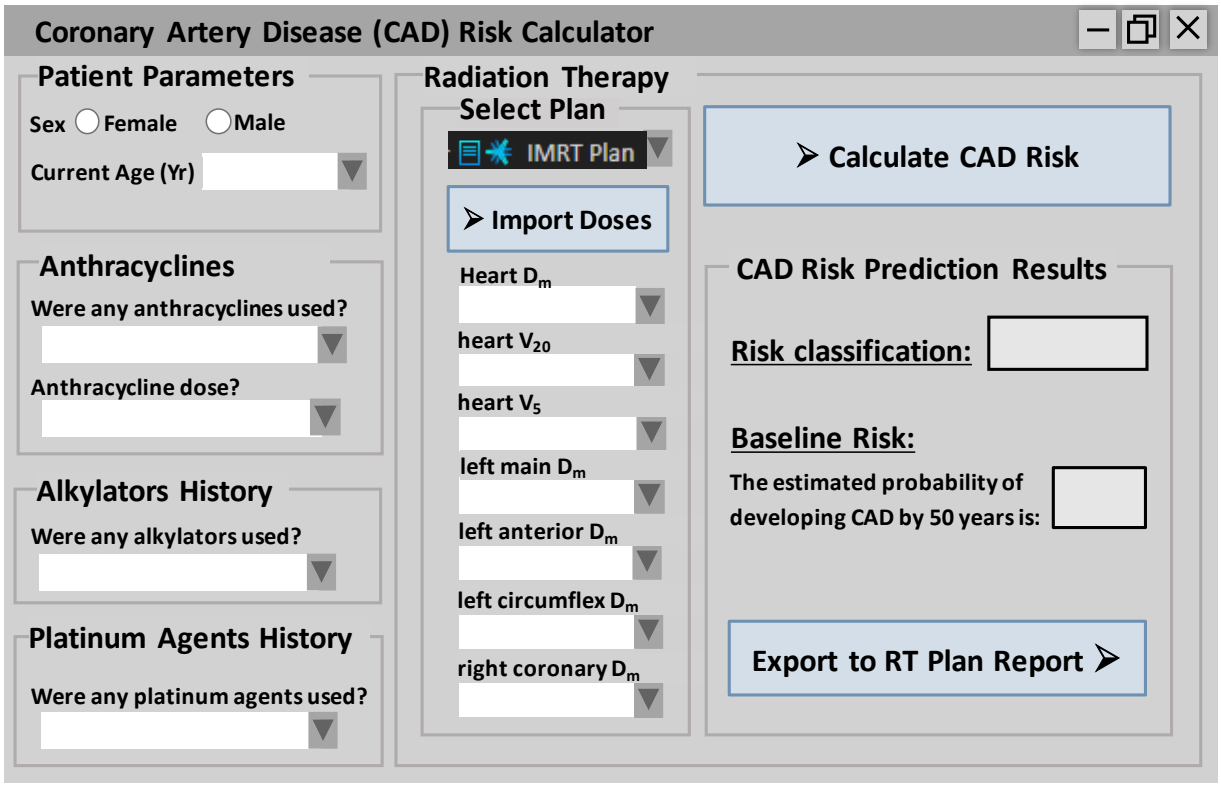

Figure 2. Example of a graphical user interface (GUI) for the coronary artery disease (CAD) risk calculator. The user would (1) execute the script within the treatment planning system to open the GUI window, (2) manually enter, age, sex, and chemotherapy exposures, (3) select the treatment plan of interest, (4) execute import RT doses function, and (5) calculate CAD risk. There will also be an option that allows users to export the calculated CAD risk results to the patient's RT plan report.

Survivorship: For clinical use in the survivorship setting, both time-of-treatment and 20-years post treatment CVD risk prediction models can be made available through risk calculators on CCSS website for use in the survivorship setting. There is a well-established precedence and infrastructure for sharing data and web-based risk prediction calculators through the CCSS website. Currently published risk calculators include models predicting risk of subsequent thyroid and breast cancers, acute ovarian failure, heart failure, and ischemic heart disease (based on whole heart and body region doses).

In-silico Study: This study will include 30 children and adolescents diagnosed with Hodgkin lymphoma based on International Classification of Diseases diagnosis codes and treated at MD Anderson with thoracic RT between January 01, 2018 and December 31, 2020; patients will be consecutively sampled to achieve an equal

sex distribution. We will use the CVD risk calculators to determine predicted risk of cardiomyopathy, CAD, and valve disease at time-of-treatment for the patients' treated plans. This aspect of the project will be carried out at MD Anderson using the RayStation treatment planning system. Patient data will be fully de-identified. This patient cohort is included in an MD Anderson IRB protocol (PI: Howell).

We selected 30 patients for this in-silico study based on power calculations using data from a treatment planning study, which demonstrated that contemporary RT can be optimized to specifically reduce dose to cardiac substructures. The proof-of-concept study and power calculations are described in Supplementary Materials (Section VII).

V. Analysis Framework

Population: *The cohorts for this study will be the* SJLIFE and CCSS (original and expanded). We reconstructed, the RT fields for irradiated CCSS and SJLIFE participants on our age-scaled phantom and calculated mean doses for the aorta, coronary arteries, atria, valves, ventricles, pericardium, and whole heart (Table 2) and dose-volume metrics (V_5, V_{10}, V_{15}, and V_{20}) for whole heart. In total we calculated heart doses for 14,526 individuals with nearly 280,000 unique dose and dose-volume metrics. We have successfully developed a comprehensive radiation dosimetry dataset, which enables the research proposed in the specific aims section; the cardiac dosimetry methods are described in the literature[28].

Table 2. Cardiac Structure Mean Doses for the CCSS and SJLIFE

	CCSS* (N=11,211)		SJLIFE (N=3,315)	
	Mean dose (Gy)		Mean dose (Gy)	
Cardiac structure	**Mean**	**SD**	**Mean**	**SD**
Aorta	10.27	13.52	9.58	12.70
Left main artery	10.47	16.64	9.75	12.83
Left anterior artery	7.34	10.44	7.18	10.42
Left circumflex artery	9.47	12.64	9.05	12.14
Right coronary artery	5.89	8.18	6.06	9.31
Left atrium	10.05	13.90	9.56	12.61
Right atrium	6.97	9.10	6.95	9.58
Aortic valve	9.64	12.84	9.26	12.41
Mitral valve	9.90	13.06	9.41	12.52
Pulmonary valve	9.86	13.18	9.42	12.69
Tricuspid valve	9.02	12.20	8.79	11.98
Left ventricle	6.05	7.69	5.96	7.91
Right ventricle	9.28	12.34	9.04	12.13
Pericardium	7.25	9.19	7.09	9.32
Heart (whole)	7.85	10.09	7.63	10.07

**Excluded SJLIFE participants who are also in CCSS*

Table 3. CTCAE Grade 3-5 CVD Outcomes in CCSS and SJLIFE for all Participants and ≥ 20-year Survivors

	All survivors		≥ 20-year survivors	
Cardiac outcome	**SJLIFE N=5,229**	**CCSS* N=22,270**	**SJLIFE N=2,686**	**CCSS* N=22,270**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Cardiomyopathy	244 (4.7)	567 (2.5)	121 (4.5)	504 (2.2)
CAD	198 (3.8)	504 (2.3)	159 (5.9)	447 (2.0)
Valve disease	61 (1.3)	177 (0.79)	46 (1.7)	171 (0.7)

**SJLIFE participants that are also in CCSS were excluded*

Outcome(s) of Interest: This study will include the following CVD outcome data from the SJLIFE and CCSS cohorts: cardiomyopathy, coronary artery disease, and heart valve disease. For both cohorts these outcomes were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Table 2). To ensure comparability across cohorts, only conditions graded 3 (severe/ disabling),

4 (life-threatening), or 5 (death), thus, requiring significant medical intervention, will be included in our prediction models.

To demonstrate feasibility, we conducted a proof-of-concept prediction modeling for heart valve disease, which is, by far, the least prevalent grade 3-5 cardiac outcome in both the SJLIFE and CCSS. We developed a preliminary 20-year post RT risk prediction model for heart valve disease in SJLIFE and independently validated the model in the CCSS. Specifically, we examined if adding heart valve doses to the prediction model increased the predictive power beyond what was observed with mean whole heart dose only. In SJLIFE, the area under the curve (AUC) values at age 45 improved from 87.6 (mean heart dose) to 89.2 with adding heart valve doses (p=0.003). Validation in the CCSS, similarly demonstrated model improvement from AUC from 78.4 to 79.6 (p=0.005).

Adjustment Variables: Adjustment variables used for this study are: gender, race, ethnicity, age at primary cancer diagnosis, attained age, year of initial diagnosis, primary cancer diagnosis, alkylating agent use (yes/no), doses of anthracycline, alkylating agents, platinum agents (using equivalent dosing[20-22] for each chemotherapeutic category), heart dose and dose volume metrics, cardiac substructure mean doses, smoking history (yes/no), diabetes (yes/no), hypertension (yes/no).

VI. Tables and Figure Examples

Table 4: Patient Characteristics

	Training Dataset [SJLIFE Cohort]	Validation Dataset [CCSS Cohort]
Characteristics	**Number (%)**	**Number (%)**
Age at Diagnosis		
0-4		
5-9		
10-14		
15-20		
Gender		
Male		
Female		
Primary Cancer Diagnosis		
Leukemia		
Hodgkin-Lymphoma		
Non-Hodgkin Lymphoma		
CNS Tumor		
Kidney Tumor		
Neuroblastoma		
Soft Tissue Sarcoma		
Bone Cancer		
Others		
Race		
White		
Black		
Other		
Ethnicity		
Hispanic		
Non-Hispanic		
Smoking Status		
Smoker		
Never Smoker		
Diabetes		
Yes		
No		
Hypertension		
Yes		
No		

Cumulative Anthracycline Dose†		
None		
1-249 mg/m2		
≥300 mg/m2		
Alkylating Agent Exposure		
Yes		
No		
Whole Heart Dose and Dose Volume Metrics		
Mean Heart Dose		
No RT		
0.1-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
≥30 Gy		
Volume of Heart ≥ 5 Gy when V_{20} = 0% ($V_{5V20=0\%}$)		
No RT		
0%		
0.1-49.9%		
≥ 50%		
Volume of Heart ≥ 20 Gy (V_{20})		
No RT		
0%		
0.1-29.9%		
30-79.9%		
≥ 80%		
Right Coronary Artery Mean Dose		
No RT		
0.1-4.9 Gy		
5-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
≥30 Gy		
Left Anterior Descending Artery Mean Dose		
No RT		
0.1-4.9 Gy		
5-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
≥30 Gy		
Left Ventricle Mean Dose		
No RT		
0.1-4.9 Gy		
5-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
≥30 Gy		
** Other substructure Doses		

†Anthracycline, alkylator, and platinum equivalent dosing will be used.

**In specific aim one we hypothesize RT-dose response relationships for coronary arteries (listed in the table) ventricles (left and right), and valves (Aortic, mitral, pulmonary and tricuspid valves[28]) and will include additional substructure dose categories if they are identified as influential predictors of CVD's under study.

Table 5: Cardiac Disease Risk Score and Corresponding Model Discrimination and Predictive Power
(Example: For Coronary Artery Disease Risk Prediction Model)

Characteristics	Dose-Volume Model	Substructure Dose Model
Age at Diagnosis		
0-4		
5-9		
10-14		
15-20		
Gender		
Male		
Female		
Cumulative Anthracycline Dose†		
None		
1-249 mg/m^2		
≥300 mg/m^2		
Alkylating Agent Exposure		
Yes		
No		
Whole heart		
Mean Heart Dose		
No RT		
0.1-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
0.1-29.9%		
≥30 Gy		
($V5_{V20=0\%}$)		
No RT		
0%		
0.1-49.9%		
≥ 50%		
V20		
No RT		
0%		
0.1-29.9%		
30-79.9%		
≥ 80%		
Right Coronary Artery Mean Dose	NA	
No RT		
0.1-4.9 Gy		
5-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
≥30 Gy		
Left Anterior Descending Artery Mean Dose	NA	
No RT		
0.1-4.9 Gy		
5-9.9 Gy		
10-19.9 Gy		
20-29.9 Gy		
≥30 Gy		
** Other substructure Doses	NA	
CCSS Cohort		
AUC		
C-Statistics		
SJLIFE Cohort		
AUC		
C-Statistics		

Note: The list of RT-related covariates for the Dose-Volume model includes whole-heart dose and dose-volume metrics. The list of RT-related covariates for the substructure-dose model includes whole-heart dose, dose-volume metrics, and individual substructure doses. Two variations of this table will be created based on two variations of substructure-based risk prediction models detailed in specific aim 1.
†Anthracycline, alkylator, and platinum equivalent dosing will be used.

Table 6: Risk Group Classification Based on Summed Risk Scores (adapted from Chow et al[19])

Risk Group	Risk Score	No. of Events	No. of at Risk	Cumulative Incidence at age 50 years	95% CI	RR vs. preceding group*	95% CI
Dose-Volume Model							
Low							
Moderate						-	-
High							
Substructure Model							
Low							
Moderate						-	-
High							
Very High							

Note: We will create separate variations of Table 6 for each CVD outcome. *Comparisons are versus the immediately preceding group (e.g., moderate- *vs* low-risk group, high- *vs* moderate-risk group etc.).

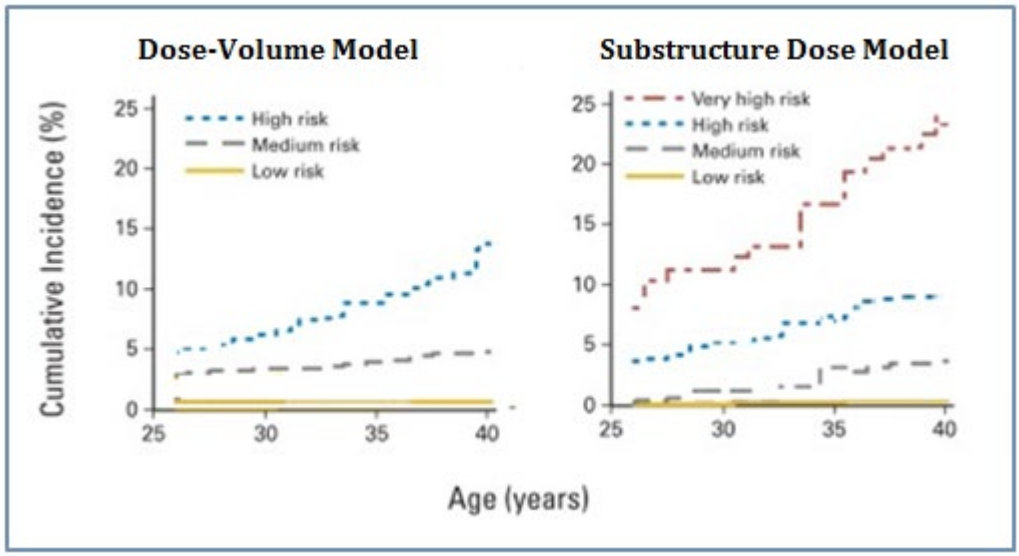

Figure 3. Cumulative incidence of cardiac disease (CVD) by risk group (Example shows synthetic data, adapted from Chow et. al.[19]).

VII. Other General Comments

The analysis proposed in this concept proposal is a subset of an R01 proposal submitted to the NCI (July 30, 2021) by Drs. Rebecca Howell, Daniel Mulrooney, and Yutaka Yasui (Co-PIs). Should that proposal be funded, we would carry-out the larger scope project described in the R01 as opposed to the smaller scope project described here.

Mr. Suman Shrestha is fourth year doctoral student in the MD Anderson UT Health graduate program in medical physics working under the supervision of Rebecca Howell. After graduation (anticipated December 2022), he will complete a post-doctoral fellowship in Dr. Howell's lab. Dr. Howell is funding his doctorate research and will also support his post-doctoral fellowship through her institutional support. Mr. Shrestha has published two first authored manuscripts[28,29] related to the cardiac dosimetry methods used to calculate the heart and substructures doses for the CCSS and SJLIFE cohorts.

VIII. Publication Plan:

We will consider drafting two manuscripts describing the CVD prediction models (based on study findings), the first with the time-of-treatment models and the second with the 20-year post treatment models targeted to different journals and readership (radiation oncology [first author: Shrestha] and survivorship communities [first author: Mulrooney], respectively). Similarly, the clinical translation script and results of the in-silico study would be published in a journal targeted to the radiation oncology community (first author: Shrestha). Based on contributions to the studies, Drs. Howell, Mulrooney, and Yasui will be senior authors on the proposed publications.

IX. Supplementary Data

Proof of Concept Treatment Planning Study:

To demonstrate that patients' RT plans can be optimized with cardiac substructure dose constraints, we carried-out a proof-of-concept study. We selected 13 young adult patients previously treated at MD Anderson for Hodgkin lymphoma or non-Hodgkin lymphoma with bulky mediastinal disease. These patients were treated with chest-directed intensity modulated radiation therapy (IMRT) with breath hold technique but their plans were not optimized to reduce cardiac substructure doses. Their IMRT treatment plans were optimized to ensure 98% CTV coverage with the prescribed dose of 30.6 Gy. Here, we considered VMAT, specifically optimized to reduce the dose to the coronary arteries. Where possible, we aimed to limit mean coronary artery doses < 5 Gy because our preliminary data showed no increased incidence of CAD associated with doses below 5 Gy. However, for some patients, the coronary arteries were in very close proximity to the CTV and a 5 Gy dose constraint would have compromised CTV coverage. In those cases, we aimed to reduce the doses as low as possible without compromising CTV coverage. These same patients were considered in a proton verses photon study that broadly examined proton therapy for reducing dose to various organs at risk.[30]

We examined heart and coronary artery doses for IMRT (baseline plan), VMAT (new plan), and proton therapy (recently published)[30] treatment plans. We observed that RT and specifically VMAT and proton therapy can be optimized to reduce coronary artery doses. Specifically, we considered dose reductions for individual patients in the context of "were the coronary artery optimized plans able to achieve dose reductions sufficiently large to result in categorical shifts to dose ranges associated with lower incidence of RT-related cardiac disease?" (Table 2), i.e., dose to one or more coronary arteries reduced from ≥ 5 Gy, ≥ 10 Gy, ≥ 20 Gy, and ≥30 Gy to < 5 Gy, < 10Gy, < 20 Gy, and < 30 Gy, respectively. Compared to the baseline IMRT, VMAT achieved lower doses for at least one coronary artery in 9 of 13 patients (Agresti-Coull 95% CI 42.0-87.6%)[31]; among those patients, there were five patients for whom VMAT achieved lowered doses for two arteries. Compared to the baseline IMRT, proton therapy achieved lower doses for at least one coronary artery in 11 of 13 patients (Agresti-Coull 95% CI 56.5-96.9%)[31]; there were five patients for whom proton therapy achieved lowered doses for two arteries. For both VMAT and proton therapy, there was one patient for whom lower doses were achieved for all three coronary arteries (note that left main and left anterior descending arteries were contoured together as a single organ at risk). Dose distributions for one representative patient are shown in Fig. 4. Broadly, these data suggest that RT may be optimized to reduce cardiac substructure doses, and for some patients, doses can be reduced below 5 Gy or to doses with lower risk CVD risk estimates.

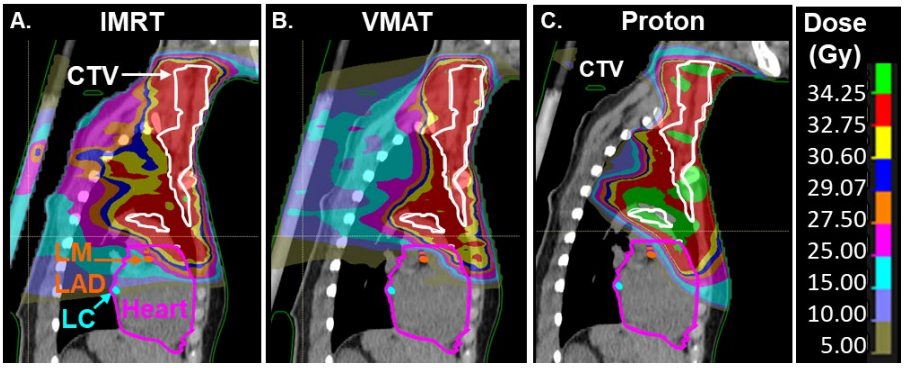

Figure. 4. Comparison multiple Hodgkin lymphoma treatment plans A. intensity modulated radiation therapy (IMRT), B. volumetric modulated arc therapy (VMAT), and C. proton therapy. Dose distributions are shown as color washes, isodose legend on the right. Doses to the whole heart (magenta), left main (LM)/left anterior descending (LAD), and left circumflex (LC, cyan) were lower for VMAT and proton plans compared to the baseline IMRT. Compared to IMRT, VMAT achieved LC dose to < 5 Gy while proton therapy achieved doses of < 5 Gy for the LC and LM/LAD arteries. Both VMAT and proton therapy reduced mean whole heart dose < 10 Gy.

Importantly, these data highlight that each patient's cardiac substructure RT dose profile is unique, and that personalized approaches are needed for both plan optimization and subsequent determination of CVD risk from the treated plan.

The risk prediction models that we develop in this study will identify cardiac substructures dose constraints that can be used for treatment plan optimization. Furthermore, our models will allow direct input of patients' actual substructure doses for CVD risk prediction to determine personalized risk profiles, and will classify patients as being at low, moderate, or high risk, for developing specific types treatment-related CVD. Patients' CVD risk classifications could be added to their survivorship care plans and would be valuable for risk counseling and future surveillance.

Power Analysis:

Let π be the (true) proportion of Hodgkin disease patients for whom the proposed dose optimization will achieve sufficiently large enough substructure dose reductions that result in categorical dose shifts associated with lower incidence of RT-related cardiac disease. Our preliminary study of 13 adult Hodgkin and non-Hodgkin lymphoma patients demonstrated that dose categories to one or more coronary arteries was reduced using VMAT or proton therapy in 9 and 11 patients, respectively, estimating π as approximately 70% and 85%, respectively. Based on our clinical experience, we expect these planning techniques can also be optimized to reduce ventricle and valve doses. We deem that achieving π=1/3 of the patient population with the dose and risk reduction would be of clinical significance. With 27 pediatric Hodgkin disease patients, we will have 80% power to reject the null hypothesis of π = 1/3 with Type I error probability of 5%, even if the true underlying π is as low as 60%: if π is 70%, this power is over 98%. Thus, we propose N=27.

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