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Project Requirements and Description

A comprehensive review of previously published data has been completed	Yes
The specific aims are clear and focused	Yes
The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator.	Yes
The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months	Yes

Project Title

Genetic Predisposition and Risk Prediction for Cardiovascular Disease Following Treatment for Hodgkin Lymphoma

Planned research population (eligibility criteria)

Inclusion Criteria:

Treated for Hodgkin Lymphoma when >15 years of age
Have germline genome-wide genotyping or whole-genome sequencing available
Have completed at least one survey to ascertain cardiovascular outcomes

Exclusion Criteria:
Unknown whether radiotherapy received
Unknown whether chemotherapy received

Proposed specific aims

The 10-year survival probability after Hodgkin Lymphoma (HL) diagnosis is >75%. There are over 500,000 survivors of HL in the United States and Europe, of whom >60% have already survived >10 years from diagnosis. The combination of treatments for HL are effective, but also increase the long-term risk of serious cardiovascular disease (CVD). We have shown that >5-year survivors treated in the Netherlands from 1965-

1995 had a 3.2-times greater risk of any coronary heart disease and a 6.8-times increased risk of heart failure relative to the general population. The increased risk is associated with radiation dose to the heart and anthracycline exposure, as well as pre-existing cardiovascular risk factors. Accordingly, HL treatment in recent decades has sought to reduce cardiotoxicity; nonetheless, HL survivors treated after 2000 still have a significantly increased risk of death from CVD compared to the general population.

The genetic factors modifying risk of treatment-associated CVD are incompletely understood. Several variants associated with anthracycline-associated cardiotoxicity have been described and could improve risk assessment. In contrast, there is insufficient evidence of genetic factors modifying radiation-associated CVD. In studies of breast cancer survivors, who also frequently receive radiation therapy and anthracyclines, genetic scores capturing predisposition to CVD modify the risk of heart disease. Therefore, based on promising data in other populations of survivors, there is an opportunity to characterize the genetic and clinical factors that predict risk of treatment-associated CVD for survivors of HL.

The purpose of this study is to understand genetic factors that modify the risk of treatment-associated CVD (namely, coronary heart disease and heart failure) and develop accurate risk prediction tools for HL survivors. The rationale is that HL survivors have a high risk of CVD, but differences in risk between patients are not well understood. We designed an international study based on existing cohorts of HL survivors across several decades to accurately stratify CVD risk to guide survivorship care. The expected outcomes of this work are (1) actionable insights into the genetic factors that influence CVD risk for HL survivors; and (2) a risk prediction model that will have clinical value for HL survivors. Our specific aims are as follows.

Specific Aim 1. Identify genetic features that modify the risk of CVD for survivors of HL

1.1. Determine whether general predisposition to CVD modifies risk of CVD for HL survivors. Using an external population-based general population sample, we will develop a score capturing genetic predisposition to CVD. We will then measure genome-wide germline genetic variants from peripheral blood or normal tissue samples from 3,100 >5-year HL survivors in the Dutch HL Late Effects Cohort. Applying this CVD predisposition score to this cohort, we will test whether risk of CVD after HL (heart failure, coronary heart disease, myocardial infarction) is modified by the general predisposition to CVD.

1.2. Identify variants that modify the treatment-specific risk of CVD. Using a unique study design we developed previously, we will capture the genetic variants associated specifically with treatment-associated CVD. Five-hundred five Dutch HL Late Effects Cohort participants who developed CVD will be age- and sex-matched to 1,515 cancer-free participants from the LIFELINES Study that developed CVD. This approach will enable us to isolate the genetic variants that specifically modify the radiation- and anthracycline-associated CVD pathways. We will combine these variants to capture treatment-associated genetic risk. Promising findings will be replicated in the CCSS/SJLIFE Study of childhood/adolescent HL survivors.

Specific Aim 2. Develop and validate a clinical tool for CVD risk prediction for HL survivors. Existing guidelines for CVD screening for HL survivors14,15 do not yet incorporate genetic variation for risk stratification. By integrating clinical data, treatment characteristics, and the genetic predisposition to CVD in general (1.1) and CVD related to treatment (1.2), we will determine whether genetic information meaningfully improves CVD risk prediction. In external populations of HL survivors in the United Kingdom and Canada, we will validate these models and determine the clinical utility of risk models for HL survivorship care.

Expected impact for survivors. Survival after HL continues to increase. However, the excess mortality for survivors relative to population controls remains high, largely due to cardiovascular late effects. To reduce this burden, personalized screening and early intervention is necessary. This personalized care will only be possible with accurate risk assessment, taking into account patient data, treatment information, and genetic factors. In the long-term, this risk stratification could even impact HL treatment decisions. This study will substantially advance CVD risk assessment and prediction for HL survivors, enabling personalized screening, and, ultimately, reduced mortality due to CVD.

Will the project require non-CCSS funding to complete? Yes

If yes, what would be the anticipated source(s) and timeline(s) for securing funding?

Dutch Cancer Society (KWF), anticipated funding date January 2026

Does this project require contact of CCSS study subjects for:

Additional self-reported information	No
Biological samples	No
Medical record data	No

If yes to any of the above, please briefly describe.

What CCSS Working Group(s) would likely be involved? (Select all that apply)

	Primary	Secondary
Second Malignancy		
Chronic Disease		✓
Psychology/Neuropsychology		
Genetics	✓	
Cancer Control		
Epidemiology/Biostatistics		✓

Outcomes or Correlative Factors

	Primary	Secondary	Correlative Factors
Late Mortality		✓	
Second Malignancy			✓

Health Behaviors

	Primary	Secondary	Correlative Factors
Tobacco			✓

	Primary	Secondary	Correlative Factors
Alcohol			✓
Physical Activity			✓
Medical Screening			✓
Other			

If other, please specify

Psychosocial

	Primary	Secondary	Correlative Factors
Insurance			✓
Marriage			✓
Education			✓
Employment			✓
Other			

If other, please specify

Medical Conditions

	Primary	Secondary	Correlative Factors
Hearing/Vision/Speech			
Hormonal Systems			
Heart and Vascular	✓		
Respiratory			
Digestive			
Surgical Procedures	✓		
Brain and Nervous System			
Other			

If other, please specify

Medications

Describe medications

medications for treatment or prevention of heart failure or coronary heart disease

Psychologic/Quality of Life

	Primary	Secondary	Correlative Factors
BSI-18			
SF-36			
CCSS-NCQ			
PTS			
PTG			
Other			

If other, please specify

Other

	Primary	Secondary	Correlative Factors
Pregnancy and Offspring			
Family History			
Chronic Conditions (CTCAE v3)		✓	
Health Status			✓

Demographic

	Primary	Secondary	Correlative Factors
Age			✓
Race			✓
Sex			✓
Other			

If other, please specify

Cancer Treatment

	Correlative Factors
Chemotherapy	✓
Radiation Therapy	✓
Surgery	

Anticipated Sources of Statistical Support

CCSS Statistical Center	No
Local Institutional Statistician	Yes

If local, please provide the name(s) and contact information of the statistician(s) to be involved.

Will this project utilize CCSS biologic samples? No

If yes, which of the following?

If other, please explain

Other General Comments

Agree I agree to share this information with St. Jude

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