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Project Requirements and Description

Requirements to submit AOI

Requirements to submit AOI (all answers must be "yes" to proceed)

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 Rare Structural Variants and their Associations with Risks of Late Effects and Mortality in Long-term Survivors of Childhood Cancer

Planned research population (eligibility criteria)

Five-year survivors of childhood cancer participating in the Childhood Cancer Survivor Study (CCSS) or the St. Jude Lifetime Cohort (SJLIFE) with whole exome sequencing data.

Proposed specific aims

Aim 1a: To characterize rare structural variants (large indels, copy number gains, losses, copy neutral loss of heterozygosity, etc.) among five-year survivors of childhood cancer.

Aim 1b: To compare prevalence of the structural variants in survivors with that from apparently healthy controls from the general population (e.g., gnomAD non-cancer controls, TOPMed and All of Us controls, SJLIFE community controls).
Aim 1c: To assess if the prevalence of specific structural variants (their global burden or carrier status) differs in survivors with corresponding late effects compared to survivors without these late effects.

- Because we are considering rare structural variants, we will also conduct similar analyses after collapsing specific chronic health conditions into broader disease groups, e.g., cancer, cardiovascular disease, and other miscellaneous diseases.
- These analyses will also be conducted in subgroups stratified by sex, cancer treatment exposures, and genetic ancestry.

Aim 2: To evaluate the association between carrying structural variants and risks of incident corresponding chronic health conditions (see Aim 1c), accounting for demographic and cancer treatment exposures.

Aim 3: To examine association between structural variants (carrier status or global burden) with lifespan and all-cause and cause-specific (cancer, cardiovascular disease, and other miscellaneous diseases) mortality risks.

We have an approved dbGaP study to use whole exome data of the CCSS Original cohort and have access to whole exome data from the CCSS Expansion cohort and SJLIFE.

Results from this analysis of structural variants among long-term childhood cancer survivors will identify those at risks and the underlying mechanisms of late effects.

Will the project require non-CCSS funding to complete?

No

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

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	✓	

	Primary	Secondary
Cancer Control		
Epidemiology/Biostatistics		✓

Outcomes or Correlative Factors

	Primary	Secondary	Correlative Factors
Late Mortality	✓		
Second Malignancy	✓		

Health Behaviors

	Primary	Secondary	Correlative Factors
Tobacco			✓
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

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			

	Primary	Secondary	Correlative Factors
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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