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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 Actionable Genetic Variants and their Associations with Late Effects Risks and Mortality among 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 St. Jude Lifetime Cohort (SJLIFE) with whole-exome sequencing data.

Proposed specific aims

Aim 1a: To characterize the prevalence and distribution of documented “actionable variants” in genes in the

most current American College of Medical Genetics and Genomics (ACMG) Secondary Findings list (v3.2) among 5-year survivors of childhood cancer.
- "Actionable variants" include those with a clinical significance interpretation of pathogenic/likely pathogenic (P/LP) in ClinVar with a high aggregate review status (at least 2 stars).

Aim 1b: To compare prevalence of the actionable 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) and individuals with non-cancer diseases (e.g., sickle cell disease).

Aim 1c: To assess if the prevalence of specific actionable variants differs in survivors with corresponding late effects compared to survivors without these late effects.
- Because actionable variants are rare, 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 relevant actionable 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 actionable variants (carrier status) with lifespan and all-cause and cause-specific (cancer, cardiovascular disease, and other miscellaneous diseases) mortality risks.

Results from this analysis of ACMG Secondary Findings among long-term childhood cancer survivors will inform decisions as to whether these findings should be reported to pediatric cancer patients in the future.

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)

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

Outcomes or Correlative Factors

Late Mortality	Primary
Second Malignancy	Primary

Health Behaviors

Tobacco	
Alcohol	
Physical Activity	
Medical Screening	
Other	

If other, please specify

Psychosocial

Insurance	
Marriage	
Education	
Employment	
Other	

If other, please specify

Medical Conditions

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

If other, please specify

Medications

Describe medications

Psychologic/Quality of Life

BSI-18	
SF-36	
CCSS-NCQ	
PTS	
PTG	
Other	

If other, please specify

Other

Pregnancy and Offspring	
Family History	
Chronic Conditions (CTCAE v3)	Primary
Health Status	

Demographic

Age	Correlative Factors
Race	Correlative Factors
Sex	Correlative Factors
Other	Correlative Factors

If other, please specify

Cancer Treatment

Chemotherapy	Correlative Factors
Radiation Therapy	Correlative Factors
Surgery	Correlative Factors

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? Yes

If yes, which of the following? Buccal cell DNA

If other, please explain

Other General Comments

Agree I agree to share this information with St. Jude

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