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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

Investigating genetic and epigenetic contributors to treatment-related endocrine dysfunction among five-year survivors of childhood cancer

Planned research population (eligibility criteria)

Five-year survivors of childhood cancer in the St. Jude Lifetime Cohort (SJLIFE) and Childhood Cancer Survivor Study (CCSS) with DNA methylation array and whole genome/exome sequencing or SNP array data.

Proposed specific aims

Aim 1: To perform epigenome-wide association studies (EWAS) to identify individual CpG sites and differentially methylated regions (DMRs) associated with treatment-related endocrine phenotypes.
Aim 1a: To perform association analyses for quantitative measurements relevant to or influenced by endocrine function, including glucose, thyroid stimulating hormone (TSH), total T3, total T4, weight, height, body mass index (BMI), height for age %, weight for age %, insulin, luteinizing hormone, Insulin-like growth factor 1 (IGF-1), total testosterone, estradiol, and cortisol.
Aim 1b: To perform association analyses for incident endocrine dysfunction phenotypes, including obesity, primary hypothyroidism, central hypothyroidism, abnormal glucose metabolism, central hypogonadism, primary ovarian insufficiency (POI), Leydig cell insufficiency, growth hormone insufficiency, adrenal insufficiency, dysfunctional uterine bleeding, cervical dysplasia, endometriosis, polycystic ovarian syndrome

(PCOS), erectile dysfunction, and precocious puberty.

Aim 2: To characterize the transcriptional correlates of EWAS-identified CpG sites and DMRs through integrative analysis of DNA methylation and matched gene expression in peripheral blood mononuclear cells (PBMCs), identifying methylation-associated transcriptional differences associated with treatment-related endocrine phenotypes in childhood cancer survivors.

Aim 3: To dissect the causal architecture linking treatment-related epigenetic dysregulation to endocrine dysfunction in childhood cancer survivors.
Aim 3a. To map methylation quantitative trait loci (mQTLs) at EWAS-identified regions and apply Mendelian randomization to test whether DNA methylation at these sites causally influences risk for treatment-related endocrine dysfunction.
Aim 3b. To identify CpG sites associated with cancer treatment exposures and test whether and to what degree DNA methylation mediates the effect of specific treatment exposures on endocrine dysfunction.

Aim 4: To train and validate molecularly informed risk scores to predict risk for the treatment-related endocrine phenotypes from Aim 1.
Aim 4a: To perform genome-wide association studies (GWAS) of endocrine phenotypes among childhood cancer survivors and train polygenic risk scores (PRS) using the resulting summary statistics. Performance of these survivor-specific PRS will be compared with scores trained in the general population.
Aim 4b: To train methylation risk scores (MRS) of endocrine phenotypes among survivors and evaluate their performance both with and without PRS included.

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		
	Primary	**Secondary**
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			
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

Endocrine conditions

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	No

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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