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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 Pathway-based Analysis of Genetic Interactions Underlying Risk for Subsequent Neoplasms in Childhood Cancer Survivors

Planned research population (eligibility criteria)

For discovery of novel genetic associations with risk of developing subsequent neoplasms (SNs) and subsequent malignant neoplasms (SMNs), we will use data from the Childhood Cancer Survivor Study (CCSS) including all 5-year survivors of childhood cancer diagnosed between 1970-1999 with genotype data. For replication, we will use data including all 5-year survivors participating in the St. Jude Lifetime Cohort

(SJLIFE) who also have genotype data, excluding participants enrolled in CCSS who were included in discovery analyses. Risk prediction model development and validation (Aim 2) will use the same data sets.

Proposed specific aims

Most phenotypes, including common human diseases, are complex in the sense that multiple genetic variants can interact to cause disease. However, commonly applied methods for developing polygenic risk scores (PRS) primarily rely on collections of individual genetic variants identified through traditional GWAS analysis. The hypothesis driving our proposed work is that genetic risk scores can be improved through the incorporation of genetic interaction information. We recently developed a method, called BridGE (Bridging Gene sets with Epistasis), that provides a new, computational approach for discovering genetic interactions from GWAS data by incorporating knowledge of biological pathways. BridGE has been applied successfully to identify interactions for six diseases to date but has not yet been incorporated into individual disease risk prediction models.

In the proposed work, we aim to apply our BridGE method to build more accurate genetic-based risk prediction models for specific subsequent neoplasms (SNs) and subsequent malignant neoplasms (SMNs) in childhood cancer survivors. We will leverage a state-of-the-art graph neural network deep learning approach that is specifically designed to capture interaction effects and enables joint learning of multiple outcomes simultaneously. Our specific aims are as follows:

Aim 1: Using our BridGE algorithm, identify novel pathway-based genetic interactions associated with risks for developing the most common SNs and SMNs in survivors (i.e., non-melanoma skin cancers, meningiomas, breast cancer, thyroid cancer), as well as overall risk for developing a SN or SMN.

Aim 2: Develop and validate BridGE-based deep learning risk prediction models for SN/SMN outcomes incorporating clinical features and pathway-based genetic interaction predictors.

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?

We are currently preparing a proposal targeting the Minnesota Lions Childhood Cancer Foundation Survivorship Research Award. If successful, this award will provide us with initial funds to pursue this project.

Longer term, with strong preliminary results, we will seek additional funding from the NIH.

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	Primary
Chronic Disease	
Psychology/Neuropsychology	

Genetics	Secondary
Cancer Control	
Epidemiology/Biostatistics	Secondary

Outcomes or Correlative Factors

Late Mortality	
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	
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	Correlative Factors
Chronic Conditions (CTCAE v3)	Correlative Factors
Health Status	Correlative Factors

Demographic

Age	Correlative Factors
Race	Correlative Factors
Sex	Correlative Factors
Other	

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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