

Section: Contact Information

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Section: Project Requirements and Description

Group: Requirements to submit AOI

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 : **Late Effects Prediction using Clinical Phenotypes and Whole Genome Sequencing**

Planned research population (eligibility criteria) :

CCSS participants with DNA samples

Proposed specific aims :

We would like to utilize CCSS for Specific Aim 2 for validating prediction models for meningiomas, BCC, and multiple subsequent neoplasms as the primary validation sample and for validating prediction models for the other late effects outcomes listed below as the secondary validation sample.

Specific Aim 1 (Primary): Utilizing genetic profiles of 3,010 individual survivors (St. Jude Lifetime Cohort Study) characterized by whole genome sequence data, along with quantitative therapeutic exposures and their interactions, build individual risk prediction models that have clinically-appropriate degrees of precision, for the following 11 late effects outcomes: meningioma; basal cell carcinoma; multiple subsequent neoplasms; cardiomyopathy; obstructive lung disease; restrictive lung disease; diabetes mellitus; oligo/azoospermia; primary hypogonadism; memory deficit; and executive function deficit.

Specific Aim 2 (Primary): Validate the risk prediction models developed in Aim 1

with an independent cohort of 1,500+ long-term childhood cancer survivors (CCSS) whose late effects outcomes and therapeutic exposures are characterized by the same methodologies as the discovery cohort in Aim 1; for subsequent neoplasms (SNs), a larger cohort study with higher SN counts that verifies self-reported SN occurrences by pathology reports will be used. DNA samples are available from both validation cohorts for targeted sequencing for validation.

Specific Aim 3 (Primary): Functionally validate the genetic elements included in the risk prediction models, either as a main effect or a modifier of a therapeutic exposure effect, developed by Specific Aim 1, through in vitro experiments appropriate for each predicted outcome's tissue type, including CRISPR-mediated genome editing experiments.

Secondary Aim: Upon completion of model building for the “primary” late effects outcomes under Specific Aim 1, extend the model building, validation, and functional/biological validation work to the following 9 late effects: stroke, arrhythmia, growth hormone deficiency, hypothyroidism, central hypogonadism, processing speed deficits, attention deficits, hearing loss, and bone mineral density deficits.

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? : **NIH funding starting in 2017 or 2018**

Group: 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. :

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

Second Malignancy : **Secondary**

Chronic Disease : **Secondary**

Psychology / Neuropsychology : **Secondary**

Genetics : **Primary**

Cancer Control :

Epidemiology / Biostatistics :

Section: Outcomes or Correlative Factors

Late mortality :

Second Malignancy : **Primary**

Group: Health Behaviors

Tobacco :

Alcohol :

Physical activity :

Medical screening :

Other :

If other, please specify :

Group: Psychosocial

Insurance :

Marriage :

Education :

Employment :

Other :

If other, please specify :

Group: Medical Conditions

Hearing/Vision/Speech : **Secondary**

Hormonal systems : **Primary**

Heart and vascular : **Primary**

Respiratory : **Primary**

Digestive :

Surgical procedures :

Brain and nervous system : **Primary**

Other :

If other, please specify :

Group: Medications

Describe medications :

Group: Psychologic/Quality of Life

BSI-18 :

SF-36 :

CCSS-NCQ :

PTS :

PTG :

Other : **Primary,Secondary**

If other, please specify : **memory deficit, executive function deficit, processing speed deficits, attention deficits**

Group: Other

Pregnancy and offspring :

Family history :

Chronic conditions (CTCAE v3) : **Primary**

Health status :

Group: Demographic

Age : **Correlative Factors**

Race : **Correlative Factors**

Sex : **Correlative Factors**

Other :

If other, please specify :

Group: Cancer treatment

Chemotherapy : **Correlative Factors**

Radiation therapy : **Correlative Factors**

Surgery : **Correlative Factors**

Section: Anticipated Sources of Statistical Support

CCSS Statistical Center :

Local institutional statistician : **Yes**

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

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Will this project utilize CCSS biologic samples? : **Yes**

If yes, which of the following? : **Buccal cell DNA**

If other, please explain :

Section: Other General Comments

Other General Comments :