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 Whole Genome**

Sequencing

Planned research population (eligibility criteria) :

As a collaborative project of CCSS and St. Jude Children's Research Hospital (SJCRH), we propose to build and validate prediction models of late effects listed below, using whole genome sequencing (WGS) data of the CCSS expansion cohort (approximately N=4,500) and St. Jude Lifetime Cohort Study (SJLIFE) (approximately N=3,000). This proposal entails WGS of the CCSS expansion cohort utilizing institutional funding of SJCRH, which will significantly enhance the WGS data availability and usage for childhood cancer survivorship research. This proposal is an extension of an NCI-funded study entitled "Late Effects Prediction Using Clinical Phenotypes and Whole Genome Sequencing" (1R01CA216354-01, PI: Yutaka Yasui and Jinghui Zhang) which utilizes WGS data of SJLIFE.

Proposed specific aims :

Specific Aim 1: Utilizing genetic profiles of approximately 5,000 individual survivors (CCSS expansion 3,000 + SJLIFE 2,000), characterized by WGS data, along with quantitative therapeutic exposures and their interactions, build individual risk prediction models that have clinically-appropriate degrees of precision, for the following late effects outcomes: basal cell carcinoma; multiple subsequent neoplasms; meningiomas; cardiomyopathy; obstructive lung disease; restrictive lung disease; diabetes mellitus; male and female infertility/primary hypogonadism; memory deficit; executive function deficit; stroke; arrhythmia; growth hormone deficiency; hypothyroidism; central hypogonadism; processing speed deficits; attention deficits; hearing loss; and bone mineral density deficits. The 3,000 CCSS expansion samples and 2,000 SJLIFE expansion samples will be selected by a stratified sampling, stratified by childhood cancer survivor characteristics including dx, dx age, treatment exposures, and sex. Special statistical considerations will be exercised to the handling of potential accuracy differences in the ascertainment of late effects between SJLIFE (clinical assessment) and CCSS (survey assessment): for example, if appropriate, we will apply the Mean Score Method or similar approaches for the analysis of a cohort where a subset of the cohort has a validated outcome ascertainment.

Specific Aim 2: Validate the risk prediction models developed in Specific Aim 1 with an independent set of 2,500 individual survivors (CCSS expansion 1,500 + SJLIFE 1,000) using the same models as Specific Aim 1.

Specific Aim 3: 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.

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? :
This proposal is an extension of an NCI-funded study entitled "Late Effects Prediction Using Clinical Phenotypes and Whole Genome Sequencing" (1R01CA216354-01, PI: Yutaka Yasui and Jinghui Zhang). SJCRH institutional funds will be used to WGS the CCSS-expanded-cohort samples.

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 : **Primary**

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 : **Primary**

Hormonal systems : **Primary**

Heart and vascular : **Primary**

Respiratory : **Primary**

Digestive : **Primary**

Surgical procedures :

Brain and nervous system :

Other :

If other, please specify :

Group: Medications

Describe medications :

Group: Psychologic/Quality of Life

BSI-18 : **Primary**

SF-36 :

CCSS-NCQ : **Primary**

PTS :

PTG :

Other :

If other, please specify :

Group: Other

Pregnancy and offspring : **Primary**

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. :
Yutaka Yasui, Yadav Sapkota, Wonjong Moon, Cindy Im

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 :