| | |
|---|---|
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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**

Multi-trait genetic analytic approach to understanding chemotherapy- and radiotherapy-associated late effects in childhood cancer survivors

### Planned research population (eligibility criteria)

Five-year survivors from Childhood Cancer Survivor Study (CCSS) and the St. Jude Lifetime Cohort (SJLIFE) with available genetic data.

## Proposed specific aims

Survivors of childhood cancer face a higher risk of late effects due to chemotherapy and radiotherapy. The mechanisms behind these late effects have been investigated through various genetic studies in survivors. Traditionally, these studies have focused on a single late effect of interest in all survivors, followed by examinations of how treatment exposures might modify these effects. However, it's possible that multiple late effects share common underlying mechanisms due to similar treatment exposures. Identifying genetic variants linked to these shared mechanisms requires analyzing multiple late effects simultaneously. The objective of this study is to utilize a novel approach to identify common genetic mechanisms underlying multiple late effects related to common chemotherapy/radiotherapy exposures among 5-year survivors of childhood cancer from both the Childhood Cancer Survivor Study (CCSS) and the St. Jude Lifetime Cohort (SJLIFE). Analyses will be conducted separately in the CCSS and SJLIFE cohorts, with results combined through a meta-analysis approach.

1) Among survivors exposed to chemotherapies (with and without radiotherapy exposures), we will conduct multi-trait genetic analyses to examine associations of both common and rare variants associated with multiple late effects. To do this, we will consider multiple composite phenotypes, based on various combination of late effects, including any late effect, organ-specific, or other combinations, depending on the sample size.

a. The primary analysis will focus on chemotherapies with similar mechanisms of action and associated late effects, examining them as a composite phenotype. We will also consider any chemotherapy and specific chemotherapy exposures (anthracyclines, alkylating agents, platinum, etc.), depending on the sample size.

b. Variants will also be assessed for potential effect modifications by cancer treatment exposures, genetic ancestry, and other relevant factors.

2) Among survivors exposed to radiotherapies (with and without chemotherapy exposures), we will conduct multi-trait genetic analyses to examine associations of both common and rare variants associated with multiple late effects. To do this, we will consider multiple composite phenotypes, based on various combination of late effects, including any late effect, organ-specific, or other combinations, depending on the sample size.

a. The primary analysis will focus on radiotherapies with similar mechanisms of action and associated late effects, examining them as a composite phenotype. We will also consider any radiotherapy and specific radiotherapy exposures, depending on the sample size.

b. Variants will also be assessed for potential effect modifications by cancer treatment exposures, genetic ancestry, and other relevant factors.

## 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** | Yes |
| **Biological samples** | Yes |
| **Medical record data** | Yes |

## 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 | | ✓ |
| 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

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# 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 | 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?

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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