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: Genetic risk prediction profiles for fracture among childhood cancer survivors
Planed research population (eligibility criteria):
The study population will include up to 5,156 long-term survivors of childhood cancer with genotype data and of European ancestry enrolled in the Original CCSS Cohort. European ancestry will be determined via principal components analysis, using the 1000 Genomes Phase III EUR cohort as a reference. Among the entire study sample with genotype and phenotype data (N=5,264), 46.3% (N=2,438) reported occurrence of at least one fracture. For this analysis, we will only include study participants with both genotype and phenotype data, and who also meet inclusion criteria typically applied in GWAS (i.e., meets missingness, heterozygosity, sex discordance, and relatedness thresholds).

Proposed specific aims:
Aim 1: Identify common and low-frequency genetic variants (minor allele frequency [MAF] ≤1%) associated with fracture risk among 5,156 long-term survivors of childhood cancer of European ancestry enrolled in CCSS (specified study cohort).

Aim 2: Identify common and low-frequency genetic variants (MAF ≤1%) and
complex genetic variants (e.g., SNP interactions) that modify treatment effects on fracture risk in the specified study cohort.

Aim 3: Assess the extent to which specific sets of genetic predictors improve the discriminatory performance of standard clinical prediction models for fracture risk in childhood cancer survivors.

Goal 3a: Develop and validate individual prediction models that consider standard clinical indicators (e.g., sociodemographic and lifestyle factors, cancer treatment history) to predict fracture risk among survivors.

Goal 3b: Investigate whether the inclusion of a genetic risk profile based on common/low-frequency variants associated with fractures (Aim 1 results) substantively improves clinical prediction modeling for fracture risk.

Goal 3c: Investigate whether the inclusion of a genetic risk profile based on common/low-frequency variants (Aim 1 results) and single/complex variants that modify treatment effects on fracture risk (Aim 2 results) substantively improves clinical prediction modeling for fracture risk.

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? :

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:
Chronic Disease : Secondary
Psychology / Neuropsychology :
Genetics : Primary
Cancer Control :
Epidemiology / Biostatistics : Secondary

Section: Outcomes or Correlative Factors
Late mortality :
Second Malignancy :

Group: Health Behaviors
Tobacco : Correlative Factors
Alcohol :
Physical activity : Correlative Factors
The outcome of interest is self-reported occurrence of fracture from questionnaires collected at Follow-Up 4 (2007, question F11) and Follow-up 5 (2014, question G11). Participants are asked whether they had “ever broken a bone”, and to provide details about all occurrences of fractures. A secondary outcome of interest is self-reported osteoporosis.
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:

Section: Anticipated Sources of Statistical Support
CCSS Statistical Center: Yes
Local institutional statistician: Yes
If local, please provide the name(s) and contact information of the statistician(s) to be involved:
Yutaka Yasui, Ph.D.
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yutaka.yasui@stjude.org (Email)
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:
I agree to share this information with St. Jude: Yes