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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: Shortened telomere length and defects in telomere maintenance associated with thyroid second malignant neoplasm in childhood cancer survivors

Planned research population (eligibility criteria): 1. For analysis of genotyping data, CCSS subjects with thyroid SMN (n=76) compared with remainder of CCSS population, 2. For biological studies, CCSS subjects with and without thyroid SMN (n=48 in each group, already identified cases and controls from previous CCSS proposal, now published), 3. For replication cohort, COG ALTE03N1 patients with and without thyroid SMN (n=90 in each group), 4. Healthy control population (n=254).

Proposed specific aims: Specific Aim 1: To leverage genome-wide SNP array data made available by the CCSS to determine whether SNPs related to telomere maintenance are enriched in survivors with thyroid SMN compared to those without SMN, and to investigate if these SNPs improve thyroid SMN risk prediction compared with telomere content alone by: a) Comparing SNPs related to telomere biology networks in participants with thyroid SMN (n=76) and those without SMN, to explore both gene-gene and gene-environment interactions and determine those at highest risk of developing radiation-related thyroid SMN b) In a subset of CCSS subjects with thyroid SMN and matched controls who have previously undergone telomere content analysis (n=48 in each group), assessing the association between both telomere maintenance SNPs enriched in thyroid SMN and SNPs previously associated with telomere content. Specific Aim 2: To investigate the impact of defects in telomere maintenance genes upon telomerase function in childhood cancer survivors with thyroid SMN by: a) Performing targeted DNA sequencing of 30 genes related to telomere maintenance in CCSS subjects with thyroid SMN, compared with survivor controls matched by age, gender, treatment exposures, and length of follow up who did

not develop SMN (n=48 in each group), and healthy controls (n=254). b) Functionally analyzing in vitro rare missense mutations in telomere maintenance genes for effects on telomerase activity or evidence of telomere damage compared with matched no-SMN survivor controls. c) Comparing absolute telomere length in lymphocytes from CCSS in thyroid SMN survivors (n=48) with matched no-SMN survivors (n=48). Specific Aim 3: To build and validate a predictive model for thyroid SMN inclusive of genotyping and telomere content that will strengthen a previously validated model by: a) Measuring the added value of incorporating (1) telomere content from a subset of CCSS thyroid SMN cases and matched survivor controls, (2) the top SNPs found by the CCSS to be associated with SMN, (3) the top telomere maintenance SNPs identified in Aim 2, and (4) SNPs previously associated with telomere length upon a previously validated risk prediction model for thyroid SMN. b) Replicating this model for thyroid SMN, including telomere content estimates and targeted genotyping of confirmed SNPs, in a distinct childhood cancer survivor cohort through the Children's Oncology Group study ALTE03N1 (n=90 with thyroid SMN).

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?: Submitting R01, deadline JUNE 2014 (Bhatia and Lupo, co-investigators), in response to NCI provocative question: Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naive population?

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.: For SA2 C, will request lymphocytes for telomerase functional analyses on previously identified thyroid SMN subjects and matched controls.

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

Second Malignancy: Secondary

Chronic Disease:

Psychology / Neuropsychology:

Genetics: Primary

Cancer Control:

Epidemiology / Biostatistics: Secondary

To describe the anticipated scope of the study, please indicate the specific CCSS data to be included as outcome (primary or secondary) or correlative factors. (Check all that apply)

Late mortality:

Second Malignancy: Primary

Health Behaviors

Tobacco: Correlative Factors

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:

Pregnancy and offspring:

Family History: Correlative Factors

Psychologic/Quality of Life

BSI-18:

SF-36:

CCSS-NCQ:

PTS:

PTG:

Other:

If other, please specify:

Chronic conditions (CTCAE v3):
Health status:

Demographic

Age: Correlative Factors
Race: Correlative Factors
Sex: Correlative Factors
Others:
If others, please specify:

Cancer treatment

Chemotherapy: Correlative Factors
Radiation therapy: Correlative Factors
Surgery:

Anticipated sources of statistical support

CCSS Statistical Center: Yes
Local institutional statistician:
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:
Peripheral blood:
Lymphoblastoid cell lines:
Second malignancy pathology samples:
Other requiring collection of samples:
If other, please explain: viably frozen blood for lymphocytes from thyroid SMN subjects and matched controls.

Other general comments: Please note that cases with thyroid SMN and controls without thyroid SMN have already been identified and will be the same population as previous Gramatges proposal. This Concept expands upon the biology behind the observation of shorter constitutional telomere length as predictive of thyroid SMN and also utilizes the upcoming genotyping data combined with telomere length to build an improved risk prediction model.