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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 Cognition, Frailty, and Subsequent Mortality in Survivors of Childhood Cancer

Planned research population (eligibility criteria)

All CCSS survivors and siblings from the original and expansion cohorts who completed at least one Neurocognitive Questionnaire (NCQ)

Proposed specific aims

Aim 1: Examine the association between cognitive impairment with subsequent mortality and whether it is modified by attained age or chronic health conditions.
Hypothesis 1.1: We hypothesize that cognitive impairment will be associated with an increased risk of all-cause and health-related mortality. Specifically, we hypothesize that survivors impaired in either or both memory and task efficiency (executive function) or survivors impaired in multiple domains will have an increased risk of mortality.
Hypothesis 1.2: We hypothesize the associations between cognition and mortality will be modified by attained age, with a greater association between cognitive impairment and mortality noted for older survivors.
Hypothesis 1.3: We hypothesize that the association between cognition and mortality will be modified by chronic health conditions, where the association will be stronger among survivors in the high or very high severity/burden CHC score compared to those in moderate, low, or none groups. (Note severity/burden score will be calculated using methods Dr. Williams has previously adapted from Geenen et al, JAMA 2007).
Hypothesis 1.4: The association between cognition and mortality will be stronger among survivors compared

with their siblings.

Aim 2: Examine the association between change in cognitive function over time and subsequent mortality.
Hypothesis 2.1: We hypothesize that survivors whose cognitive function declines over time will experience an increased risk of all-cause and health-related mortality compared to survivors who do not.
Hypothesis 2.2: We hypothesize the associations above will be modified by attained age at first assessment, with a greater association between change in cognitive function and mortality noted for older survivors.
Hypothesis 2.3: We hypothesize the associations above will be modified by chronic health conditions at first assessment, where the association will be stronger among survivors in the high or very high severity/burden CHC score compared to those in moderate, low, or none groups.
Hypothesis 2.4: The association between cognitive decline and mortality will be stronger among survivors compared with their siblings.

Aim 3: Examine if cognitive impairment mediates the association between burden of chronic health conditions and Mortality.
Hypothesis 3.1: Cognitive impairment in any domain will partially mediate the association between a high severity/burden CHC score and all-cause mortality or health-related mortality.

Aim 4: To describe the prevalence of cognitive frailty and examine the combined effect of cognition and frailty (cognitive frailty) on the risk of subsequent mortality.
Hypothesis 4.1: We hypothesize that survivors who have a cognitive frailty phenotype (meet criteria for both cognitive impairment and frailty) will have a greater risk of all-cause and health-related mortality compared to survivors with only one or neither of these phenotypes.
Hypothesis 4.2: We hypothesize the associations above will be modified by attained age, with a greater association between cognitive frailty and mortality noted for older survivors.
Hypothesis 4.3: The association between cognitive frailty and mortality will be stronger among survivors compared with their siblings.

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	No
Biological samples	No
Medical record data	No

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			✓

	Primary	Secondary	Correlative Factors
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

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			
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	Yes
Local Institutional Statistician	No

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

Other General Comments: This AOI uses and expands on the proposed work by Dr. Stephanie Dixon in Concept Proposal 20-15 (see below), with her permission and collaboration.

Concept Proposal 20-15:
Aim 4: Examine the association between cognitive impairment associated with aging (memory and executive function) and mortality, We will present these data overall and by attained age in 10 year increments (5-15 years, 16-25 years, 26-35 years, 36-45 years and 45+ years). Of note, if any survivors contribute neurocognitive questionnaire responses at multiple timepoints (FU-2, FU-5, FU-6), we will consider treating this as a time-varying predictor and use each survey response in the analysis.
We hypothesize that survivors with impairment in memory and/or executive function will have increased all-cause and health-related mortality when compared to survivors without impairment. Further, we anticipate that survivors with impairment in both memory and executive function will have higher risk for mortality than those without impairment or with impairment in only single domain. Finally, we expect those with more severe impairment will be at highest risk.

Agree

I agree to share this information with St. Jude

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