

**AOI: Received 6/5/08**

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**Project Title** Genetic Predictors of Impaired and Enhanced Neurocognitive and Psychological Functioning among Survivors of Childhood Leukemia and Lymphoma

**Planned research population (eligibility criteria)** -CCSS cases with previous history of Leukemia and Lymphoma AND banked biological specimens -history of completing FU2 (the survey that contains the standardized instruments for neurocognitive and psychological functioning) -sibling controls with banked biological specimens

**Proposed specific aims** The goal of this study is to identify the genetic factors that contribute to neurocognitive and emotional functioning in survivors of leukemia and lymphoma. Specifically, differences among individuals may be explained by inherited factors in the enzymes responsible for chemotherapy metabolism or inherited factors that result in a general vulnerability to these outcomes. We hypothesize that greater cognitive impairment, anxiety, and depression will be associated with heritable variables in: 1) enzymes responsible for folate metabolism (methylene tetrahydrofolate reductase, methionine synthase, methionine synthase reductase, cystathionine beta-synthase) and detoxification (glutathione S-transferases GSTM1, GSTP1, and GSTT1 and endothelial nitric acid synthase), 2) neurotransmitter metabolic pathways associated with anxiety and depression (alpha-2A adrenergic gene, serotonin transporter gene, brain-derived neurotrophic factor gene, dopamine receptor type 4 gene, and dopamine transporter gene), and 3) presenile dementia (apolipoprotein E4 and insulin-degrading enzyme). To test these hypotheses, we will: Specific Aim 1: Genotype genes of the folate metabolism pathway, detoxification pathways, neurotransmitter pathways, and genes related to presenile dementia. Specific Aim 2: Test for association between DNA sequence variations and quantitative measures of neurocognitive and psychological impairment identified by standardized instruments on the CCSS FU2, adjusted for age, gender, and type of cancer treatment. By achieving these two Specific Aims, this study will identify risk factors for long-term neurocognitive impairment in children successfully treated for leukemia and lymphoma. Ultimately these studies will lead to the development of a genetic risk panel to guide clinical decisions such as choice of chemotherapy.

**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?** The investigators plan to apply for external funding through NIH, American Cancer Society, and Leukemia/Lymphoma Society.

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Does this project require contact of CCSS study subjects for . . .

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**Additional self-reported information** No

**Biological Samples** Yes

**Medical record data** No

**If yes to any of the above, please briefly describe.**

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

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**Second Malignancy**

Primary - No                      Secondary - No

**Chronic Disease**

Primary - No                      Secondary - No

**Reproductive**

Primary - No                      Secondary - No

**Neurologic**

Primary - No                      Secondary - No

**Psychology / Neuropsychology**

Primary - Yes                      Secondary - No

**Genetics**

Primary - No                      Secondary - No

**Cancer Control**

Primary - No                      Secondary - No

**Epidemiology / Biostatistics**

Primary - No                      Secondary - No

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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)

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**Late mortality**

Primary - No                      Secondary - No                      Correlative Factors - No

**Second Malignancy**

Primary - No                      Secondary - No                      Correlative Factors - No

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Health Behaviors

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**Tobacco**

Primary - No                      Secondary - No                      Correlative Factors - No

**Alcohol**

Primary - No                      Secondary - No                      Correlative Factors - No

**Physical activity**

Primary - No                      Secondary - No                      Correlative Factors - No

**Medical screening**

Primary - No                      Secondary - No                      Correlative Factors - No

**Other**

Primary - No                      Secondary - No                      Correlative Factors - No

**If other, please specify**

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Psychosocial

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**Insurance**

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Primary - No                      Secondary - No                      Correlative Factors - No

**Marriage**

Primary - No                      Secondary - Yes                      Correlative Factors - No

**Education**

Primary - No                      Secondary - Yes                      Correlative Factors - No

**Employment**

Primary - No                      Secondary - Yes                      Correlative Factors - No

**Other**

Primary - No                      Secondary - Yes                      Correlative Factors - No

**If other, please specify** special education history, use of psychotropic drugs, psychiatric hospitalizations, history of living independently in adulthood

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Medical conditions

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**Hearing/Vision/Speech**

Primary - No                      Secondary - No                      Correlative Factors - Yes

**Hormonal systems**

Primary - No                      Secondary - No                      Correlative Factors - No

**Heart and vascular**

Primary - No                      Secondary - No                      Correlative Factors - No

**Respiratory**

Primary - No                      Secondary - No                      Correlative Factors - No

**Digestive**

Primary - No                      Secondary - No                      Correlative Factors - No

**Surgical procedures**

Primary - No                      Secondary - No                      Correlative Factors - No

**Brain and nervous system**

Primary - No                      Secondary - Yes                      Correlative Factors - No

**Other**

Primary - No                      Secondary - No                      Correlative Factors - No

**If other, please specify**

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Medications

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**Describe medications** stimulants, anxiolytics, antidepressants, antipsychotic drugs, anticonvulsants

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**Pregnancy and offspring**

Primary - No                      Secondary - No                      Correlative Factors - No

**Family History**

Primary - No                      Secondary - No                      Correlative Factors - No

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Psychologic/Quality of Life

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**BSI-18**

Primary - Yes                      Secondary - No                      Correlative Factors - No

**SF-36**

Primary - Yes                      Secondary - No                      Correlative Factors - No

**CCSS-NCQ**

Primary - Yes                      Secondary - No                      Correlative Factors - No

**PTS**

Primary - No                      Secondary - No                      Correlative Factors - No

**PTG**

Primary - No                      Secondary - No                      Correlative Factors - No

**Other**

Primary - No                      Secondary - No                      Correlative Factors - No

**If other, please specify**

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**Chronic conditions (CTCAE v3)**

Primary - No                      Secondary - No                      Correlative Factors - No

**Health status**

Primary - No                      Secondary - No                      Correlative Factors - No

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Demographic

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**Age**

Primary - No                      Secondary - No                      Correlative Factors - Yes

**Race**

Primary - No                      Secondary - No                      Correlative Factors - Yes

**Sex**

Primary - No                      Secondary - No                      Correlative Factors - Yes

**Others**

Primary - No                      Secondary - No                      Correlative Factors - No

**If others, please specify**

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Cancer treatment

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**Chemotherapy**

Correlative Factors - Yes

**Radiation therapy**

Correlative Factors - Yes

**Surgery**

Correlative Factors - Yes

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Anticipated sources of statistical support

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**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.** This proposal is of the scope that would require external funding to perform the genetic lab studies. We would also request funding for statistical support as part of the proposal. We are flexible about whether we should request support for CCSS statistical center effort vs. local stastician support, depending on what is most feasible and helpful for the study.

**Will this project utilize CCSS biologic samples?** No

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If yes, which of the following?

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**Buccal cell DNA** Yes

**Peripheral blood** Yes

**Lymphoblastoid cell lines**

**Second malignancy pathology samples**

**Other requiring collection of samples**

**If other, please explain**

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**Other general comments** Dr. M.Fatih Okcu and Dr. Krull have previously expressed interested in being co-investigators on this proposal.