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CHILDHOOD CANCER SURVIVAL STUDY
CONCEPT PROPOSAL

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I- **Title:** Executive Functioning in Long-Term Survivors of Non-CNS Childhood Cancers: Two Phase Concept Proposal

II- **Working Group and Investigators:** Psychology Working Group. Proposed investigators will include:

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III- **Background and Rationale:**

The impressive gains in survival from childhood cancer have led to an obligation to assess long-term complications in the growing population of childhood cancer survivors. Outcome studies suggest that, compared to their siblings and normative populations, survivors are more likely to live with their parents as adults [1], need special education services [2], have lower educational attainment [3], and not to marry [4]. One model hypothesized in the literature suggests that the failures in adaptive functioning are due to observed changes in neurocognitive functioning, particularly problems in executive functioning. Executive functioning, the bringing together and coordinating of information for a purpose, is a multifaceted process with at least two clearly identified elements: attention and working memory.

Several treatment exposures have been associated with impaired neurocognitive functioning in survivors of childhood cancer, but their individual contribution has been difficult to ascertain. These therapies include cranial radiation, methotrexate, cytarabine, and intrathecal therapy. Histological changes associated with cranial radiation include subacute leukoencephalopathy, mineralizing microangiopathy, and cortical atrophy, most often becoming apparent several months to years after cranial radiation [5-7]. Domains of neurobehavioral impairment after cranial radiation include attention, short term memory

impairment, distractibility, fine motor coordination; visual-spatial ability, and somatosensory functioning [8-13]. These deficits were most severe among children treated at younger ages (<5 years) and those who were female.

Previous reviews of the literature suggest that about 25-33% childhood cancer patients who were not exposed to cranial radiation will still experience impairment in some aspect of executive functioning [14]. Patients previously treated with methotrexate without cranial radiation experience significant declines in attention, verbal and non-verbal memory as well as nonsignificant declines in visual-spatial abilities. Glucococorticoid therapy, another mainstay of many pediatric cancer protocols, has been associated with attentional problems in non-cancer pediatric populations, including premature infants and asthmatics [15, 16]. Because glucocorticoids are rarely administered without methotrexate for childhood cancer, the independent effect of this agent has been difficult to study.

Similar specific patterns of neurocognitive impairment in memory and attention have been observed among cancer patients treated in adulthood which suggests that a similar process may be occurring. These studies have included adults exposed to methotrexate. However, chemotherapy regimens not containing methotrexate or corticosteroids have also been associated with neurocognitive deficits in adults [17]. Agents in these regimens included doxorubicin, cyclophosphamide, fluorouracil, and/or tamoxifin. Non-methotrexate chemotherapy exposures have been largely unexamined in terms of neurocognitive outcomes among individuals treated for childhood cancer. Studies in which different chemotherapies are associated with adverse neurocognitive outcomes suggest that the brain injury in response to chemotherapy is related to the individual's vulnerability rather than a mechanism specific to the agent.

Even among children who are given identical therapy, there is considerable individual variation in cognitive outcomes. Differences among individuals may be explained by inherited factors that may make some children more vulnerable to insults to the brain. One possibility is that there are individual differences in the ability to metabolize neurotoxic drugs. For example, for methotrexate-treated patients, polymorphisms in methylene tetrahydrofolate reductase (MTHFR) which amplifies the folate-depleting effects of methotrexate, may predict neurocognitive impairment. Alternatively, patients vary in resiliency to the neurotoxic exposures in general. Polymorphisms in human x-ray cross-complementing groups 1 and 3 (XRCC1,2,3) which determines DNA repair after radiation exposure, apolipoprotein E4 which is important for neuronal repair and plasticity, and insulin-like growth factors which may protect against ischemia are potential mediators for a lack of resiliency [18] .

There are several limitations in the currently available literature in childhood cancer survivors that can be overcome using the Childhood Cancer Survivor Study (CCSS) cohort. Most previous studies included relatively small sample sizes that were further limited by heterogeneous treatment exposures. Therefore, there is inadequate power to determine the role of individual treatment exposures to neurocognitive outcomes. Evaluations were often done soon after completing therapy, potentially too soon to measurable differences in neurocognitive functioning which may take several years to manifest. Also, patients were often compared to published normative data. This approach may not be ideal since the incidence of childhood cancer is highly associated with factors representative of higher socioeconomic status, which in itself is associated

with better neurocognitive functioning. Most previous studies did not simultaneously screen for psychological conditions which could confound performance on tests of attention and memory. No adequately powered study has yet associated neurocognitive functioning with genetic factors.

The CCSS cohort is an informative sample to study the prevalence and contributing individual and treatment risk factors for executive functioning impairment among survivors of childhood cancer. We propose to accomplish this goal with a two phase approach.

Phase I:
Analysis of existing data from the CCSS Follow-Up 2 survey to determine the prevalence of impaired executive functioning compared to sibling controls, in the non-CNS cancer cohort. We will then conduct multivariate analysis to determine the contribution of individual treatment modalities to executive functioning. Specifically, we are interested in the independent effect of methotrexate, separate from intrathecal therapy or steroids or cranial radiation. This analysis requires inclusion of the entire non-CNS cancer cohort to have a sample with the necessary distribution of treatment exposures. We are excluding CNS cancers so to remove the confounding effect of space-occupying lesions. Our results from this analysis will help us construct a model of brain injury in childhood cancer patients. In particular, we hope to understand if neurocognitive impairment is best predicted by exposure to a specific therapy and/or if it is due to individual vulnerability to nonspecific brain injury

Phase II.
Based on the results of Phase I, the goal of this phase of the investigation is to determine the role of genetic factors in an individual's vulnerability to neurocognitive impairment after childhood cancer therapy. We proposed to use stored buccal cells. Results of the Phase I analysis will guide whether we will utilize a candidate gene approach or a whole genome approach. This phase will involve a RO1 grant application or similar mechanism for external funding. We will submit a separate concept for Phase II when the data from Phase I are known.

We propose to complete Phase I at the soonest opportunity with the assistance of the CCSS Statistical Center. We anticipate that Phase I results will provide the necessary preliminary data for the Phase II grant application. We describe the aims and analysis plan for Phase I below.

IV- Phase I: Treatment Predictors of Executive Functioning among Long-Term Survivors of Non-CNS Childhood Cancers

A- Primary Aim: Describe the risk and pattern of executive functioning impairment among long-term survivors of non-CNS childhood cancers, overall and stratified by treatment exposures.

B- Objectives:

1. Calculate the prevalence of impairment in executive functioning, overall and for specific domains of executive function (i.e. memory, organization, etc.)
2. Calculate the relative risk of impairment in executive functioning compared to siblings, overall and stratified by treatment exposures.
3. Identify patient and treatment characteristics independently associated with an increased risk of developing impairment in executive functioning.
4. Get necessary data to design and power a larger study to identify the role of genetic factors in executive functioning.

C- Hypotheses:

1. There is an increased risk of impairment in executive functioning survivors of non-CNS childhood cancers compared to sibling controls.
2. Survivors of non-CNS childhood cancers will be at increased risk for developing impairment in executive functioning if they have the following attributes:
   - Younger age at diagnosis (<5 years)
   - History of increasing cranial radiation
   - History of greater methotrexate therapy
   - History of intrathecal chemotherapy
   - History of glucocorticoid therapy
   - History of any chemotherapy (versus no chemotherapy)
   - Evidence of anxiety or depression from the BSI
3. Methotrexate exposure will be the most robust predictor of impaired neurocognitive functioning in patients who have not had cranial radiation.

C. Analysis Framework:

1. Outcomes of interest:
   The primary outcome of interest is executive functioning as measured by the validated Behavior Rating Inventory of Executive Function (BRIEF) instrument (Questions I 1-25 on the FU2) which yields the following scales: Inhibit, Self-Monitor, Plan/organize, shift, initiate, task monitor, emotional control, working memory, organization of materials. Surrogate outcome variable to be examined will be self-report of stimulants in the open-field medication open-field section (Q9).

2. Study population:
   The entire CCSS cohort except for the CNS tumor population. We are excluding children with brain tumor because of the confounding effect of the presumed injury to the brain with a mass previously being present.

3. Predictor variables to be analyzed:

a. Patient and treatment characteristics which are associated with an increased risk of developing neurocognitive impairment
    i. Age at diagnosis
    ii. Female Gender
    iii. Time elapsed since diagnosis (more impairment with greater time elapsed)
    iv. History of cranial radiation
    v. History of greater methotrexate therapy (continuous; and none, low, medium, high in tertiles)
    vi. History of glucocorticoid therapy (continuous; and none, low, medium, high in tertiles)
    vii. History of intrathecal chemotherapy (yes/no)
    viii. History of anthracycline therapy (yes/no)
    ix. History of alkylator therapy (yes/no)
    x. History of any chemotherapy (vs. no chemotherapy)
    xi. Evidence of psychological difficulties from the BSI on the FU2 instrument

4. Analysis:

    a. We will calculate the prevalence of executive functioning impairment among cases compared to sibs, overall and by specific executive functioning sub-scale.
    b. We will calculate relative risk of executive functioning impairment, overall and by patient and treatment characteristics
    c. We will construct multivariate regression models to determine the independent role of treatment factors (cumulative dosage as well as dichotomous variables) in executive functioning outcomes, adjusted for age at diagnosis and gender and psychological impairment.

V. Other considerations.

Dr. Kadan-Lottick will do this work in the context of her ongoing K grant focused on neurocognitive and psychosocial outcomes in children with cancer. Dr. Schultz (Yale Child Study Center) is her primary mentor and Dr. Meadows is her co-mentor for the K grant. For the K grant, Dr. Kadan-Lottick had proposed to limit her analyses to patients with acute lymphoblastic leukemia. However, the distribution of therapy exposures among leukemia patients, namely in methotrexate exposure without intrathecal chemotherapy or cranial radiation, would make an analysis limited to this diagnosis less informative.

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