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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

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Project Title: Adult Neurobehavioral Late Effects of Pediatric Low Grade Brain Tumors
Planned research population (eligibility criteria): D. 2.2 Low Grade Study Participants. Eligible CCSS participants were identified in the following way: (a) were active participants in the CCSS and (b) corresponding to WHO Grades I and II (Kleihuens, 2000), had astroctyoma/glioma tumor diagnoses of Pilocytic Astrocytoma, Fibrillary Astrocytoma, Subependymal Giant Cell Astrocytoma, Oligodendroglioma NOS, Subependymal Glioma, and Astrocytoma NOS. This resulted in the final list of 503 eligible participants (see flow chart below). Two hundred and sixty four of these were treated with surgery only (LGA-RT) while 288 were treated with surgery plus focal radiotherapy (LGA+RT). Upon re-review of the original records, we expect that approximately 10% of those receiving RT will be found to have high grade tumors, leaving a final eligible pool from the CCSS of 259 receiving RT. While tumor location information was not gathered by the CCSS, based upon the tumor types, we expect that one third of the eligible participants will have cerebellar locations. We also expect that about 28% of our sample of brain tumor survivors will have had a relapse requiring further therapy. Detailed information about relapse has been collected by the CCSS and we intend to retain these individuals in our models as a variable of interest (see D.6.3.2 & D.6.3.6). The table below shows the age at surgery distributions of eligible participants, while the maps below show the current geographic distribution of these eligible participants, 44% of the eligible brain tumor survivors residing in close proximity to the 14 testing sites described below. The CCSS has well-developed methods, including contacting relatives, tracking social security numbers, etc. used by an experienced national survey research firm (Westat Inc.) for locating subjects who move without notice (See Robison, et al., 2002 for a description of the tracing protocol). For those eligible subjects who

cannot be located using such methods, comparisons will be made to the eventual participants to determine whether ascertainment bias may have influenced the results. Based upon prior recruitment rates for the CCSS, other long-term follow-up brain tumor research (Sands et al., manuscript in preparation), and aggressive plan for acquiring these data, it is estimated that 50%, or 260 eligible participants will be enrolled in the Low Grade Study. An additional 156 active participants from the CCSS control group will be randomly sampled as well, matched on gender, age and education of their families of origin (i.e., parent with the highest educational attainment) to the brain tumor group. With this 20% over-recruitment for the control group, we are able to increase power while not over-allocating limited research resources to this presumptively normal group of participants. Over-sampling of Controls also assures precision in matching with brain tumor subgroups (LGA-RT, LGA+RT). For methodological (i.e. matching for age) and pragmatic (i.e. geographic dispersion) reasons, matching tumor patients with their own siblings will not be attempted. Rather, comparison subjects will be recruited from the large CCSS control pool based upon geographic proximity to the participants with brain tumors. More specifically, from the pool of 3378 active in the CCSS control group, those within 50 miles of the 14 Testing Sites will be identified. Random selection will be made from the subgroup meeting the following matching criteria with the brain tumor participants in the same geographic region: (a) gender, (b) age (within 5 years), and (c) parent education of family of origin (within 2 years). These matching criteria were selected because of the possible gender variance in the effects of neurologic insults and cognitive aging; the obvious need to compare similar brain tumor and control age groups; and the need to equate the two groups for premorbid/contextual factors during childhoodâ€”the parent highest educational attainment serving as a proxy for these factors.

Proposed specific aims: Specific Aim A. Ascertain the presence, degree, and nature of neuropsychological as well as SES effects in adults treated as children for low grade astrocytoma (LGA) as compared to healthy controls. Hypothesis. A. 1: Participants with LGA (n=260) will be impaired compared to Controls (n=156) on measures of Composite Neuropsychological Functioning and Estimated IQ as well as SES as measured by Educational Attainment, Income, and Occupational Prestige Hypothesis A. 2: Both the subgroup of LGA participants treated with surgery only (LGA-RT; n=130) and those treated with surgery plus focal radiotherapy (LGA+RT; n=130) will be impaired compared to Controls (n=156) on measures of Composite Neuropsychological Functioning and Estimated IQ. as well as Socioeconomic Status (SES) as measured by Educational Attainment, Income, and Occupational Prestige Specific Aim B. Within the LGA group, determine disease- and subject-related predictors of outcome Hypothesis. B. 1: Degree of intellectual and neuropsychological impairment will correspond to tumor site, with cerebellar and cerebral hemisphere tumors (estimated n=152) associated with the least, and supratentorial midline and brainstem tumors (estimated n=108) the most impairment on Estimated IQ, Composite Neuropsychological Index, as well as SES as measured by Income, Educational Attainment, and Occupational Prestige Hypothesis .B. 2: Compared to the LGA-RT subgroup (n=130), the LGA+RT (n=130) subgroup will evince lower Composite Neuropsychological Functioning and Estimated IQ as well as SES as measured by Educational Attainment, Income, and Occupational Prestige Hypothesis .B.3.: Compared to those treated at age 8 years and above (estimated n=130), LGA patients treated at age 7 years and below (estimated n=130) will evince lower Composite Neuropsychological Functioning and Estimated IQ as well as SES as measured by Educational Attainment, Income, and Occupational Prestige. Hypothesis B. 4: Composite Neuropsychological Functioning and Estimated IQ will correlate

inversely with SES as measured by Educational Attainment, Income, and Occupational Prestige Secondary Aims will explore: (A) Multivariate prediction models of outcome partitioning unique variance attributable to the predictors: treatment, tumor site, age at surgery, as well as an exploration of moderating variables such as Gender and Education of Family of Origin as a proxy measure of Cognitive Reserve. (B) The relationship between site of tumor and specific neuropsychological functions. (C) Accelerated cognitive aging using structural equation modeling. (D) The relationship between objective and subjective measures of neurobehavioral functioning.
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?: Funded through and RO1 from NCI to me/Baylor.

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

Additional self-reported information: Yes
Biological Samples: No
Medical record data: Yes
If yes to any of the above, please briefly describe.: Neuropsychological evaluations will be conducted at 14 sites in the US and Canada. We will use previous CCSS medical and other data to augment the dataset for relevant predictors.

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

Second Malignancy:
Chronic Disease:
Psychology / Neuropsychology: Primary
Genetics:
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: Correlative Factors

Health Behaviors

Tobacco:
Alcohol:
Physical activity:
Medical screening:
Other:
If other, please specify:

Psychosocial

Insurance:
Marriage:
Education: Correlative Factors
Employment: Correlative Factors
Other:
If other, please specify: Most of the variables will be collected as part of the individual evaluations.

Medical conditions

Hearing/Vision/Speech: Correlative Factors
Hormonal systems:
Heart and vascular:
Respiratory:
Digestive:
Surgical procedures:
Brain and nervous system: Correlative Factors
Other:
If other, please specify:

Medications

Describe medications: chemotherapy, psychotropic medications

Pregnancy and offspring:
Family History:

Psychologic/Quality of Life

BSI-18: Correlative Factors
SF-36:
CCSS-NCQ:
PTS:
PTG:
Other: Primary
If other, please specify: Collected as part of the individual evaluations

Chronic conditions (CTCAE v3):
Health status: Correlative Factors

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: Correlative Factors

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?: No

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:

Other general comments: