1. STUDY TITLE: The Effect of Neurofibromatosis Type 1 on Late Outcomes in Adult Survivors of Childhood Cancer

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3. BACKGROUND AND RATIONALE

Neurofibromatosis type 1 (NF1) is a common hereditary cancer predisposition syndrome, affecting approximately 1 in 3000 children.[1,2] Children and adults with NF1 are predisposed to developing both benign and malignant tumors, but are also at risk to develop a spectrum of orthopedic and neurologic disorders that include cognitive deficits, bone disorders, and vascular abnormalities. While many of the complications of NF1 have been previously described in the general population, no prior study has investigated the effects of NF1 on long-term survivors of childhood cancer.

NF1 is a disorder caused by mutations or deletions in the *NF1* gene at chromosome 17q11.2. Although the inheritance pattern is autosomal dominant, approximately half of new cases are sporadic in nature. *NF1* encodes the protein neurofibromin, a GTP-ase inactivator of the RAS signaling pathway.[3] Absence of neurofibromin leads to stimulation of MAP kinases and PI3 kinases, resulting in cell proliferation and survival.[4] *NF1* is therefore a tumor suppressor gene and loss of neurofibromin results in tumorigenesis.[5] NF1 is expressed ubiquitously in different cells and tissue types,[6,7] and can cause tumors in any body region as well as a variety of non-malignant complications.

Malignancy is the most common cause of death in individuals with NF1 and reduces life expectancy by 10-15 years.[8] The incidence of cancer in NF1 is 2.7 times the rate found in the general population.[9] Among children less than 20 years old, the relative rate of a cancer diagnosis is 27.8 times that in the age-matched general population.[9] The most common tumors associated with NF1 include aggressive malignant peripheral nerve sheath tumors (MPNSTs) and low-grade gliomas of the optic pathway and hypothalamus; however, other malignancies have been found more frequently in individuals with NF1, including rhabdomyosarcoma,[10] pheochromocytoma,[11] breast cancer,[9] and leukemia.[12]

NF1 status may also modify the outcome after therapy for these tumors, although the effect is not uniform between tumor types. For instance, NF1-associated MPNST is associated with significantly worse overall survival and disease specific survival compared to sporadic cases,[13] but NF1-associated optic pathway gliomas have improved overall survival and event-free survival compared to sporadic cases.[14] It is unclear whether differences in survival are due to a biological effect of the *NF1* gene or differences in surveillance and presentation between NF1 and non-NF1 patients.

Non-malignant complications of NF1 are common but extremely variable in their presentation and severity. Although most individuals with NF1 are mildly affected, it is estimated that approximately a third develop serious complications.[15] The most obvious complications of NF1 involve the skin and nervous system. Dermal neurofibromata affect virtually all individuals with NF1 by adulthood, but larger plexiform neurofibromas occur in at least 25% of individuals with NF1 and can cause disfigurement and complications due to compression.[16] Cognitive deficits can be measured in most children with NF1 to a variable degree and can include lower IQ,[17,18] specific cognitive impairments (such as memory, attention and executive dysfunction),[17] and lower academic achievement.[19] Children with NF1 are also more frequently diagnosed with attention deficit hyperactivity disorder[20] and may be at increased risk for behaviors similar to autistic spectrum disorder.[21] In addition, individuals with NF1 are at increased risk for bone abnormalities (including pseudoarthrosis,[22] scoliosis[23,24] and increased fracture risk[25]) and vascular complications (including hypertension, arterial stenosis[26] and cerebrovascular abnormalities[27]). Survivors of childhood cancer may also suffer from complications of their disease, particularly vision loss and pituitary dysfunction in gliomas occurring in the optic pathway and hypothalamus.[28]

Individuals with NF1 are predisposed to tumors and at risk for psychological dysfunction, socioeconomic impairment and chronic disease. Survivors of childhood cancer with NF1 may be at increased risk for adverse late outcomes compared to survivors without NF1. Describing the complications and adverse outcomes found in long-term survivors with NF1 and measuring the relative risk of adverse late outcomes in survivors with NF1 may help guide early intervention efforts to reduce the impact of childhood cancer and its therapies in this population.

The CCSS cohort is an ideal sample with which to study adverse outcomes in survivors with NF1. The size of the CCSS cohort ensures that adequate numbers of survivors with NF1 are available. By adjusting for key characteristics in survivors with NF1 and without NF1 (such as age, diagnosis, and type and intensity of prior therapies), we will be able to isolate the effect of NF1 on late outcomes.

The design of this study will attempt to mitigate potential limitations. Survivors with NF1 are self-identified in the CCSS cohort and false-negatives are inevitable. However, because NF1 subjects make up a small minority of total survivors, the effect of these false negatives is expected to be minimal. Questions regarding NF1 status were posed differently in the original and the expansion cohort, likely leading to differences in prevalence of NF1 in these two cohorts. We have further mitigated this effect and reduced misclassification of NF1 status by examining raw data for subjects that have positive or equivocal responses to NF1 status, history of genetic counseling or family history of NF1. In subjects where raw data suggests a different NF1 status (decided by

consensus with PdB and SB), data will be reclassified. This review has resulted in identification of 182 cases of NF1. If substantial differences remain between the original and expansion cohort after examination of raw data, the analysis may be further limited to the expansion cohort alone.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:
   - 4.1. Primary Aim:
     - 4.1.1. Determine the effect of NF1 status on long-term functional outcomes (i.e. emotional, cognitive, and learning problems, and pain) in survivors of childhood cancer. Note: This aim will be assessed twice, once in all diagnoses and once in those with astrocytoma alone.
   - 4.2. Secondary Aims:
     - 4.2.1. Examine the association between NF1 status and socioeconomic attainment (i.e. marital status, employment, independent living, household income, educational attainment) in survivors of childhood cancer. Note: This aim will be assessed twice, once in all diagnoses and once in those with astrocytoma alone.
     - 4.2.2. Explore the association between NF1 status and chronic health conditions and overall survival.
   - 4.3. Primary Hypothesis:
     - 4.3.1. NF1 status will be associated with impaired long-term functional outcomes compared to survivors without NF1 after matching for diagnosis and decade of diagnosis and adjusting for prior treatment, age, gender and race.
   - 4.4. Secondary Hypotheses:
     - 4.4.1. NF1 status will be associated with inferior socioeconomic attainment compared to survivors without NF1 after matching for diagnosis and decade of diagnosis and adjusting for diagnosis, prior treatment, age, gender and race.
     - 4.4.2. In this exploratory aim, we will examine whether NF1 status is associated with an increased number of chronic health conditions and decreased overall survival after matching for diagnosis and decade of diagnosis and adjusting for diagnosis, prior treatment, age, gender and race.

5. Subject population:
   - 5.1. The CCSS survivor cohort who completed the Baseline survey (Original or Expansion cohort).
     - 5.1.1. Inclusion criteria: CCSS survivors who completed the Baseline survey of the Original cohort or Expansion cohort.
     - 5.1.2. NF1 survivors ("Exposed"): NF1 positivity will be determined by: (a) answering "yes" to the question "Have you ever been told by a doctor that you have Neurofibromatosis (type 1)" [Q1a(j) in Expansion Baseline Survey], OR "not sure" to the question above AND "yes" to the question "were you born with large or multiple birthmarks (any 1 larger than a quarter or 6 larger than a dime)"

AND diagnosed with a malignancy more frequently seen in NF1, including astroglial tumor, malignant nerve sheath tumor, rhabdomyosarcoma, or leukemia.

5.1.3. Survivors without NF1 ("Unexposed"): 4 non-NF1 survivors will be selected for each NF1 survivor, matching on diagnosis and decade of diagnosis. Additional covariates (age at diagnosis, age at survey, gender, race, treatment (section 6.3.6.1)) will be included in multivariable analysis.

5.1.4. Sibling cohort: the entire sibling cohort for both the baseline and expansion cohort will be used in this study

5.2. Population subgroups will be analyzed depending on the age range for which each measure is defined.

5.2.1. Adolescent respondents (13-17years at time of survey) will be analyzed for questions involving BPI (6.1.1.1.2)

5.2.2. Adult respondents (>17years at time of survey) will be analyzed for questions involving BSI-18 (6.1.1.1.1.), marital status (6.1.1.2.1), independent living status (6.1.1.2.2), household income (6.1.1.2.4).

5.2.3. Repondents >24years at time of survey will be analyzed for questions involving employment (6.1.1.2.3) and educational attainment (6.1.1.2.5).

ANALYSIS FRAMEWORK:

6.1 Primary Outcome Variables:

6.1.1. Functional outcome variables

6.1.1.1. Psychological

6.1.1.1.1. BSI-18 (adults): Emotional distress will be measured with the Brief Symptom Inventory-18 (BSI-18). Subscales of depression, anxiety and somatization will be dichotomized with impairment defined as a performance falling at or below the 10^{th} percentile based on sibling norms. Scores will be derived from the baseline survey for the original and expansion cohort (for subjects >18yo).

6.1.1.1.2. BPI (adolescents): Emotional and cognitive problems in adolescents will be measured with the Behavior Problem Index (BPI). Subscales of depression/anxiety and attention deficit will be dichotomized with impairment defined as a performance falling at or below the 10^{th} percentile of sibling norms. Scores will derive from the baseline survey for the original and expansion cohort (for subjects <18yo).

6.1.1.1.2. Learning and Memory Problems: A frequency count will examine the number of survivors with grade 1, 2, 3 and 4 memory

problems (variable 28 from the Matrix for Chronic Conditions 20151202.xlsx). The definition for learning and memory problems will derive from this frequency and may be categorical (none, mild, moderate-severe) or boolean (any CTCAE 4.0 grade 1-4 memory problems vs none).

6.1.1.2. Socioeconomic (adults)

6.1.1.2.1. Married: Married will be dichotomized as yes/no. A negative response will be defined as "single, never married or never lived with partner as married." [original cohort: baseline survey question L2; expansion cohort: Baseline survey question M2]

6.1.1.2.2. Independent living: Independent living will be dichotomized as yes/no. Living Independently (no) will be defined as responses that include "live with parents." [original cohort: baseline survey question A9; expansion cohort: Baseline survey question A9]

6.1.1.2.3. Employment: A frequency count will be requested to examine the employment status of survivors included in the study. Based on these frequencies, Employment will be categorized as working full-time/working part-time/not working, or dichotomized as yes/no. Employed (yes) will be defined as responses that include "yes" to the question of working in the last 12 months in the original cohort and "working full-time" and "working part-time" in the expansion cohort [original cohort: baseline survey question O6; expansion cohort: Baseline survey question S2]

6.1.1.2.4. Household Income: Income will be dichotomized based on household income. Income <$20,000 (yes) will be defined as responses that include "less than $9,999", "$10,000 - $19,999" in the original cohort or "less than $19,999" or "none" in the expansion cohort. [Original cohort: baseline survey Q8; expansion cohort Baseline survey question T1]

6.1.1.2.5. Education: Educational attainment will be dichotomized based on any college attendance or beyond. "< College" (yes) will be defined as responses that include "1-8 years (grade school)," "9-12 years (high school)," "completed high school/GED," "Training after high school, other than college." [original cohort: baseline survey question O1; expansion cohort: baseline survey question R1]

6.1.2. Medical Conditions excluding second malignant neoplasm (medical conditions coded according to CTCAE 4.0 (excluding SMN, variable 1) will be used for this section. Variables defined from Matrix for Chronic Conditions 20151202.xlsx).

6.1.2.1 Chronic Medical Conditions excluding SMN: The following will be defined:

6.1.2.1.1. Number of subjects with chronic medical conditions (grade 1-5): defined for both the NF1 and non-NF1 populations of survivors.

6.1.2.1.2. Number of subjects with a chronic medical condition (grade 3 - 5): defined for both the NF1 and non-NF1 population of survivors.

6.1.2.1.3. Number of subjects with more than one chronic medical condition (grade 1-5): defined for both the NF1 and non-NF1 population of survivors.

6.1.2.1.4. Number of subjects with more than one chronic medical condition (grade 3-5): defined for both the NF1 and non-NF1 population of survivors.

6.1.2.2 Specific Chronic Medical Conditions: The following specific chronic medical conditions will be defined dichotomously:

6.1.2.2.1. Vision: CTCAE 4.0 grade 1-4 for vision (variables 3-6a)

6.1.2.2.2. Speech: CTCAE 4.0 grade 1-3 for stammering (variable 7)

6.1.2.2.3. Abnormal Thyroid: CTCAE 4.0 grade 1-2 for hyperthyroid (variable 10) or hypothyroid (variable 11)

6.1.2.2.4. Osteoporosis: CTCAE 4.0 grade 2 for osteoporosis (variable 38)

6.1.2.2.5. Diabetes: CTCAE 4.0 grade 1-5 for diabetes (variable 36)

6.1.2.2.6. Hypertension: CTCAE 4.0 grade 1-5 for hypertension (variable 17)

6.1.2.2.7. Hyperlipidemia: CTCAE 4.0 grade 1-2 for cholesterol (variable 18b)

6.1.2.2.8. Heart disease: CTCAE 4.0 grade 1-5 for myocardial infarction (variable 14), congestive heart failure (variable 15), or arrhythmia (variable 16)

6.1.2.2.9. Lung disease: CTCAE 4.0 grade 1-5 for any respiratory (variables 13a-13c)

6.1.2.2.10. GI disease: CTCAE 4.0 grade 1-5 for any GI (variables 20, 20a, 21, 22, 22a)

6.1.2.2.11. Epilepsy: CTCAE 4.0 grade 1-5 for epilepsy (variable 29)

6.1.2.2.12. Balance: CTCAE 4.0 grade 1-4 for balance (variable 30)

6.1.2.2.13. Motor: CTCAE 4.0 grade 1-2 for weakness in arms (variable 33) or legs (variable 32), tremors (variable 31) or paralysis (variable 32a)

6.1.2.2.14. Sensory: CTCAE 4.0 grade 1 for sensory neuropathy (variable 34)

6.1.2.2.15. Pain: dichotomized as yes/no, defined as "medium amount of pain," "a lot of pain," or "very bad, excruciating pain" as a result of cancer or similar illness [original cohort: baseline survey question J36; expansion cohort: baseline survey question K19]

6.1.2.2.16. Headache: defined as migraine or severe headaches. [original cohort: baseline survey question J6-7; expansion cohort: Baseline survey question J3-J4]

6.1.2.2.17. Hearing loss: CTCAE 4.0 grade 1-4 for hearing loss (variable 2)

6.1.3. Procedures

6.1.3.1 Breast Surgery: defined as <u>any</u> history of breast biopsy, lumpectomy or mastectomy. Note: a yes in this outcome will be defined as a positive response indicating that a condition is still present or is no longer present. [original cohort: baseline survey question I18; expansion cohort: baseline survey question I20-I22]

6.1.3.2. Ventriculoperitoneal shunt: defined as <u>any</u> history of surgery for a VPS. Note: a yes in this outcome will be defined as a positive response indicating that a condition is still present or is no longer present. [original cohort: baseline survey question I17; expansion cohort: baseline survey question I19]

6.1.3.3. Scoliosis surgery: defined as <u>any</u> history of scoliosis surgery. Note: a yes in this outcome will be defined as a positive response indicating that a condition is still present or is no longer present. [original cohort: baseline survey question I2; expansion cohort: baseline survey question I2]

6.1.4. Services

6.1.4.1. Personal Care: Personal care will be dichotomized as impaired or not. Impaired personal care will be defined as needing help in personal care needs, such as eating, bathing, dressing or getting around the home. [original cohort: baseline survey question N10; expansion cohort: baseline survey question O16]

6.1.4.2. Routine Needs: The ability to perform routine needs will be dichotomized as impaired or not. Impairment in routine needs will be defined as needing help handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes. [original cohort: baseline survey question N11; expansion cohort: baseline survey question O17]

6.2. Primary Predictors:

6.2.1. NF1 status: NF1 status will be defined by consensus by Dr. de Blank and Dr. Bhatia based on self report [original cohort: baseline P1; expansion cohort: baseline Q1a(j)], with review of raw data for subjects who responded "yes" or "not sure" to these questions, have an immediate family member with NF1 [P2-P6 of the baseline survey of the original cohort or other follow up surveys; Q1b in the baseline survey of the expansion cohort] or met with a genetic counselor for cancer risk [Q2 of the expansion cohort's baseline survey]. For online responses, NF1 will also be defined as positive if subjects responded "not sure" to the self report of NF1 AND "yes" to the question "were you born with large or multiple birthmarks (any 1 larger than a quarter or 6 larger than a dime)" AND diagnosed with a malignancy more frequently seen in NF1, including astroglial tumor, malignant nerve sheath tumor, rhabdomyosarcoma, or leukemia.

6.3. Covariates

6.3.1. Age at tumor diagnosis: Age at diagnosis will be defined continuously in years.

6.3.2. Age at survey

6.3.3. Gender

6.3.4. Race

6.3.5. Diagnosis

6.3.6. Treatment exposure

6.3.6.1 Treatment will be defined categorically as (1) surgery only, (2) chemotherapy, (3) radiation therapy, (4) chemotherapy and radiation therapy, and (5) other. This covariate will be used in multivariable analysis. Radiation therapy will be defined dichotomously as yes/no.

6.3.6.2 Chemotherapy exposure (yes/no to categories: any, anthracycline, alkylating agent, antimetabolite, steroid, plant alkyloid, epipodophyllotoxin, and other). This variable will be described in Tables 1 and 2.

6.3.7. Decade of Diagnosis

6.4. Related to the specific hypotheses, the following analyses will be conducted in this study:

6.4.1. Frequency distributions will be examined to categorize relevant outcome variables and covariates including diagnosis according to reasonable groupings and consistent with previous CCSS manuscripts to determine whether above categories define a reasonable distribution.

6.4.2. Descriptive statistics will be reported for all predictors and covariates among NF1 survivors, selected controls, sibling cohort and all non-NF1 survivors (See Table 1). Evidence for NF1 (self-report vs chart review) will also be examined in the NF1 cohort. A second analysis will report predictors and covariates among NF1 survivors, selected controls and all non-NF1 survivors with astroglial tumors.

6.4.3. The three most common chronic medical conditions (or three most common organ systems involved) will be compared for each cohort.

6.4.4. Comparisons of outcome measures will be performed with a χ^2 test between groups (Table 3 for all cancer survivors, Table 4 for survivors of astrocytoma). An additional analysis will adjust for relevant covariates.

6.4.5. The overall survival of both NF1 survivors and selected non-NF1 survivors will be graphed vs. age and time since diagnosis. Secondary plots will examine overall survival of NF1 survivors and selected non-NF1 survivors (1) that did and did not receive radiation, (2) that did and did not received an alkylating agent.

6.4.6. The cumulative incidence of (1) grade 3 or 4 chronic medication conditions and (2) any chronic medical condition (grades 1-4) of both NF1 survivors, selected non-NF1 survivors and sibling cohort will be graphed and compared.

6. TABLES

Table 1. Description of the cohort of survivors of childhood tumors

Characteristic	NF1 Survivors	Selected Non-NF1 Survivors	All Non-NF1 Survivors	Sibling Cohort
	N=	N=	N=	N=
Age at Dx, years (mean ± st dev)				
<1 yr				
1-3				
4-7				
8-10				
11-14				
5-20				
unknown				
Sex (n, %)				
Male				
Female				
Race (n, %)				
White				
Black				
API				
Other				
Unknown				
Diagnosis (n, %)				
ALL				
AML				
Other leukemia				
Astrocytoma				
Medulloblastoma, PNET				
Other CNS tumor				
Hodgkin Lymphoma				
non-Hodgkin Lymphoma				
Kidney tumors				
Neuroblastoma				
Soft Tissue Sarcoma				
Ewing Sarcoma				
Osteosarcoma				
Other bone tumor				
Unknown				
Decade of Diagnosis				
1970-1979				
1980-1989				

1990-1999				
Treatment				
Surgery only				
Radiation				
Chemotherapy				
Radiation and chemotherapy				
Chemotherapy agents				
Alkylating Agent				
Anthracycline				
Antimetabolite				
Steroid				
Plant alkyloid				
Epipodophyllotoxin				
Other				

Table 2. Description of the cohort of survivors of childhood astroglial tumors

Characteristic	NF1 Astroglial Survivors	Selected Non-NF1 Astroglial Survivors	All Non-NF1 Astroglial Survivors
	N=	N=	N=
Age at Dx, years (mean ± st dev)			
<1 yr			
1-3			
4-7			
8-10			
11-14			
15-20			
unknown			
Sex (n, %)			
Male			
Female			
Race (n, %)			
White			
Black			
API			
Other			
Unknown			
Decade of Diagnosis			
1970-1979			
1980-1989			
1990-1999			
Treatment			
Surgery only			
Radiation			
Chemotherapy			
Radiation and chemotherapy			
Chemotherapy agents			
Alkylating Agent			
Anthracycline			
Antimetabolite			
Steroid			
Plant alkyloid			
Epipodophyllotoxin			
Other			

Table 3. Comparison of outcomes among survivors of childhood cancer with and without NF1, matched for diagnosis and diagnosis decade, adjusted for age at diagnosis, age at survey, gender, race, and treatment.

	NF1 N=	Non-NF1 N=	OR NF1 vs nonNF1 [95% CI]	P value	Sibling N=	OR NF1 vs siblings [95% CI]	P value
Impaired Psychological Outcomes							
Psychological Distress (BSI-18)							
Global Distress Index							
Depression							
Anxiety							
Somatization							
Behavioral Problem Index (BPI)							
Depression/Anxiety							
Headstrong Behavior							
Social Deviance							
Attention Deficit							
Peer Conflict							
Learning/Memory Problems							
Impaired Socioeconomic Outcomes							
Married							
Living Independently							
Employed							
Income ≤ $20,000							
Education ≥ College							
Medical Conditions							
Hearing Loss							
Vision Loss							
Speech Deficit							
Abnormal Thyroid							
Osteoporosis/Osteopenia							
Diabetes							
Hypertension							
Hyperlipidemia							
Heart Disease							
Lung Disease							
GI Disease							
Epilepsy							

Impaired balance							
Motor impairment							
Sensory impairment							
Pain							
Headache							
Procedures							
History of Breast Surgery							
History of VPS Surgery							
History of Scoliosis Surgery							
Services							
Personal Care Needs							
Routine Needs							
Chronic Medical Conditions							
Any CMC							
>1 CMC							
Any specific medical condition (SMC)							
>1 SMC							

Table 4. Comparison of outcomes among survivors of childhood astrocytoma with and without NF1, matched for diagnosis decade, adjusted for age at diagnosis, age at survey, gender, race, and treatment.

	NF1 N=	Non-NF1 N=	OR NF1 vs nonNF1 [95% CI]	P value	Sibling N=	OR NF1 vs sibling [95%CI]	P value
Impaired Psychological Outcomes							
Psychological Distress (BSI-18)							
Global Distress Index							
Depression							
Anxiety							
Somatization							
Behavioral Problem Index (BPI)							
Depression/Anxiety							
Headstrong Behavior							
Social Deviance							
Attention Deficit							
Peer Conflict							
Learning/Memory Problems							
Impaired Socioeconomic Outcomes							
Married							
Living Independently							
Employed							
Income ≤ $20,000							
Education ≥ College							
Medical Conditions							
Hearing Loss							
Vision Loss							
Speech Deficit							
Abnormal Thyroid							
Osteoporosis/Osteopenia							
Diabetes							
Hypertension							
Hyperlipidemia							
Heart Disease							
Lung Disease							
GI Disease							
Epilepsy							

Impaired balance							
Motor impairment							
Sensory impairment							
Pain							
Headache							
Procedures							
History of Breast Surgery							
History of VPS Surgery							
History of Scoliosis Surgery							
Services							
Personal Care Needs							
Routine Needs							
Chronic Medical Conditions							
Any CMC							
>1 CMC							
Any specific medical condition (SMC)							
>1 SMC							

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