Analysis Concept Proposal

1. **Study title:** Psychosocial outcomes in adolescent survivors of Wilms Tumor

2. **Working group:** Psychology (primary), Chronic Disease (secondary)

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3. **Background and Rationale:**

Little is known about psychosocial late effects (i.e., internalizing and externalizing behaviors, problems with social relationships) experienced by survivors of Wilms tumor or whether specific physical late effects of treatment, such as endocrine, pulmonary, and/or cardiac problems, may relate to poorer psychosocial outcomes. Higher frequency of impaired physical health, functional impairment, and activity limitations have been identified in survivors of Wilms tumor at rates two- to four-times higher than sibling controls per the Childhood Cancer Survivor Study (CCSS).[1, 2] Termuhlen et al[1] reported 65.4% of Wilms tumor survivors in the CCSS reported chronic health conditions, with 24.2% endorsing severe conditions. Cardio-pulmonary, endocrine, and renal problems were frequently identified, including increased risk for congestive heart failure, renal failure, and hypertension compared to sibling controls. In contrast to these high rates of physical late effects, studies suggest that survivors of Wilms tumor experience few psychosocial late effects of treatment as compared to survivors of other childhood cancers, including central nervous system (CNS) malignancies, leukemias, lymphomas, and other solid tumors.[3] Other research indicated survivors of Wilms tumor endorsed similar emotional health as survivors of neuroblastoma, bone tumors, and other solid tumors.[2] Health-related quality of life (QOL) of survivors of Wilms tumor is reported to be similar to survivors of neuroblastoma, with both groups indicating no greater physical QOL problems and poorer emotional health ratings compared to population norms,[4] though mental health outcomes are similar to siblings.[1] Risk factors for poorer mental health included being female, unemployed, having low household

income, and being of Native American descent.[4] Most of these prior studies have been conducted in adult survivors, who were many years post-diagnosis and who may have adapted to psychosocial late effects over time. Little is known regarding functional outcomes during adolescence.

Because no CNS-directed therapy is given as part of standard treatment for Wilms tumor, survivors have frequently been considered as comparison or control groups in studies assessing the effects of CNS-directed therapies for treatment of other childhood cancers.[5,6] Such studies have concluded that children surviving Wilms tumor demonstrate no substantial cognitive functioning deficits,[7] fewer physical growth problems than children who underwent cranial irradiation or intrathecal chemotherapy,[8] and visual motor and attentional functioning similar to healthy controls.[5,6] In terms of behavioral and academic concerns, it has been suggested that survivors of Wilms tumor demonstrate concerns at relatively low rates that are similar to sibling and population controls and that are significantly less frequent than survivors of acute lymphoblastic leukemia (ALL)[9] or lymphoma.[10] Despite this, the most recent research on Wilms tumor contradicts these findings and indicates that a third of survivors report at least one academic difficulty[11] with survivors of Wilms tumor being less likely to graduate college or be employed than their siblings.[1] Socially, survivors of Wilms tumor reported significant problems with peer and romantic relationships as compared to non-cancer controls but at lower rates than survivors of ALL.[12] Survivors of Wilms tumor are also at risk for gonadal dysfunction/risks to fertility,[13] which has been linked to poorer social and mental health outcomes in studies including but not restricted to Wilms' tumor survivors.[14] No investigation has yet examined how physical late effects among survivors of Wilms tumor may relate to psychosocial dysfunction.

The Behavior Problems Index (BPI)[15] will be utilized to explore psychosocial functioning in the proposed study. The BPI is comprised of a subset of questions from the Child Behavior Checklist (CBCL)[16] and was initially developed for the National Health Survey. For each item, parents were asked to indicate their child's functioning on a Likert Scale ranging from 1 ("Not True") to 3 ("Often True"). An evaluation of the validity and reliability of the BPI within the CCSS cohort suggested five domains comprised of a total of 27 items from the CBCL including 1) Depression/Anxiety, 2) Headstrong, 3) Attention Deficit, 4) Peer Conflicts/Social Withdrawal, and 5) Antisocial Behaviors.[17] Two additional items collected with the BPI will be utilized to describe aspects of social competence (i.e., the number of close friends the adolescent has and the frequency of interacting with these close friends).

We propose to investigate demographic, treatment, and medical predictors of psychosocial difficulties in the large sample of survivors of Wilms Tumor in the combined CCSS cohort. We will examine prevalence and predictors of problems reported by parents on the BPI for survivors compared to siblings who completed the < 18 Baseline surveys. Of importance, since the treatment of Wilms tumor has not substantially changed over the last three decades, factors that are associated with poor psychosocial outcomes in the CCSS cohort are likely to have relevance to the population of children diagnosed and treated currently.

4. Specific Aims/Objectives/Research Hypotheses:

Aim 1: To estimate the prevalence of psychosocial difficulties in adolescent survivors of Wilms tumor compared to the adolescent sibling cohort.

> **Hypothesis 1a:** Survivors of Wilms tumor will demonstrate higher frequency of depression/anxiety, headstrong behaviors, attention problems, antisocial behaviors and peer conflict/social withdrawal compared to siblings.
>
> **Hypothesis 1b:** Survivors of Wilms tumor will have fewer close friends and will interact with these friends less often compared to siblings.
>
> **Hypothesis 1c:** Survivors of Wilms tumor will be more likely to have received special education services for low test scores and/or problems learning or concentrating compared to siblings.

Aim 2: To identify demographic and treatment-related predictors of psychosocial outcomes, friendship variables, and involvement in special education services in adolescent survivors of Wilms tumor.

> **Hypothesis 2:** Impairment on psychosocial outcomes (depression/anxiety, headstrong behaviors, attention problems, antisocial behaviors and peer conflict/social withdrawal), number of friends, time spent with friends, and involvement in special education services will be associated with gender, lower household income, earlier treatment era, history positive for scoliosis, dose and location of radiation exposure (e.g., chest radiation), and cumulative dose of anthracyclines.

Aim 3: To examine the association between cardiac, pulmonary, and endocrine chronic conditions and psychosocial outcomes in adolescent survivors of Wilms tumor. These three systems will be assessed individually and as an overall composite.

> **Hypothesis 3a:** Impairment on psychosocial outcomes will be associated with the severity of chronic cardiac, pulmonary, and endocrine conditions (CTCAE grade).
>
> **Hypothesis 3b:** Having any severe, disabling, and/or potentially life limiting chronic condition, defined as CTCAE grade 3 or greater, across any of the three systems under investigation will be associated with greater impairment on psychosocial outcomes.

Aim 4: Within females, to explore the association between gonadal function (as reflected through menstruation status and age at menarche) and psychosocial outcomes in adolescent survivors of Wilms tumor. This aim will include only females within the original cohort, as these data are unavailable in the expanded cohort.

Hypothesis 4: Females with gonadal dysfunction (as defined by menstruation status and early or delayed menarche) will show greater likelihood of impaired psychosocial outcomes.

5. Analysis framework:

Population: The planned research population will include participants from the original and expanded cohort who were 1) survivors of Wilms tumor, 2) under 18 years of age at the time of participation, and 3) and whose parents completed the Baseline survey (*n* = 702 per the CCSS enrollment table). Participants will also include the sibling data from the original cohort for those under 18 years of age. Currently, only sibling data from the original cohort is available. Sibling data from the Expansion cohort will be included if it becomes available. For the psychological variables under investigation, we do not have reason to believe that sibling data from the original cohort will be substantially different from the expanded cohort; therefore, it is reasonable to compare the original cohort sibling data to the combined original and expanded cohort patient data. Overall, however, this will need to be considered as a possible limitation of the study.

Outcomes of interest

- Behavior Problems Index (BPI) – The BPI measures emotional, behavioral, cognitive, and social functioning and is comprised of five domains including Depression/Anxiety, Headstrong, Attention Deficit, Peer Conflict/Social Withdrawal, and Antisocial Behaviors.
  - Original Cohort Baseline <18: **Items J.19 through J.21**
  - Original Cohort Baseline Sibling < 18: **Items J.19 through J.21**
  - Expansion Baseline < 18: **Items K.4 through K.6**
- Social competence items
  - Original Cohort Baseline <18: **Items J.16 and J.17**
  - Original Cohort Baseline Sibling < 18: **Items J.16 and J.17**
  - Expansion Baseline < 18: **Items K.1 and K.2**
- Special education services
  - Original Cohort Baseline <18: **Items O.3**
  - Original Cohort Baseline Sibling < 18: **Items O.3**
  - Expansion Baseline < 18: **Items R.3**

Predictors and covariates

- **Age**
  - Original Cohort Baseline <18: **Age at Survey**
  - Original Cohort Baseline Sibling < 18: **Age at Survey**
  - Expansion Baseline < 18: **Age at Survey**

- **Sex**
  - Original Cohort Baseline <18: **Item A.2**
  - Original Cohort Baseline Sibling < 18: **Item A.2**
  - Expansion Baseline < 18: **Item A.2**

- **Race** – *To which one of the following groups does he/she belong?*
  - Original Cohort Baseline <18: **Item A.4**
  - Original Cohort Baseline Sibling < 18: **Item A.4**
  - Expansion Baseline < 18: **Item A.5**

- **Ethnicity** – *Is he/she Hispanic?*
  - Original Cohort Baseline <18: **Item A.4a**
  - Original Cohort Baseline Sibling < 18: **Item A.4a**
  - Expansion Baseline < 18: **Item A.5a**

- **Use of Birth Control Pills**
  - Original Cohort Baseline <18: **Item B.8.2**

- **Use of Estrogens or Progesterones**
  - Original Cohort Baseline <18: **Item B.8.3**

- **Use of antidepressants or other prescribed drugs for depression or other mental health disorders**
  - Original Cohort Baseline <18: **Item B.8.15**
  - Original Cohort Baseline Sibling < 18: **Item B.7.15**
  - Expansion Baseline < 18: **Item B.8.9**

- **History of Scoliosis**
  - Original Cohort Baseline <18: **Item I.2**
  - Original Cohort Baseline Sibling < 18: **Item I.2**
  - Expansion Baseline < 18: **Item I.2**

- **Treatment Era** – Medical Record Abstraction Form [MRAF[)
  - Will code each participant from the Original Cohort<18 and Expansion Baseline as having received treatment for the initial cancer diagnosis in one of the following three decades: 1) 1970-1979, 2) 1980-1989, or 3) 1990-1999

- **Chemotherapy** - (MRAF)
  - Will request cumulative doses for each of the agents listed below, and we will also code each of the following as *administered* or *not administered*

for inclusion as a covariate in some analyses, indicating all that apply for the Original Cohort <18 and Expansion Baseline <18.

- Vincristine
- Dactinomycin
- Doxorubicin
- Cyclophosphamide
- Etoposide
- Carboplatin
- Other chemotherapy

- **Radiation** – (MRAF)
  - Will code as four mutually exclusive categories using Original Cohort <18 and Expansion Baseline <18: 1) no radiation treatment, 2) radiation to the abdomen only, 3) radiation to the abdomen and chest, or 4) other radiation treatment location/s. For participants who received any radiation, the cumulative dose will also be recorded.

- **Surgical Procedures** – (MRAF)
  - Will code as five categories utilizing the Original Cohort <18 only, as CPT-coded information is not available in the Expanded Cohort: 1) partial nephrectomy (ICD-9 Code: 55.4), 2) complete unilateral nephrectomy (ICD-9 Code: 55.5), 3) nephrectomy of remaining kidney (ICD-9 Code: 55.52), 4) bilateral nephrectomy (ICD-9 Code: 55.54), or 5) anephric (V45.73)
  - Note that some participants may have more than one of the preceding surgical codes

- **Endocrine System** – (CTCAE 4.03 grading)
  - Mutually exclusive categories will be created to capture the highest grade of all conditions within the category (e.g., if a participant has one endocrine condition of grade 1/2 and one endocrine condition of grade 3/4, the participant will be coded as grade 3/4).
  - **Gonadal function**
    - Original Cohort Baseline <18: **Items E.16 through E.18**
    - Expansion Baseline < 18: **N/A – data not available for expansion cohort**

- **Cardiac System** – (CTCAE 4.03 grading)
  - Mutually exclusive categories will be created to capture the highest grade of all conditions within the category (e.g., if a participant has one cardiac

condition of grade 1/2 and one cardiac condition of grade 3/4, the participant will be coded as grade 3/4).

- **Respiratory System** – (CTCAE 4.03 grading)
  - Mutually exclusive categories will be created to capture the highest grade of all conditions within the category. (e.g., if a participant has one respiratory condition of grade 1/2 and one respiratory condition of grade 3/4, the participant will be coded as grade 3/4).

- **Relapse/Recurrence**
  - Original Cohort Baseline <18: **Item K.1 and K.4**
  - Original Cohort Baseline Sibling < 18: **N/A**
  - Expansion Baseline < 18: **Item L.1 and L.5**

- **Health Status**
  - Original Cohort Baseline <18
    - Health Practices: **Item N.11**
  - Original Cohort Baseline Sibling < 18: **Item N.11**
  - Expansion Baseline < 18: **Item O.7**

- **Education** – correlative variables
  - Original Cohort Baseline <18: **Items O.1, O.3**
  - Original Cohort Baseline Sibling < 18: **Items O.1, O.3**
  - Expansion Baseline < 18: **Items R.1, R.3**

- **Income** – correlative variables
  - Original Cohort Baseline <18: **Item Q.8**
  - Original Cohort Baseline Sibling < 18: **Item P.8**
  - Expansion Baseline < 18: **Item T.1**

Data Analysis Plan

Outcome variables and predictors will be categorized into groupings consistent with previous CCSS manuscripts. Differences between survivors and siblings will be examined using *t*-tests or chi-square where appropriate (Table 1).

- ***Aim 1:*** Means, standard deviations, and ranges for the five domains of the BPI will be calculated and compared between survivors and siblings utilizing *t*-tests (Table 2). For the survivors, percent impairment on the BPI will also be developed, with impairment defined as a score of ≥ the top 90th percentile of symptoms reported by siblings (as previously delineated by Schultz et al[17]). Chi square analyses will be conducted to determine survivor and sibling differences in

number of friends, time spent with friends, and involvement in special education services.

- ***Aim 2:*** Multivariate logistic regression models will be developed to determine demographic and treatment-related predictors of: 1) psychosocial outcomes, as measured by the five domains of the BPI; 2) number of friends and time spent with friends; and 3) involvement in special education services. Results will be presented as odds ratios (OR) with 95% confidence intervals (Table 3).

- ***Aim 3:*** Multivariate logistic regression models will be developed to determine relationships between cardiac, pulmonary, and endocrine dysfunction and psychosocial outcomes, as measured by the five domains of the BPI. Results will be presented as odds ratios (OR) with 95% confidence intervals (Table 4).

- ***Aim 4:*** Multivariate logistic regression models will be developed to determine the relationships between gonadal dysfunction among female survivors and psychosocial outcomes, as measured by the BPI. Results will be presented as odds ratios (OR) with 95% confidence intervals (Table 4). We will adjust these models to include any necessary demographic or treatment-related predictor variables ($p < .10$) identified in Aim 2. We will conduct sensitivity analyses to determine whether use of hormone replacement or oral contraceptives contribute to these models. Given that data collection for hormone replacement and oral contraceptives includes only the past two years prior to report of psychosocial outcomes, this will be an exploratory analysis and an acknowledged limitation of the study within the discussion section of the manuscript. As noted previously in the aims, these analyses will include only female survivors within the original cohort, as these data are unavailable in the expanded cohort.

Example Tables

- Please see on the following pages

Table 1.

Descriptive Statistics

	Survivor *n* (%)	Sibling *n* (%)	*p*-value
Sex			
Female			
Male			
Race			
Caucasian			
Non-Caucasian			
Ethnicity			
Hispanic			
Non-Hispanic			
Family Income			
<60,000			
≥ $60,000			
Education			
In Elementary/Middle School			
In High School			
Learning Disabilities			
Yes			
No			
Advanced Classes			
Yes			
No			
History of Homebound Education			
Yes			
No			
Hormonal Systems			
Grade 0			
Grade 1/2			
Grade 3/4			
Heart and Vascular Systems			
Grade 0			
Grade 1/2			
Grade 3/4			

	Survivor *n* (%)	Sibling *n* (%)	*p*-value
Grade 0			
Grade 1/2			
Grade 3/4			
Composite			
Grade 0			
Grade 1/2			
Grade 3/4			
Use of Birth Control Pills*			
Yes		--	--
No		--	--
Use of Estrogens or Progesterones*			
Yes		--	--
No		--	--
History of Scoliosis			
Yes			
No			
Health Rating/Practices			
Excellent/Very Good			
Good			
Fair/Poor			
Use of psychoactive medications			
Yes			
No			
Age at Diagnosis			
≤ 2 year		--	--
3-6 years		--	--
≥ 7 years		--	--
Treatment Era			
1970-1979		--	--
1980-1989		--	--
1990-1999		--	--
Wilms Tumor Treatment Modalities			
Surgery			
Partial nephrectomy		--	--
Total nephrectomy		--	--

Bilateral nephrectomy	--	--
Chemotherapy**		
Vincristine	--	--
Dactinomycin	--	--
Doxorubicin	--	--
Cyclophosphomide	--	--
Carboplatin	--	--
Etoposide	--	--
Other chemotherapy	--	--
Radiation		
No radiation treatment	--	--
Radiation to the abdomen	--	--
Radiation to the abdomen and chest	--	--
Radiation to another location		
Second Malignancy or Recurrence	--	--
Yes	--	--
No	--	--

*Note that these data only include females in the Original Cohort
**Note that these may be collapsed into a smaller number of categories for later analyses.

Table 2.
BPI Comparisons for Survivor and Siblings

Variable	Survivor *M (SD)*	Sibling *M (SD)*	*t*	*p*-value
Depression/Anxiety				
Headstrong				
Attention Deficit				
Peer Conflict/Social Withdrawal				
Antisocial Behaviors				

Table 3.

Multivariable Model of Demographic and Treatment Related Predictors of Internalizing and Externalizing Behaviors among Survivors of Wilms Tumor

	Depression/Anxiety (*OR, 95% CI, p*)	Headstrong (*OR, 95% CI, p*)	Attention Deficit (*OR, 95% CI, p*)	Peer Conflict (*OR, 95% CI, p*)	Antisocial Behaviors (*OR, 95% CI, p*)
Sex					
Female	1.0	1.0	1.0	1.0	1.0
Male					
Race					
Caucasian	1.0	1.0	1.0	1.0	1.0
Non-Caucasian					
Ethnicity					
Hispanic					
Non-Hispanic	1.0	1.0	1.0	1.0	1.0
Family Income					
< $60,000	1.0	1.0	1.0	1.0	1.0
≥ $60,000					
Education					
In Elementary School/Middle School	1.0	1.0	1.0	1.0	1.0
In High School					
History of Scoliosis					
Yes					
No	1.0	1.0	1.0	1.0	1.0

	Depression/Anxiety (*OR, 95% CI, p*)	Headstrong (*OR, 95% CI, p*)	Attention Deficit (*OR, 95% CI, p*)	Peer Conflict (*OR, 95% CI, p*)	Antisocial Behaviors (*OR, 95% CI, p*)
Health Rating/Practices					
Excellent/Very Good	1.0	1.0	1.0	1.0	1.0
Good					
Fair/Poor					
Use of psychoactive medications					
Yes					
No	1.0	1.0	1.0	1.0	1.0
Age at Diagnosis					
≤ 2 year	1.0	1.0	1.0	1.0	1.0
3-6 years					
>7 years					
Treatment Era					
1970-1979	1.0	1.0	1.0	1.0	1.0
1980-1989					
1990-1999					
Treatment Modalities*					
Surgery					
Partial nephrectomy					
Total nephrectomy					
Bilateral nephrectomy					
Chemotherapy*					

Vincristine					
Dactinomycin					
Doxorubicin					
Cyclophosphomide					
Carboplatin					
Etoposide					
Other chemotherapy					
Radiation					
No radiation treatment					
Radiation to the abdomen					
Radiation to the abdomen and chest					
Radiation to another location					
Second Malignancy or Recurrence					
Yes					
No	1.0	1.0	1.0	1.0	1.0

*Note that treatment categories will likely be collapsed depending on the numbers of participants treated with each modality and their combinations; the reference categories for these variables will thus be determined at that time.

Table 4.

Multivariable model for the prediction of psychological function based on endocrine, cardiac, or pulmonary dysfunction with adjustment for all listed variables among survivors of Wilms tumor

	Depression/Anxiety (*OR, 95% CI, p*)	Headstrong (*OR, 95% CI, p*)	Attention Deficit (*OR, 95% CI, p*)	Peer Conflict (*OR, 95% CI, p*)	Antisocial Behaviors (*OR, 95% CI, p*)
Endocrine System					
Grade 0	1.0	1.0	1.0	1.0	1.0
Grade 1/2					
Grade 3/4					
Cardiac System					
Grade 0	1.0	1.0	1.0	1.0	1.0
Grade 1/2					
Grade 3/4					
Pulmonary System					
Grade 0	1.0	1.0	1.0	1.0	1.0
Grade 1/2					
Grade 3/4					
Composite					
Grade 0	1.0	1.0	1.0	1.0	1.0
Grade 1/2					
Grade 3/4					

Table 5.

Multivariable model for the prediction of psychological function based on gonadal dysfunction among females with adjustment for all listed variables among survivors of Wilms tumor

	Depression/Anxiety (*OR, 95% CI, p*)	Headstrong (*OR, 95% CI, p*)	Attention Deficit (*OR, 95% CI, p*)	Peer Conflict (*OR, 95% CI, p*)	Antisocial Behaviors (*OR, 95% CI, p*)
Achieved Expected Menstruation					
Yes	1.0	1.0	1.0	1.0	1.0
No					
Early Menstruation					
Yes					
No	1.0	1.0	1.0	1.0	1.0
Delayed Menstruation					
Yes					
No	1.0	1.0	1.0	1.0	1.0

6. **Special consideration:** N/A

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