1) **Study title**
Incidence of and Risk Factors for Late End Stage Renal Disease in Survivors of Childhood Cancer

2) **Working group and investigators:** The study will be performed with the assistance of the Chronic Disease Working Group. Secondary oversight will be provided by the Epidemiology/Biostatistics Working Group.

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3) **Background and rationale**

Over 80% of children treated for childhood cancer will become long-term survivors.[1] Currently, there are approximately 380,000 survivors in the United States and between 300,000 and 500,000 in Europe, equating to an estimated 1 in 530 young adults between the ages of 20 and 39 years.[2-3] Previously published data from the Childhood Cancer Survivor Study (CCSS) demonstrated that survivors are at increased risk for chronic health disease, especially severe or life-threatening conditions. End stage renal disease is among these conditions and has been observed to occur amongst 0.5% of childhood cancer survivors by a mean age of 27 years, representing a nearly nine-fold increased risk compared to their siblings.[4]

Late development of end stage renal disease among survivors of childhood cancer may be related to a variety of etiologies including direct effects of the cancer, exposure to toxic chemotherapeutic agents, radiation therapy to the abdomen or retroperitoneum and surgical interventions. Multiple chemotherapeutic agents have been implicated as causal agents of chronic renal insufficiency. Cisplatin induces renal tubular injury via production of reactive oxygen species, generally reversible, though may result in interstitial fibrosis and persistent reductions in the glomerular filtration rate (GFR) years after treatment.[5] Carboplatin has also been associated with nephrotoxicity at myeloablative doses.[6] Ifosfamide and cyclophosphamide have been implicated in persistent GFR reduction several months after therapy.[7, 8] Additionally, tumor lysis syndrome, sepsis, and other complications of multi-modal cancer therapy

can cause acute renal cellular injury and may also contribute to long term development of end stage renal disease.[9-10]

Given the relative infrequency of end stage renal disease in childhood cancer survivors, efforts to understand the factors associated with its development, which survivors may be at particular risk, and how to best mitigate this risk require studying large numbers of survivors. For this reason, we intend leverage the large CCSS cohort to clarify this issue. Furthermore, as an exploratory aim, we will seek to combine data available through the CCSS with data from the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) cohort, which includes 33,160 one-year survivors from Denmark, Iceland, and Sweden diagnosed between 1943 and 2008. Late development of chronic conditions in this cohort are identified based on robust hospital admission data available from high-quality, nationwide health registries.[11] Previous studies within the ALiCCS have documented a number of severe late adverse conditions occurring in survivors including renal and urinary tract, gastrointestinal, autoimmune, and cardiovascular diseases.[12-15]

Previous survivorship research has implicated nephrotoxic therapies, specifically cisplatin, ifosfamide and nephrectomy, as exposures that place survivors at risk for persistent, long-term renal dysfunction.[8] To date, the specific risk factors associated with end stage renal disease remain unknown.

This study will be conducted as a multi-disciplinary collaboration investigating the effect of childhood cancer treatments on the long-term risk for end stage renal disease. Our intention is to quantify the risk of end state renal disease and identify associated risk factors in an effort to 1) individualize off-therapy surveillance in long term survivors and 2) inform strategies to reduce toxicity in future therapeutic protocols.

4) Specific aims:

a) Specific aim 1

To determine the 35-year cumulative incidence of late end stage renal disease, defined as any CTCAE grade 4 chronic kidney disease or renal transplant occurring >5 years after primary cancer diagnosis, in childhood cancer survivors and a sibling comparison group.

Hypothesis: Survivors are at increased risk for end stage renal disease compared with siblings.

b) Specific aim 2

To determine risk factors for late end stage renal disease in survivors of childhood cancer, specifically evaluating the impact of: chronic conditions (diabetes, hypertension and genitourinary disease), tumor characteristics, cancer treatment factors (treatment era, primary cancer diagnosis, chemotherapy agents, radiotherapy dose to the kidneys, nephrectomy status) and treatment for second malignant neoplasm.

Hypothesis: Bilateral renal tumors, nephrotoxic chemotherapeutic agents, radiotherapy directed to the kidney/renal fossa, nephrectomy status and chronic renal and cardiovascular conditions are associated with increased risk for late end stage renal disease in survivors of childhood cancer.

c) Specific aim 3 (exploratory)

We will explore the feasibility of merging datasets with the ALiCCS to determine cumulative incidence in a larger cohort given the relative infrequency of end stage renal disease.

Hypothesis: Combining datasets with the ALiCCS will facilitate estimation of 35-year cumulative incidence and, if feasible, allow evaluation of any associations between specific cancer diagnoses and late end stage renal disease.

5) Analysis framework:

a) Outcomes of interest

The primary outcome is occurrence of late end stage renal disease (≥5 years post-diagnosis), defined as chronic renal dysfunction requiring dialysis. Late end stage renal disease will be a composite outcome including CTCAE grade 4 chronic kidney disease and renal transplantation. This will be ascertained in the following manner:

- Any grade 4 CTCAE chronic kidney disease (binary; yes/no); affirmative response to #D4 on the baseline survey ("Dialysis?") or write-in response coded as grade 4 CTCAE chronic kidney disease from #D5 on the baseline survey ("Any other kind of kidney or urinary tract disorder?"), #D3 on the expanded baseline ("Dialysis?") or write-in response coded as grade 4 CTCAE chronic kidney disease from #D6 on the expanded baseline ("Any other kind of kidney, bladder or urinary tract disorder?"), #E3 on FU4 ("Dialysis?") or write-in response coded as grade 4 CTCAE chronic kidney disease from #E6 on FU4 ("Any other kind of kidney, bladder or urinary tract disorder?"), #E3 on FU5 ("Dialysis?") or write-in response coded as grade 4 CTCAE chronic kidney disease from #E6 on FU5 ("Any other kind of kidney, bladder or urinary tract disorder?").

OR

- Renal transplant (binary; yes/no); affirmative response to #I25 on the baseline survey ("Kidney transplant?"), #I27 on the expanded baseline ("Kidney transplant?"), #J27 on FU4 ("Kidney transplant?"), #J29 on FU5 ("Kidney transplant?").

Note: multiple imputation will be used (if required) for age at event among participants who reported the outcomes.

b) Subject Population

All five-year survivors in the CCSS baseline and expansion cohorts and all nearest-age siblings will be included.

If feasible:
ALiCCS: All five-year survivors will be included. Data will be collected for all survivors with a childhood cancer diagnosis before 21 years of age and ranging from 1943-2008. Patients may be excluded in order to facilitate merging the cohorts.

> Note: We intend to collect data for all survivors included within the ALiCCS cohort but will censor those patients who did not survive beyond five years from their initial cancer diagnosis.

Exclusions: Data on survivors or siblings with congenital conditions predisposing to renal failure (Genetic syndromes? EX Q1a. FU5) or those who endorse a congenital abnormality of kidney, bladder, or genitals (EX Q3an. FU5 W3an) will be collected but may be excluded. All survivors who developed end stage renal disease within 5 years of their cancer diagnosis will be included for cumulative incidence calculations but excluded from subsequent analyses.

c) Exploratory variables

- <u>Demographic and social variables</u>
  - Age at diagnosis (continuous and categorical; Baseline #A1; ExpBaseline #A1)
  - Sex (categorical; Baseline #A2; ExpBaseline #A2)
  - Race (categorical; Baseline #A4; ExpBaseline #A5)

- <u>Additional Variables</u>
  - Underlying cancer diagnosis (categorical; ALL, AML, Other leukemia, CNS tumors, Hodgkin disease, Non-Hodgkin lymphoma, Wilms, Neuroblastoma, Soft tissue sarcoma, Bone tumors)
  - Treatment era (categorical: 1970-1979, 1980-1989, 1990-1999)
    - Treatment periods may change based on years specific nephrotoxic agents emerged
  - Age at 'end stage renal disease'
  - Body mass index (BMI; categorical: <18.5, 18.5-30, >30; Baseline #A10-11, ExpBaseline #A3-4, LTFU 2003 #7-8, LTFU 2007 #A1-2, LTFU 2014 #A1-2)
    - Calculated as BMI = (weight [kg]) / (height [m])^2
  - Tobacco use (categorical: never smoker, former smoker, current smoker; Baseline #N1-2, ExpBaseline #O1-8, LTFU 2003 #L1-8, LTFU 2007 #N7-14, LTFU 2014 #N7-14) and binary (ever/never)
  - Diabetes (binary; yes/no); baseline E5-7. EX E5-7.FU4 F5-7. FU5 G5-7.
  - HTN (binary; yes/no); baseline F7-8. EX F5. FU4 G5. FU5 F5.

- Cardiovascular disease (composite including any one of the following):
    - Coronary artery disease (binary; yes/no); baseline F6. EX F4. FU1 10f. FU4 G4. FU5 F4.
    - Angina (binary; yes/no); baseline F10, F17. EX F6, F11. FU1 10h. FU4 G6, G11. FU5 F6, F11.
    - Myocardial infarction (binary; yes/no); baseline F5. EX F2. FU1 10e. FU4 G2. FU5 F2
    - Hardening of arteries or arteriosclerosis (binary; yes/no); baseline F2. FU1 10b
    - CABG (binary; yes/no); baseline I7. EX I7. FU4 J7. FU5 J7.
- Repeated kidney infections? (binary; yes/no); baseline D2. EX D2. FU4 E2. FU5 E2.
- Repeated bladder infections? (binary; yes/no); baseline D3. EX D2. FU4 E2. FU5 E2.
- Kidney stones (binary; yes/no); baseline D1. EX D1. FU4 E1. FU5 E1.
- Genetic syndromes (WAGR, Denys-Drash, Beckwith-Wiedemann) EX Q1a. FU5
- Second malignant neoplasm (binary; yes/no)
    - The subgroup of 'renal second malignant neoplasm' will be explored separately as well

Note: comorbidity variables will be included if they occur prior to the outcome

- <u>Treatment variables (within 5 years of cancer diagnosis)</u>
    - Any chemotherapy (binary)
        - Alkylating agent (binary)
            - Ifosfamide (binary)
        - Cyclophosphamide equivalent dose (CED) (categorical: 0, 1-3999, 4000-7999, ≥8000mg/m^2)
        - Busulfan (binary)
        - Anthracycline (categorical: 0, <250, ≥250 mg/m^2)
        - Platinum agents
            - Stratify by agents (binary + categorical by dose range)
        - Antimetabolites (binary)
        - Epipodophyllotoxins (binary)
    - Any radiotherapy
        - Body region dosimetry:
            - Any (binary)
            - Renal (categorical; Left kidney/Right kidney/Both/None >X Gy)
                - Dose cutoff to be determined at time of analysis
            - TBI (binary)
    - Surgery

- Any nephrectomy (binary and categorical; none, unilateral partial, bilateral partial, unilateral total, bilateral total)

d) Statistical methods

We will describe demographic and clinical characteristics among childhood cancer survivors (and siblings) that do and do not develop the primary outcome of late end stage renal disease **[Table 1]**. We will define the cumulative incidence of late end stage renal disease among survivors and siblings overall **[Figure 1]** and by individual cancer diagnoses in survivors alone **[Figure 2]**. The relative risk for late end stage renal disease will be determined for survivors, using the sibling cohort as the referent group.

Among those cohorts of survivors with primary cancer diagnoses associated with higher cumulative incidence of end stage renal disease (excluding siblings), we will evaluate the association between treatment factors and end stage renal disease in a univariate model (controlling for relevant factors if indicated) **[Tables 2-3]**. We will then use piecewise exponential models to evaluate those factors that are independently associated with late end stage renal disease **[Table 4]**. For time-to-event analyses involving siblings, time-since-diagnosis will be used as the time scale with participants entering the analysis at their entry to the cohort (five years post diagnosis for survivors and corresponding age of siblings) and exiting with development of the primary outcome, death, or censoring (i.e., time of last survey). Death will be considered a competing risk for all time-dependent analysis

As an exploratory aim (if feasible), we will look to merge the CCSS and ALiCCS databases to calculate the cumulative incidence of late end stage renal disease. All ALiCCS survivors who developed the outcome or died within 5 years of their initial cancer diagnosis will be excluded.

e) Examples of tables and figures

Table 1. Demographic and treatment characteristics of childhood cancer survivors and siblings who did and did not develop late end stage renal disease.

	Survivors		**Siblings**	
Characteristics	**ESRD N=*** (%)**	**No ESRD N=*** (%)**	**ESRD N=*** (%)**	**No ESRD N=*** (%)**
Sex				
Male				
Female				
Race/Ethnicity				
White, NH				
Black, NH				
Hispanic/Latino				
Other				
Year of diagnosis				
1970-1979				
1980-1989				

1990-1999				
Diagnosis				
ALL				
AML				
Other Leukemia				
CNS				
HD				
NHL				
Kidney (Wilms)				
Unilateral				
Bilateral				
Neuroblastoma				
Soft tissue sarcoma				
Bone cancer				
Age at cancer diagnosis (y)				
0-3				
4-9				
10-14				
15-20				
Smoking Status				
Current				
Former				
Never				
Alcohol Status				
Current				
Former				
Never				
BMI (kg/m2)				
<18.5				
18.5-24.99				
25-29.99				
30-39.99				
40+				
Diabetes*				
Hypertension*				
Cardiovascular disease*				
Repeated bladder or kidney infections*				
Nephrolithiasis*				
Other kidney or urinary tract disorder*				
Renal SMN (n = X)				
Any SMN (n = X)				
Age at onset of ESRD, median (IQR)				
Chemotherapy				
CED				
None				
0-<4000mg/m2				
>=4000-<8000mg/m2				
>=8000mg/m2				
Ifosfamide				
None				

0-40 g/m2				
40-80 g/m2				
>80 g/m2				
Epipodophyllotoxins (n=X)				
Cisplatin				
None				
0-500 mg/m2				
>500 mg/m2				
Carboplatin				
None				
0-4000 mg/m2				
>4000 mg/m2				
Anthracyclines (n=X)				
Antimetabolites (n=X)				
Radiotherapy				
None				
Unilateral kidney				
Bilateral kidney				
Maximum total dose to kidneys (Gy)				
None				
0-10				
10-20				
>30				
TBI				
Yes				
No				
Nephrectomy				
None				
Unilateral partial				
Bilateral partial				
Unilateral total				
Bilateral total				

*reported to have occurred prior to the primary endpoint

Figure 1: Cumulative incidence of late end stage renal disease in survivors and siblings

Figure 2: Cumulative incidence of late end stage renal disease in survivors by cancer diagnosis

Table 2: Factors associated with late end stage renal disease in Wilms survivors adjusted for age at diagnosis, sex, race/ethnicity, and decade of diagnosis.

	ARR (95%CI)
Type	
Unilateral	ref
Bilateral	
Cancer predisposition syndrome	
Yes	
No	ref
Chemotherapy	
CED	

None	ref
0-<4000mg/m2	
>=4000-<8000mg/m2	
>=8000mg/m2	
Ifosfamide	
None	ref
0-40 g/m2	
40-80 g/m2	
>80 g/m2	
Epipodophyllotoxins	
Yes	
No	ref
Cisplatin	
None	ref
0-500 mg/m2	
>500 mg/m2	
Carboplatin	
None	ref
0-4000 mg/m2	
>4000 mg/m2	
Anthracyclines	
Yes	
No	ref
Antimetabolite	
Yes	
No	ref
Radiotherapy	
None	ref
Unilateral kidney	
Bilateral kidney	
Maximum total dose to kidneys (Gy)	
None	ref
0-10	
10-30	
>30	
TBI	
Yes	
No	ref
Nephrectomy	
None	ref
Unilateral partial	
Bilateral partial	
Unilateral total	
Bilateral total	
Chronic conditions	
Diabetes*	Ref ‘no’
Hypertension*	Ref ‘no’
Cardiovascular disease*	Ref ‘no’
Any renal disease*	Ref ‘no’
Second Malignant Neoplasm	
None	ref
Any	

Renal	

*reported to have occurred prior to the primary endpoint

Table 3 (if applicable): Treatment factors associated with late end stage renal disease in *other cancer diagnosis* survivors adjusted for age at diagnosis, sex, race/ethnicity, and decade of diagnosis.

Table 4: Multivariable analysis of factors associated with late end stage renal disease among all childhood cancer survivors

Variable	ARR (95%CI)
Sex	
Male	Ref
Female	
Race	
White, NH	Ref
Black, NH	
Hispanic/Latino	
Other	
Smoking	
Current	
Former	
Never	Ref
BMI (kg/m2)	
<18.5	
18.5-30	Ref
>30	
Decade of diagnosis	
1970-1979	Ref
1980-1989	
1990-1999	
Age at cancer diagnosis (y)	
0-3	Ref
4-9	
10-14	
15-20	
Cancer predisposition syndrome	
Yes	
No	Ref
Chemotherapy	
CED	
None	Ref
0-8000mg/m2	
>=8000mg/m2	
Ifosfamide	
None	Ref
0-40 g/m2	
40-80 g/m2	
>80 g/m2	
Cisplatin	
None	Ref
0-500 mg/m2	

>500 mg/m2	
Carboplatin	
None	Ref
0-4000 mg/m2	
>4000 mg/m2	
Radiotherapy	
None	Ref
Unilateral	
Bilateral	
Maximum total dose to kidneys (Gy)	
None	Ref
0-10	
10-20	
>30	
TBI	
Yes	
No	Ref
Nephrectomy	
None	Ref
Unilateral partial	
Bilateral partial	
Unilateral total	
Bilateral total	
Chronic conditions	
Diabetes*	
No	Ref
Yes	
Hypertension*	
Yes	
No	Ref
Second Malignant Neoplasm	
None	Ref
Any	
Renal	

*reported to have occurred prior to the primary endpoint

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