1) Study title

Thirty-Five Year Follow-Up of Childhood Wilms Tumor: Impact of Treatment Era on Long-Term Health Outcomes*

* Title chosen to remain consistent with associated AOI, but may change

2) Working group and investigators

Name	Contact information
Brent Weil	Brent.Weil@childrens.harvard.edu
Christopher Weldon	Christopher.Weldon@childrens.harvard.edu
Andrew Murphy	Andrew.Murphy@stjude.org
Eric Chow	ericchow@u.washington.edu
Wendy Leisenring	wleisenr@fredhutch.org
Elizabeth Mullen	Elizabeth_Mullen@dfci.harvard.edu
Rebecca Howell	rhowell@mdanderson.org
Joseph Neglia	jneglia@umn.edu
Arin Madenci	Arin.Madenci@childrens.harvard.edu
Bryan Dieffenbach	Bryan.Dieffenbach@childrens.harvard.edu
Amanda Termuhlen	atermul@umn.edu
Sogol Mostoufi-Moab	moab@email.chop.edu
Jennifer Levine	Jel9022@med.cornell.edu
Kevin Krull	Kevin.Krull@stjude.org
Yutaka Yasui	Yutaka.Yasui@stjude.org
Gregory Armstrong	Greg.Armstrong@stjude.org
Kevin Oeffinger	Kevin.Oeffinger@duke.edu
Leslie Robison	Les.Robison@stjude.org
Daniel Green	Daniel.Green@stjude.org
Saro Armenian	SArmenian@coh.org

The primary working group for this project will be "**Chronic Disease**." Secondary working groups will be "**Biostatistics/Epidemiology**" and "**Second Malignancy**."

3) Background and rationale

It is expected today that over eighty percent of children and adolescents treated for cancer will become long-term survivors, representing an approximately 30% absolute increase in overall survival since the 1970s[1]. With survivors now regularly living well into adulthood, the often detrimental impact that cancer therapies may have on later health has become well-recognized[2,3]. A full understanding of the implications of childhood cancer therapy requires continued study of health and long-term outcomes as these individuals continue to age and modern therapies evolve. It remains largely unknown, for example, how early generations of survivors will fare as they enter their sixth, seventh, and eighth decades. Likewise, it will be important to understand how health risks to survivors of contemporary treatment regimens will compare to those of previous generations from whom much of our current understanding is derived. Since cancer therapies will continue to advance, it is imperative to continue to systematically follow long-term survivors to understand changes in patterns and risk of late-effects.

Wilms Tumor (WT), once an almost uniformly fatal disease, can now be successfully treated with long-term survival expected in greater than 90% of cases. The transformation of WT into a highly curable cancer in North America can be attributed in large part to efforts by the National Wilms Tumor Study Group (NWTS)[4–6]. This multi-institutional and multidisciplinary collaborative organized in the late 1960s, through careful study, identified ways to improve treatment and overall outcomes for patients with WT for nearly 40 years before continuing as the renal tumor committee of the Children's Oncology Group as it exists today. Even as the initial NWTS studies were underway, it was recognized that WT therapies may negatively impact long-term health. Indeed, survivors of WT are known to experience higher rates of overall chronic health conditions, a wide range of cardiac and pulmonary disease, subsequent neoplasms, infertility, and excess late mortality attributable to the hazardous effects of treatments such as anthracyclines and radiotherapy[7–15]. With sequential iterations of NWTS, it became clear that work was needed to identify who could safely be spared or receive reduced doses of therapies with known long-term toxicities while maintaining excellent oncologic outcomes.

Prior to the NWTS, most individuals underwent nephrectomy followed by postoperative abdominal radiotherapy with or without single-agent chemotherapy. With the advent of NWTS-1 in the early 1970s, the combination of vincristine and actinomycin D was shown to be more effective than either agent alone[16]. These two agents have since served as the backbone for all WT chemotherapy regimens. It was also demonstrated with NWTS-1 that children with localized tumors could be safely spared abdominal radiotherapy, and future dosages for those who did benefit from radiotherapy would continue to be modified over time to identify the least toxic and most effective combinations of multimodal therapy. Anthracyclines (doxorubicin) were also shown to be effective and associated with improved recurrence free survival for higher stage WT patients during NWTS-2, but as subsequent NWTS studies would prove, could be safely eliminated for patients with lower risk disease. As treatment for WT continued to evolve during the NWTS studies, so too did our understanding of critical negative prognostic factors such as tumor spillage, lymph node involvement, unfavorable histology (anaplasia), and loss of heterozygosity (LOH) at chromosomes 1p and 16q[17–19]. As a result, it is now well-established that stages 1 and 2 WT patients whose tumors lack unfavorable features such as anaplasia or LOH can be treated with two-drug chemotherapy (and in some case, with no chemotherapy) and avoid radiotherapy, while introduction of a third-drug (doxorubicin) and abdominal radiotherapy is reserved for those with stage 3, and the further addition of whole lung radiotherapy for those with stage 4 disease and pulmonary metastases. More

intensive regimens such as addition of higher disease of radiotherapy and additional agents including cyclophosphamide, platinum-based agents and etoposide are reserved for tumors possessing unfavorable features or for recurrent tumors, for which outcomes are measurably poorer.

In summary, clinical trials for WT have strived to limit treatment-related toxicity by making it possible to determine which patients can safely receive reduced chemotherapy (two versus three or more drug regimens and at minimal effective doses), who can be spared radiotherapy to the abdomen and/or lungs, and which limited groups of patients will require more intensive multimodal therapy. With many survivors of WT now achieving advanced age, it is critical to understand the health conditions they face, whether efforts to minimize detrimental long-term health impact have been successful and where further work may be needed. With this knowledge, lifelong care and follow-up can be tailored and optimized for survivors, and strategies that precisely address and work to minimize known long-term health consequences of therapy can continue to be incorporated into the design of future treatment algorithms. Outcomes associated with twenty-five-year follow-up for WT survivors in the CCSS baseline cohort were previously reported by Termuhlen and colleagues, confirming that survivors were at increased risk for several chronic health conditions, cardiac disease, subsequent malignant neoplasms (SMNs) and excess late mortality[7]. The CCSS expanded cohort now includes children treated for their cancers through 1999, thereby including children treated during all five NWTS eras. By re-examining the CCSS cohort at present, we aim to report up to thirty-five-year follow-up among WT-survivors and examine outcomes of those treated from 1970-1999 with an emphasis on evaluating how therapy received has impacted the long-term health of WT survivors.

4) Specific aims:

Specific aim 1

To estimate and compare incidence of all-cause and cause-specific late mortality among 1) all eligible WT survivors and their siblings in the complete cohort and 2) among participants stratified by treatment group.

Hypothesis:
Survivors of WT will experience a higher incidence of late mortality compared to siblings attributable to death from late recurrence of the primary cancer as well as increased incidence of health-related late mortality. Increased intensity of therapy received will be directly associated with increased all-cause and cause-specific late mortality.

Specific aim 2

To estimate and compare the cumulative incidence of CTCAE grade 2-5 chronic health conditions due to and other health-related outcomes among WT survivors and 1) their siblings in the complete cohort and 2) stratified by treatment group.

Aim 2.1
To estimate and compare the cumulative incidence of subsequent neoplasms (SNs) and subsequent malignant neoplasms (SMNs) among all WT survivors and stratified by treatment group.

Aim 2.2
To estimate and compare the cumulative incidence of Grade 2-5 chronic cardiac conditions among WT survivors and 1) their siblings in the complete cohort and 2) stratified by treatment group. Grade 5 chronic cardiac conditions will be included in this cumulative incidence and reported separately to specifically assess incidence of death due to cardiac conditions.

Aim 2.3
To estimate and compare the cumulative incidence of Grade 2-5 chronic pulmonary conditions among WT survivors and 1) their siblings in the complete cohort and 2) stratified by treatment group. Grade 5 chronic pulmonary conditions will be included in this cumulative incidence and reported separately to specifically assess incidence of death due to pulmonary conditions.

Aim 2.4
To estimate and compare rates of pregnancy/child siring, miscarriages, premature/early (non-surgical) menopause among WT survivors and 1) their siblings in the complete cohort and 2) stratified by treatment group.

Hypothesis:
Survivors of WT will experience a higher cumulative incidence of CTCAE grade 2-5 chronic health conditions compared with siblings. Increased intensity of therapy received will be directly associated with an increased cumulative incidence of CTCAE grade 2-5 chronic health

conditions, miscarriages, and premature/early (non-surgical) menopause; and inversely associated with successful pregnancy.

Specific aim 3

To estimate and compare neurocognitive, psychosocial, educational, economic, and health status outcomes among all eligible WT survivors and their siblings among all WT survivors and stratified by treatment group.

Hypothesis:
WT survivors will demonstrate more neurocognitive and psychosocial problems, and have lower social attainment compared to siblings. Associated outcomes with be worse in proportion to increasing intensity of therapy received among WT survivors.

5) Analysis framework:

a) Outcomes of interest

Primary outcomes will include the following:

- Late mortality
  - Any-cause (binary: yes/no): using National Death Index
  - Mortality secondary to recurrent or progressive WT (binary: yes/no)
  - Mortality due to subsequent malignant neoplasms (binary: yes/no)
  - Mortality due to cardiovascular disease (binary: yes/no)
  - Mortality due to any health-related cause (binary: yes/no)
- Late SNs
  - All late SNs (malignant and non-malignant; binary: yes/no)
  - All late SMNs (binary: yes/no)
- Late CTCAE grade 2-4 chronic conditions
  - Any late CTCAE grade 2-5 chronic condition (binary: yes/no)
  - Multiple (≥ 2) late CTCAE grade 2-5 conditions (binary: yes/no)
  - Late grade 2-5 cardiac conditions (binary: yes/no)
  - Late CTCAE grade 2-5 pulmonary conditions (binary: yes/no)
- Ever pregnant (defined as becoming pregnant[13] or siring a pregnancy[14]; binary/yes no): Response of "Yes" to baseline M9. EX N6. FU1 8. FU2 N1. FU4 Q1. FU5 V1 (females) or V3 (males).
- Primary ovarian insufficiency (defined as cessation of menses ≥ 6 months in duration occurring 5 years after diagnosis and before age 40, not due to surgery, pregnancy or medications[20]; binary: yes/no). "Yes" is defined as response of < 40 years on question 19b and answer of "Normal" on question 19d on FU1, and/or response of < 40 years to question G14 and answer of "Normal or early menopause" on question G16 on FU5.

- Miscarriage (defined as and report of a miscarriage on baseline or follow-up surveys). "Yes" to "Stillbirth" and/or "Miscarriage" on original baseline M.11, expansion baseline N8, FU1 8a, FU2 N3, FU4 Q5, FU5 V5
- Education attainment (categorical yes/no; OrBL O1, ExpBL R1, FU1 page 3 #1, FU2 Page 3 #1, FU4 A3, FU5 A4)
- Ever employed (categorical yes/no; OrBL O5, ExpBL S1, FU1 page 3 #3b, FU2 Page 3 #4, FU4 A4, FU5 A5)
- Ever married (categorical yes/no; OrBL L1, ExpBL M2, FU1 page 3 #2, FU2 Page 3 #2, FU4 M2, FU5 M2)
- Personal income (categorical; OrBL Q9, ExpBL T3, FU2 S3, FU4 A8, FU5 A9)
- Health insurance (categorical yes/no)
- *SF-36* (categorical; divided into physical and mental components as in table 7, defined as "impaired" vs. "not impaired" as described in "Statistical Methods")

Note: multiple imputation will be used (if required) for age at event among participants who reported the primary and/or secondary outcomes, but not the age at which the respective outcome occurred.

b) Subject Population

Population: All survivors treated for WT from 1970-1999 and their siblings.

- Entire WT survivor cohort
- Categorized by "treatment group"
    - surgery only
        - includes all WT survivors who received surgery only, and no chemo- or radiotherapy
    - two drugs and no radiotherapy
        - includes all WT survivors receiving vincristine and actinomycin D ONLY and no radiotherapy
        - Can be referred to as "Stage 1/2 favorable histology (FH)-like therapy"
    - three drugs and abdominal radiotherapy only
        - includes all WT survivors receiving vincristine, actinomycin D AND doxorubicin ONLY and abdominal radiotherapy ONLY
        - Can be referred to as "Stage 3 FH-like therapy"
    - three drugs, abdominal and whole lung radiotherapy
        - includes all WT survivors receiving vincristine, actinomycin D AND doxorubicin ONLY, abdominal radiotherapy and whole lung radiotherapy
        - Can be referred to as "Stage 4 FH-like therapy"
    - more than 3 drugs
        - includes all WT survivors receiving vincristine, actinomycin D, doxorubicin AND an additional agent (etoposide, cyclophosphamide, and/or cisplatin)
        - These patients would also likely have received abdominal and possibly whole lung radiotherapy
        - Can be referred as "High risk and/or recurrent disease-like therapy"

Exclusions: None

c) Exploratory variables

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

- Additional Variables
  - Treatment era (categorical: 1970-1979, 1980-1989, 1990-1999)
  - Relapsed WT (binary; yes/no)*
  - Bilateral WT (binary; yes/no)

*depending on quality of data, and if available

- Treatment variables (within 5 years of cancer diagnosis)
  - Chemotherapy
    - Single agent (binary yes/no)
    - Vincristine and actinomycin D only (binary yes/no)
    - Doxorubicin (categorical: 0, 0.1 - 250, >250 mg/m^2)[12]
    - Cyclophosphamide (binary yes/no)
    - Platinum agent (binary yes/no)
    - Epidophyllotoxins (binary yes/no)
  - Radiotherapy (binary)
    - Flank radiotherapy (none, 0.1 - 25 Gy, > 25 Gy)
    - Whole abdomen radiotherapy (none, 0.1 - 25 Gy, > 25 Gy)
    - Whole lung radiotherapy (binary yes/no)
  - Treatment groups
    - all WT survivors
    - surgery only
    - two drugs and no radiotherapy
    - three drugs and abdominal radiotherapy only
    - three drugs and whole lung radiotherapy
    - more than three drugs

d) Statistical methods

Demographic and treatment characteristics for all WT survivors will be reported **(Table 1)**. Development of primary outcomes will be reported for both WT survivors and their siblings **(Table 2)**. Piecewise exponential models will be used to estimate multivariable-adjusted rate ratios and associated

95% confidence intervals and p values for late mortality due to any cause, WT recurrence or progression, SMN, cardiac cause, or other health-related cause for WT survivors according to treatment group (**Table 3**). Specific types of SNs developing in WT survivors will be displayed **(Table 4)**. Piecewise exponential models will be used to estimate multivariable-adjusted rate ratios and associated 95% confidence intervals and p values for development of at least one CTCAE grade 2-5 chronic condition, multiple (≥2) conditions, any grade 2-5 cardiac condition, and any grade 2-5 pulmonary condition for WT survivors according to treatment groups (**Table 5**). Piecewise exponential models will be used to estimate multivariable-adjusted rate ratios and associated 95% confidence intervals and p values for becoming pregnant (at least one pregnancy), developing premature/early menopause, and experiencing a miscarriage (at least one miscarriage) among female WT survivors (**Table 6a**); and for successfully siring at least one pregnancy among male WT survivors (**Table 6b**). Age-adjusted frequencies of social, educational, economic, physical health and mental health outcomes (according to most recent survey response) among WT survivors will be estimated and compared to their siblings and among treatment groups (**Table 7)**[21,22]. Physical and mental health outcomes will be ascertained using the SF-36 instrument, WT survivors to their siblings. Outcomes will be dichotomized into impaired (vs. not impaired) using tenth percentile values of population normative data as thresholds. Multivariable log binomial regression will be used to estimate the association (prevalence ratios) between WT survivor and relevant WT treatment groups with the aforementioned outcomes.

Up to 35-year cumulative incidence curves of late mortality will be displayed for WT survivors vs. siblings, and for survivors stratified by treatment groups and by occurrence of WT relapse vs. no relapse **(Figure 1)**. Up to 35-year cumulative incidence curves for development of any CTCAE grade 3-5 chronic condition will be displayed for WT survivors vs. siblings, and for survivors stratified by treatment groups and by occurrence of WT relapse vs. no relapse **(Figure 2)**. Up to 35-year cumulative incidence curves for development of any CTCAE grade 2-5 chronic cardiac condition will be displayed for WT survivors vs. siblings, and for survivors stratified by treatment groups and by occurrence of WT relapse vs. no relapse **(Figure 3)**. Up to 35-year cumulative incidence curves for development of any CTCAE grade 2-5 chronic pulmonary condition will be displayed for WT survivors vs. siblings, and for survivors stratified by treatment groups and by occurrence of WT relapse vs. no relapse **(Figure 4)**. Up to 35-year cumulative incidence curves for development of any SN will be displayed for WT survivors stratified by treatment groups and by occurrence of WT relapse vs. no relapse **(Figure 5)**.

e) Examples of tables and figures

Table 1. Demographic and treatment characteristics of Wilms tumor survivors

Variable	***All survivors*** *N=*	***1970s*** *N=*	***1980s*** *N=*	***1990s*** *N=*
Female	# (%)	# (%)	# (%)	# (%)
Race/ethnicity				
Non-Hispanic white				
Non-Hispanic black				
Hispanic				
Other				
Age at diagnosis, years				
0-3				
4-9				
10-14				
15-20				
Age at latest questionnaire or death, years				
5-9				
10-19				
20-29				
30-39				
40-49				
≥ 50				
Follow-up from diagnosis, years				
5-14				
15-24				
25-34				
≥ 35				
Bilateral WT				
Relapsed WT (Early or late*)				
Treatment group				
Surgery only				
2 drugs, no radiotherapy				
3 drugs, abdominal radiotherapy only				
3 drugs, whole lung radiotherapy				
> 3 drugs				
Chemotherapy				
None				
Single agent				
VCR + AMD				
Doxorubicin				
None				
0.1 - 249 mg/m^2				
≥250 mg/m^2				
Cyclophosphamide				

- No
- Yes

Epipodophyllotoxins
- No
- Yes

Platinum
- Yes
- No

Radiotherapy

None

Whole abdomen
- None
- 0.1 – 25 Gy
- > 25 Gy

Flank
- None
- 0.1 – 25 Gy
- > 25 Gy

Whole lung
- No
- Yes

Surgery

Unilateral nephrectomy

Other[#]

VCR=vincristine; AMD = actinomycin D

*Relapsed disease generally requires more intense therapy. As such would be interested in relapse regardless of timing. This is relevant in the designing new treatment protocols that attempt to balance maintaining good long-term survival, reducing therapies, and preventing relapse.

[#]Will have to determine the number of "other" and what granularity is available before further categorizing, or we may consider dropping this as it may ultimately not correspond with the outcomes we are evaluating in this project

Table 2. 35-year cumulative incidence of late mortality, chronic health conditions, secondary malignant neoplasms, and late recurrence among Wilms tumor survivors and their siblings

Variable	***Survivors*** *N=*	***Siblings*** *N=*	***P***
Late mortality	%	%	
Secondary malignant neoplasm			
CTCAE chronic condition			
None			
Any condition			
Any Grade 2 – 5 condition			
≥ 2 conditions			
≥ 3 conditions			
Cardiovascular disease			
Pregnancy*		-	
Any miscarriage[#]			
Premature/early menopause[#]			

*Defined as "any pregnancy" for females and "siring any pregnancy" for males; [#]Females only

Table 3. Multivariable rate ratios of all-cause and cause specific mortality in WT survivors.

	Any-cause		Recurrence or progression		SMN		Cardiac cause		Other health-related cause	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Treatment group										
All survivors										
Surgery only										
2 drugs, no XRT										
3 drugs, abdominal XRT only										
3 drugs, WL XRT										
> 3 drugs										

XRT=radiotherapy; WL=whole lung

Table 4. SNs among WT survivors*

Any SN	CI
Any SMN	
Leukemia	
ALL	
AML	
Other	
Lymphoma	
HL	
NHL	
Other	
CNS	
Glial	
Medullo/PNET	
Meningioma	
Other	
Skin	
Melanoma	
NMSC	
Head and Neck	
Solid Organ	
Breast	
Bone	
STS	
Thyroid	
Lung	
Gastrointestinal	
Other	

SN=subsequent neoplasm; SMN=subsequent malignant neoplasm; ALL= acute lymphoblastic leukemia; AML = acute myeloid leukemia; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; CNS = central nervous system; Medullo/PNET = medulloblastoma/primitive neuroectodermal tumor; NMSC = non-melanoma skin cancer; STS = soft tissue sarcoma; CI=cumulative incidence

*May need to simplify/lump diagnoses for final version

Table 5. Multivariable rate ratios of overall and specific chronic health conditions in WT survivors.

	At least one Grd 2-5		**Multiple Grd 2-5**		**Grd 2-5 cardiac**		**Grd 2-5 pulmonary**	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Treatment group								
All survivors								
Surgery only								
2 drugs, no XRT								
3 drugs, abdominal XRT only								
3 drugs, WL XRT								
> 3 drugs								

XRT=radiotherapy; WL=whole lung

Table 6a. Multivariable analysis of factors associated with infertility, miscarriage, or premature menopause among female WT survivors.

Variable	***Pregnancy***			***Miscarriage***			***Premature menopause***		
	RR	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*
Siblings	Ref						-		
Race									
White									
Black									
Other									
Doxorubicin									
None									
0.1 - 250 mg/m^2									
>250 mg/m^2									
Cyclophosphamide									
Epipodophyllotoxins									
Platinum agent									
Radiotherapy									
Whole Abdomen									
0.1 – 25 Gy									
> 25 Gy									
Flank									
0.1 – 25 Gy									
> 25 Gy									

RR = rate ratio

Table 6b. Multivariable analysis of factors associated with successful siring of pregnancy among male WT survivors.

Variable	***Siring pregnancy***		
	RR	*95% CI*	*P*
Siblings			
Race			
White			
Black			
Other			
Doxorubicin			
None			
0.1 - 249 mg/m^2			
≥250 mg/m^2			
Cyclophosphamide			
Epipodophyllotoxins			
Platinum agent			
Radiotherapy			
Whole Abdomen			
0.1 – 25 Gy			
> 25 Gy			
Flank			
0.1 – 25 Gy			
> 25 Gy			

RR = rate ratio

Table 7. Social, educational, economic, physical health, and mental health outcomes among WT survivors compared to their siblings (according to most recent survey response).

	Siblings	**All WT survivors**	**WT Survivors by Treatment Group**				
			Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
	OR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
	(Ref)						
Education							
Not a high school graduate							
High school graduate/GED							
College graduate							
Ever employed							
No							
Yes							
Ever married							
No							
Yes							
Personal income ($)							
<19,999							
20,000 – 39,999							
40,000 – 59,999							
≥ 60,000							
Health insurance							
No							
Yes							
Canadian resident							
***SF-36* physical component**							
Physical health							
Physical role							
Bodily pain							
General health							
Physical component (summary)							
***SF-36* mental component**							
Vitality							

Emotional role							
Social function							
Mental health							
Mental component (summary)							

RR: relative risk; Group 1: surgery only; Group 2: two drugs and no radiotherapy; Group 3: three drugs and abdominal radiotherapy only; Group 4: three drugs and whole lung radiotherapy; Group 5: more than three drugs; *SF-36*, Medical Outcomes Study 36-Item Short-Form Health Survey

Figure 1. 35-year cumulative incidence curves of all-cause late mortality: (a) in WT survivors vs. siblings; (b) in survivors stratified by treatment group; (c) in survivors stratified by occurrence of WT relapse vs. no relapse (if possible).

Figure 2. 35-year cumulative incidence curves for development of any CTCAE grade 2-5 chronic condition: (a) in WT survivors vs. siblings; (b) in survivors stratified by treatment group; (c) in survivors stratified by occurrence of WT relapse vs. no relapse (if possible).

Figure 3. 35-year cumulative incidence curves for development of any CTCAE grade 2-5 chronic cardiac condition: (a) in WT survivors vs. siblings; (b) in survivors stratified by chemotherapy received (single agent, VCR + AMD only, DOX 0.1 - 250 mg/m^2, DOX >250 mg/m^2); (c) in survivors stratified by radiotherapy received (none, flank only, whole abdomen only, flank + whole lung, whole abdomen + whole lung); (d) in survivors stratified by occurrence of WT relapse vs. no relapse (if possible).

Figure 4. 35-year cumulative incidence curves for development of any CTCAE grade 2-5 chronic pulmonary condition: (a) in WT survivors vs. siblings; (b) in survivors stratified by radiotherapy received (none, flank only, whole abdomen only, flank + whole lung, whole abdomen + whole lung); (c) in survivors stratified by occurrence of WT relapse vs. no relapse (if possible).

Figure 5. 35-year cumulative incidence curves for development of SNs*: (a) in survivors stratified by treatment group; (b) in survivors stratified by occurrence of WT relapse vs. no relapse (if possible).

*Based on data, may request additional curves for specific neoplasms and/or specifically for malignant neoplasms.

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