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Second Tumors Working Group

CCSS Investigators Meeting
June 2015

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Second Tumors Working Group
Committee Membership

- Joseph Neglia
- Sue Hammond → Mike Arnold
- Greg Armstrong
- Smita Bhatia
- Tara Henderson
- Marilyn Stovall
- Peter Inskip

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Second Tumors Working Group
Interactions

- **Breast Cancer Calls**
  - **Ongoing calls (approx. q month)**
  - **Troubleshooting, looking for duplication**

- **NCI GWAS study**
  - **Location to facilitate radiation groupings**

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Second Tumors Working Group
Concepts to Products

Concept	Investigator	Year	Publication / Status
Second malignant neoplasms following childhood cancer.	Joe Neglia	1998	J Natl Cancer Inst 2001 Apr 18;93(8):618-29
Second primary neoplasms (SPNs) of the central nervous system among long-term survivors of childhood cancer.	Joe Neglia	1999	J Natl Cancer Inst 2006 Nov 1;98(21):1528-37
Second thyroid carcinomas.	Alice Sigurdson	2000	Lancet 2005 Jun 11-17;365(9476):2014-23
Non-treatment risk factors for breast cancer.	Lisa Kenney	2000	Ann Intern Med 2004 Oct 19;141(8):590-7
Second malignant neoplasms after Wilms tumor.	Norman Breslow	2001	Int J Cancer 2010 Aug 1;127(3):657-66
Treatment-related breast cancer.	Peter Inskip	2002	J Clin Oncol 2009;27:3901-07
Genotypes in Hodgkin's disease second malignancies.	Ann Mertens	2002	Cancer 2004 Sep 15;101(6):1463-72
Occurrence of nonmelanoma skin cancer (NMSC) in survivors.	JoAnna Perkins	2002	J Clin Oncol 2005 Jun 1;23(16):3733-41
Association of CYP3A5 and breast cancer following Hodgkin disease.	Debra Friedman	2002	No update
Risk of a carcinoma as a second primary neoplasm.	Mylene Bassal	2003	J Clin Oncol 2006 Jan 20;24(3):476-83
Outcome after second malignancy neoplasm in adult survivors.	Rob Goldsby	2004	Dropped
Second primary sarcomas in survivors of pediatric malignancy.	Tara Henderson	2004	J Natl Cancer Inst 2007 Feb 21;99(4):300-8 Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):224-30
Sun sensitivity, sun exposure, sun protection behavior and risk of skin cancer (melanoma and NMSC).	Ann Mertens	2004	Cancer 2009 Sept 15;115(18 Suppl):4374-84
The risk of disease recurrence and second malignancies following pregnancy in female survivors.	Berrin Ergun-Longmire	2005	Dropped

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Concepts to Products

Concept	Investigator	Year	Publication / Status
Radiation and thyroid cancer in the CCSS: Cohort analysis and alternative methods for dosimetry.	Cecile Ronckers	2006	Radiated Res 2006 Oct;166(4):618-28, Radiat Res 2010;174:741-52, CEBP 2012;21:92-101
Subsequent salivary gland carcinomas in the Childhood Cancer Survivor Study cohort.	Houda Boukheris	2008	Int J Radiat Oncol Biol Phys 2013 Mar 1;85(3):776-83
Second Malignancies of the Gastrointestinal Tract.	Tara Henderson	2009	Ann Intern Med 2012 Jun 5;156(11):757-66
Multiple Subsequent Neoplasms.	Les Robison	2009	J Clin Oncol 2011 Aug 1;29(22):3056-64
Late Occurring Secondary Leukemia in Survivors of Childhood Cancers.	Kerri Nottage	2009	Blood 2011 Jun 9;117(23):6315-8
Incidence of breast cancer among women treated with chest radiation therapy for a pediatric malignancy.	Kevin Oeffinger	2010	J Clin Oncol 2014 Jul 20;32(21):2217-23
Melanoma as a Second Malignant Neoplasm in Survivors of Childhood Cancer.	Alberto Pappo	2010	Pediatr Blood Cancer 2013 Mar;60(3):461-6

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Concepts to Products

Concept	Investigator	Year	Publication / Status
Development and validation of an absolute risk prediction model for thyroid cancer in childhood cancer survivors.	Alice Sigurdson	2011	J Clin Oncol 2013 Jan 1;31(1):119-27
Second primary breast cancers among childhood cancer survivors: joint effects of treatment and host factors.	Peter Inskip	2011	Radiation dosimetry is in progress and expected to be completed in a month.
Risk of Breast Cancer Following Spinal Irradiation for a Pediatric Malignancy.	Chaya Moskowitz	2011	Manuscript under review
Breast Cancer in Survivors Not Exposed to Chest Radiation: A Report from the Childhood Cancer Survivor Study.	Tara Henderson	2011	Platform Presentation ASCO 2014 – Manuscript under review
Renal Carcinoma following therapy for cancer in childhood.	Carmen L. Wilson	2011	J Natl Cancer Inst. 2013;105(7):504-508.
Second neoplasms in the 5th and 6th decades in long term survivors of childhood cancer.	Lucie Turcotte	2012	In press, J Clin Oncol 2015
Pooled International Study of Radiation-related Tumors of the Brain and Nervous System.	Peter Inskip	2013	Data pooling underway; analysis underway
Subsequent Neoplasms in Survivors of Central Nervous System Tumors.	Karen Tsui	2013	Neuro Oncol, 2014, Epub Nov 13, 2014
Prediction Model: Breast Cancer in Women Irradiated for a Pediatric Malignancy.	Chaya Moskowitz	2014	ongoing
Changing Patterns of Second Neoplasms in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study.	Lucie Turcotte	2014	awaiting data

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Concepts to Products

Concept	Investigator	Year	Publication / Status
NF1 and Second Malignant Neoplasms	Smita Bhatia	2014	Funded, ongoing

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Second Tumors Working Group
Ongoing AOIs

Date Received	Title	Author/ Institution	Primary Working Group	Secondary Working Group(s)	AOI Outcome	Concept to Publication Committee
2011	Development of Radiobiologic Models of Second Cancer Risk for Childhood Cancer Patients Treated with Radiation Therapy	Hodgson/Princess Margaret	SMN	Epi/Biostats	Approved	Circulating
2012	Second Malignant Neoplasm in Down syndrome survivors of childhood cancer	Xavier/MUSC	SMN	Genetics	Approved	Pending
2013	Beyond radiation: Understanding thyroid cancer risk in childhood cancer	Turcotte/University of Minnesota	SMN	Epi/Biostats	Approved	Pending
2013	HPV-related SMNs in childhood cancer survivors	Alexander/University of Chicago	SMN		Approved	Pending

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Second Tumors Working Group
Active AOIs

Date Received	Title	Author/ Institution	Primary Working Group	Secondary Working Group(s)	AOI Outcome	Concept to Publication Committee
2014	**Breast Cancer in the Modern Treatment Era**	**Henderson/Univ. of Chicago**	**SMN**		**Approved**	**Pending**
2014	**The Impact of Radiation Dose Uncertainty and Hetergeneity Breast Cancer Risk**	**Berrington/NCI**	**SMN**	**Epi/Biostats**	**Approved**	**Pending**
2015	**Cause-specific Mortality among Survivors with Thyroid Subsequent Malignant Neoplasm**	**Barnea/MSKCC**	**SMN**	**Epi/Biostats**	**Approved**	**Pending**

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Second Tumors Working Group
Recent Publications

- **Turcotte et al: Risk of Subsequent Neoplasms in the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort, J Clin Oncol, 2015 In Press**

- **Tsui et al: Subsequent Neoplasms in Survivors of Childhood Central Nervous System Tumors: Risk After Modern Multimodal Therapy, Neuro Oncol, 2014, Epub Nov 13, 2014**

- **Moskowitz et al: Breast Cancer After Chest Radiation Therapy for Childhood Cancer, J Clin Oncol, 2014, 32(21):2217-23**

- **Patterson et al: Growth Hormone Exposure as a Risk Factor for the Development of Subsequent Neoplasms of the Central Nervous System: A Report from the Childhood Cancer Survivor Study, J Clin Endocrinol Metab, 2014, 99(6):2030-7**

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Second Tumors Working Group
Recent Publications

Concept

- **Incidence of breast cancer among women treated with chest radiation therapy for a pediatric malignancy.**

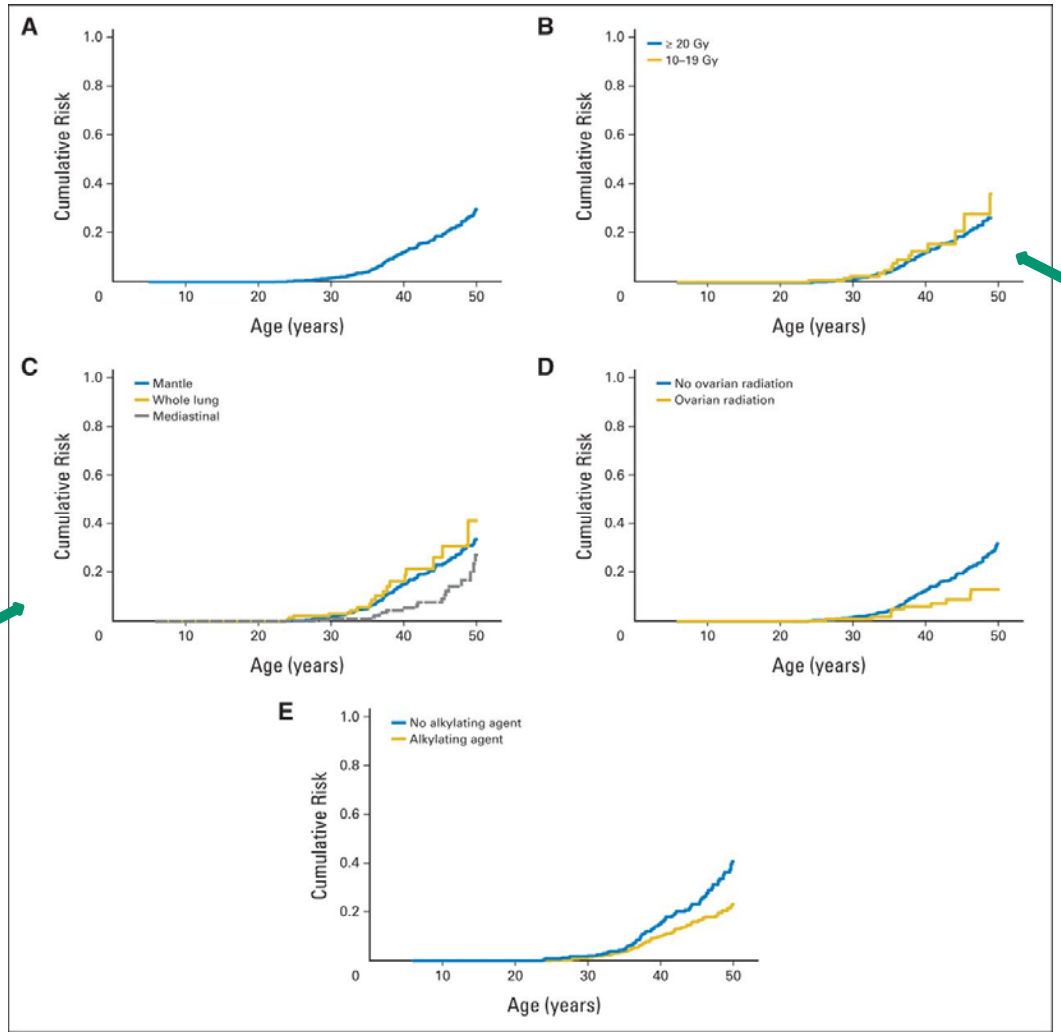
PI

- **Chaya Moskowitz, Kevin Oeffinger**

Aims

- **To evaluate the risk of breast cancer in women who were treated with radiotherapy to the chest**
    - **a. All women in the CCSS cohort who received chest radiation**
    - **b. Subgroups defined by the primary childhood cancer diagnosis:**
        - **i. Hodgkin lymphoma**
        - **ii. All other diagnoses grouped together**
    - **c. Subgroups defined by the chest radiation fields and prescribed doses**

Cumulative risk of breast cancer among women treated for childhood cancer with chest irradiation (A) overall and by childhood cancer therapy: (B) chest radiation dose; (C) chest irradiation field; (D) ovaries in concurrent irradiation field; (E) alkylating agents



Dose curves are overlapping

Risk reduced with limited field

Chaya S. Moskowitz et al. JCO 2014;32:2217-2223

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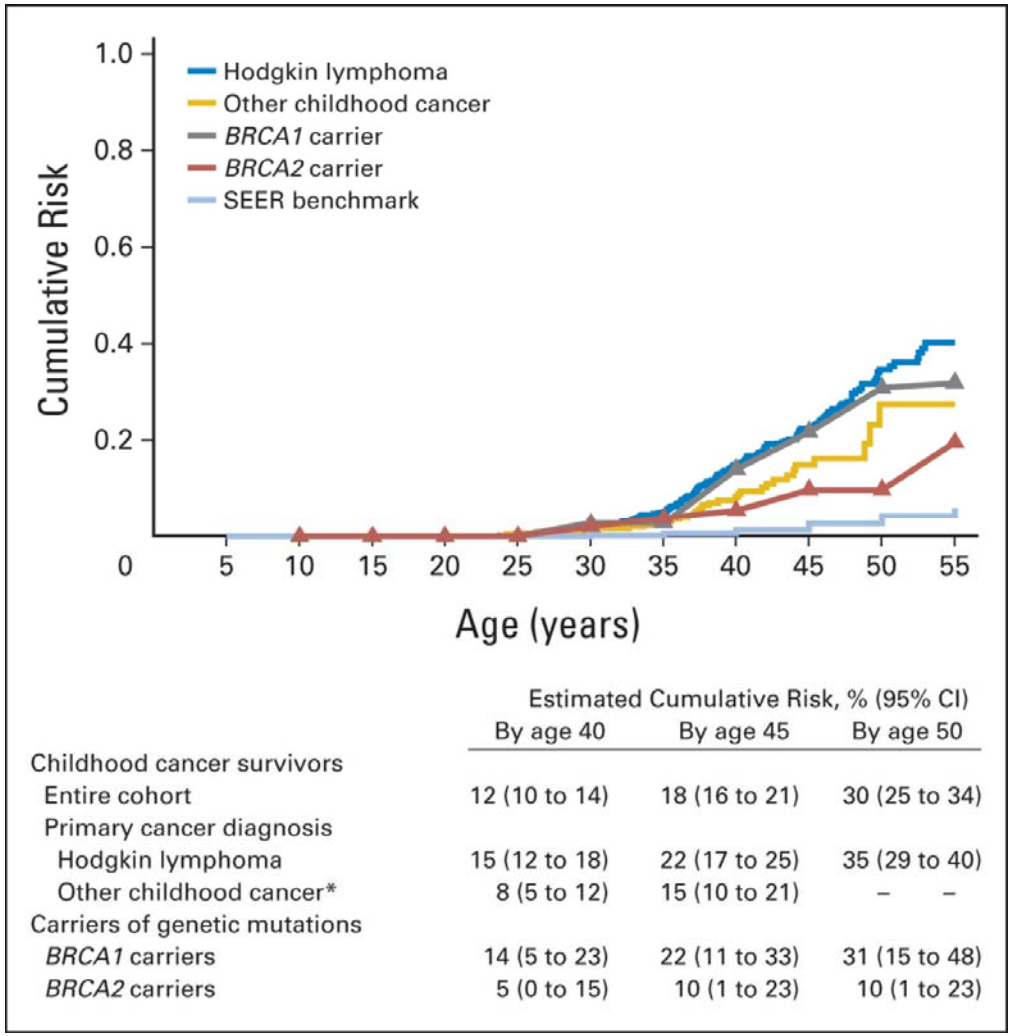
Recent Publications

Characteristic	No. of Participants	No. of Breast Cancer Cases		SIR	95% CI
		Observed	Expected		
Total group	1,230	203	9.3	21.9	19.1 to 25.2
Primary field of chest irradiation, dose in Gy					
Mantle (median, 40; range, 5 to 54)	603	156	6.5	24.2	20.7 to 28.3
Mediastinal (median, 30; range, 3 to 54)	239	20	1.5	13.0	8.4 to 20.2
Whole lung (median, 14; range, 2 to 20)	116	17	0.4	43.6	27.1 to 70.1
Total body (median, 12; range, 4 to 16)	69	4	0.2	19.3	7.3 to 51.5
Abdominal (median, 20; range, 4 to 40)[*]	77	2	0.2	10.8	2.7 to 43.2
Posterior chest (median, 31; range, 6 to 54)[†]	54	0	0.2	0.0	—
Other one-sided anterior (median, 41; range, 10 to 61)	53	3	0.3	9.9	3.2 to 30.6

Note: Table is incomplete

Chaya S. Moskowitz et al. JCO 2014;32:2217-2223

Cumulative risk of breast cancer.



	Estimated Cumulative Risk, % (95% CI)		
	By age 40	By age 45	By age 50
Childhood cancer survivors			
Entire cohort	12 (10 to 14)	18 (16 to 21)	30 (25 to 34)
Primary cancer diagnosis			
Hodgkin lymphoma	15 (12 to 18)	22 (17 to 25)	35 (29 to 40)
Other childhood cancer*	8 (5 to 12)	15 (10 to 21)	– –
Carriers of genetic mutations			
BRCA1 carriers	14 (5 to 23)	22 (11 to 33)	31 (15 to 48)
BRCA2 carriers	5 (0 to 15)	10 (1 to 23)	10 (1 to 23)

Chaya S. Moskowitz et al. JCO 2014;32:2217-2223

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Second Tumors Working Group
Recent Publications

Conclusions

- **Volume is important; risk of lower doses and larger volumes is not dissimilar from higher doses / smaller volumes**

- **The magnitude of breast cancer risk by age 50 years in childhood cancer survivors is comparable to that of BRCA mutation carrier**

- **Breast cancer after childhood cancer is associated with substantial mortality – *intervention opportunity?***

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Second Tumors Working Group
Recent Publications

Concept

- **Growth Hormone Exposure as a risk factor for the development of Subsequent Central Nervous System Neoplasms**

PI

- **Briana Patterson**

Hypothesis

- **Treatment with GH is associated with development of a meningioma, glioma, and other subsequent CNS neoplasms.**

Methods

- **The study was designed with a retrospective cohort with longitudinal follow-up**
- **A total of 12 098 5-year pediatric cancer survivors from the Childhood Cancer Survivor Study, diagnosed with cancer prior to age 21 years, of whom 338 self-reported GH treatment, which was verified through medical record review**

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Recent Publications

Findings

- **Among GH-treated survivors, 16 (4.7%) developed CNS-SN,**
  - **10 with meningioma and six with glioma**
- **203 survivors without GH treatment (1.7%) developed CNS-SN,**
  - **138 with meningioma, 49 with glioma, and 16 with other CNS-SNs**
- **Adjusted rate ratio in GH-treated compared with untreated survivors for development of any CNS-SN was 1.0 [95% confidence interval (CI) 0.6-1.8, P = .94]**
  - **Meningiomas, 0.8 (95% CI 0.4-1.7, P = .61)**
  - **Gliomas, 1.9 (95% CI 0.7-4.8, P = .21).**

No statistically significant increased overall risk of the occurrence of a CNS-SN associated with GH exposure.

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Updated and Consolidated Second Neoplasm Data

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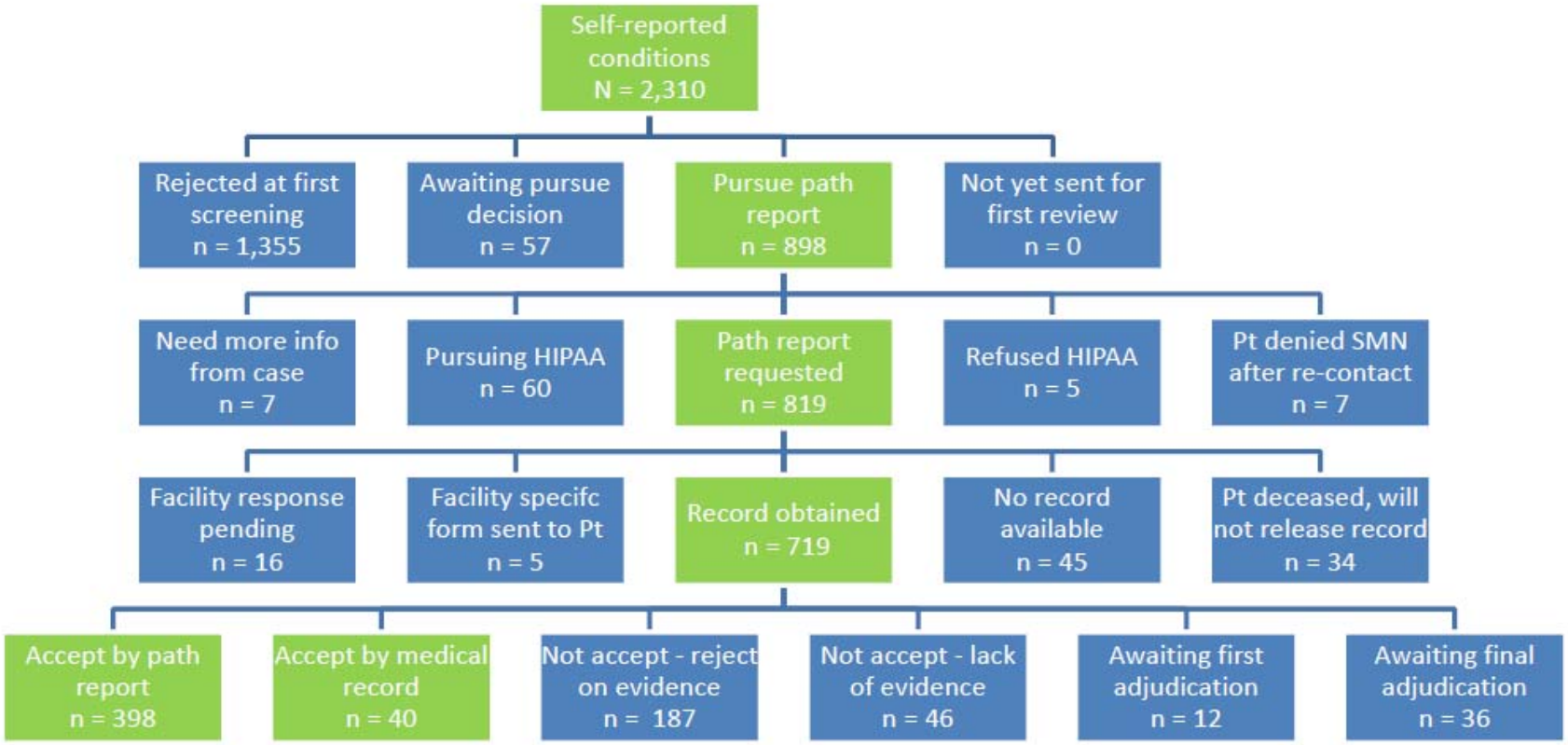
Expansion Cohort

Expansion Cohort Subsquent Neoplasm Confirmation – Baseline Survey



Report Date: 5/2015

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Second Tumors Working Group
SNs in Expanded Cohort

	Primary Cancer Diagnosis								
Subsequent Neoplasm*	**Leukemia**	**CNS**	**HD**	**NHL**	**Kidney**	**Neuro-blastoma**	**Soft tissue sarcoma**	**Bone cancer**	***Total***
Breast	1	2	33	2	_	_	_	7	***45***
Meningioma	6	16	1	_	_	3	1	_	***27***
Other CNS	14	19	0	2	_	_	2	1	***38***
Thyroid	11	12	18	3	2	5	1	4	***56***
Soft tissue sarcoma	1	15	4	5	2	4	4	3	***38***
Leukemia	10	2	2	2	_	1	1	3	***21***
Bone	2	_	3	_	_	2	1	1	***9***
Melanoma	1	3	1	3	_	_	_	4	***12***
Lymphoma	1	1	3	3	1	1	_	2	***12***
Renal carcinoma	2	1	1	1	_	2	1	_	***8***
Other carcinoma	7	6	7	2	1	_	_	7	***30***
NMSC	42	22	19	2	1	9	_	6	***101***
All others	4	12	4	2	2	5	3	4	***36***
Total	***102***	***111***	***96***	***27***	***9***	***32***	***14***	***42***	***433***

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Second Tumors Working Group
SNs in Expanded Cohort (& original)

Primary Cancer Diagnosis										
Subsequent Neoplasm*	**Leukemia**	**CNS**	**HD**	**NHL**	**Kidney**	**Neuro-blastoma**	**Soft tissue sarcoma**	**Bone cancer**	***Total***	***Number in first look at orig cohort***
Breast	1	2	33	2	_	_	_	7	***45***	***60***
Meningioma	6	16	1	_	_	3	1	_	***27***	
Other CNS	14	19	0	2	_	_	2	1	***38***	***36***
Thyroid	11	12	18	3	2	5	1	4	***56***	***43***
Soft tissue sarcoma	1	15	4	5	2	4	4	3	***38***	***34***
Leukemia	10	2	2	2	_	1	1	3	***21***	***20***
Bone	2	_	3	_	_	2	1	1	***9***	***28***
Melanoma	1	3	1	3	_	_	_	4	***12***	***19***
Lymphoma	1	1	3	3	1	1	_	2	***12***	***13***
Renal carcinoma	2	1	1	1	_	2	1	_	***8***	
Other carcinoma	7	6	7	2	1	_	_	7	***30***	
NMSC	42	22	19	2	1	9	_	6	***101***	
All others	4	12	4	2	2	5	3	4	***36***	
Total	***102***	***111***	***96***	***27***	***9***	***32***	***14***	***42***	***433***	

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SNs in Overall Cohort

	Primary Cancer Diagnosis								
Subsequent Neoplasm*	**Leukemia**	**CNS**	**HD**	**NHL**	**Kidney**	**Neuro-blastoma**	**Soft tissue sarcoma**	**Bone cancer**	***Total***
Breast	30	7	249	15	11	3	18	46	***379***
Meningioma	113	93	4	8	_	3	7	2	***230***
Other CNS	59	45	9	7	1	2	7	3	***133***
Thyroid	46	29	69	14	5	15	10	17	***205***
Soft tissue sarcoma	17	29	30	9	11	12	26	11	***145***
Leukemia	23	5	20	7	2	6	5	10	***78***
Bone	7	5	9	6	6	2	14	11	***60***
Melanoma	12	10	14	4	2	_	10	14	***66***
Lymphoma	11	5	23	7	1	3	4	3	***57***
Renal carcinoma	5	3	5	4	1	11	3	3	***35***
Other carcinoma	38	17	42	15	8	5	21	20	***166***
NMSC	416	148	562	83	31	17	40	45	***1342***
All others	24	22	46	11	5	9	13	18	***148***
Total	***801***	***418***	***1082***	***190***	***84***	***88***	***178***	***203***	***3044***

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Second Tumors Working Group
5 Year Plan

- **Second Neoplasm Patterns Over Time (3 decades of therapy)**
  - **Overall cancer risk**
  - **Specific subpopulations**
  - **Correlation with exposures**
    - **i.e. Ifosfamide**
    - **Reduction of radiation dose**
- **Genomic Associations with Second Neoplasm Risk**
  - **Modifications / Associations with Therapeutic Exposures**
- **Further identification of the “not at risk” population**
- **Identifying and Acting on International opportunities**
- **New Investigators**