Genetics Working Group

A Report from the Childhood Cancer Survivor Study

Monica Gramatges

Yadav Sapkota

Smita Bhatia

June 2023

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Scope of Research

CCSS

The Genetics Working Group, in collaboration with the Second Neoplasm, Chronic Disease, Psychology, and Epidemiology/ Biostatistics Working Groups, is charged with understanding the role of genetic susceptibility in understanding the pathogenesis of treatment-related adverse events and explaining the inter-individual variability in the association between treatment and adverse events.

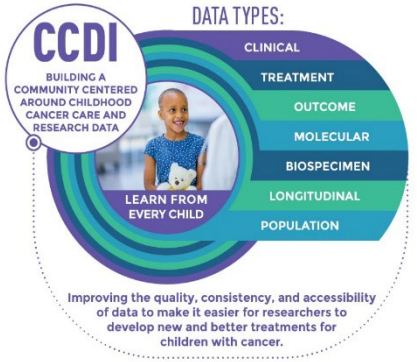
Resource for Genetic Investigation

CCSS

Characteristic	Genotype Data Diagnosed 1970-1986 (N=5,739)	WES Data Diagnosed 1970-1986 (N=5,451)	WGS and WES Data Diagnosed 1987-1999 (N=2,641)
Sex	n	n	n
Male	2,781 (49%)	2,630 (48%)	1,240 (47%)
Female	2,958 (51%)	2,821 (52%)	1,401 (53%)
Ancestry (based on genotype)			
European	5324 (93%)	5105 (94%)	2114 (80%)
Non-European	415	346	527
Data Access	**Available in dbGaP**	**Available in dbGaP**	**WGS Available in the St. Jude Cloud**

Phenotype data on all **25,665 CCSS** participants is available in **dbGaP** (diagnosis, treatment, and long-term outcome data

Expanding the Genomic and Biospecimen Resource: Supplemental Funding 2021



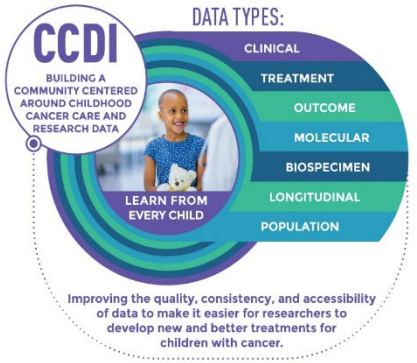
- SMN somatic tissues with matched germline specimens
  - 218 breast cancer, 116 thyroid, 111 meningioma
  - WGS, WES (Hudson Alpha), and RNAseq (St. Jude)
  - Approved concept to examine the effects of prior therapy on the genomic landscape, timing of mutation acquisition and immune infiltration signatures (Zhang)

Expanding the Genomic and Biospecimen Resource: Supplemental Funding

CCSS

	Breast Tissue		Thyroid Tissue		Meningioma Tissue		Melanoma Tissue	
Initial Cases with Tissue in CCSS BioPathology Center	**218**		**116**		**111**		**12**	
Cases Meeting Criteria and Submitted to HudsonAlpha	**127 (58%)**		**85 (73%)**		**109 (98%)**		**12 (100%)**	
	WGS	**WES**	**WGS**	**WES**	**WGS**	**WES**	**WGS**	**WES**
Adequate nucleic acid quantity/ quality from tumor tissue	**90 (42%)**	**83 (36%)**	**66 (56%)**	**71 (63%)**	**71 (70%)**	**71 (69%)**	**11 (92%)**	**3 (25%)**
Current Status								
In Library prep	0	0	0	0	0	0	0	0
In Sequencing	0	0	0	0	0	0	0	0
Sequencing Complete	90	82	66	71	71	71	11	3
Matched Pairs with Germline	78	76	51	65	54	57		
RNA Seq	42		49		34			

Expanding the Genomic and Biospecimen Resource: Supplemental Funding 2021



- 1,350 Survivors with CTCAE grade 3 or 4 chronic health conditions
  - At high risk for mortality
  - Banking 40ml specimen
  - Enhance the resource to understand the molecular basis of disease

COMPLETED

Biospecimen Resource

CCSS

Characteristic	Blood Specimen Available (n=4,426)		No Blood, But Oragene Available (n=6,769)		Overall: Either Blood or Oragene Available (n=11,195)	
	N	(%)	N	(%)	N	(%)
Sex						
Female	2,450	54.3	3,341	49.2	5,791	51.2
Race						
White	4,009	89.7	6,014	87.7	10,023	88.5
Black	238	5.8	345	5.3	583	5.5
American Indian/Alaska Nat.	16	0.4	33	0.5	49	0.4
Asian or Pacific Islander	41	1.0	111	1.9	152	1.6
Mixed race/Other	108	2.8	246	4.3	354	3.7
Unknown	14	0.3	20	0.2	34	0.3
Ethnicity						
Hispanic	206	5.0	526	8.5	732	7.1
Non-Hispanic	4115	93.0	6064	89.3	10179	90.8
Unknown	105	2.0	179	2.2	284	2.1
Age at Cancer Diagnosis						
0-4 yrs	1,428	35.9	2,832	45.1	4,260	41.4
5-9 yrs	984	24.2	1,560	24.5	2,544	24.3
10-14 yrs	1,116	22.7	1,362	17.8	2,478	19.7
15-20 yrs	898	17.3	1,015	12.7	1,913	14.5

Biospecimen Resource

CCSS

Characteristic	Blood Specimen Available (n=4,426)		No Blood, But Oragene Available (n=6,789)		Overall: Either Blood or Oragene Available (n=11,195)	
Primary Cancer Diagnosis						
ALL	1,233	39.3	1,730	37.8	2,963	38.4
AML	161	3.1	260	3.2	421	3.2
Other leukemia	56	1.1	73	0.9	129	1.0
Astrocytoma	300	5.7	756	9.3	1,056	7.9
Medulloblastoma/PNET	179	3.4	291	3.6	470	3.5
Other CNS malignancy	96	1.8	195	2.4	291	2.2
Hodgkin lymphoma	711	13.5	752	9.3	1463	10.9
Non-Hodgkin lymphoma	356	6.8	568	7.0	924	6.9
Kidney tumors	319	6.1	718	8.9	1037	7.8
Neuroblastoma	226	4.3	564	7.0	790	5.9
Soft tissue sarcoma	310	5.9	434	5.4	744	5.6
Ewing sarcoma	153	2.9	152	1.9	305	2.3
Osteosarcoma	306	5.8	243	3.0	549	4.1
Other bone malignancy	20	0.4	33	0.4	53	0.4

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Resource

Biospecimen Resource

CCSS

Characteristic	Blood Specimen Available (n=4,426)		No Blood, But Oragene Available (n=6,789)		Overall: Either Blood or Oragene Available (n=11,195)	
Vital status						
Alive	4,089	93.2	6,270	93.7	10,359	93.5
Dead	337	6.8	499	6.3	836	6.5
Treatment						
Chemo + RT + Surgery	1,728	35.1	2,031	26.0	3,759	29.6
Chemo + RT	503	12.7	557	8.9	1,060	10.4
Chemo + Surgery	899	20.3	1,630	22.4	2,529	21.5
Chemo Only	406	14.8	879	21.5	1,285	18.9
RT + Surgery	393	7.5	513	6.3	906	6.8
RT Only	9	0.2	16	0.2	25	0.2
Surgery Only	206	3.9	715	8.8	921	6.9
No treatment	11	0.2	22	0.3	33	0.2
Med. Rec. Not Available	271	5.3	406	5.6	677	5.4

Biospecimen Resource

CCSS

Characteristic	Blood Specimen Available (n=4,426)		No Blood, But Oragene Available (n=6,789)		Overall: Either Blood or Oragene Available (n=11,195)	
Age at sample collection						
<20 yrs	30	1.3	100	1.9	130	1.6
20-29 yrs	939	28.6	2,322	40.0	3,261	35.5
30-39 yrs	1,581	34.1	2,719	37.9	4,300	36.4
40-49 yrs	1,236	23.9	1,351	16.9	2,587	19.6
50-59 yrs	519	9.9	266	3.3	785	5.9
60+	121	2.3	11	0.1	132	1.0
Genomic data Available						
Genotype Array (Original Cohort	2,072	39.4	2,656	32.8	4,728	35.4
WES (Original Cohort)	1,542	29.3	2,654	32.8	4,196	31.4
WGS (Expansion Cohort)	565	12.9	2,123	34.1	2,688	25.8

Biospecimen Resource

CCSS

Characteristic	Blood Specimen Available (n=4,426)		No Blood, But Oragene Available (n=6,789)		Overall: Either Blood or Oragene Available (n=11,195)	
CTCAE grade and condition						
Max grade 3	1757	37.3	1223	16.3	2,980	24.6
Max grade 4	1020	20.9	742	9.9	1,762	14.2
Max grade 5	155	3.0	189	2.3	344	2.6
Multiple grade 3-5 conditions	1256	25.3	936	12.2	2,192	17.4
Diabetes requiring insulin	176	3.9	125	1.7	301	2.6
Emphysema	40	0.9	30	0.4	70	0.6
Lung fibrosis	49	1.0	45	0.6	94	0.7
Gonad dysfunction	355	7.2	222	2.9	577	4.6
Myocardial infarct	181	3.6	142	1.8	323	2.5
Congestive heart failure	204	4.0	167	2.1	371	2.8
Arrhythmia with pacemaker	100	2.1	63	0.8	163	1.3
Heart valve replacement	58	1.2	66	0.8	124	0.9
Stroke	231	4.9	217	3.0	448	3.7
Obesity	1228	28.2	1695	24.8	2,923	26.1
SMN	857	17.3	349	4.5	1,206	9.5
≥1 of the listed 11 health conditions listed	2421	52.6	2444	34.4	4,865	41.6
Grade 3-5 but none of the 11 conditions listed	933	19.4	813	11.0	1746	14.3
No grade 3-5 condition or obesity	1057	27.5	3478	54.0	4,535	43.5

Working Group Progress

CCSS

9	**Published/In Press Manuscripts (since 1/1/2022)**
2	**Currently Submitted Manuscripts**
8	**Approved Concepts/ analyses in progress**
1	**New AOIs (total, since 1/1/2022)**
8	**Ancillary studies in Progress**

Published (since January 2022)

ccss

1. Wang X, Singh P, Zhou L, Sharafeldin N, Landier W, Hageman L, Burridge P, Yasui Y, Sapkota Y, Blanco JG, Oeffinger KC, Hudson MM, Chow EJ, Armenian SH, Neglia JP, Ritchey AK, Hawkins DS, Ginsberg JP, Robison LL, Armstrong GT, Bhatia S. Genome-Wide Association Study Identifies ROBO2 as a Novel Susceptibility Gene for **Anthracycline-Related Cardiomyopathy** in Childhood Cancer Survivors. ***J Clin Oncol.*** 2023 Mar 20;41(9):1758-1769.

2. Sapkota Y, Ehrhardt MJ, Qin N, Wang Z, Liu Q, Qiu W, Shelton K, Shao Y, Plyler E, Mulder HL, Easton J, Michael JR, Burridge PW, Wang X, Wilson CL, Jefferies JL, Chow EJ, Oeffinger KC, Morton LM, Li C, Yang JJ, Zhang J, Bhatia S, Mulrooney DA, Hudson MM, Robison LL, Armstrong GT, Yasui Y. A Novel Locus on 6p21.2 for Cancer Treatment-Induced **Cardiac Dysfunction** Among Childhood Cancer Survivors. ***J Natl Cancer Inst.*** 2022 Aug 8;114(8):1109-1116.

Published (since January 2022)

ccss

3. Sapkota Y, Qiu W, Dixon SB, Wilson CL, Wang Z, Zhang J, Leisenring W, Chow EJ, Bhatia S, Armstrong GT, Robison LL, Hudson MM, Delaney A, Yasui Y. Genetic risk score enhances the risk prediction of **severe obesity** in adult survivors of childhood cancer. ***Nat Med.*** 2022 Aug;28(8):1590-1598.

4. Richard MA, Mostoufi-Moab S, Rathore N, Baedke J, Brown AL, Chanock SJ, Friedman DN, Gramatges MM, Howell RM, Kamdar KY, Leisenring WM, Meacham LR, Morton LM, Oeffinger K, Robison LL, Sapkota Y, Sklar CA, Armstrong GT, Bhatia S, Lupo PJ. Germline Genetic and Treatment-Related Risk Factors for **Diabetes Mellitus** in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study and St Jude Lifetime Cohorts. ***JCO Precis Oncol.*** 2022 Dec;6:e2200239.

Published (since January 2022)

ccss

5. Lu D, Sapkota Y, Valdimarsdóttir UA, Koenen KC, Li N, Leisenring WM, Gibson T, Wilson CL, Robison LL, Hudson MM, Armstrong GT, Krull KR, Yasui Y, Bhatia S, Recklitis CJ. Genome-wide association study of **posttraumatic stress disorder** among childhood cancer survivors: results from the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort. ***Transl Psychiatry.*** 2022 Aug 23;12(1):342.

6. Man, T. K., Aubert, G., Richard, M. A., LeJeune, W., Hariri, E., Goltsova, T., Gaikwad, A., Chen, Y., Whitton, J., Leisenring, W. M., Arnold, M. A., Neglia, J. P., Yasui, Y., Robison, L. L., Armstrong, G. T., Bhatia, S., & Gramatges, M. M. (2022). Short NK- and Naïve T-Cell Telomere Length Is Associated with **Thyroid Cancer** in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study. ***CEBP***, 31(2), 453–460. https://doi.org/10.1158/1055-9965.EPI-21-0791

Published (since January 2022)

ccss

7. Rotz SJ, Worley S, Hu B, Bazeley P, Baedke JL, Hudson MM, Kuo DJ, Oeffinger KC, Robison LL, Sahoo D, Wang F, Yasui Y, Armstrong GT, Bhatia S. Genome-Wide Association Study of **Pregnancy** in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study. ***CEBP***. 2022 Sep 2;31(9):1858-1862.

8. Chen C, Song N, Dong Q, Sun X, Mulder HL, Easton J, Zhang J, Yasui Y, Bhatia S, Armstrong GT, Wang H, Ness KK, Hudson MM, Robison LL, Wang Z. Association of Single-Nucleotide Variants in the Human Leukocyte Antigen and Other Loci With **Childhood Hodgkin Lymphoma**. ***JAMA Netw Open***. 2022 Aug 1;5(8):e2225647.

9. Im,…,Turcotte. Polygenic risk and **chemotherapy-related subsequent malignancies** among long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study and St. Jude Lifetime Cohort Study, ***JCO*** (In Press)

Manuscripts under review

CCSS

1. Im,…, Wilson, Sapkota. Trans-ancestral genetic study of **diabetes mellitus** risk in survivors of childhood cancer: a report from the St. Jude Lifetime Cohort and the Childhood Cancer Survivor Study, (Under Review)

2. Chen,….Wang. Cancer Predisposing Variants and **Late-Mortality from Subsequent Malignant Neoplasms** Among Long-Term Survivors of Childhood Cancer: A Report from the St. Jude Lifetime Cohort and the Childhood Cancer Survivor Study (Revise/Resubmit ***Lancet Oncology***)

Approved Concepts (in progress)

CCSS

1. Whole genome sequencing of the youngest osteosarcoma cases (Mirabello)
2. Risk prediction of menarche and menopause-related phenotypes in childhood cancer survivors using polygenic risk scores and clinical predictors (Yuan)
3. Long-term cost-effectiveness of the identification of cancer predisposition syndromes in survivors of pediatric leukemia, brain tumors or bone/soft-tissue sarcomas(Goudie)
4. Genetic association study of cardiac toxicity following chest radiotherapy (Kerns)

Approved Concepts (in progress)

CCSS

5. Autoimmune genetic variation to identify survivors at risk of chemotherapy-associated subsequent malignant neoplasms (Watt)
6. Neurocognitive outcomes and genetic susceptibility (Scheurer/Richard/Krull)
7. GWAS for dyslipidemia (Pluimakers)
8. GWAS for frailty in adult survivors of childhood cancer (Gramatges)

Concepts under development

CCSS

1. GWAS of dyslipidemia (lipid traits) and risk prediction model
    - Discovery (SJLIFE); Replication (CCSS) (Kateryna/Sapkota)

Approved Ancillary Studies

CCSS

1. Epigenetic Approach in Understanding the Risk of Cardiometabolic Conditions (Z. Wang)
2. Trajectories of Epigenetic Aging and Health Outcomes in Survivors of Childhood Cancer (Z. Wang)
3. Developing and validating race-specific cardiomyopathy risk prediction model in African American survivors of childhood cancer (Sapkota/Im)
4. Communication of Skin Cancer Risk Profiles to Childhood Cancer Survivors (Im)
5. Leveraging High-Fidelity Sequencing to Define the Impact of Chemotherapy and Radiotherapy on Mutation in Normal Cells (Shoag)
7. Investigation of Predisposition to Pediatric Radiation-Induced Glioma (Green)
8. Immune phenotype and chronic health conditions (Dhodapkar/Bhatia)

Career Development Award

CCSS

Gordon P. Watt, Ph.D.
Memorial Sloan Kettering Cancer Center

Mentor: Jonine Bernstein, PhD

Aim 1. Conduct SNP-by-SNP tests of interaction to identify autoimmune SNPs that interact with chemotherapy to modify risk of SMNs.

Aim 2. Develop and test an autoimmune PRS to predict risk of chemotherapy-associated SMNs.

Career Development Award

CCSS

Catherine Goudie, MD
McGill University

Mentor: Paul Nathan, MD

Long-term cost-effectiveness of cancer predisposition syndrome identification strategies in survivors of pediatric leukemia, brain tumors or bone/soft-tissue sarcomas

Aim: To inform a cost-effectiveness model which estimates the long-term impact of CPS detection, and which compares three CPS detection strategies in survivors of acute lymphoblastic leukemia (ALL), bone/soft tissue sarcomas (bone/STS) and brain tumors.

Highlights of Recently Completed Research

CCSS

Obesity

CCSS

ARTICLES
https://doi.org/10.1038/s41591-022-01902-3

nature medicine

Check for updates

Genetic risk score enhances the risk prediction of severe obesity in adult survivors of childhood cancer

Yadav Sapkota[1]✉, Weiyu Qiu[2], Stephanie B. Dixon[1], Carmen L. Wilson[1], Zhaoming Wang[1], Jinghui Zhang[1], Wendy Leisenring[3], Eric J. Chow[3], Smita Bhatia[4], Gregory T. Armstrong[1], Leslie L. Robison[1], Melissa M. Hudson[1], Angela Delaney[1] and Yutaka Yasui[1]✉

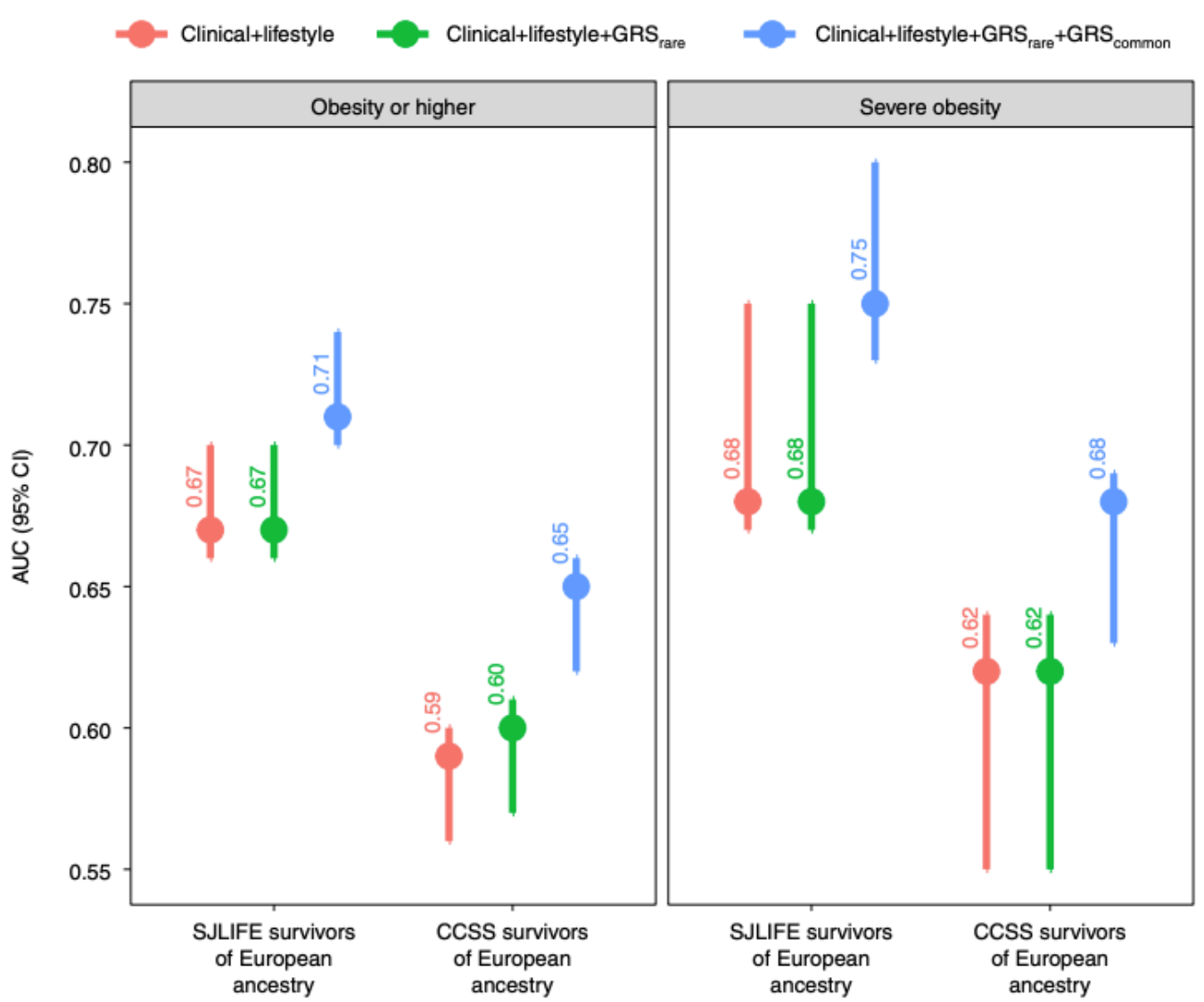
- 2,548 EUR survivors from SJLIFE
  - model development
- 6,064 EUR survivors from CCSS
  - model validation

In survivors, general population genetic risk scores for BMI

- **Showed 53-fold odds of severe obesity**
- **Increased AUC from 0.68 (Clinical + lifestyle) to 0.75**
- **Identified 4.3-times more high-risk survivors than Clinical + lifestyle factors alone**

Obesity

CCSS



Childhood Cancer Survivor Study

An NCI-funded resource

Treatment-specific genetic risk scores for late effects prediction in CAYA cancer survivors (NCI R21CA261833)

MPIs: Cindy Im, Yan Yuan

Specific Aim 1: Create a catalog of treatment-specific genetic effects (i.e., gene-treatment interactions) for selected chronic health conditions

Specific Aim 2: Construct and evaluate novel survivor-/therapy-specific polygenic risk scores (PRS) that appropriately account for treatment-specific genetic effects

Chronic health conditions:

Subsequent cancer
- Breast cancer
- Thyroid cancer
- Basal cell carcinoma
- SMN (any)

Cardiovascular
- Heart failure
- Hypertension
- Coronary artery disease

Endocrine
- Diabetes mellitus

Progress to date (NCI R21CA261833)

MPIs: Cindy Im, Yan Yuan

CCSS

Publications:

Leveraging therapy-specific polygenic risk scores: Predicting **restrictive lung defects** in childhood cancer survivors (Im *et al*., *Cancer Res* 2022)

In press:

Polygenic risk and **chemotherapy-related subsequent malignancies** in childhood cancer survivors: a CCSS and SJLIFE report (Im and Sharafeldin *et al*., *J Clin Oncol*)

Manuscripts under review:

Trans-ancestral genetic study of **diabetes mellitus risk** in survivors of childhood cancer: a report from SJLIFE and CCSS (Im *et al*.)

Predicting **primary ovarian insufficiency** in long-term survivors of childhood cancer: a report from CCSS (Lu and Im, *et al*.; Yuan, senior author)

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal
ORIGINAL REPORTS | Pediatric Oncology

Genome-Wide Association Study Identifies *ROBO2* as a Novel Susceptibility Gene for Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors

Xuexia Wang, PhD[1]; Purnima Singh, MSc, PhD, MSPH[2]; Liting Zhou, MS[2]; Noha Sharafeldin, MD, MSc, PhD[2]; Wendy Landier, PhD[2]; Lindsey Hageman, MPH[2]; Paul Burridge, PhD[3]; Yutaka Yasui, PhD[4]; Yadav Sapkota, PhD[4]; Javier G. Blanco, PhD[5]; Kevin C. Oeffinger, MD[6]; Melissa M. Hudson, MD[4]; Eric J. Chow, MD, MPH[7]; Saro H. Armenian, DO, MPH[8]; Joseph P. Neglia, MD, MPH[9]; A. Kim Ritchey, MD[10]; Douglas S. Hawkins, MD[7]; Jill P. Ginsberg, MD[11]; Leslie L. Robison, PhD[4]; Gregory T. Armstrong, MD, MSCE[4]; and Smita Bhatia, MD, MPH[2]

GWAS with focus on GxE interactions

SNP rs17736312 (*ROBO2*) was successfully replicated

AA genotype + >250mg/m^2: 2.2-fold higher risk of CHF in Discovery (CCSS)

8.2-fold higher risk in Replication (COG)

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

ROBO2 encodes Robo receptors that bind Slit ligands

Slit-Robo signaling pathway promotes cardiac fibrosis by interfering with the TGFβ1/Smad pathway

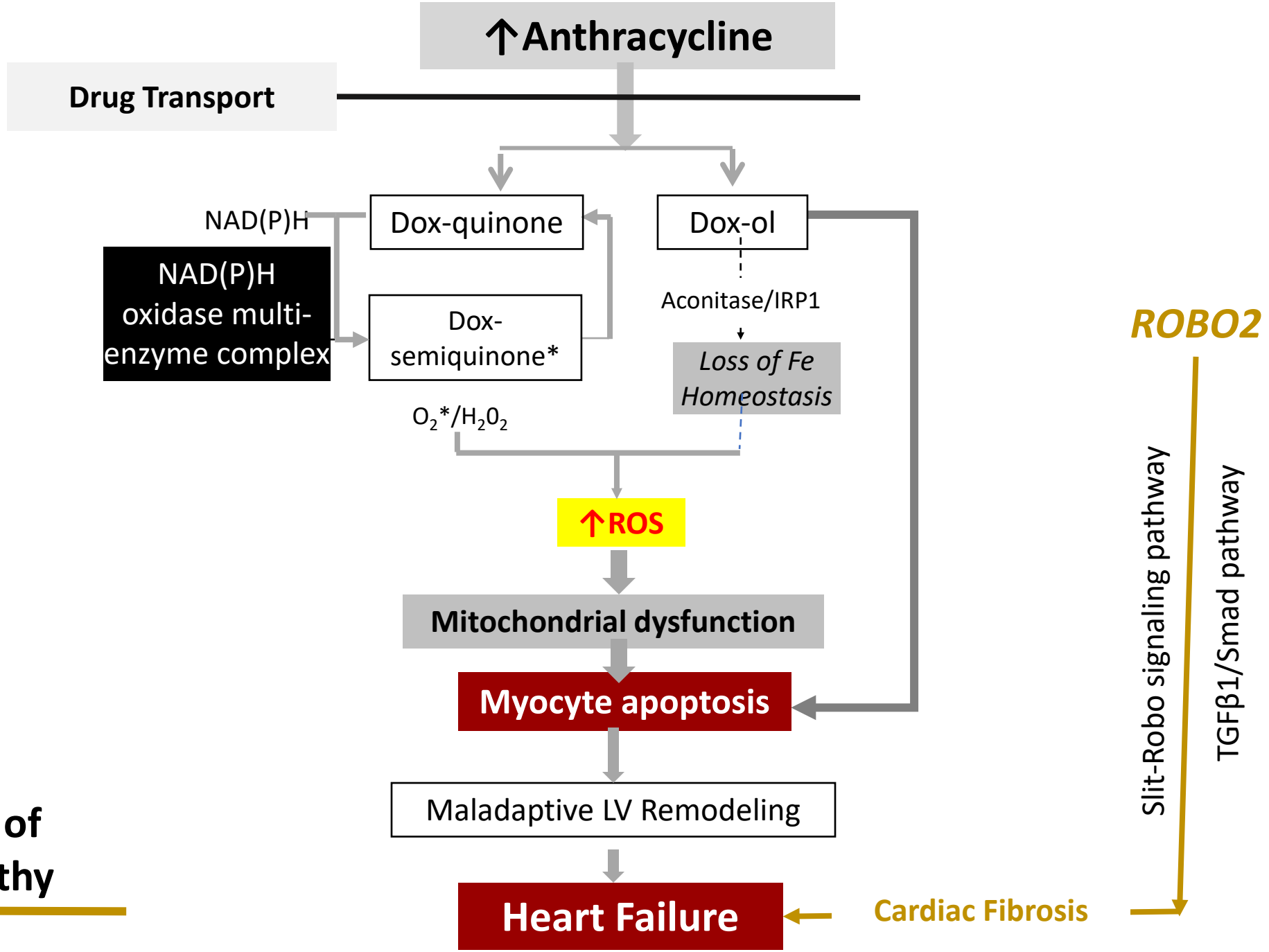
Results in disordered remodeling of ECM and potentiates heart failure

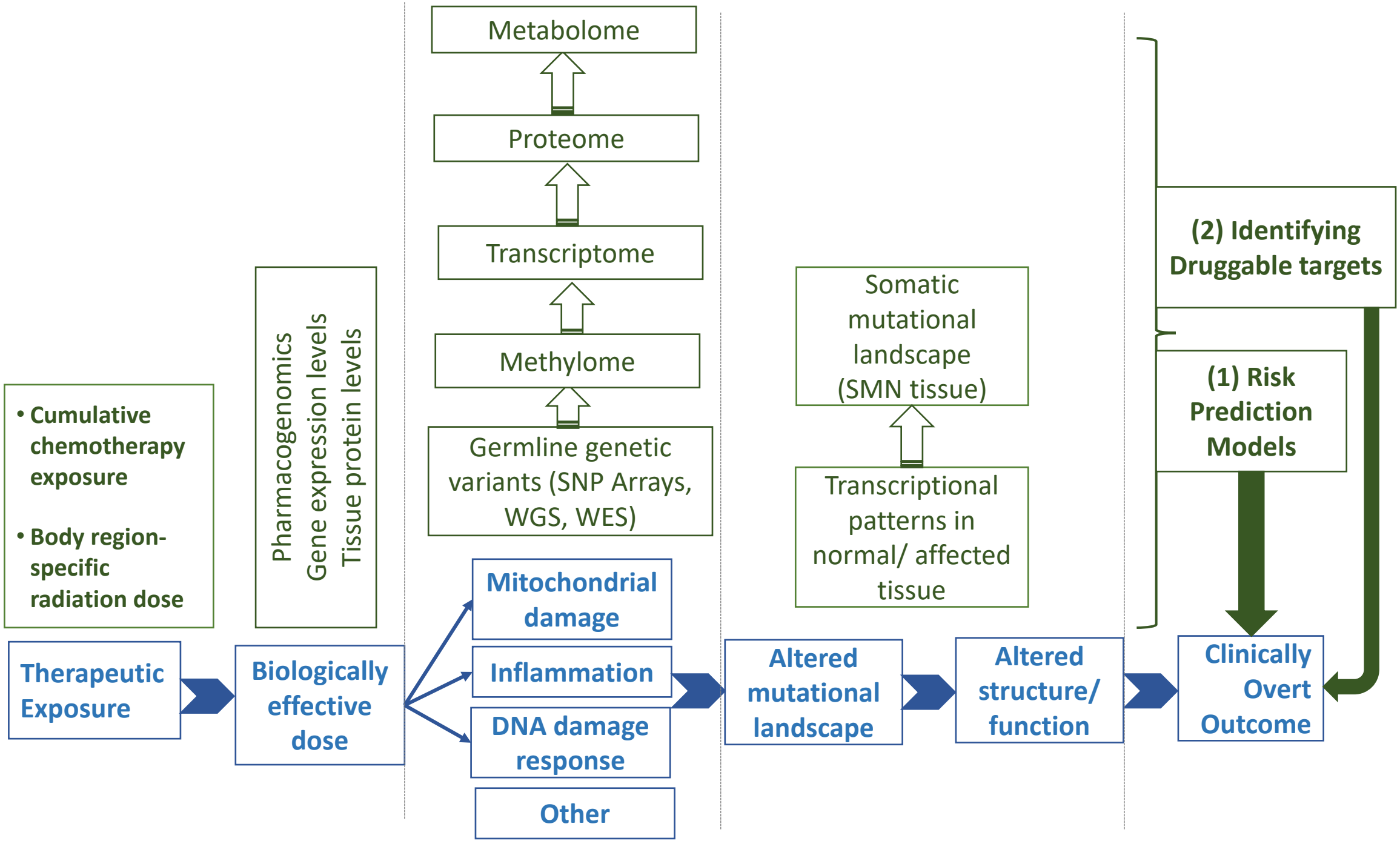
We found significant gene-level associations with heart failure

- main effect (*TGF-β1*, *P* = .007);
- gene*anthracycline (*ROBO2**anthracycline, *P* = .0003)
- gene*gene*anthracycline (*SLIT2***TGF-β1***anthracycline, *P* = .009)

Implications: High-dose anthracyclines combined with genetic variants involved in the profibrotic Slit-Robo signaling pathway promote cardiac fibrosis via the TGF-β1/Smad pathway, providing credence to the biologic plausibility of the association between SNP rs17736312 (*ROBO2*) and anthracycline-related cardiomyopathy.

Pathogenesis of Cardiomyopathy

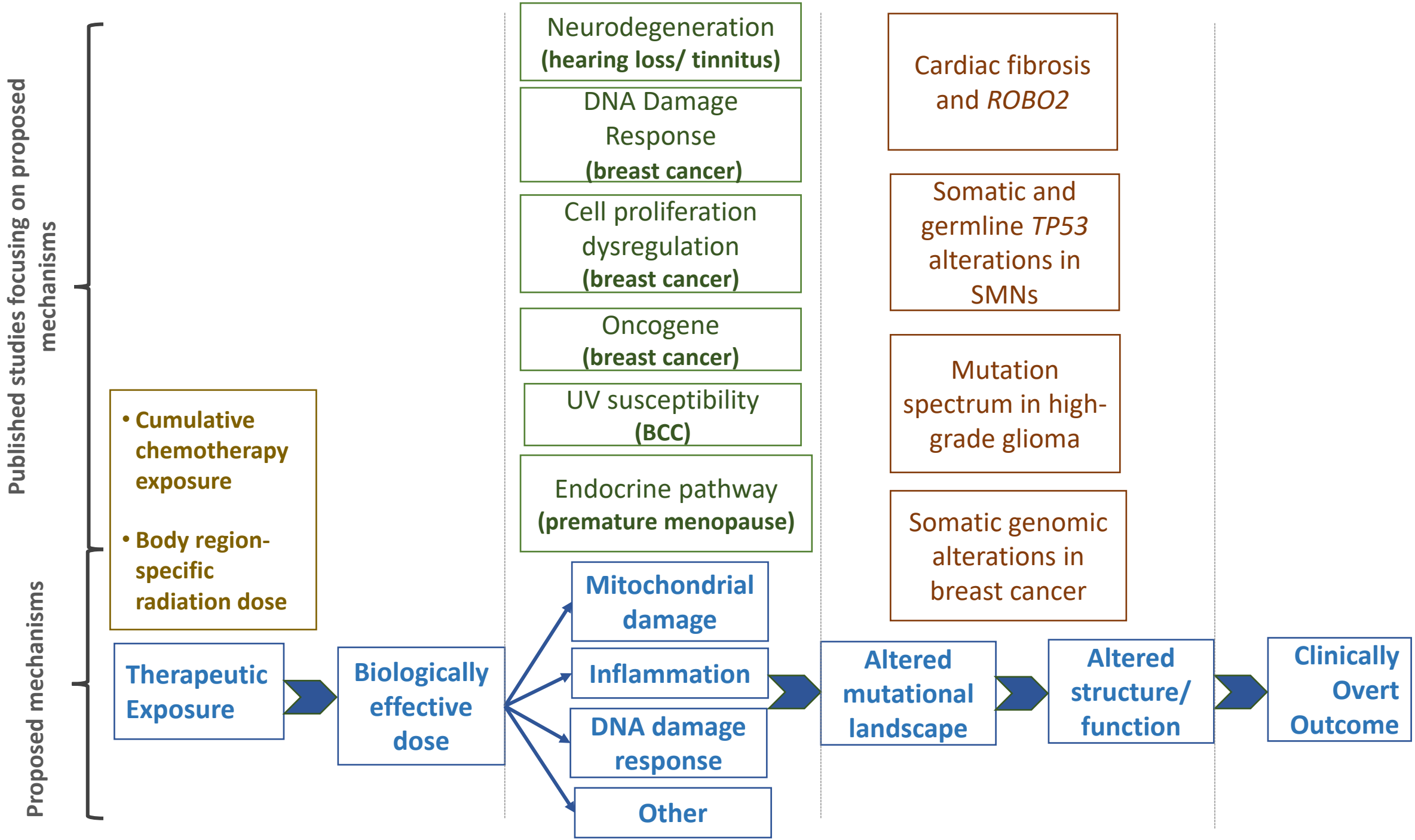



Metabolome
Proteome
Transcriptome
Methylome
Germline genetic variants (SNP Arrays, WGS, WES)
Pharmacogenomics
Gene expression levels
Tissue protein levels
• Cumulative chemotherapy exposure
• Body region-specific radiation dose
Therapeutic Exposure
Biologically effective dose
Mitochondrial damage
Inflammation
DNA damage response
Other
Somatic mutational landscape (SMN tissue)
Transcriptional patterns in normal/ affected tissue
Altered mutational landscape
Altered structure/ function
(2) Identifying Druggable targets
(1) Risk Prediction Models
Clinically Overt Outcome

Genetic Working Group

CCSS

Thank you


Published studies focusing on proposed mechanisms
Proposed mechanisms
Neurodegeneration (hearing loss/ tinnitus)
DNA Damage Response (breast cancer)
Cell proliferation dysregulation (breast cancer)
Oncogene (breast cancer)
UV susceptibility (BCC)
Endocrine pathway (premature menopause)
Cardiac fibrosis and ROBO2
Somatic and germline TP53 alterations in SMNs
Mutation spectrum in high-grade glioma
Somatic genomic alterations in breast cancer
• Cumulative chemotherapy exposure
• Body region-specific radiation dose
Therapeutic Exposure
Biologically effective dose
Mitochondrial damage
Inflammation
DNA damage response
Other
Altered mutational landscape
Altered structure/ function
Clinically Overt Outcome

One-year deliverables

CCSS

Leverage

- Germline samples from selected survivor populations
- Somatic tissue from patients with SMNs

Understand mechanistic pathways associated with the development of treatment-related adverse events.

sequenced data for ~11000 childhood cancer survivors diagnosed 1970-1999

- Identify rare variants, multi-allelic substitutions, insertions/ deletions

5-year plan – prioritize hypothesis-driven research

CCSS

Develop an integrated approach to understand mechanistic pathways associated with treatment-related complications

- Extend beyond genomics to other “omics”
  1. Transcriptomics
  2. Proteomics
  3. Metabolomics
  4. Microbiome
- Functional studies stemming from genomic leads
  - iPSC derived models
  - *Pre-clinical* animal models
  - Utilization of somatic tissue (SMNs) integrated with germline variants/ mutations

Develop integrated risk-prediction models for precision prevention

Use mechanistic pathways to identify druggable target

Genetics WG – NCI collaboration

Supplements awarded by the NCI

CCSS

Leverage somatic tissue with matched germline DNA for SMN cases

- Support WGS, WES, RNASeq
- Overarching goal
  - create a rich and unique resource to examine mutational landscape in SMNs
  - undertake hypothesis-driven approaches to understand pathogenesis of SMNs and carcinogenesis at large

Collect 40 mL peripheral blood sample from survivors with CTCAE grade 3 or 4 non-malignant events at high risk for premature mortality.

- Support WGS, WES, RNASeq, Methylation, Proteomics, Metabolomics, etc.
- Overarching goal
  - understand the molecular basis of disease in this population

Resource

CCSS

1) SNP array data

- 5,739 childhood cancer survivors diagnosed 1970-1986 (5,324 [93%] of European ancestry)
  - Illumina HumanOmni5Exome microarray
  - 4.1 million loci passed quality control thresholds

2) WES data

- 8,092 childhood cancer survivors diagnosed 1970-1999

3) WGS

- 2,641 childhood cancer survivors diagnosed 1987-1999

4) Accompanying **phenotype** data

- **~7,500 European survivors with CCSS genotype data and 5% with late effect of interest (n=375) can detect**
  - OR=1.96-2.50 for common variants (risk allele frequency (rAF) >5%)
  - OR=2.69-4.84 for low-frequency variants (rAF=1-5%)