Genetics Working Group

A Report from the Childhood Cancer Survivor Study

Smita Bhatia, MD, MPH

CCSS
Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

An NCI-funded Resource

Scope of Research

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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 explaining the inter-individual variability in the therapy-adverse event association.

Working Group Membership

CCSS

Greg Armstrong

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Les Robison

Joshua Sampson

Peggy Tucker

Lucie Turcotte

Yutaka Yasui

Working Group Progress

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Genetics WG

NCI collaboration

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1) SNP array data

- 5,739 childhood cancer survivors diagnosed 1970-1986 (5,324 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 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%)

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

Initiate collection of a 40 mL peripheral blood sample on survivors with CTCAE grade 3 or 4 non-malignant events at high risk for premature mortality.

- Overarching goal
  - understand the molecular basis of disease in this population from genome, methylome and transcriptome, to metabolome and proteome

Research Projects Using CCSS Genetic Resource

Germline genetic variants associated with SMNs

CCSS

Study Title	PI/ Institution	Funding	Status
XRCC1 and *GST* gene polymorphisms and susceptibility to **radiotherapy-related malignancies** in survivors of Hodgkin disease	Mertens/Univ. of Minnesota	Internal funding	Mertens AC et al, **Cancer** 2004; 101(6): 1463-72
Variants at 6q21 implicate *PRDM1* in the etiology of therapy-induced **second malignancies** after Hodgkin lymphoma	Onel/University of Chicago	NIH R21	Best T et al, **Nat Med** 2011;17:941-3
Subsequent neoplasm risk associated with rare variants in DNA damage response and clinical radiation sensitivity syndrome genes	Morton/NCI	NIH intramural funds	Morton LM et al, **JCO Precis Oncol** 2020;4:PO.20.00141

Research Projects Using CCSS Genetic Resource

Germline genetic variants associated with breast SMNs

CCSS

Study Title	PI/ Institution	Funding	Status
GWAS identifies susceptibility loci that modify **radiation-related risk for breast cancer** after childhood cancer	Morton/NCI	NIH intramural funds	Morton LM et al, **J Natl Cancer Inst** 2017; 109(11)
Genetic susceptibility to **radiation-induced breast cancer** after Hodgkin lymphoma	Van Leeuwen/ Princess Maxima Ctr	Internal funding	Opstal-van Winden AWJ et al, **Blood** 2019; 133:1130-1139

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with Thyroid SMNs

CCSS

Study Title	PI/ Institution	Funding	Status
Telomere length-associated genetic variants and risk of **thyroid cancer** in survivors of childhood cancer	Gramatges/ Baylor	NIH R01	Gramatges MM et al, **CEBP.** 2018; 28(2):417-419
Genetic variation in POT1 and risk of **thyroid SMN**	Gramatges/ Baylor	NIH R01	Richard MA et al, **PLOS ONE** 2020; 15(2)
Polygenic risk score for **subsequent thyroid cancer**	Wang/ St. Jude	Internal funding	Manuscript under review
Telomere content and risk of **SMNs** in survivors of childhood cancer	Gramatges/ Baylor	Institutional training grant	Gramatges et al, **Clin Cancer Res** 2014; 20(4):904-11

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with BCC SMNs

CCSS

Study Title	PI/ Institution	Funding	Status
GWAS in irradiated childhood cancer survivors identifies *HTR2A* for subsequent **basal cell carcinoma**	Morton/NCI	NIH intramural funds	Sapkota Y et al, **J Invest Dermatol** 2019; 139:2042-2045

Research Projects Using the CCSS Genetic Resource

Somatic mutations associated with SMNs

CCSS

Study Title	PI/ Institution	Funding	Status
Characterization of genomic alterations in **radiation-associated breast cancer** among childhood cancer survivors using comparative genomic hybridization (CGH) arrays	Yang/NCI	NIH intramural funds	Yang XR et al, **PLoS ONE** 2015; 12;10(3)
Somatic and germline TP53 alterations in **second malignant neoplasms** from pediatric cancer survivors	Nakamura/ UCSF	St. Baldrick's Foundation	Sherborne AL et al, **Clin Cancer Res** 2017; 23(7): 1852-1861
Comprehensive molecular characterization of pediatric treatment-induced **high-grade glioma**: a distinct entity despite disparate etiologies with defining molecular characteristics and potential therapeutic targets	Lucas/St. Jude	Internal funding	**Nature Communications**. 2021, in press

Research Projects Using the CCSS Genetic Resource

Genetics / epigenetics of Obesity/ BMI

CCSS

Study Title	PI/ Institution	Funding	Status
Genetic variation in the leptin receptor gene and **obesity** in ALL survivors	Ross/Univ. of Minnesota	Internal funding	Ross JA et al, **J Clin Onc** 2004; 22(17):3558-62
DNA methylation and **obesity** in survivors of pediatric acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study	Lupo/Baylor	CCSS CDA	Lupo PJ et al, **Genes Chromosomes** Cancer 2019; 58(1):52-59
Genetic variation in **body mass index** of adult survivors of childhood acute lymphoblastic leukemia	Kamdar/Texas Children's Hospital	Leukemia Lymphoma Society	Richard MA, et al. **Cancer.** 2021 Jan 15;127:310-318.
Protein-altering variants (PAV) associated with **BMI** in the general population and their roles in survivors of childhood cancer.	Sapkota/ St. Jude	Internal funding	Analysis Underway

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with cardiac disorders

CCSS

Study Title	PI/ Institution	Funding	Status
Genetic polymorphisms in *CBR3* and *NQO1* in patients who developed anthracycline-related congestive **heart failure**	Blanco/Univ. of Buffalo	Internal funding	Blanco JG et al, **Cancer** 2008; 112(12): 2789-95
Cardiomyopathy Simulation Model	Yeh/Boston Children's Hospital	NIH R01	Analysis Underway
Genome Wide Investigation of **Anthracycline Cardiomyopathy**	Bhatia/UAB	Internal funding	Analysis Underway – MS under prep
Genome Wide Investigation of **Myocardial Infarction, stroke**	Morrison and Bowers/Univ. Texas Health Science Ctr, UTSW	Internal funding	Replication unsuccessful
iPSC-Cardiomyocyte RNAseq Identified Genes and **Cardiomyopathy**	Reyes/ MD Anderson	Internal funding	Replication unsuccessful

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with neuropsychological outcomes

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Study Title	PI/ Institution	Funding	Status
Antioxidant enzyme polymorphisms and **neuropsychological outcomes** in medulloblastoma survivors	Brackett/Texas Children's Hospital	Internal funding	Brackett J et al, **Neuro Oncol** 2012; 14(8): 1018-25
Genetic Susceptibility to **Neurocognitive Impairment**	Scheurer/ Baylor College of Medicine	Internal funding	Analysis Underway
Genetic Determinants of **PTSD**	Recklitis/Dana Farber Cancer Institute	Internal funding	MS under prep

Research Projects Using the CCSS Genetic Resource

Germline Genetic Variants associated with reproductive health

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Study Title	PI/ Institution	Funding	Status
A high-risk haplotype for **premature menopause** in childhood cancer survivors exposed to gonadotoxic therapy	Brooke/ St. Jude	Internal funding	Brooke RJ et al, **J Natl Cancer Inst** 2018; 110: 895-904
Genetic Polymorphisms of **pregnancy** in Cyclophosphamide Exposed Survivors	Rotz/Cleveland Clinic	Internal funding	Analysis Underway

Research Projects Using the CCSS Genetic Resource

Germline Genetic Variants associated with CVRFs

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Study Title	PI/ Institution	Funding	Status
Contribution of Polygenic Risk to **Hypertension** Among Long-Term Survivors of Childhood Cancer	Sapkota/ St. Jude	Internal funding	**JACC: CardioOncology**, 2021;3: 85-87
Genome Wide Investigation of **Diabetes Mellitus**	Lupo/Baylor College of Medicine	Internal funding	Oral presentation at **ASCO** (2021) MS under prep
Developing a Clinical and Genetic Risk Prediction Model for **Diabetes Mellitus** among Survivors of Childhood Cancer	Lupo/Baylor College of Medicine	Internal funding	Analysis Underway
Genome-wide Investigation of **Dyslipidemia**	Pluimakers/ Princess Maxima Ctr	Internal funding	Analysis Underway

Research Projects Using the CCSS Genetic Resource

Germline Genetic Variants associated with Frailty/ Fracture

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Study Title	PI/ Institution	Funding	Status
Genome-wide Association Studies Reveal Novel Locus With Sex-/Therapy-Specific **Fracture** Risk Effects in Childhood Cancer Survivors.	Im/ St. Jude	Internal funding	**J Bone Miner Res.** 2020 Dec 18.
GWAS for **Frailty** in adult survivors of childhood cancer	Gramatges/ Baylor	Internal funding	Awaiting replication in SJLIFE

Research Projects Using the CCSS Genetic Resource

Germline Genetic Variants associated with non-malignant disorders

CCSS

Study Title	PI/ Institution	Funding	Status
Clinical and genetic risk factors for radiation-associated **ototoxicity**	Dolan/ University of Chicago	Internal funding	Revised/ resubmitted to **Cancer,** 2021

Study Title	PI/ Institution	Funding	Status
Genome Wide Investigation of **Intestinal Obstruction**	Madenci/ Boston Children's Hospital	Internal funding	Did not find any SNPs that exceeded the threshold for genome-wide significance

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with primary cancer

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Study Title	PI/ Institution	Funding	Status
Frequency of pathogenic germline variants in **pediatric cancer survivors**	Kim and Mirabello/NIH	NIH intramural funds	MS under review

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with primary sarcoma

CCSS

Study Title	PI/ Institution	Funding	Status
Evaluation of polymorphisms in EWSR1 and risk of **Ewing Sarcoma**	DuBois/UCSF	Institutional training grant	Dubois S et al, **Pediatr Blood Cancer** 2012; 59:52-6
Chimeric *EWSR1-FLI1* regulates the **Ewing sarcoma** susceptibility gene EGR2 via a GGAA microsatellite	Grunewald/ Institut Curie	-	Grunewald TG et al, **Nat Genet** 2015; 47(9):1073-8
Genome-wide association study identifies multiple new loci associated with **Ewing sarcoma** susceptibility	Machiela/NCI	NIH intramural funds	Machiela MJ et al, **Nat Commun** 2018; 9(1): 3184
Low-frequency variation near common germline susceptibility loci are associated with risk of **Ewing sarcoma.**	Lin and Machiela/NCI	NIH intramural funds	Lin et al, **PLoS One.** 2020 Sep 3;15(9):e0237792.
Frequency of pathogenic germline variants in cancer-susceptibility genes in patients with **osteosarcoma**	Mirabello/NIH	NIH intramural funds	Mirabello L et al, **JAMA Oncol.** 2020 May 1;6(5):724-734.

Research Projects Using the CCSS Genetic Resource

Germline genetic variants associated with Lymphoma

CCSS

Study Title	PI/ Institution	Funding	Status
A genome-wide meta-analysis of **Nodular Sclerosing Hodgkin Lymphoma** identifies risk loci at 6p21.32.	Cozen/ USC	Multiple Awards	Cozen W et al, **Blood** 2012; 119 (2):469-475
A meta-analysis of **Hodgkin lymphoma** reveals 19p13.3 TCF3 as a novel susceptibility locus	Cozen/ USC	Multiple Awards	Cozen W et al, **Nat Commun** 2014; 5:3856
Meta-analysis of genome-wide association studies reveals genetic overlap between **Hodgkin lymphoma** and multiple sclerosis	Cozen/ USC	Internal funding	Khankhanian P et al, **Int J Epidemiol** 2016; 45(3): 728-40
Association of germline *BRCA2* mutations with the risk of pediatric or adolescent **non-Hodgkin lymphoma**	Wang/St. Jude	Internal funding	Wang Z et al, **JAMA Oncol** 2020; 5(9):1362-1364

Research Projects Using the CCSS Genetic Resource

Additional studies

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Study Title	PI/ Institution	Funding	Status
Successful use of whole genome amplified DNA from multiple source types for high-density Illumina SNP microarrays	Morton/NCI	NIH intramural funds	Dagnall CL et al, **BMC Genomics** 2018; 19(1): 182
Generalizability of GWAS hits in clinical populations	Im/Univ. of Alberta	Internal funding	**Am J Hum Genet.** 2020 Oct 1;107(4):636-653.

Research Projects Using the CCSS Genetic Resource

Concepts

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Study Title	PI/ Institution	Funding	Status
Multiple SMNs & genomic instability/DNA repair	Bhatia/UAB	Internal funding	Pending concept development
Genetic Association Study of **Cardiac Toxicity Following Chest Radiotherapy**	Kerns/ University of Rochester	Internal funding	Pending concept development
Long-Term Cost-Effectiveness of the Identification of **Cancer Predisposition Syndromes** in Survivors of Pediatric Leukemia, Brain Tumors and Bone/Soft-Tissue Sarcomas	Goudie/McGill University	CCSS CDA	Pending concept development
Clinical and Genetic Profiling of **Cataract Risk**	Sharafeldin/ UAB	Internal funding	Pending concept development
Robust Genetic Predictors of **Secondary Cancer** Risks (Ancillary Study)	Ostrer/Einstein College of Medicine	NIH R01	Pending procurement of funding

Highlights of Recently Completed Research

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Subsequent Neoplasm Risk associated with rare variants in DNA Damage Response and Clinical Radiation Sensitivity Syndrome

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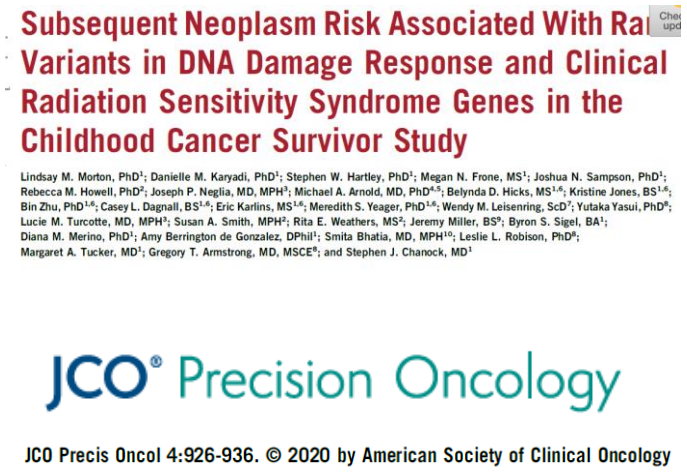
Subsequent Neoplasm Risk Associated With Rare Variants in DNA Damage Response and Clinical Radiation Sensitivity Syndrome Genes in the Childhood Cancer Survivor Study

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Goal

- Examine SN risk associated with potentially protein damaging rare variants in 476 DDR or radiation-sensitivity genes

Methods

- Whole-exome sequencing in a cohort of 5,105 childhood cancer survivors originally diagnosed during 1970 to 1986 (mean follow-up, 32.7y)
- Reconstruction of doses to body regions from radiotherapy records
- 1108 survivors with RT related SNs (BCC, breast ca, meningioma, thyroid ca, sarcoma)
- Matched controls (age, sex, survival, RT dose

Results

- Out-of-field RT-SN risk, excluding BCC, was associated with homologous recombination repair (HRR) gene variants (OR=2.6; 95% CI, 1.7 to 3.9; $P = 4.79 \times 10^{-5}$)
- Irrespective of radiation dose, risk for RT-SNs was also associated with *EXO1* variants ($P = 3.31 \times 10^{-}5$), another gene implicated in DNA double-strand break repair

Conclusions

- Novel associations between RT-SN risk after childhood cancer and potentially protein-damaging rare variants in genes involved in DNA double-strand break repair, particularly HRR

GWAS to identify susceptibility Loci that modify Radiation-related risk for breast cancer after Childhood Cancer

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Genome-Wide Association Study to Identify Susceptibility Loci That Modify Radiation-Related Risk for Breast Cancer After Childhood Cancer

Lindsay M. Morton*, Joshua N. Sampson*, Gregory T. Armstrong*, Ting-Huei Chen, Melissa M. Hudson, Eric Karlins, Casey L. Dagnall, Shengchao Alfred Li, Carmen L. Wilson, Deo Kumar Srivastava, Wei Liu, Guolian Kang, Kevin C. Oeffinger, Tara O. Henderson, Chaya S. Moskowitz, Todd M. Gibson, Diana M. Merino†, Smita Bhatia‡, Stephen J. Chanock‡, Margaret A. Tucker‡, Leslie L. Robison‡

JNCI J Natl Cancer Inst (2017) 109(11): djx058

Goal

- To examine the role of genetic susceptibility to breast after chest-directed radiotherapy for childhood cancer

Methods

- GWAS of breast cancer in female survivors of childhood cancer, pooling two cohorts : the Childhood Cancer Survivor Study and St. Jude Lifetime Cohort.
  - 207 survivors who developed breast cancer and 2774 who had not developed any subsequent neoplasm as of last follow-up.
- Genotyping and subsequent imputation yielded 16,958 466 high quality variants
- Tested associations in the overall population and in subgroups stratified by receipt of lower than 10 and 10 or higher gray breast radiation exposure.

Results

- Common variant: ≥10 Gy: rs4342822, nearest gene *PROX1*, RAF = 0.46, HR= 1.92, 95% CI=1.49-2.44, P = 7.09×10^{-9}
- Two rare variants: ≥10Gy: rs74949440, T*AGLN*, P = 5.84×10^{-8}; <10 Gy: rs17020562, *RPS6KC1*, P = 6.68×10^{-8})

Conclusions

- Germline genetics could modify the effect of radiation exposure on breast cancer risk after childhood cancer.

Genetic Variation in BMI of Adult Survivors of Childhood ALL

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Genetic Variation in the Body Mass Index of Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort

Melissa A. Richard, PhD, MS [1]; Austin L. Brown, PhD, MPH [1]; John W. Belmont, MD, PhD[2]; Michael E. Scheurer, PhD, MPH[1]; Vidal M. Arroyo, BS[1]; Kayla L. Foster, MD[1]; Kathleen D. Kern, MD[1]; Melissa M. Hudson, MD[3,4]; Wendy M. Leisenring, ScD [5]; M. Fatih Okcu, MD, MPH[1]; Yadav Sapkota, PhD [4]; Yutaka Yasui, PhD[4]; Lindsay M. Morton, PhD[6]; Stephen J. Chanock, MD[6]; Leslie L. Robison, PhD, MPH[4]; Gregory T. Armstrong, MD, MSCE[4]; Smita Bhatia, MD, MPH [7,8]; Kevin C. Oeffinger, MD[9]; Philip J. Lupo, PhD, MPH [1]; and Kala Y. Kamdar, MD, MS[1]

***Cancer* 2021;127:310-318**. *© 2020 American Cancer Society*

Goal

Characterize genetic variation related to adult BMI among survivors of childhood ALL.

METHODS

- 1458 adult survivors of childhood ALL (time from dx, 20y)
- 2-stage GWAS in the CCSS and SJLIFE (meta-analysis)
- Within known loci, BMI percent variance explained estimated
- Additive interactions with CRT in CCSS were evaluated

RESULTS

- 2 novel loci associated with adult BMI (*LINC00856* rs575792008 and *EMR1* rs62123082; $P_{Meta} < 5E^{-8}$)
- >700 known loci explained 6.2% of the variation in adult BMI in childhood ALL survivors.
  - Within known loci, main effects for 23 loci and interactions with CRT at 9 loci ($P < 7.0E^{-5}$) were identified.

CONCLUSIONS

- Adult survivors of childhood ALL have genetic heritability for BMI similar to that observed in the general population.
- Treatment with CRT can modify the effect of genetic variants on adult BMI in childhood ALL survivors.

Genetic Variation in BMI of Adult Survivors of Childhood ALL

CCSS

Contribution of Polygenic Risk to Hypertension Among Long-Term Survivors of Childhood Cancer

Yadav Sapkota, PhD,[a] Nan Li, PhD,[a] Jeanne Pierzynski, PhD,[a] Daniel A. Mulrooney, MD,[a,b] Kirsten K. Ness, PhD,[a] Lindsay M. Morton, PhD,[c] J. Robert Michael, PhD,[d] Jinghui Zhang, PhD,[d] Smita Bhatia, MD,[e] Gregory T. Armstrong, MD,[a] Melissa M. Hudson, MD,[a,b] Leslie L. Robison, PhD,[a] Yutaka Yasui, PhD[a]

JACC: CARDIOONCOLOGY VOL. 3, NO. 1, 2021

Goal

- Determine contribution of a blood pressure polygenic risk score (PRS) from general population and its interplay with cancer therapies

Methods

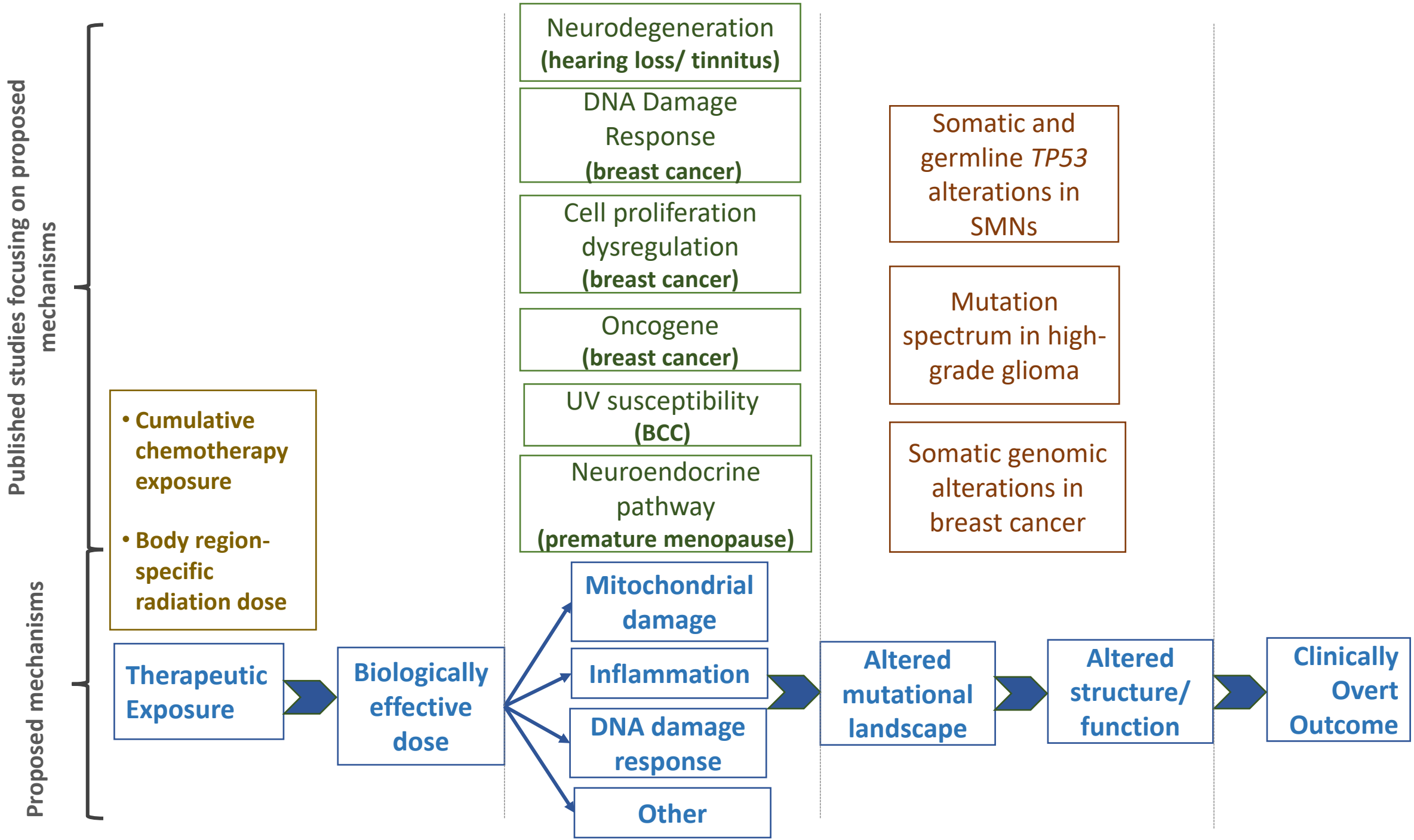
- Using 895 established blood pressure loci from the general population, we calculated a PRS for 3,572 childhood cancer survivors from CCSS original cohort, 1,889 from the CCSS expansion cohort, and 2,534 from the SJLIFE.
- Hypertension was assessed using National Cancer Institute criteria based on self-report of a physician diagnosis in CCSS and based on blood pressure measurement in SJLIFE

Results

- Top decile of PRS: OR=2.66 (95% CI: 2.03 - 3.48) for hypertension compared with bottom decile
- PRS-hypertension association was modified by being overweight/obese (per SD interaction OR: 1.13; 95% CI:1.01-1.27) and exposure to hypothalamic-pituitary axis radiation (per SD interaction OR: 1.18; 95% CI: 1.05-1.33)
- Attributable fractions for hypertension to PRS and cancer therapies were 21.0% and 15.7%, respectively
  - jointly accounted for 40.2% of hypertension among survivors

Conclusions

- findings highlight importance of screening for hypertension and identifying higher risk subgroups


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)
Neuroendocrine pathway (premature menopause)
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

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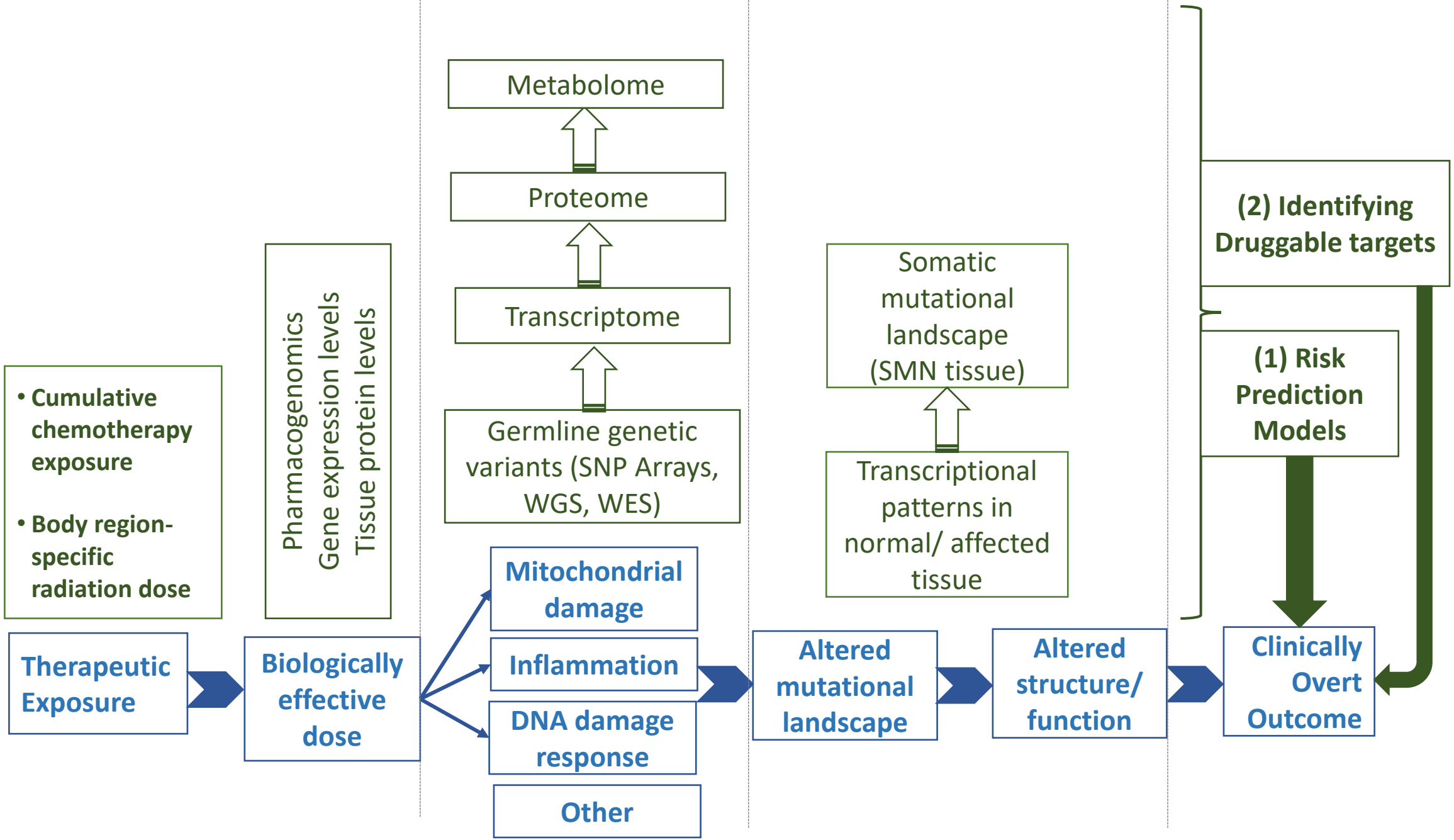
Leverage

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

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

WES data for ~8000 childhood cancer survivors diagnosed 1970-1999

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


• Cumulative chemotherapy exposure
• Body region-specific radiation dose
Therapeutic Exposure
Pharmacogenomics
Gene expression levels
Tissue protein levels
Biologically effective dose
Metabolome
Proteome
Transcriptome
Germline genetic variants (SNP Arrays, WGS, WES)
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

5-year plan

CCSS

Prioritize hypothesis-driven research

- develop an integrated approach to understand mechanistic pathways associated with treatment-related complications
- develop integrated risk-prediction models for precision prevention
- where possible, use mechanistic pathways to identify druggable target

5-year plan

CCSS

Prioritize hypothesis-driven research

- develop an integrated approach to understand mechanistic pathways associated with treatment-related complications
- develop integrated risk-prediction models for precision prevention
- where possible, use mechanistic pathways to identify druggable target

Genetics WG – Opportunities

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1. Utilization of this resource to determine molecular pathogenesis of treatment-related complications
    1. GWAS, WES, WGS data
    2. Paired germline DNA/ SMN tissue
2. Develop integrated risk-prediction models
3. Druggable targets
4. Extend beyond genomics to other “omics”
    1. Transcriptomics
    2. Proteomics
    3. Metabolomics
    4. Microbiome

Genetics – Limitations

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i) Self-reported outcomes (without source validation)
   i) Exception: SMNs
   ii) Certain outcomes more susceptible to misclassification

1. 5y survivors – survival bias
2. Representativeness of the sample cohort to the overall CCSS cohort
3. Small absolute numbers of racial/ethnic minorities with sequencing/ genotype data
4. Need for large replication cohorts
5. Analyses, interpretation is resource-intensive
6. Paucity of expertise in
   1. Analyzing and interpreting genomic data
   2. Functional analyses
   3. Integrative molecular pathogenesis

Current Top Priorities

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Identify opportunities for genomic data for non-malignant outcomes

- Ensure that the current-approved concepts are progressing in a timely fashion
- Facilitate addressing relevant research questions and analyses of WES/ WGS data

Future Top Priorities

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Develop integrated (clinical + genetic) risk prediction models that identify cancer survivors at highest risk for specific outcomes

Develop interventions that target those at highest risk of complications – personalized/ targeted interventions

Focus on pathogenesis of treatment-related complications

- Functional studies stemming from the genomic leads
  - iPSC derived models
  - *Pre-clinical* animal models
  - Utilization of somatic tissue (SMNs) integrated with germline variants/ mutations