ANALYSIS CONCEPT PROPOSAL

1. Title: Genetic determinants of posttraumatic stress disorder in pediatric cancer survivors

2. Investigators and Working Groups

2.1 Working groups

Psychology (primary), Genetics (primary), and Biostatistics (secondary)

2.2 Investigators

Name	Email	Affiliation
Donghao Lu, MD, PhD	nhdlu@channing.harvard.edu	Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA
Unnur A. Valdimarsdóttir, PhD	unnurav@hi.is	Center of Public Health Sciences, University of Iceland, Reykjavik, Iceland
Melissa Hudson, MD	Melissa.Hudson@stjude.org	Cancer Survivorship Division, St. Jude Children's Research Hospital, Memphis, TN
Les Robison, PhD	Les.Robison@stjude.org	Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN
Yutaka Yasui, PhD	Yutaka.Yasui@stjude.org	Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN
Todd Gibson, PhD	todd.gibson@stjude.org	Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN
Gregory Armstrong, MD, MSCE	Greg.Armstrong@stjude.org	Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN
Wendy M. Leisenring, ScD	wleisenr@fredhutch.org	Clinical Research Division, Fred Hutch Cancer Research Center, Seattle, WA
Smita Bhatia, MD, MPH	sbhatia@peds.uab.edu	Institute for Cancer Outcomes and Survivorship, UAB Comprehensive Cancer Center, University of Alabama Birmingham, Birmingham, AL
Kevin Krull, PhD	Kevin.Krull@stjude.org	Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN
Christopher J. Recklitis, PhD, MPH	Christopher_Recklitis@dfci.harvard.edu	Perini Family Survivors' Center, Dana-Farbear Cancer Institute and Harvard Medical School, Boston MA

3. Background and Rational:

Cancer patients face significant stress during treatment, including aversive and painful medical procedures and possible death or disfigurement. Pediatric cancer survivors are

particularly vulnerable to psychological late-effects of treatment, as cancer profoundly disrupts their physical and emotional development[1,2]. Our work has found significantly elevated risk of suicide ideation[3] and behavior[4] among pediatric cancer survivors. Moreover, studies using gold standard measures show high rates of posttraumatic stress disorder (PTSD), with as many as 20% affected even many years after treatment[1,2]. PTSD is a stress-related mental disorder characterized by re-experiencing, avoidance, negative cognitions and mood, and arousal following a traumatic life event. It is a chronic debilitating disorder that has a significant impact on health and quality of life, including impaired education, employment, income, life-satisfaction, depression, emotional distress, and quality of life among pediatric cancer survivors[5].

A four-time higher risk of PTSD symptoms was previously reported for childhood cancer survivors in the Childhood Cancer Survivor Study (CCSS), as compared to their cancer-free siblings[6]. Risk for PTSD symptoms was associated with demographic and psychosocial outcome variables; specifically, these symptoms were more commonly reported by older survivors, unmarried survivors, and those with poor education, employment, and income. Significant PTSD symptoms were also associated with cranial radiation in those treated before age 4 (odds ratio [OR]=2.05) and those who received more intensive treatment (OR=1.36), but no relationship with recurrence or second malignant neoplasm was identified. ***Overall, this leaves researchers with only a limited understanding of why some childhood cancer patients go on to develop PTSD symptoms and other do not—information that would greatly enhance efforts to identify survivors at risk and provide them with appropriate treatment.***

In studies of PTSD conducted in large veterans- and population-based cohorts, data has increasingly shown evidence of genetic predisposition to PTSD. It is reported that the heritability of PTSD is up to 71%[7]. So far, the largest genome-wide association (GWA) study including 30,000 PTSD patients has identified six genetic markers of PTSD[8]. However, the majority of participants are limited to veteran populations. It is unclear whether these markers are generalizable to the cancer population. ***Large study samples homogenous with respect to exposure to specific highly stressful circumstances, such as diagnosis of cancer in childhood, will add significantly to the evidence base for the genetic signature of PTSD, and offer first-hand evidence of prevention and early detection for PTSD in the childhood cancer population.***

4. Specific Aims and Research Hypotheses

We hypothesize that genetic polymorphisms play an important role in the development of PTSD symptom among pediatric cancer survivors. By leveraging the genetic data of adult survivors in the Childhood Cancer Survival Study who answered the Posttraumatic Stress Diagnostic Scale (PDS), ***the overarching aim of this proposal is to further our understanding of the genetic contribution to the varying risk of PTSD after receiving a cancer diagnosis in childhood***.

Primary Aim 1: Using a GWAS approach in the CCSS cohort, identify genetic markers associated with PTSD symptom among adult survivors of childhood cancer.

Primary Aim 2: Using the genotype data of the CCSS cohort, examine the associations of candidate genetic markers with PTSD symptom among adult survivors of childhood cancer.

Primary Aim 3: Using the genotype data of the CCSS cohort, assess the associations of polygenic risk scores for PTSD (from the Psychiatric Genomic Consortia), functional markers related to stress, and common psychiatric disorders (e.g. depression and anxiety) with PTSD symptom among adult survivors of childhood cancer.

Primary Aim 4: Examine whether these genetic markers of PTSD identified in Aim 1 are specific to childhood cancer survivors, rather than to survivors of adulthood cancer or other trauma.

Secondary Aim 1: Determine if SNPs reaching genome-wide significance in Primary Aim 1 may be replicated in an independent cohort from the St. Jude Lifetime Cohort Study (SJLIFE; n=4398). We will also replicate our findings in the deCODE Genetics in Iceland (referred as Icelandic cohort below. The Icelandic cohort holds sequenced and imputed genetic data of up to 80% of the entire Icelandic population). Childhood cancers are identifiable through the Icelandic Cancer Registry (n=333 during 1954-2008) and clinical diagnosis of PTSD could be obtained from the Patient Register. Although number of clinical diagnoses may be few, PTSD symptoms are assessed by PTSD Checklist for DSM-5 during 2018-2019 in the SAGA Cohort, a nationwide Icelandic cohort study led by Prof. Unnur A. Valdmarsdóttir, University of Iceland. It covers about 40% of the whole female population and can be linked to genetic data at deCODE Genetics. A similar cohort recruiting a male population is being planned.

Secondary Aim 2: Determine if SNPs reaching genome-wide significance in Primary Aim 2 may be replicated in an independent cohort from the SJLIFE cohort. We will also replicate our findings in the deCODE Genetics in Iceland cohort noted above.

5. Analysis framework:

5.1 Study population

The CCSS is a longitudinal cohort study that enrolled 20,691 survivors of childhood cancer diagnosed between 1970 and 1999 from 26 collaborating centers in USA and Canada, and tracks the long-term health status, including behavioral and sociodemographic outcomes[9]. Subjects were recruited from persons treated for an initial diagnosis of leukemia, central nervous system (CNS) malignancy, Hodgkin's disease, non–Hodgkin's lymphoma (NHL), kidney cancer, neuroblastoma, soft tissue sarcoma, or malignant bone tumor at 1 of 26 institutions across the United States and Canada, survivors >5 years. This analysis will utilize the original cohort of the CCSS who were diagnosed between 1970 and 1986 when younger than 21 years of age. Among the 20,267 eligible individuals, 17,273 were located; 14,024 (81.2%) survivors were enrolled. The CCSS is estimated to have captured about 45% of all U.S. 5-year survivors at baseline. The institutional review board at each collaborating center reviewed and approved the CCSS protocol. All study participants provided informed consent for participation in the study. We will include all participants in the CCSS who were previously genotyped for the CCSS GWAS study (N=5739), and answered the Posttraumatic Stress Diagnostic Scale (PDS; N=5148).

Note: After completing Primary Aims 1 and 2, we will determine if SNPs which meet genome-wide significance (i.e., $P<5e-8$) in the CCSS cohort (the discovery setting) remain significant (i.e., $P<0.05$) in the SJLIFE cohort (excluding the CCSS participants) and in survivors from the deCODE Genetics data set (the replication settings). Replication analyses

will be conducted by the St. Jude analytic team with oversight by Dr. Yasui. Dr. Valdimarsdóttir will assist the team in accessing data from the SAGA and deCODE cohorts.

5.2 Primary outcome

The primary outcome is PTSD symptom, assessed by the Posttraumatic Stress Diagnostic Scale (PDS). As part of the psychosocial portion of the second follow-up survey, the PDS was sent to all eligible survivors (N= 9308) to assess PTSD symptoms specifically related to the cancer in 2003, and 7040 (76%) survivors completed. This measure includes 17 questions covering the three categories of symptoms described above. Each symptom was rated on a 0 to 3 scale for frequency in the past month (0=Not at all or only one time, 1=Once in a while, 2=Half the time, and 3=Almost always). Symptoms rated at 1 or above are counted as present. Using these scoring criteria, the PDS has been shown to have good internal consistency and test-retest reliability, as well as satisfactory convergent and concurrent validity[10].

We will analyze PTSD symptoms using ***continuous scores*** as well as a ***dichotomous case/ control variable***. As previously described[6], a dichotomous (yes/no) variable will be created using the full diagnostic criteria for PTSD (Table 1) – a probable case has to meet all Criteria from A to F. This includes the number and distribution of symptoms specified in the DSM-IV (Criteria B to E), as well as assessment of functional impairment or clinical distress. The Brief Symptom Inventory–18 (BSI-18) will be used to evaluate psychological distress, whereas the RAND Health Status Survey, Short Form-36 (RAND SF-36) will be employed to assess functional impairment. Performance on the BSI-18 and the SF-36 role limitations due to emotional health are used to determine whether survivors meet the Criteria F (Table 1).

All questions were assessed in the follow-up survey 2003.

Table 1. Definition of PTSD.

	DSM-IV criteria	**Proposed PTSD criteria**
Criteria A	Exposure to event threatening life or body integrity of self or loved one	Diagnosed with cancer
Criteria B	Re-experiencing: (1 symptom required) *	Uncontrollable upsetting thoughts/images Having bad dreams/nightmares Reliving your illness Feeling upset when reminded about illness Physical reactions when reminded about illness
Criteria C	Avoidance: (3 symptoms required)*	Not thinking/talking/feeling about illness Avoiding activities/people/places that are reminders about illness Forgetting important experiences about illness Less interest in important activities Feeling distant/cut off from people Feeling numb Believing future plans/hopes will not come true
Criteria D	Arousal (2 symptoms required)*	Trouble falling/staying asleep Feeling irritable/having fits of anger Trouble concentrating Overly alert Jumpy/easily startled
Criteria E	Duration	More than 30 days after the traumatic event
Criteria F	Functional Impairment or Significant Distress	Significant distress defined as T-score $\geq$ 63 on the Global Status Index (GSI) scale from the BSI or T-score $\geq$ 63 on any two of the following three BSI factors: Depression, Anxiety, Somatization. Functional Impairment defined as T-score $\leq$ 40 on the "role limitations due to emotional health" factor from the SF-36.

5.3 Genotyping and imputation

5739 participants of the CCSS have been genotyped. DNA was extracted using standard methods from blood, saliva (Oragene), or buccal cells (collected using mouthwash). For samples with insufficient DNA, whole-genome amplification (WGA) was performed. Genotyping of study samples and quality control replicates was conducted at the Cancer Genomics Research Laboratory of the National Cancer Institute on the Illumina (San Diego,

CA) HumanOmni5Exome array. Ancestry was estimated using the Genotyping Library and Utilities (GLU) struct.admix module with HapMap data as the fixed reference population. The imputation was then performed based on the 1000 Genomes Project release version 3 reference haplotypes using IMPUTE version 2.3.0, resulting in a total of 26,135,905 high-quality single nucleotide polymorphisms (SNPs) and small insertions or deletions (InDels).

5.4 Variables

In addition to the outcome variables of the **PDS**, the **BSI-18**, and the **SF-36** taken from the Follow-up Survey 2003, we plan to use the following descriptive and exploratory variables:

	Baseline Survey	Follow-up Survey 2003
Age at interview		X
Race	X	
Gender	X	
Education		X
Employment		X
Personal income		X
Marital status		X
Cigarette smoking		X
Physical activity		X
Health insurance		X
Cancer type	X	
Age at diagnosis	X	
Year of diagnosis	X	
Chemotherapy: none, anthracyclines or alkylating agents, or others	X	
Radiation therapy: no or yes (total body irradiation and CNS radiation)	X	
Surgery: no or yes	X	

5.5 Analytic approach

5.5.1 Primary Aim 1 and Secondary Aim 1

1. Descriptive characteristics: We will first describe the distribution of exploratory variables between survivors with and without probable PTSD. (**Table 1**)
2. GWA analysis: We will first perform quality control for the 26 million imputed SNPs (INFO>0.8 and MAF>0.01), and then identify genetic variants associated with PTSD symptoms. Linear regression will be used for the continuous scores, whereas logistic regression will be employed for the dichotomous outcome. All association tests will be adjusted for sex and population stratification in the primary model, and additionally controlled for cancer type and cancer treatment in the secondary model. $P<5\times10^{-8}$ will be considered as genome-wide significance (**Figure 1**). In case no markers would reach the genome-wide significance, we will go forward to the meta-analysis (described below in Point 6) instead of replication analysis.
3. Replication: Significant SNPs will be validated using the SJLIFE cohort and deCODE Genetics data using the same statistical models.
4. Stratified analysis: To identify gene-environment interaction, for the validated SNPs, we will perform stratified analysis by sex, race, age at cancer diagnosis, cancer types, chemotherapy, radiation therapy, marital status (at interview), education attainment (at

interview), and employment status (at interview). Namely, we will add an interaction term between the validated SNP and potential risk modifier, and assess the interaction by testing the significance of the term.
5. Functional annotation: Any SNPs that meet genome-wide significance as well as any SNPs with at least suggestive significance (P<1e-6) and in high LD (r^2>0.7) with these lead SNPs in the discovery cohort, will undergo functional annotation, including: 1) evaluation as possible expression QTLs in brain tissue and blood samples in GTEx; 2) assessment of Human Omni 5 annotations including exonic, splice site, and promoter markers; 3) evaluation of overlap with DNA regulatory regions found in the ENCODE database as well as microRNA and lncRNA coding regions; 4) pathway analysis using position and eQTL mapped genes against pathway databases including KEGG, Reactome, and GO Biological Process.
6. Meta-analysis: To gain statistical power and maximize the precision of estimates, we will also meta-analyze the summary statistics from the CCSS, SJLIFE, and Icelandic cohorts. By doing meta-analysis, the most significant markers are usually not heterogenous across cohorts and could be considered as a proxy of replication.
7. Heritability and genetic correlations with common psychiatric disorders: to shed light on the overall genetic architecture of PTSD in childhood cancer survivors, we will also calculate SNP-based heritability using the Genome-wide Complex Trait Analysis as well as genetic correlations with common psychiatric disorders using LD score regression and summary statistics obtained from the Psychiatric Genomics Consortium (PGC). **(Figure 2)**
8. Power: Given 5148 participants who were genotyped and surveyed for the PDS, we will have >95% power to detect an association between variants with a MAF of 0.15 and quantitative score of PTSD symptom with an additive effect of 0.20 at a P value of 5×e-8.

5.5.2 Primary Aim 2 and Secondary Aim 2

Using a candidate gene approach will significantly reduce the risk of false positive results, and allow the testing of a specific hypothesis.

1. The candidate SNPs: We will specifically examine the association between PTSD symptoms and a collection of candidate alleles from novel genetic markers of PTSD based on the findings from the PGC-PTSD[11] (PI: Prof. Karestan Koenen, Havard T.H. Chan School of Public Health) and SAGA Cohort (PI: Prof. Valdmarsdóttir), 282 functional genetic markers related to stress (through the collaboration with Prof. Elisabeth B. Binder, Max Planck Institute of Psychiatry)[11], as well as two SNPs from a longevity gene klotho (rs9315202 and rs9563121) that are associated with PTSD severity[12].
2. Association analysis: The same statistical models will be used for the association analysis in the CCSS cohort first, and, for the significant ones, replicated in the SJLIFE cohort and Icelandic cohort. Given about 300 candidate SNPs, P<0.00016 will be considered as significance based on the Bonferroni correction. **(Table 2)**
3. Stratified analysis: To identify potential risk modifiers, for the validated SNPs, we will perform stratified analysis by sex, race, age at cancer diagnosis, cancer types, radiation therapy, marital status (at interview), education attainment (at interview), and employment status (at interview). Namely, we will add an interaction term between the validated SNP and potential risk modifier and assess the interaction by testing the significance of the term (P<0.05 as a secondary analysis). If an interaction is significant, we will present associations stratified by that stratification factor.

5.5.3 Primary Aim 3

1. Polygenic risk scores: We will calculate polygenic risk scores based on a collection of associated alleles from independent GWA studies on PTSD based on the general or veteran-

dominated populations (e.g. results from the PGC-PTSD and SAGA Cohort), and determine the extent to which these scores can be used to predict variation of PTSD symptom in childhood cancer population. We believe that, although PTSD in childhood cancer survivors may be different from other trauma-related PTSD, the genomic architecture of PTSD in general would still help to predict the PTSD development among childhood cancer survivors and provide useful information for clinicians. We will first filter out overlapping SNPs between the summary statistics (i.e., the base) and the CCSS cohort (i.e., using QC-ed imputed SNPs as the target), and then perform LD clumping (r^2<0.1 in 500kb window). Next, polygenic risk scores will be constructed from the original effect sizes (provided in the GWAS summary statistics) for the subset of loci that yield P-values below some arbitrary threshold of significance (as a standard approach, we will use cut-offs including 5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 1×10^{-3}, 0.01, 0.05, 0.1, 0.2, and 0.5). The regression of the polygenic risk score against the PTSD trait provides information about the predictive power of these sequence variants for this phenotype. Since PTSD is genetically correlated with depression, anxiety, insomnia, neuroticism, and schizophrenia[8], we will also calculate polygenic risk scores for these psychiatric disorders and examine the prediction value for PTSD symptom in the childhood cancer population. The GWA results of these disorders are publicly available from PGC.

2. Statistical analysis: The score will be analyzed as continuous and quantiles. Linear regression will be used for the continuous scores of PTSD, whereas logistic regression for the probable PTSD cases. Demographic and population stratification will be adjusted in the primary model. To improve the prediction, socioeconomic and clinical characteristics will be added in secondary models. **(Tables 3 and 4)**

3. Stratified analysis: To identify potential risk modifiers, we will examine the interactions with socioeconomics, marital status, and intensive cancer treatment.

5.5.4 Primary Aim 4

We speculate that some genetic markers of PTSD are specific to childhood cancer survivors, although many markers are shared with PTSD due to adulthood cancer or other trauma. Thus, we will compare our GWA results with the GWA summary statistics of PTSD in adulthood cancer survivors from deCODE Genetics (PI: Prof. Valdmarsdóttir), as well as PTSD after all kinds of trauma from PGC-PTSD (PI: Prof. Koenen), using METAL and reporting P for heterogeneity as indication of difference. We aim to identify genetic markers that are specific to PTSD development among childhood cancer survivors, namely the effect size of these markers is statistically different from that in survivors of adulthood cancer or other trauma. **(Table 5)** Moreover, we will test if the effect of such markers is particularly driven by or explained by early-life exposure (i.e., age at cancer diagnosis), certain cancer types, or exposures to intensive cancer treatment, through mediation analysis.

References

1. Michel G, et al: Psychological distress in adult survivors of childhood cancer: the Swiss Childhood Cancer Survivor study. J Clin Oncol, 2010.
2. Zeltzer LK, et al: Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Clin Oncol, 2009.
3. Recklitis CJ, et al: Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol, 2010.
4. Lu D, et al: Suicide and suicide attempt after a cancer diagnosis among young individuals. Ann Oncol, 2013.
5. Brinkman TM, et al: Psychological Symptoms, Social Outcomes, Socioeconomic Attainment, and Health Behaviors Among Survivors of Childhood Cancer: Current State of the Literature. J Clin Oncol, 2018.
6. Stuber ML, et al: Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. Pediatrics, 2010.

7. Duncan LE, et al: Robust Findings From 25 Years of PSTD Genetics Research. Curr Psychiatry Rep, 2018.
8. Nievergelt CM, et al: Largest genome-wide association study for PTSD identifies genetic risk loci in European and African ancestries and implicates novel biological pathways. bioRxiv, 2018.
9. Leisenring WM, et al: Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. J Clin Oncol, 2009.
10. Zeltzer LK, et al: Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev, 2008.
11. Arloth J, et al: Genetic Differences in the Immediate Transcriptome Response to Stress Predict Risk-Related Brain Function and Psychiatric Disorders. Neuron, 2015.
12. Wolf EJ, et al: The goddess who spins the thread of life: Klotho, psychiatric stress, and accelerated aging. Brain Behav Immun, 2019.

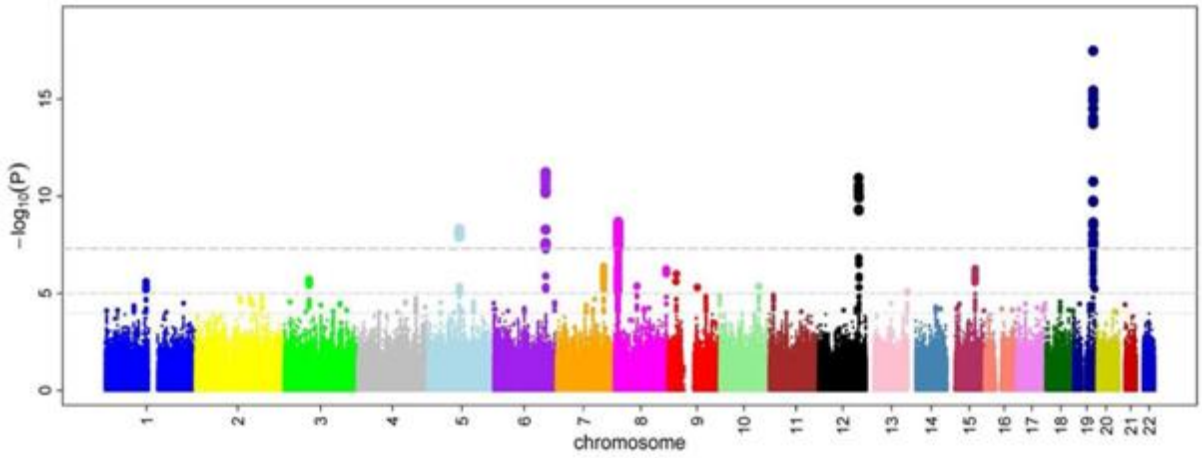
TABLES/ FIGURES

Table 1. Demographic and clinical characteristics of childhood cancer survivors with and without posttraumatic stress disorder (PTSD).

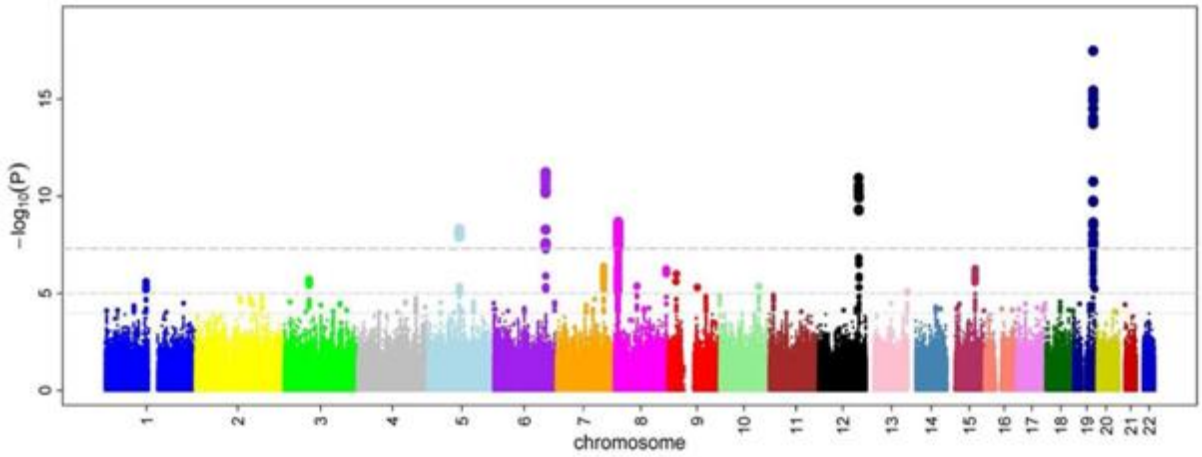
	Survivors without PTSD	Survivors with PTSD	P
	M (SD) or N (%)	M (SD) or N (%)	
Age at diagnosis, year			
Age at interview, year			
Race			
White			
Black			
Hispanic			
Other			
Gender			
Female			
Male			
Education			
High school graduate or less			
Some college			
College graduate or more			
Employed			
No			
Yes			
Personal income			
Below $20,000			
$20,000-39,999			
$40,000 or above			
Marital status			
Single,			
Married or living as married			
Widowed, divorced, or separated			
Cigarette smoking			
Never			
Ever			
Current			
Physical activity			
Active			
Inactive			
Health insurance			
Insured			
Uninsured			
Cancer type			
Bone			
Central nervous system			
Hodgkin’s lymphoma			
Kidney			
Leukemia			
Non-Hodgkin’s lymphoma			

Neuroblastoma			
Soft-tissue sarcoma			
Year of diagnosis			
1970-1975			
1976-1980			
1980-1986			
Chemotherapy			
No			
Anthracyclines or alkylating agents			
Other drugs			
Radiation therapy			
No			
Radiation to brain			
Radiation but not to brain			
Radiation, site unknown			
Surgery			
No			
Yes			

Figure 1. Manhattan plots showing genome-wide association analyses of PTSD symptom score and probable cases.
A. PTSD symptom score

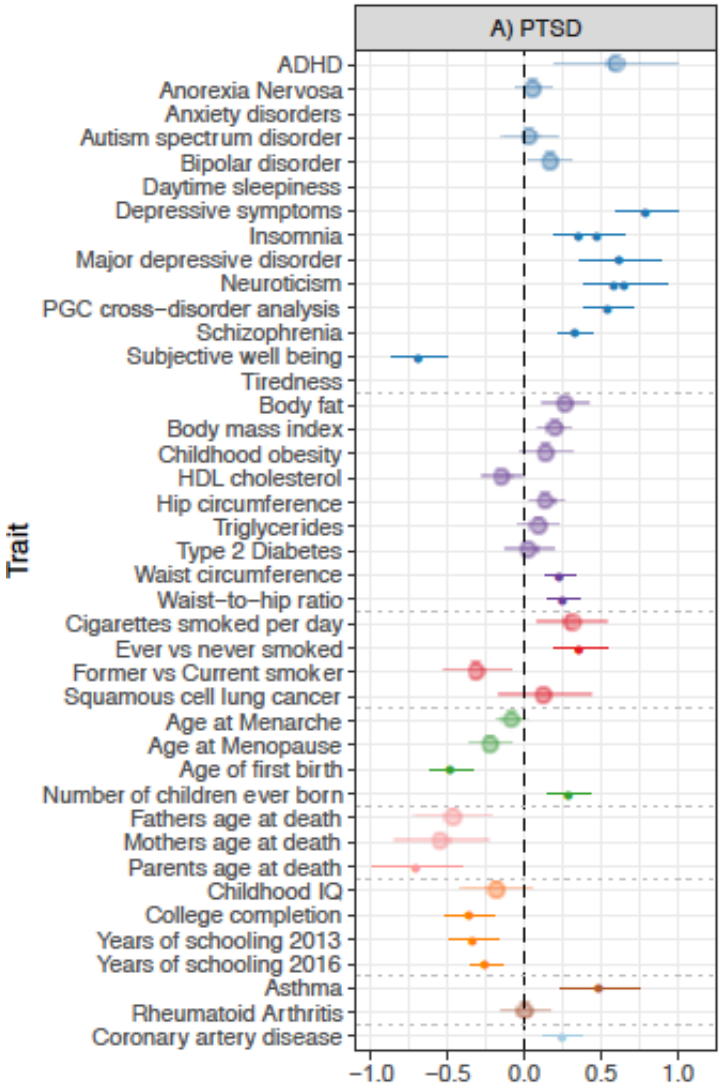


B. PTSD probable cases



Examples from https://en.wikipedia.org/wiki/Manhattan_plot.

Figure 2. Genetic correlations of PTSD symptom score and probable cases with common psychiatric traits, including ADHD, anorexia nervosa, anxiety disorder, autism spectrum disorder, bipolar disorder, daytime sleepiness, depressive symptoms, insomnia, major depressive disorder, neuroticism, PGC cross-disorder analysis, schizophrenia, subjective wellbeing, and tiredness.



Example from Nievergelt CM, et al: Largest genome-wide association study for PTSD identifies genetic risk loci in European and African ancestries and implicates novel biological pathways. bioRxiv, 2018.

Table 2. Associations of candidate SNPs with PTSD symptom score and probable cases. Total of 288 SNPs.

						Symptom score		Probable cases	
Chr	Position	SNP	A1/A2	MAF	Gene	Beta	Corrected P	OR	Corrected P
PTSD markers (n=6)									
1	15436223	rs148757321	CTGTG/C		KAZN				
6	157789333	rs34517852	A/T		ZDHHC14				
6	162163506	rs9364611	T/C		PARK2				
6	31294290	rs142174523	A/G		HLA-B				
19	53988841	rs571848662	T/TATAC		ZNF813				
13	55759209	rs115539978	T/C		MIR5007				
Functional markers related to stress (n=282)									
1	148440425		T/G		PLEKHO1				
1	155229343		C/T		ARHGEF11				
3	188427399	rs1001073	A/G		MASP1				
4	47653436	rs10002500	C/T		CNGA1				
5	150498092	rs10039049	T/C		ANXA6				
7	50152625	rs10234768	C/T		C7orf72				
12	38732017	rs10784359	C/T		SLC2A13				
20	30809662	rs1007122	C/T		PLUNC				
…									

Table 3. Polygenic risk scores for major psychiatric disorders from independent samples and risk of PTSD development (probable cases) among childhood cancer survivors. GWAS summary statistics of major psychiatric disorders are available at the website of Psychiatric Genomics Consortium.

Threshold	PTSD		Stress		Depression		Anxiety		Insomnia		Neuroticism		Schizophrenia	
P-value	R^2	P	R^2	P	R^2	P	R^2	P	R^2	P	R^2	P	R^2	P
P< 5×10^{-8}														
P< 1×10^{-6}														
P< 1×10^{-4}														
P< 0.001														
P< 0.01														
P< 0.05														
P< 0.1														
P< 0.2														
P< 0.5														

R^2, variance explained by the polygenic model.

Table 4. Odds ratios (ORs) of PTSD development (probable cases) among childhood cancer survivors with different polygenic risk scores (PRS) for major psychiatric disorders. GWAS summary statistics of major psychiatric disorders are available at the website of Psychiatric Genomics Consortium.

	PTSD	Stress	Depression	Anxiety	Insomnia	Neuroticism	Schizophrenia
PRS percentile	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
$<20^{th}$							
20^{th} to 39^{th}							
40^{th} to 59^{th}	Reference	Reference	Reference	Reference	Reference	Reference	Reference
60^{th} to 79^{th}							
80^{th} +							

Table 5. PTSD-associated genetic markers across survivors of childhood, adulthood cancer, and other trauma.

					PTSD GWAS in			P for heterogeneity		
					Childhood cancer (CC)	Adulthood cancer (AC)	Other trauma (OT)	CC vs. AC	CC vs. OT	AC vs. OT
Chr	Position	SNP	A1/A2	Gene	OR (95% CI)	OR (95% CI)	OR (95% CI)			
Genetic markers associated with PTSD after other trauma										
1	15436223	rs148757321	CTGTG/C	KAZN						
6	157789333	rs34517852	A/T	ZDHHC14						
6	162163506	rs9364611	T/C	PARK2						
6	31294290	rs142174523	A/G	HLA-B						
19	53988841	rs571848662	T/TATAC	ZNF813						
13	55759209	rs115539978	T/C	MIR5007						
Genetic markers associated with PTSD in childhood cancer survivors										
Genetic markers associated with PTSD in adulthood cancer survivors										