1. Study Title: GWAS of cisplatin-induced, radiation-induced, and *de novo* hearing loss

2. Working Group and Investigators

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3. Background and Rationale

Ototoxicity, leading to auditory complications like hearing loss or tinnitus, is an adverse event of childhood cancer treatment, especially common in individuals treated with platinum chemotherapy or cranial radiation (1-3). In a study reported in 2011 evaluating auditory complications from the Childhood Cancer Survivor Study (CCSS), survivors were at significant risk of problems hearing sounds, hearing loss requiring a hearing aid and hearing loss not corrected by a hearing aid when compared to siblings due primarily to cranial radiation and cisplatin (1). Studies have shown that 45%-60% of childhood cancer survivors treated with cisplatin develop irreversible hearing loss and almost half of them require hearing aids (4-6). In addition to platinum based therapies, cranial radiation can cause ototoxicity, particularly if the dose exceeds 30Gy (1). Ototoxicity resulting from cisplatin or radiation can create functional limitations in long-term survivors such as speech development and academic achievement in children, quality of life, socialization, and cognitive abilities/dementia in older adults (2). Hearing loss is bilateral and permanent after completion of therapy (7, 8).

Risk factors associated with cisplatin-induced ototoxicity include young age at treatment, exposure to additional ototoxic therapies and cumulative dose (5, 9-13). Similarly, the dose of radiation is important for radiation-induced ototoxicity with the majority of toxicity seen with radiation doses ≥30Gy, although problems hearing sounds were also observed at doses <30Gy (1, 14-17). Previous reports indicate that males are more likely to have de novo hearing loss than females and Blacks are less likely than Whites to have hearing loss (18-20). In pediatric cancer patients, males appear to be more susceptible to cisplatin-induced hearing loss than females (9) although analysis of gender and race on susceptibility of cisplatin- and radiation-induced hearing loss are currently being evaluated in CCSS by Dr. Austin Brown.

Although there have been a number of candidate gene or metabolic chip analyses of hearing loss (21), the first genome-wide association study (GWAS) of cisplatin-induced hearing loss in 238 pediatric brain tumor patients identified an association with a genetic variant in *ACYP2* (rs1872328, hazard ratio (HR)=4.5, 95% CI 2.63-7.69, $P=3.9 \times 10^{-8}$), and results were replicated in a second cohort of 68 pediatric patients (22). Further, increased *ACYP2* expression highly correlated with cisplatin sensitivity in lymphoblastoid cell lines *in vitro* ($P=6.5\times10^{-5}$), but the genotype at the SNP rs1872328 position was not associated with sensitivity *in vitro*, nor was it related to expression of *ACYP2* and other genes 300 kb within this index SNP. Nevertheless, three studies have replicated this association with cisplatin-induced hearing loss in 156 osteosarcoma patients (23), 149 pediatric cancer patients (24) and 229 testicular cancer patients (25). *ACYP2* encodes for an enzyme that catalyzes phosphate hydrolysis in membrane pumps, most notably the Ca^{2+}/Mg^{2+} ATPase from the sarcoplasmic reticulum of skeletal muscle (26). Importantly, *ACYP2* is expressed in the cochlea for ATP-dependent Ca^{2+} signaling that is critical for hair cell development and has been directly implicated in hair cell damage (27, 28), providing a rationale for its association with cisplatin-induced hearing loss.

In addition, we have performed a GWAS on cisplatin treated testicular cancer survivors, which also represented the largest, most comprehensive and quantitative evaluation of cisplatin-associated ototoxicity in adult-onset cancer survivors. Our patients were young men with a median age at testicular cancer diagnosis of 32 years old and a median of 55 months between treatment completion and clinical evaluation. Chemotherapy regimens consisted largely of bleomycin, etoposide, and cisplatin (61%) or etoposide and cisplatin (30%). Hearing loss at frequencies of 4-12 kHz was significantly associated with increasing cumulative cisplatin dose (29, 30). Using American Speech Language-Hearing Association (ASHA)-defined criteria, we identified 25% survivors with mild, 16% with moderate, 21% with moderately-severe and 18% with severe/profound hearing loss (29, 30). In an analysis of 511 testicular cancer survivors, we identified a genome-wide significant SNP, rs62283056 ($P=1.4\text{x}10^{-8}$), located at the 5' end in the first intron of wolframin ER transmembrane glycoprotein localized to the ER gene (*WFS1*) (31). The minor allele confers cisplatin-induced hearing loss risk, as higher cumulative cisplatin doses exacerbated hearing loss in patients with the minor allele (P=0.035). Recently, we evaluated rs62283056 in an additional 317 testicular cancer survivors and found a significant association with the same direction of effect (P = 0.032). Using GCTA's variance component method (32) we showed that all SNPs explained a large proportion of variance in cisplatin-induced hearing loss ($h^2 = 0.92 \pm 0.62$, P = 0.039). The association between rs62283056 and cisplatin-induced hearing loss was replicated in a Canadian study of 229 testicular cancer patients when evaluating the same phenotype, that is, the geometric mean of hearing thresholds at 4-8 kHz ($P=5.67\text{x}10^{-3}$, OR=3.2), although it was not replicated using a phenotype of audiologist-defined hearing loss (25).

CCSS approved proposal #16-15 by Dr. Austin Brown that aims to evaluate cumulative incidence and rate of hearing impairment among long-term childhood cancer survivors relative to siblings without a history of cancer. To this end, his team will assess the effects of treatment-related factors on hearing impairment among childhood cancer survivors and potential academic and psychosocial consequences. The Expanded Cohort is included in his study.

CCSS also approved proposal #17-20, by our group, to identify the nongenetic factors and genetic variants associated with de novo and treatment related tinnitus. *Complementing both previously approved projects, this proposal is focused on identifying the genetic factors associated with de novo hearing loss, cisplatin-induced hearing loss and radiation-induced hearing loss using the original (Discovery) and Expanded cohort (diagnosed 1987-1999 with whole genome sequencing; Replication). As per a call with Dr. Brown on 4/12/19, we will use the same classification of hearing impairment proposed in #16-15 (CTCAE grades, see* ***Table 1****) and a similar GWAS approach as in our proposal (#17-20).* We will compare our results to additional GWAS that we are performing: 1) We have a total of 1664 Testicular Cancer Survivors with genotype and exome sequencing data that will be evaluated and compared to results from the CCSS cisplatin-induced hearing loss dataset in this proposal. 2) We will compare our de novo hearing loss results to studies we are performing within the eMERGE dataset (a large DNA biobank linked to the electronic health records of > 85,000 individuals) with ICD-9 codes for hearing loss.

Significance*.* This proposal represents an unprecedented opportunity to make inroads into identifying genetic risk factors associated with cisplatin- and radiation-induced hearing loss and to determine shared genetic architecture with de novo hearing loss. Variability in cisplatin- and radiation-induced ototoxicity can be explained in part by pharmacogenomics, which aims to provide the foundation for genetically guided treatment regimens that maximize efficacy and minimize toxicity. One of the challenges in pharmacogenomics is that most cancers are treated with a multi-drug regimen, making it difficult to ascertain the genetic variants associated with a specific chemotherapeutic toxicity; however hearing loss is primarily due to cisplatin or cranial radiation. Therefore, the genetic variants identified are most likely associated with exposure to either of these therapies if we subgroup patients into those treated only with either cisplatin or radiation. Novel therapeutic strategies by which to reduce adverse effects such as ototoxicity are supported through an understanding of the genetic underpinnings associated with these toxicities. Selecting genetically supported targets could double the success rate of drugs in clinical development as demonstrated in a study published in Nature Genetics (33). By investigating the shared genetic burden of hearing loss with Mendelian forms and the biological functions of associated SNPs and genes, our work has far-reaching implications for the millions suffering from hearing loss worldwide.

Specific aims/objectives/research hypothesis

1. To perform GWAS of cisplatin-induced hearing loss using the Original cohort with genotype data as a discovery set and the Expanded cohort with sequencing data as the replication set. We will compare to GWAS of self-reported cisplatin-induced hearing loss in 1664 Testicular Cancer Survivors. Previous analysis of hearing loss measured by audiometry in a subset from the Platinum Study has been reported (31). Both SNP-based and gene-based (PrediXcan) analysis will be performed.
2. To perform GWAS of radiation-induced hearing loss using the Original cohort with genotype data as a discovery set and the Expanded cohort with sequencing data as the replication set. Both SNP-based and gene-based (PrediXcan) analysis will be performed.
3. To perform GWAS of de novo hearing loss using the Original cohort with genotype data as a discovery set and the Expanded cohort with sequencing data as the replication set. We will then compare the results to our GWAS of the eMERGE dataset in which we have ICD-9 codes for bilateral sensorineural hearing loss (3,511 cases and 80,701 controls). Both SNP-based and gene-based (PrediXcan) analysis will be performed.
4. To evaluate whether there is an enrichment of SNPs identified in the GWAS of de novo hearing loss at different p-value cutoffs with GWAS of cisplatin-induced or radiation-induced hearing loss. Both SNP-based and gene-based (PrediXcan) analysis will be performed.

We hypothesize that

1) Inherited genetic variants are associated with de novo, cisplatin-induced and radiation-induced hearing loss.
2) Treatment (cisplatin and/or radiation)-induced hearing loss shares genetic architecture with de novo forms of hearing loss.

V. Analysis Framework

Outcomes of interest

The primary outcome of interest for aim #1 and #2 is the genetics associated with the occurrence of hearing loss in cancer survivors following treatment with cisplatin and radiation, respectively. The primary outcome of interest for aim #3 is the genetics of de novo hearing loss in those survivors with hearing loss that were not treated with cisplatin or radiation nor were they diagnosed with a brain tumor.

Subject population

The analysis will utilize existing data within CCSS and dbGAP to address each aim. The primary analysis described below will be based on those with and without hearing loss following treatment with either cisplatin (aim #1), radiation (aim #2) or neither treatment and did not present with a brain tumor (aim #3).

Eligible individuals will include:

- Discovery: all survivors enrolled in the Original Cohort with genotype data who completed the Hearing Section of the questionnaire and answered the questions below.
- Expanded Cohort: All survivors with sequencing data who completed the Hearing Section of the questionnaire and answered the questions below.

Have you ever been told by a doctor or other health care professional that you have, or have had:

- **FU2007, FU5 D.1**/*C.1.* Hearing loss requiring a hearing aid?
- **FU2007, FU5 D.2/***C.2.* Deafness in both ears not completely corrected by hearing aid?
- **FU2007, FU5 D.3***C.3.* Deafness in only one ear not completely corrected by hearing aid?
- **FU2007, FU5 D.6/** *C.6.* Hearing loss, not requiring a hearing aid?
- **FU2007, FU5 D.7**/*C7***.** Any other hearing problems? If yes, describe this problem.

The base eligible population for **Discovery Cohort** will include all patients in the original cohort with genotype data who responded on baseline, and, at least one of the follow-up CCSS surveys (FU2007 or FU5) to the question: 1) Problems hearing sounds, not requiring a hearing aid? 2) Hearing loss that requires a hearing aid? or hearing loss not completely corrected by a hearing aid? 3) Deafness in both ears not completely corrected by hearing aid? They can answer, 1) yes, still present, 2) no, 3) yes, no longer present, 4) yes, not sure. We require responses to be consistent on baseline and 1 follow up survey for cases (*yes, still present)* and controls (no) and will remove all patients who responded *yes, no longer present* or *not sure*. Note: this will include a few cases of "late-onset" hearing loss (i.e., reporting at baseline and no impairment in 2007 and significant impairment by FU5). **Table 1** illustrates the proposed classification similar to that in proposal #16-15 by Dr. Austin Brown except those with CTCAE 1-2 in our proposal are also cases. **Table 2** provides the number of patients with Hearing Loss (Chronic dataset with Loss of hearing) and with genotype information. All events happened before last follow up questionnaire and are genotyped in the Original cohort. The replication cohort will include all those in the **Expanded Cohort** with whole genome sequencing data answering the same questions with the same criteria as the Discovery Cohort (**Table 3**).

Table 1. Proposed Classification of hearing impairment applying CTCAE criteria

Classified as Hearing Impaired	CTCAE	Hearing Impairment Reported	Original Baseline	2007 Follow up	Expansion Baseline
Control	0	None			
Yes	1-2	Problems hearing sounds, not requiring a hearing aid	C.6, C.7	D.6, D.7	C.6, C.7
Yes	3	Hearing loss requiring a	C.1, C.3	D.1, D.3	C.1, C.3

		hearing aid or hearing loss not completely corrected by hearing aid in either ear			
Yes	4	Deafness in both ears not completely corrected by hearing aid		D.2	C.2

Key Variables

Cases and controls for Discovery Group of Cisplatin-induced Hearing Loss:

Cisplatin-induced version 1: All who received cisplatin, but did not receive carboplatin

Cisplatin-induced version 2: Survivors who received cisplatin but did not receive carboplatin, excluding survivors with ANY or scatter dose cranial radiation and primary brain tumors.

Controls will be all those who respond No in all surveys for hearing loss (CTCAE 0) with same criteria as above.

Cases for Logistic Regression are all those with CTCAE 3-4.

Cases for Ordinal regression are all those with CTCAE 1-2 as ordinal scale 1 and CTCAE 3-4 as ordinal scale 2 (max grade across 3 surveys).

Cases and controls for Discovery Group of Radiation-induced Hearing Loss

Radiation-induced_v1: Survivors who received ANY cranial radiation, but exclude high or low scatter cranial radiation dose and either cisplatin or carboplatin.

Radiation-induced_v2: Survivors who received ANY cranial radiation and high or low scatter cranial radiation dose excluding cisplatin or carboplatin.

Controls will be all those who respond No in all surveys for hearing loss (CTCAE 0) with same criteria as above.

Cases for Logistic Regression are all those with CTCAE 3-4.

Cases for Ordinal regression are all those with CTCAE 1-2 as ordinal scale 1 and CTCAE 3-4 as ordinal scale 2.

Cases and controls for Discovery Group of de Novo Hearing Loss

De Novo hearing loss group within CCSS, we are excluding the survivors with a primary brain tumor or who received ANY cranial or high or low scatter radiation dose, or received cisplatin or carboplatin from the base population and evaluating all others with and without hearing loss. Controls will be all those who respond No in all surveys for hearing loss (CTCAE 0).

Cases for Logistic Regression are all those with CTCAE 3-4.

Cases for Ordinal regression are all those with CTCAE 1-2 as ordinal scale 1 and CTCAE 3-4 as ordinal scale 2.

Explanatory variables: Provide variables that may prove to be important or should be taken into consideration in analyzing the data (i.e., confounders and effect modifiers). The clinical and sociodemographic characteristics that may confound our analysis will be ascertained from Dr. Austin Brown's analyses for de novo hearing loss in the CCSS. Based on previous analysis, we expect that age, cumulative dose (cisplatin or radiation) and 20 Principle Compenents (PC) will be taken into consideration in analyzing the data. In addition, we will require genotypes to perform GWAS of all patients with and without hearing loss and exome data when the data is released by NCI.

Exploratory variables: To prepare a demographics table and for validation of our previously identified associations of de novo hearing loss with other variables will require answers from the following demographic and clinical questions on the CCSS questionnaires including dizziness/vertigo.

Note: Question numbers from the Original Cohort Baseline Questionnaire, FU2007 or FU5 are in bold, with survey time indicated if from FU2007 or FU5, while question numbers from the Expanded Cohort Baseline Cohort Questionnaire are italicized.

    - **A.2**/*A2*. What is your sex?
    - **A.4**/*A5*. To which one of the following groups do you belong (race)?
    - **A.4a**/*A5a*. Are you Hispanic (ethnicity)?
  - **FU2007, FU5 D.4**/*C.4*. Tinnitus or ringing in the ears?
  - **FU2007, FU5 D.5**/*C.5*. Persistent dizziness or vertigo?
  - **O.8** What kind of business or industry was this job in? **FU2007 A5a, FU5 A6a /** *S3a.* Main job title? **FU2007 A5b, FU5 A6b /** *S3b.* Please briefly describe your primary job tasks.
  - **P.1** Yourself. Medical history of cancer, birth defect, hereditary condition (provide specific type).
  -

Data from the *Medical Records Abstraction Forms or Radiation dosimetry from the Radiation Dosimetry Center*

- Year of cancer diagnosis
- Cancer diagnosis
- Ages at beginning and end of cisplatin therapy
- Cumulative dose of cisplatin
- Cumulative dose of carboplatin
- Ages at beginning and end of vincristine treatment
- Cumulative dose of vincristine
- Ages at beginning and end of cranial radiation treatment
- Maximum Cranial Radiation dose

Analytic Approach:

<u>GWAS Discovery</u>

For all analysis, we will include age and 20 principal components as co-variates. For cisplatin- and radiation-induced, we will include cisplatin dose and for radiation dose, respectively.

We will perform both logistic and ordinal regression: 1) include all of the patients without hearing loss as controls (CTCAE 0; Ordinal scale 0) and those who have severe forms of hearing loss as cases (CTCAE 3-4) for logistic regression or; 2) perform an ordinal regression based GWAS in which controls (CTCAE 0) are Ordinal scale 0 and those with “Problems hearing sounds, not requiring a hearing aid” are designated as Group 1 (CTCAE grade 1-2), and those with Hearing loss requiring a hearing aid or hearing loss not completely corrected by hearing aid and Deafness in both ears not completely corrected by hearing aid in either ear (CTCAE grades 3-4) to give us three different groups. This is similar to what we did for our GWAS of cisplatin-induced peripheral neuropathy (34), in which we had a scale consisting of none, a little, and a combined level of quite a bit/very much and for cisplatin induced tinnitus (35).

Using FU2007 and FU5, **Figure 2** and **3** provide a plot of the proportion of childhood cancer survivors with no hearing loss, hearing loss not requiring a hearing aid, and deafness in both ears not completely corrected by a hearing aid relative to the cumulative cisplatin and cranial radiation dose, respectively. For radiation-induced hearing loss, we will include age at diagnosis, radiation dose as a covariate and likewise for cisplatin-induced, we will use age at diagnosis and cisplatin dose as a covariate. Both will include 20 PCs. GWAS will be performed following quality control as previously described by the CCSS working group (36) including ancestry quantification with principal component analysis (PCA) and the exclusion of non-European and admixed samples (in comparison to 1000 Genomes Phase 3), related/duplicated samples, samples with excess heterozygosity, and samples with missing phenotypes, as well as SNP level quality-control in PLINK 1.9 (minor allele frequency, call rate, Hardy-Weinberg equilibrium etc.). The genome-wide significance threshold will be set at $\alpha = 5 \times 10^{-8}$. Multiple hypothesis testing for PrediXcan will use Bonferroni and/or Benjamini-Hochberg correction to define significance thresholds.

<u>Replication with Expanded Cohort</u>

As per Dr. Yutaka Yusai (6/13/19), the genotype data from WGS are not yet available for the Expanded Cohort. Therefore, we will request the specific SNPs' genotypes from CompBio that were hits from our discovery analysis. At this time, they are waiting for their Computational Biology colleagues to complete the processing for QC, alignment, and genotype calls. Once that is complete, we will submit a set of SNPs suggestively significant ($p<10^{-6}$) to determine if any SNPs replicate using the same models as discovery and use fixed-effects meta-analysis using METAL once the full set is available.

Replication with Additional Cohorts

Cisplatin-induced hearing loss: Replication with cisplatin-induced hearing loss will be carried out in the Platinum Study. Although the Platinum Study (R01 CA157823) ended in July 2018, additional cisplatin-treated testicular cancer survivors have been phenotyped and genotyped (full set of 1660 has been Exome sequenced and genotyped by Regeneron). Eligibility criteria included: men diagnosed with histologically or serologically confirmed germ cell tumor (GCT), age <55 years at diagnosis and >18 years at enrollment, and treatment with a first-line cisplatin-based chemotherapy regimen. Data abstracted from medical charts included age at germ cell tumor diagnosis, tumor characteristics, treatment regimen with cumulative dose and number of cycles, and BMI at the initiation of treatment. Data collected at clinical evaluation included age and physical examination (with BMI), audiometric studies, self-reported questionnaires, and genotyping. The initial subset of patients were genotyped on the Illumina HumanOmniExpressExome chip at the RIKEN Center for Integrative Medical Science (Yokohama, Japan). Samples were plated randomly with inter- and intra-plate duplicates. Standard quality control measures for GWAS genotypes were implemented using PLINK. Individuals with pairwise identity by descent (IBD) > 0.125 and excess heterozygosity (F inbreeding coefficient 6 standard deviations from the mean) were removed. To quantify hearing, pure-tone air conduction thresholds were measured bilaterally at the frequency range 0.25-12 kHz. The rank normalized geometric mean of hearing thresholds across cisplatin-affected frequencies (4-12 kHz; rnGM412) was used to quantify cisplatin-induced hearing loss and GWAS performed as previously described (31). Self-reported hearing loss and tinnitus were also assessed with validated questionnaires: the EORTC-CIPN 20 item questionnaire (37) and SCIN (38). Since it would be difficult to replicate our findings using the rnGM412 phenotype because it is a continuous variable, we will likely use self-reported hearing loss, which is reported on an ordinal scale. As such, we could format self-reported hearing loss as either an ordinal or binary variable, depending on our results from the discovery cohort. We can also use fixed-effects meta-analysis with our testicular cancer survivor's discovery cohort using the self-report hearing loss from the Platinum Study (31) and CCSS cisplatin-induced hearing loss using METAL.

De novo hearing loss: We also have a dataset from the Electronic MEdical Record and GEnomics [**eMERGE**] Network (39), representing 39 million SNPs imputed into 84,212 patient samples with ICD-9 codes for bilateral sensorineural hearing loss on 3,511 for discovery GWAS of de novo hearing loss***.*** Cases will be patients who have a reported ICD-9 code of bilateral sensorineural hearing loss, the same subtype of hearing loss as that associated with cisplatin-induced hearing loss. All others will be designated as controls. This will be a binary variable since there is no audiometry data available in eMERGE (ICD9 codes will establish cases and all those without an ICD-9 code of bilateral sensorineural hearing loss are controls. Excluded: 1) Patients with ICD-9 codes associated with a cancer diagnosis for which cisplatin could have been used; 2) with diseases/disorders associated with deafness or tinnitus such as Meniere's disease, head injury, injury of face and neck, temporomandibular joint disorders, benign neoplasm cranial nerve, malignant neoplasm of cranial nerves. We have available demographic characteristics (age, sex, self-reported race) and traits such as vertigo, and dizziness that will be included in our analysis.

PrediXcan as a gene based analysis

We will also use PrediXcan, a gene-based method that uses reference transcriptome (genotype to gene expression) data to generate models used to 'impute' gene expression levels from genotype data and associate the predicted gene expression with phenotypes of interest (40). PrediXcan will allow us to identify *genes of interest* associated with hearing loss in survivors with de novo, cisplatin-induced and radiation-induced hearing loss. Specifically, PrediXcan aggregates the effects of regulatory SNP on gene expression, allowing us to extrapolate SNP-level summary statistics to the gene-level by predicting gene expression. We will identify endophenotypes (gene expression) that is known to account for the majority of common variant heritability to common complex traits and reduce the multiple testing burden by at least 100-fold. Specifically, PrediXcan's elastic net models ($\alpha = 0.5$) trained on GTEx reference transcriptome data will be used to predict

gene expression in tissues of choice (brain, tibial nerve) from GWAS summary statistics and perform logistic regression with de novo, cisplatin-induced and radiation-induced hearing loss.

Additional analysis
We will additionally investigate the shared genetic architecture between cisplatin-induced and non-platinum-induced hearing loss by conducting a meta-analysis and identifying potential genome-wide significant variants across the phenotypes. We will assess the functions of SNPs associated with de novo, cisplatin-induced, and radiation-induced hearing loss using ENCODE and Roadmap Epigenomics to elucidate biologically plausible mechanisms.

- **Potential tables and figures**

Manuscript # 1: Genetics of cisplatin-induced hearing loss in CCSS
Table 1. Demographic features, clinical characteristics, and patient reported outcomes of CCSS according to hearing loss status.
Figure 1. Hearing loss frequency according to age (A) and dose of cisplatin (B).
Figure 2. GWAS of cisplatin-induced hearing loss in CCSS cohort (A) and Replication cohort (B).
Table 2. Comparison of GWAS of cisplatin-induced hearing loss in CCSS and the Platinum Study.
Figure 3. Enrichment of de novo hearing loss GWAS SNPs in cisplatin-induced hearing loss
Figure 4. Evaluation of expression of relevant genes and sensitivity to cisplatin from Cancer RX and Cancer Cell Line Encyclopedia
Figure 5. Functional validation study in HEI-OC1 auditory cells (modulate potential gene of interest with analysis of resultant effect on sensitivity of cells to cisplatin.

Manuscript # 2: Genetics of radiation-induced hearing loss in CCSS
Table 1. Demographic features, clinical characteristics, and patient reported outcomes of CCSS according to hearing loss status.
Figure 1. Hearing loss frequency according to age (A) and dose of radiation (B).
Figure 2. GWAS of radiation-induced hearing loss in CCSS cohort (A) and Replication cohort (B).
Table 2. Comparison of GWAS of radiation-induced hearing loss in CCSS and the Platinum Study.
Figure 3. Enrichment of de novo hearing loss GWAS SNPs in radiation-induced hearing loss.
Figure 4. Functional validation experiment either in cells or in silico.

Special consideration:

Table 2† All: The survivors who participated baseline, follow up 1, follow up 2007 or follow up 5 and with Genotyped by the Illumina SNP array information (follow up 2 didn't ask questions about hearing loss).

Classified as Hearing Impaired	CTCAE	Hearing Impairment Reported	Type of Hearing Loss					
			All (N=5739)	De Novo (N=1531)	Cisplatin-induced (N=245)	Radiation-induced v1 (N=1726)	Radiation-induced v2 (N=1735)	Cisplatin-induced version 2 (N=132)
No	**0**	**None**	4737	1368	123	1290	1494	75
No	**1-2**	Problems Hearing Sounds, not requiring a hearing aid	852 (578)	144 (108)	107 (34)	348 (223)	219(169)	53 (21)
Yes	**3**	Hearing loss requiring a hearing aid or hearing loss not completely corrected by a hearing aid in either ear	423 (279)	41 (26)	64 (24)	247 (165)	66(47)	21 (6)
Yes	**4**	Deafness in both ears not completely corrected by a hearing aid	71 (49)	1 (1)	15 (5)	53 (40)	6(2)	4(1)

† 1) The numbers in the parentheses were the number of events by excluding the events that happened before 5 years of cancer diagnosis. 2) All numbers in the table didn't consider the sample weight. 3) A survivor can have multiple events.
De Novo: All by excluding the survivors with a primary brain tumor or received ANY cranial or high or low scatter radiation dose, or received cisplatin or carboplatin
Cisplatin-induced: All and received cisplatin
Cisplatin-induced version 2: All and received cisplatin, the survivors with ANY or scatter dose cranial radiation were excluded.
Radiation-induced_v1: All and received ANY but exclude high or low scatter cranial radiation dose.
Radiation-induced_v2: All and received high or low scatter cranial radiation dose.
Hearing Loss events definition:
Chronic dataset with Loss of hearing. All events happened before last follow up questionnaire.

Table 3†. The survivors who participated baseline or follow up 5 and with Whole genome sequenced information.

Classified as Hearing Impaired	CTCAE	Hearing Impairment Reported	Type of Hearing Loss					
			All (N=3000)	De Novo (N=1174)	Cisplatin-induced (N=395)	Radiation-induced_v1 (N=562)	Radiation-induced_v1 (N=543)	Cisplatin-induced version 2 (N=180)
No	**0**	**None**	2501	1101	165	338	477	103
No	**1-2**	Problems Hearing Sounds, not requiring a hearing aid	357 (166)	59 (42)	152 (37)	146 (57)	45(26)	59 (11)
Yes	**3**	Hearing loss requiring a hearing aid or hearing loss not completely corrected by a hearing aid in either ear	251 (100)	23 (13)	131 (41)	148 (68)	28(6)	31 (6)
Yes	**4**	Deafness in both ears not completely corrected by a hearing aid	72 (26)	7 (3)	40 (10)	49 (20)	6(0)	9 (2)

† 1) The numbers in the parentheses were the number of events by excluding the events that happened before 5 years of cancer diagnosis. 2) All numbers in the table didn't consider the sample weight. 3) A survivor can have multiple events.
Population definition:
De Novo: All by excluding the survivors with a primary brain tumor or received ANY cranial or high or low scatter radiation dose, or received cisplatin or carboplatin
Cisplatin-induced: All and received cisplatin
Cisplatin-induced version 2: All and received cisplatin, the survivors with ANY or scatter dose cranial radiation were excluded.
Radiation-induced_v1: All and received ANY but exclude high or low scatter cranial radiation dose.
Radiation-induced_v2: All and received high or low scatter cranial radiation dose.
Hearing Loss events definition:
Chronic dataset with Loss of hearing. All events happened before last follow up questionnaire.

Figure 1. The proportion of childhood cancer survivors with no hearing loss, hearing loss not requiring a hearing aid, and deafness in both ears not completely corrected by a hearing aid relative to the cumulative cisplatin dose.

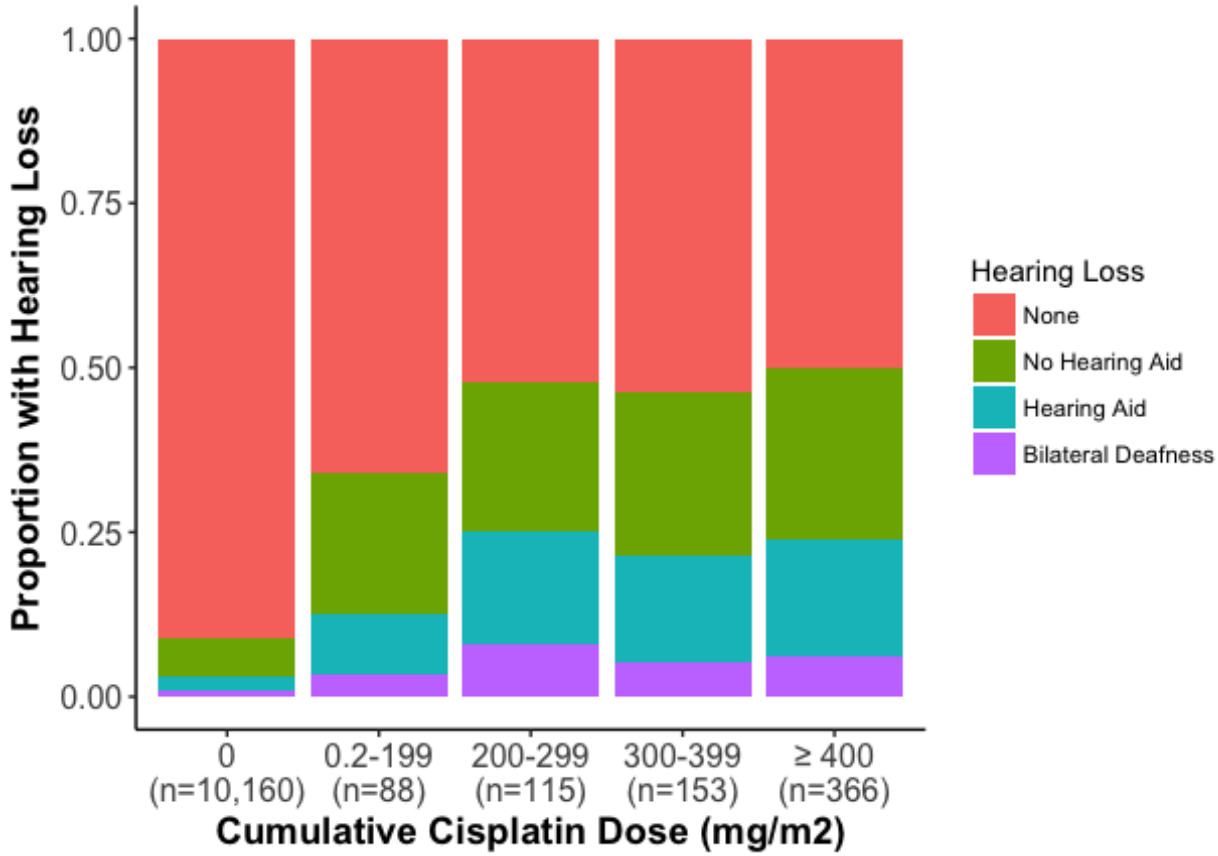
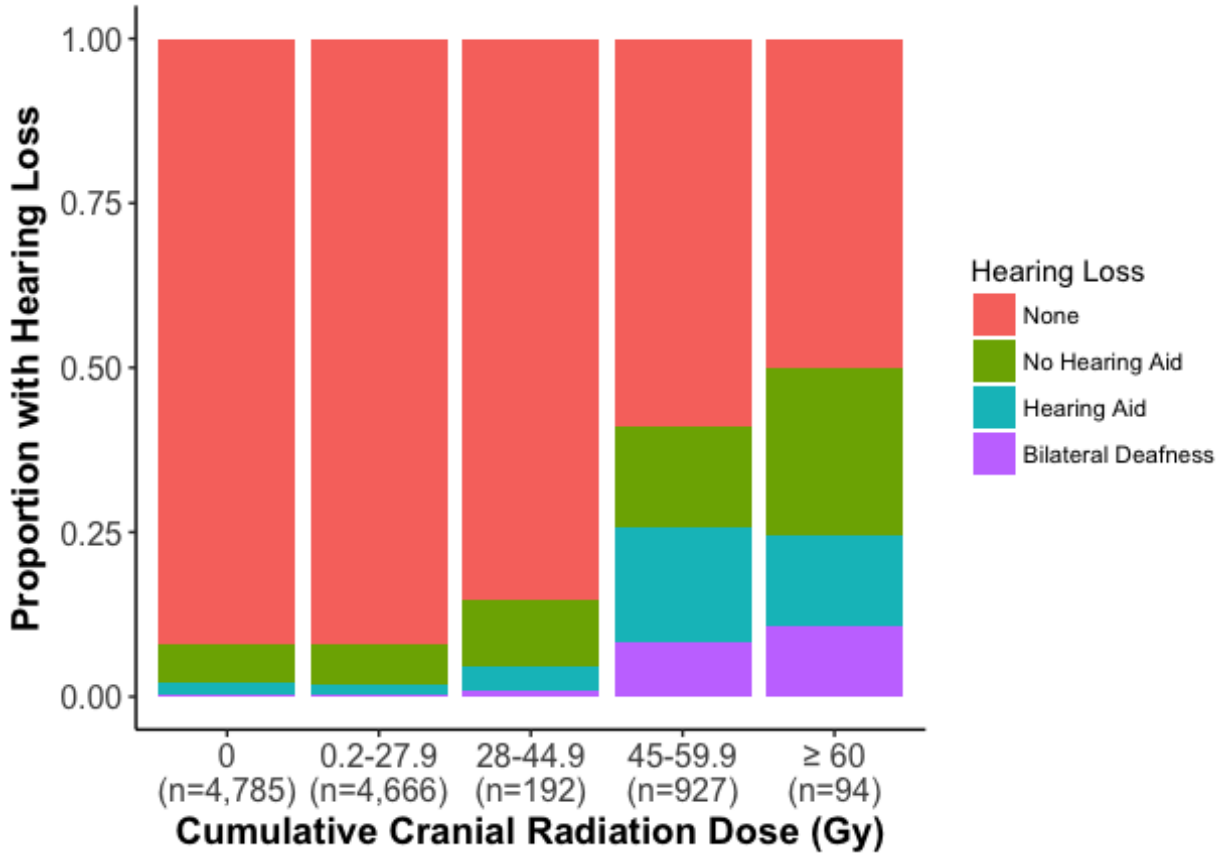


Figure 2. The proportion of childhood cancer survivors with no hearing loss, hearing loss not requiring a hearing aid, and deafness in both ears not completely corrected by a hearing aid relative to the cumulative cranial radiation dose.



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