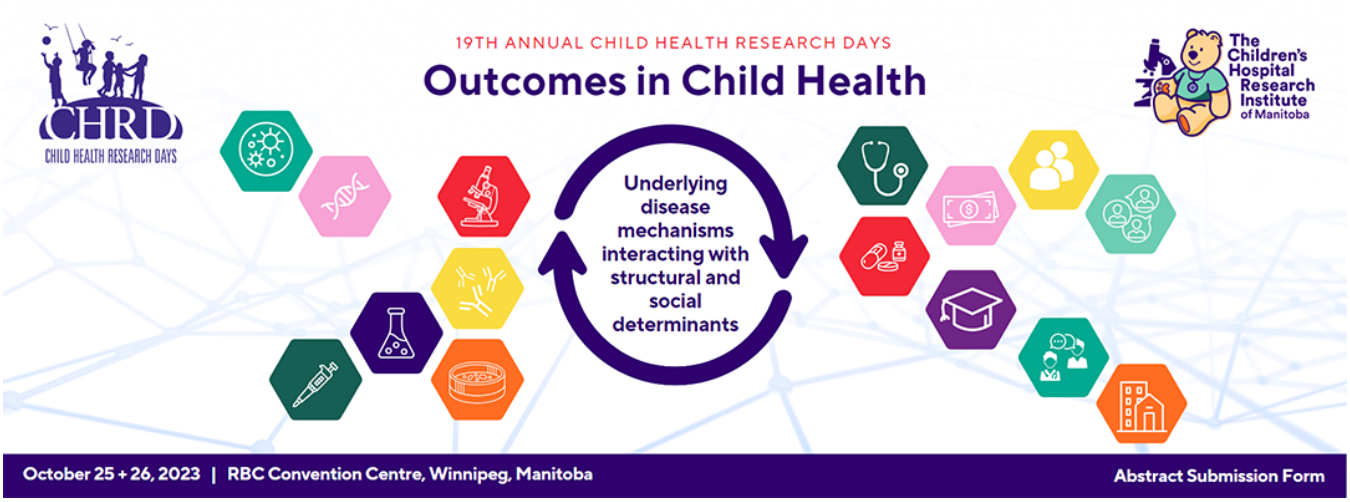

CHRD 2023: Abstract Submission Form

Submitter Name
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Presenter Name
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Presenter Status
Masters Student

Research Category
Basic Science

Role in the project
Analyze Data
Write Abstract

Title
Development of a polygenic score to predict cisplatin-induced ototoxicity in pediatric cancer patients

Background
Cisplatin, a major chemotherapeutic agent, causes hearing loss (i.e., ototoxicity) in a large number of patients, with children at a three-fold higher risk of developing this adverse drug reaction (ADR). Genetics plays a significant role in the variability observed in patient response to cisplatin treatment.

Objective
Given the importance of genetics in cisplatin-induced ototoxicity (CIO), we hypothesize that genetic data can be used to predict the occurrence of this ADR.

Methods
We developed polygenic scores (PGS) using SBayesR and various hearing phenotypes obtained from two large-scale datasets, the UKBiobank (n=353,983) and the Canadian Longitudinal Study on Aging (n=18,955). The relevance of these scores to CIO was tested in a pediatric CIO cohort (n=238) using ReAct. Enrichment analyses were conducted on murine inner ear single-cell-RNA-sequencing data from gEAR to determine whether variants annotated to genes expressed in specific inner ear cell types are more likely to be associated with hearing loss traits.

Results
The self-reported hearing loss PGS was significantly associated with CIO (P=3.8x10-3, R2 = 0.02). However, using audiogram data to more accurately phenotype hearing loss significantly enhanced the predictive capacity of this score (P=5.5x10-10, R2=0.09). Enrichment analyses revealed that variants mapping to genes expressed in cell types in the epithelial cochlea and stria vascularis, were more likely to

be associated with hearing loss (P<2.0x10-16).

Conclusion
This is the first PGS developed to predict the risk of CIO. These results have uncovered novel biology underlying this ADR and confirmed our hypothesis that genetics can be used as a tool to predict CIO.. These findings underscore the clinical relevance of our work, with future opportunities for enhanced patient care and interventions to prevent CIO. This is particularly important for children, where loss of hearing can result in delays in speech/language development, which can potentially affect academic and psychosocial outcomes.

Table/Figure File
Table (Results).pdf

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Table 1. The association between PGS for three different hearing loss phenotypes and CIO.

Hearing Loss Phenotype	Number of Variants in PGS	R^2	P-value
Self-reported	2,753,914	0.021	3.8×10^{-3}
Metabolic*	2,535,227	0.095	5.52×10^{-10}
Sensory*	2,535,227	0.028	9.76×10^{-4}

*As determined using audiogram-based phenotyping