# **Integrative Genomic Analysis of Pediatric Cancer Data from Peds-MI-OncoSeq within the NCI Childhood Cancer Data Initiative (CCDI)**

### **1. Introduction & Background**

The National Cancer Institute's Childhood Cancer Data Initiative (CCDI) was established to create a connected data ecosystem for childhood cancer research. The initiative aims to accelerate scientific discovery and improve patient outcomes by making data from diverse sources widely accessible to investigators. A primary challenge in pediatric oncology is the rarity of individual cancer types, which often results in patient data being fragmented across different institutions. This fragmentation impedes the large-scale research necessary to understand tumor biology, identify new treatments, and improve long-term survivorship.

To address the need for comprehensive genomic profiling in oncology, the University of Michigan established the Michigan Oncology Sequencing Program (MI-OncoSeq). This pioneering initiative provides in-depth sequencing for both adult and pediatric patients. Building on this foundation, the **Pediatric Michigan Oncology Sequencing Program (Peds-MI-OncoSeq)** was created as a dedicated program at C.S. Mott Children's Hospital to specifically address the unique complexities of childhood cancers. Peds-MI-OncoSeq generates high-quality genomic and transcriptomic data from pediatric patients, offering a vital resource for the CCDI. This proposal outlines a project with two primary aims: first, to construct a foundational molecular atlas of this cohort, and second, to leverage this dataset to identify molecular predictors of immunotherapy response in neuroblastoma.

### **2. Project Aims**

**Aim 1: Elucidate the multi-omic landscape of the Peds-MI-OncoSeq cohort to define the molecular architecture of pediatric malignancies.** We will perform a comprehensive and integrative analysis of the Peds-MI-OncoSeq dataset, leveraging whole-exome and transcriptome sequencing data. This aim moves beyond simple cataloging of variants to explore the interplay between different classes of molecular alterations. We will systematically characterize the landscape of somatic and germline mutations, structural variants, copy number alterations, and gene fusions, and correlate these genomic features with transcriptomic profiles to identify patterns of dysregulated gene expression and pathway activation across the cohort. This molecular atlas will serve as a durable resource for the research community, enabling the identification of novel oncogenic drivers and therapeutic vulnerabilities across diverse pediatric malignancies.

**Aim 2: Identify molecular determinants of response to anti-GD2 immunotherapy in neuroblastoma.** We will conduct a focused analysis on the neuroblastoma subset within the Peds-MI-OncoSeq cohort to discover biomarkers predictive of response or resistance to anti-GD2 immunotherapy, a standard treatment for high-risk neuroblastoma. By integrating genomic (e.g., *MYCN* amplification, *ATRX* alterations) and transcriptomic data, we will examine the relationship between tumor genotypes and their corresponding expression profiles. This analysis will specifically interrogate the tumor microenvironment by deconvolving RNA-seq data to characterize immune cell infiltration and explore how pre-existing immune states correlate with therapeutic outcomes. We hypothesize that tumors with transcriptomic signatures indicative of a non-T-cell-inflamed microenvironment will exhibit primary resistance to anti-GD2 therapy. Our goal is to test this by identifying robust, multi-omic signatures that predict patient response.

### **3. Methodology**

We will provide a comprehensive landscape of the genetic alterations in individual pediatric tumor specimens for the purpose of identifying informative and/or actionable mutations.

* Point mutations
* Insertions/deletions (indels)
* Gene fusions and rearrangements
* Gene amplifications and deletions (Copy Number Variants)
* Outlier-expressed genes

Furthermore, a critical component of this pediatric-focused analysis will be the identification and characterization of germline alterations that may predispose children to cancer or otherwise be clinically relevant for the patient and their family.

### **4. Expected Outcomes & Impact**

This project will translate a rich, high-quality pediatric clinical sequencing dataset into foundational knowledge. The expected outcomes include:

* A comprehensive molecular atlas detailing the interplay of genomic and transcriptomic alterations across the Peds-MI-OncoSeq cohort.
* The identification of novel, data-driven biomarkers and potential therapeutic targets, particularly related to the tumor microenvironment in neuroblastoma.
* The development of a clinically-relevant biomarker for anti-GD2 therapy response, providing a strong rationale for prospective validation and eventual implementation in clinical trial design to better stratify patients.
* A harmonized and deeply characterized dataset contributed to the CCDI, serving as a powerful resource for researchers globally and fulfilling the CCDI's core mission to learn from every child with cancer.