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Computational Approaches for Identifying Effective Treatments for Pediatric Brain Tumors

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Medulloblastoma (MB) is the most common pediatric brain tumor. MB standard of care includes surgery, followed by radiation of the brain and spinal cord, and adjuvant chemotherapy. Although survival benefit occurs for some patients after standard-of-care treatment, several deficits persist. Treatment sequelae include neurocognitive impairments, mutism, and hearing loss, as well as secondary malignancies that arise. Importantly, some patients are resistant to conventional therapy. Thus, there is considerable interest in identifying new therapies for treating MB patients. MB has been classified into four major subgroups: WNT, SHH, Group 3 and Group 4, each with its own histology, molecular drivers and prognoses. We have recently developed a computational pipeline to identify therapeutic combinations in a patient specific manner. This pipeline, termed SynergySeq, allows us to stratify patients based on the tumor makeup. We have used this pipeline effectively for glioblastoma, the most common adult brain tumor, to make predictions that were confirmed in preclinical models. We now would like to apply this same computational pipeline to pediatric brain tumors.

Although some children who suffer from MB go on to lead a healthy life after surgery and radiation, some children do not respond to this treatment and succumb to this disease. Therefore, we are trying to find safe and effective therapies for those patients. One of the main issues with brain tumors is that tumors are made up of many different cells and this makes it difficult to ascertain which cells to try to eliminate with a drug. We have developed a way to find this out based on sequencing each cell individually within



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MB tumors. We will use novel computational approaches we developed to identify FDA approved drugs to target the cells in medulloblastoma and test these drugs in animal models of MB. These preclinical studies will make way for clinical trials in MB.