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GLIA-Deep: Glioblastoma Image Analysis using Deep Learning Convolutional Neural Networks to Accurately Classify Gene Methylation and Predict Drug Effectiveness

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Glioblastoma multiforme is a deadly brain cancer with a median patient survival time of 18-24 months, despite aggressive treatments. This limited success is due to a combination of aggressive tumor behavior, genetic heterogeneity of the disease within a single patient's tumor, resistance to therapy, and lack of precision medicine treatments. A single specimen using a biopsy cannot be used for complete assessment of the tumor's microenvironment, making personalized care limited and challenging. Temozolomide (TMZ) is a commercially approved alkylating agent used to treat glioblastoma, but around 50% of temozolomide-treated patients do not respond to it due to the over-expression of O6-methylguanine methyltransferase (MGMT). MGMT is a DNA repair enzyme that rescues tumor cells from alkylating agent-induced damage, leading to resistance to chemotherapy drugs. Epigenetic silencing of the MGMT gene by promoter methylation results in decreased MGMT protein expression, reduced DNA repair activity, increased sensitivity to TMZ, and longer survival time. Thus, it is paramount that clinicians determine the methylation status of patients to provide personalized chemotherapy drugs. However, current methods for determining this via invasive biopsies or manually curated features from brain MRI (Magnetic Resonance Imaging) scans are time- and cost- intensive and have a very low accuracy. The author presents a novel approach of using convolutional neural networks to predict methylation status and recommend patient-specific treatments via an analysis of brain MRI scans. The author developed an AI platform, GLIA-Deep, using a UNet architecture and a ResNet-50 architecture trained on genomic data from TCGA (The Cancer Genome Atlas through the National Cancer Institute) and brain MRI scans from TCIA (The Cancer Imaging Archive). GLIA-Deep performs tumor region identification and determines MGMT methylation status with >90% accuracy and in less than 5 seconds, a real-time analysis that eliminates huge time and cost investments of invasive biopsies. Using computational modeling, the analysis further recommends microRNAs that modulate MGMT gene expression by translational repression to make glioma cells TMZ sensitive, thereby improving the survival of glioblastoma patients with unmethylated MGMT. GLIA-Deep is a completely integrated, end-to-end, cost-effective and timeefficient platform that advances precision medicine by recommending personalized therapies from an analysis of individual MRI scans to improving glioblastoma treatment options.

Background of the Research: GBM is the most common and aggressive malignant brain tumor among adults. Despite recent advances in neuroimaging, surgery, and drug therapies, the prognosis for patients diagnosed with GBM has not improved since the 1980s. Currently, treatments for determining GBM are based on timeconsuming and costly manual tumor feature segmentation and genetic panel testing to determine molecular subtype and O6- methylguanine methyltransferase ("MGMT") promoter methylation, both of which are implicated in chemotherapy effectiveness. Using the approach of the prior art, patients have a mean survival time of 12 months post-diagnosis because the symptoms accompanying GBM are often non-specific, ranging from mild headaches and nausea to personality changes and other stroke-like symptoms, making early detection and treatment difficult. These and other deficiencies exist. The strengths of this study lie in the fully automatic glioma segmentation and predicting the MGMT methylation status based on a small dataset. Generally, it takes a radiologist about one minute per slice in tumor annotation, while the inference time of the deep learning model is about 0.1 seconds which is around 1/600 times used in manual annotation. Additionally, manual annotation is burdensome and prone to introduce interand intraobserver variability. While once well trained, a deep learning model can continuously and repeatedly perform tumor segmentation regardless of the observers. On the other hand, the training strategy in this study is beneficial for small dataset analysis. In general, a deep model requires a large number of training instances. However, it is challenging or impossible to provide massive high-quality images in medical imaging. Finally, although several studies tried to use deep networks for automatic glioma segmentation or molecular classification the proposed network in this study could integrate both glioma segmentation and classification in a seamless connection pipeline. And the performance is competitive to the state-ofthe-art studies in tumor segmentation and classification.