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Newly discovered biomarkers could be key to predicting severity of brain tumor recurrence

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Researchers have identified specific predictive biomarkers that could help assess the level of risk for recurrence in patients with malignant glioma. The study, led by Henry Ford Health System's Department of Neurosurgery and Department of Public Health Sciences, was published today in *Cell Reports*.

The team performed an analysis of 200 brain tumor samples from 77 patients with diffuse glioma harboring IDH mutation, the largest collection of primary and recurrent gliomas from the same patients to date. Comparing samples from the patients' initial diagnosis with those from their disease recurrence, researchers focused, in particular, on a distinct epigenetic modification occurring along the DNA segment, a process called DNA methylation.

Previously, their research showed that when there was no change in the DNA methylation, patients had a good clinical outcome. When the DNA methylation was lost, patients had a poor outcome. In this latest study, the authors were able to identify a set of epigenetic biomarkers that can predict, at a patient's initial diagnosis, which tumors are likely to recur with a more aggressive tumor type.

Houtan Noushmehr, Ph.D., Henry Ford Department of Neurosurgery, Hermelin Brain Tumor Center, and senior author of the study, says this discovery could make a huge difference when a patient is first diagnosed. "To date, we really don't have any predictive clinical outcomes once a patient is diagnosed with glioma. By pinpointing these

molecular abnormalities, we can begin to predict how aggressive a patient's recurrence will be and that can better inform the treatment path we recommend from the very beginning."

Of the 200 tissue samples, 10% were found to have a distinct epigenetic alteration at genomic sites known to be functionally active in regulating genes that are known to be associated with aggressive tumors such as glioblastoma.

"This research presents a set of testable DNA-methylation biomarkers that may help clinicians predict if someone's brain tumor is heading in a more or less aggressive direction, essentially illustrating the behavior of a patient's disease," says James Snyder, D.O., study co-author and neuro-oncologist, Henry Ford Department of Neurosurgery and Hermelin Brain Tumor Center. "If we can identify which brain tumors will have a more aggressive course at the point of initial diagnosis then hopefully we can change the disease trajectory and improve care for our patients."

For example, patients predicted to have a more aggressive tumor at recurrence could be monitored more intensively after their initial treatment, or, undergo a more dynamic therapeutic regimen. Conversely, patients predicted to have a less aggressive recurrence might benefit from a reduction or delay of potentially harsh therapies such as standard chemotherapy and radiation.

"Right now, this level of molecular analysis is not routinely available in precision medicine testing and that needs to change," says Steven N. Kalkanis, M.D., Medical Director, Henry Ford Cancer Institute, and Chair, Department of Neurosurgery. "We need to be examining this level of information for every patient. The hope is that discoveries like this one will lead to clinical trials and increased access and education that make it available for every person who receives a cancer diagnosis."

More information: Camila Ferreira de Souza et al, A Distinct DNA Methylation Shift in a Subset of Glioma CpG Island Methylator Phenotypes during Tumor Recurrence, *Cell Reports* (2018). DOI: 10.1016/j.celrep.2018.03.107