Diagnosing brain tumors with a blood test

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Princess Margaret Senior Scientist Dr. Daniel De Carvalho and Krembil Brain Institute Medical Director Dr. Gelareh Zadeh collaborated to combine advanced technology with machine learning to develop a highly sensitive and accurate blood test to detect and classify brain cancers. Credit: UHN

A simple but highly sensitive blood test has been found to accurately diagnose and classify different types of brain tumors, resulting in more

accurate diagnosis, less invasive methods and better treatment planning for patients, in the future.

The finding, published in *Nature Medicine* on June 22, 2020, describes a non-invasive and easy way to classify brain tumors. The study is also being presented virtually today at the prestigious Opening Plenary Session of the American Association for Cancer Research Annual Meeting 2020: Turning Science into Lifesaving Care.

A major challenge in treating brain cancers is the accurate diagnosis of different types of brain cancers, and tumors ranging from low grade—which can look almost normal under a microscope—to aggressive tumors. Cancer grades are used to determine prognosis, and assist in treatment planning.

Current methods to diagnose and establish the subtype of brain cancer based on molecular information rely upon invasive surgical techniques to obtain tissue samples, which is a high-risk procedure and anxiety-provoking for patients.

The ability to diagnose and classify the type of brain tumor without the need for a tissue sample is revolutionary and practice changing. In some cases, surgery may not even be necessary.

"If we had a better and more reliable way to diagnose and subtype tumors, we could transform patient care," says Dr. Gelareh Zadeh, Medical Director of the Krembil Brain Institute, Head of Surgical Oncology at the Princess Margaret Cancer Centre, Senior Scientist at the Princess Margaret Cancer Research Institute, Professor of Surgery, University of Toronto, and a co-senior author in the study.

"It would have a tremendous impact on how we treat these cancers, and in how we plan our treatments."

Dr. Zadeh worked with Senior Scientist Dr. Daniel De Carvalho at Princess Margaret Cancer Centre, who is a world leader in the field of cancer epigenetics applied to early detection, classification and novel therapeutic interventions.

Dr. De Carvalho's lab specializes in a type of epigenetic modification called DNA methylation, which plays an important role in the regulation of gene expression (turning genes on or off) in cells. In cancer cells, DNA methylation patterns are disrupted, leading to unregulated cancer growth.

Dr. De Carvalho has previously developed a DNA methylation-based liquid biopsy approach to profile hundreds of thousands of these epigenetic alterations in DNA molecules circulating in the blood. These fragments are called circulating tumor DNA or ctDNA. Combining this new technology with machine learning, his team was able to develop a highly sensitive and accurate test to detect and classify multiple solid tumors.

Working together, Drs. Zadeh and De Carvalho decided to use this same approach in the challenging application of intracranial brain tumor classification. The clinicians and scientists tracked the cancer origin and type by comparing patient tumor samples of brain cancer pathology, with the analysis of cell-free DNA circulating in the blood plasma from 221 patients.

Using this approach, they were able to match the circulating plasma ctDNA to the tumor DNA, confirming their ability to identify brain tumor DNA circulating in the blood of these patients. Then, using a machine learning approach, they developed a computer program to classify the brain tumor type based solely on the circulating tumor DNA.

Prior to this, it was not thought possible to detect any brain cancers with

a blood test because of the impermeable blood-brain barrier, says Dr. Zadeh. This barrier exists between the brain's blood vessels and its tissue, protecting the brain from any toxins in the blood.

"But because this test is so sensitive in picking up even small amounts of highly specific tumor-derived signals in the blood, we now have a new, non-invasive way of detecting and discriminating between common brain tumors—something which was long thought impossible. This really is a tour de force," explains Dr. Zadeh.

Dr. Daniel De Carvalho, a Canada Research Chair in Cancer Epigenetics and Associate Professor at University of Toronto, adds that the field of identifying tumor-specific alterations in ctDNA with new, more sensitive tests in various body fluids—such as blood and urine—is now at a turning point because advanced technologies can detect and analyze even the smallest traces of cancer-specific molecular signatures from the vast quantities of circulating non-tumor DNA fragments.

"The possibility to map epigenetic modifications genome-wide, combined with powerful computational approaches, has brought us to this tipping point," says Dr. De Carvalho.

"Molecular characterization of tumors by profiling epigenetic alterations in addition to genetic mutations gives us a more comprehensive understanding of the altered features of a tumor, and opens the possibilities for more specific, sensitive, and tumor agnostic tests."

In an accompanying paper, also published in *Nature Medicine* on June 22, 2020, Dr. Carvalho and his collaborators from the Dana-Farber Cancer Institute at Harvard University show the same blood test can accurately identify kidney cancer from circulating cell-free DNA obtained either from plasma or from urine.

More information: Nassiri, F et al. Detection and discrimination of intracranial tumors using plasma cell-free DNA methylomes. Nat Med (2020). doi.org/10.1038/s41591-020-0932-2