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Tumor DNA in spinal fluid could help doctors better monitor childhood brain cancer

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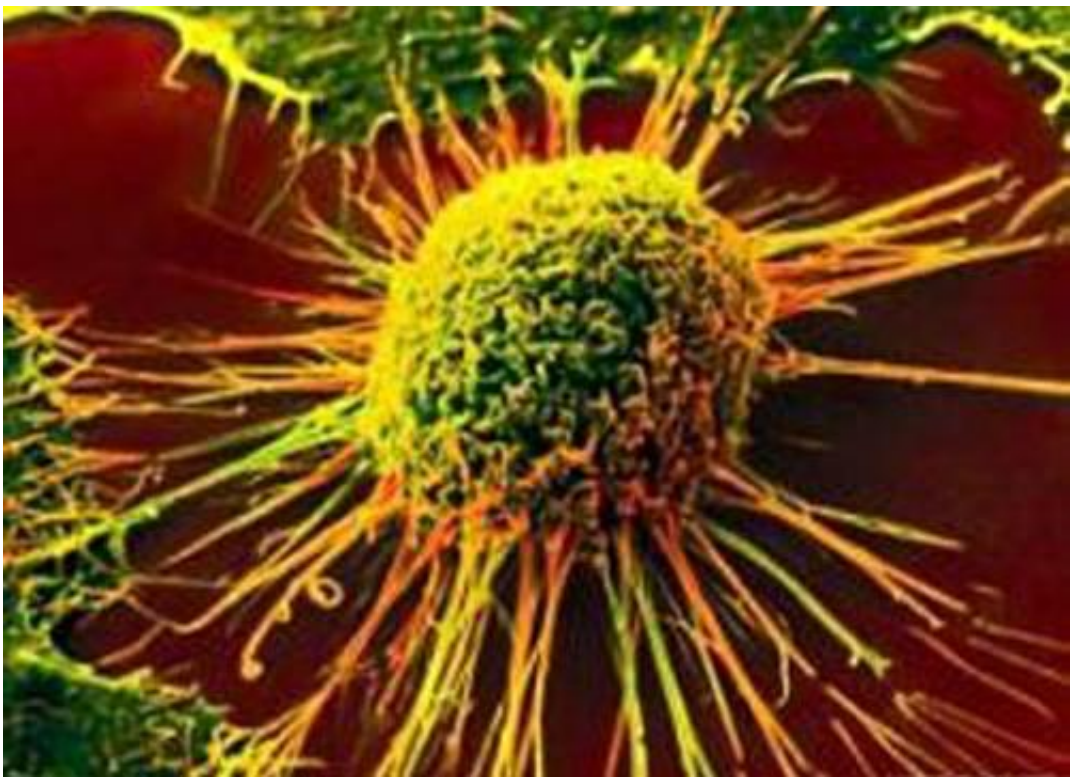

For many cancers, doctors are increasingly looking to the DNA that solid tumors shed into the blood stream to help with diagnosis and monitoring. But brain cancer has been a different story thanks to the natural blockade created by the blood-brain barrier.

Researchers at the University of Michigan Rogel Cancer Center and Michigan Medicine C.S. Mott Children's Hospital, however, were optimistic that cerebrospinal fluid could be a valuable source for tumor DNA that could help monitor and treat pediatric cancer patients with aggressive brain tumors known as high-grade gliomas.

Not only do the mutations in these tumors change over time, causing shifts in potential avenues for treatment, the amount of tumor DNA in a patient's spinal fluid can help doctor's know whether changes observed on a patient's imaging scans are true signs of a tumor's progression or a merely the body's response to cancer treatments.

"We knew from past research that the genetic sequences of these tumors, including information about the mutations that are driving them, can be found in the spinal fluid—but collecting it isn't currently part of the standard of care," says Carl Koschmann, M.D., a Mott pediatric oncologist and researcher with the Chad Carr Pediatric Brain Tumor Center at Michigan Medicine. "That's something we have been hoping to change."

A new study by Koschmann and a team of researchers from U-M suggests new, portable DNA sequencing technology could make such a "liquid biopsy" approach feasible. The team's findings, which appear in *Clinical Cancer Research*, a journal of the American Association for Cancer Research, were the first to apply nanopore genetic sequencing technology toward this purpose.

"We used a modern, handheld DNA sequencing device in a way that had never been done before," says study first author Amy Bruzek, M.D., a neurosurgery resident at Michigan Medicine. "This allowed us to analyze the tumor DNA in patients' cerebrospinal fluid quickly and with equipment that's portable enough to bring into the operating room."

The nanopore system works by measuring changes in electrical current as biological molecules pass through the tiny holes in a collection surface; different values correspond to different letters in the genetic code, thus allowing a DNA sequence to be read.

The study looked for clinically actionable alternations in samples from 12 patients with high-grade gliomas using a device made by Oxford Nanopore Technologies, a spinout from the University of Oxford. The device costs about $1,000, weighs one pound and can be connected to a laptop, the researchers note, giving it advantages over leading laboratory models, which often cost tens of thousands, require dedicated space and are more complex to operate. It also requires significantly smaller amounts of spinal fluid than other sequencing methods.

Across nearly 130 samples, the researchers found the new approach worked well, and the results were confirmed using well-established sequencing methods.

"This study shows an opportunity to efficiently monitor how well clinical trial medications are working for pediatric glioma patients by collecting spinal fluid at different points in time using a procedure known as lumbar puncture or spinal tap," Bruzek says.

Currently, after an initial surgery to remove as much of a glioma as possible, doctors track changes to a tumor by looking at imaging scans.

"Unfortunately, good responses to radiation therapy can create swelling that looks very similar to a tumor that is growing," Koschmann says. "And as doctors, we have to tell patients' families the images can't be interpreted with certainty."

Although these pediatric brain cancers are rare, the vast majority patients who are diagnosed with them live less than two years. So new,

targeted approaches to treating high-grade gliomas in children and young adults is desperately needed—including for diffuse intrinsic pontine gliomas or DIPGs, highly aggressive tumors of the brain stem.

Exploiting the specific molecular mutations these tumors carry offer doctors' best hope for attacking them. Sequencing tumor DNA found in cerebrospinal fluid would also allow doctors to monitor how a tumor's mutations were changing over time and know whether any of the mutations might make specific treatments less likely to work.

"As caregivers, we're excited about the possibility of monitoring tumors without exposing patients to potential complications from invasive surgeries," Koschmann says. "This approach suggests we can rapidly and reliably detect key tumor-driving mutations in high-grade gliomas with very small samples—overcoming some of the barriers that were preventing the use of spinal cord fluid in diagnosing and monitoring these patients. And we're optimistic about incorporating this approach into clinical trial design for pediatric brain cancer, allowing us to track molecular response across multiple genes to better understand and predict clinical outcomes."

More information: Karthik Ravi et al, Electronic DNA Analysis of CSF Cell-free Tumor DNA to Quantify Multi-gene Molecular Response in Pediatric High-grade Glioma, *Clinical Cancer Research*. DOI: 10.1158/1078-0432.CCR-20-2066

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