

Genomics-guided brain tumor treatment

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Several patients with recurring glioblastoma, a deadly brain cancer, survived for more than a year in a clinical trial believed to be the first to use comprehensive DNA and RNA sequencing of a patient's tumor to inform treatment for these patients in real-time. The study was led by the Translational Genomics Research Institute (TGen), UC San Francisco (UCSF) and the Ivy Foundation Early Phase Clinical Trials Consortium.

"This study demonstrates the feasibility of using genome-wide molecular tests to guide treatment in recurrent glioblastoma," according to a scientific paper published today in *Clinical Cancer Research*, a journal of the American Association for Cancer Research (AACR).

"To our knowledge, this is the first report of a prospective profiling study in recurrent glioblastoma to show patients with extended time to progression following treatment with genomics-informed therapy," said Dr. Sara Byron, Research Assistant Professor in TGen's Integrated Cancer Genomics Division and the study's lead author. "This is a primary example of the benefits of genomics-driven precision medicine being applied for patients with aggressive and refractory tumors."

Fifteen of 16 glioblastoma patients in the study conducted at UCSF received TGen's genomics-informed treatment recommendations, in which the therapeutics suggested by a medical review panel (UCSF's Molecular Tumor Board) were matched to each patient's particular genetic code. Of those 15, seven patients were treated by their physicians using the genomic-based recommendations.

Key to this study was the fact that all genomic sequencing (the spelling out of the chemical DNA and RNA bases for more than 20,000 genes in the human genome), genetic analysis, and recommendations for treatment were completed in less than 35 days after surgery, ensuring that suggested therapies could begin within "a clinically acceptable time frame."

Timely administration of therapeutics is critical

Glioblastoma is an aggressive disease, with a median overall survival of only 15 months for newly diagnosed patients. One of the major difficulties in treating glioblastoma is its intrusive penetration into adjoining tissues, which prevents the complete surgical removal of the tumors from the brain, even with follow-up radiation and chemotherapy. As a result, nearly all glioblastomas recur. Patients whose brain [cancer](#) returns are often encouraged to enter experimental clinical trials. However, even on [clinical trials](#), further progression of the disease is seen, on average, within 4 months.

"Notably, two of the patients experienced progression-free survival - meaning their tumor did not return or increase in size - for more than a year, with one of these patients progression-free at 21 months, three times longer than the time to progression on their previous therapy," said Dr. Michael D. Prados, the Charles B. Wilson Endowed Chair in Neurological Surgery at UCSF, and the study's senior author.

Another major challenge in treating brain tumors is finding drugs that can penetrate the blood-brain barrier, which buffers the brain from the rest of the body's blood-circulatory system. Located along small capillaries, the blood-brain barrier protects the brain from rapid changes in the body's metabolic conditions and minimizes exposure to large molecules that are toxic to neurons in the brain.

The only FDA-approved standard-of-care drugs to treat glioblastoma are temozolomide, nitrosoureas, and bevacizumab.

In this study, more than 180 FDA-approved agents were reviewed, including all FDA-approved oncology drugs and a selection of repositioned agents that are approved by the FDA for other indications but show promising activity against cancer pathways. The tumor board considered the drugs supported by the genomic data for each patient, and discussed each drug's ability to penetrate the [blood-brain barrier](#), potential opportunities to combine treatments, drug-to-drug interactions and drug-safety profiles.

Two patients survived more than a year

One of the patients was a 58-year-old woman with recurrent glioblastoma. Genomic sequencing showed several alterations with potential therapeutic relevance. Based on mutations in her NF1 and PALB2 genes, the UCSF Molecular Tumor Board recommended treatment with a combination of trametinib, olaparib and carboplatin. "This patient continued on treatment without disease progression (for more than) 665 days after surgery," according to the new paper, which adds, "Additional preclinical and clinical studies will be needed to determine the role of genomic context and combination therapy in the response observed for this patient."

Another patient was a 35-year old man with recurrent glioblastoma. The study's tumor board, focusing on the tumor's mutations in the IDH1 and ATRX genes, recommended treatment with a combination of CCNU, carboplatin, and metformin. The patient and treating oncologist decided to pursue treatment with CCNU and metformin. "This patient remained on treatment and progression-free for just over one year," the study said.

"This precision-medicine study provides one of the first prospective

demonstrations of using genome-wide molecular profiling to guide treatment recommendations for patients with recurrent glioblastoma within a clinically actionable time frame," said Dr. Michael Berens, TGen Deputy Director for Research Resources, and Professor and Director of TGen's Cancer and Cell Biology Division.

"These findings provide a rationale and framework for larger prospective studies to further assess the efficacy of employing genomics-guided treatment for patients with [recurrent glioblastoma](#)," said Dr. Berens, one of the study's authors.

Also contributing to this study, titled "Prospective feasibility trial for genomics-informed treatment in recurrent and progressive glioblastoma," were physicians and scientists at the University of Texas MD Anderson Cancer Center; the University of Utah Huntsman Cancer Institute; Dana-Farber Cancer Center; the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles; and the Memorial Sloan Kettering Cancer Center.

The study was funded by the Scottsdale, Arizona-based Ben & Catherine Ivy Foundation.

"This study shows a remarkable advance in our ability to treat this most aggressive of brain cancers, and provides [glioblastoma](#) patients with hope that we can conquer this disease," said Catherine (Bracken) Ivy, President of The Ben & Catherine Ivy Foundation.

More information: Sara A Byron et al, Prospective feasibility trial for genomics-informed treatment in recurrent and progressive glioblastoma, *Clinical Cancer Research* (2017). DOI: 10.1158/1078-0432.CCR-17-0963

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