



## RESEARCH ARTICLE

## Real World Utility of Next-Generation Sequencing in Neuro-oncology Patients

Kent R. Richter<sup>1\*</sup>; Ali R. Tafreshi<sup>1</sup>, Alejandro Bugarini<sup>1</sup>, Zachary Hoffer<sup>2</sup>, Manjari Pandey<sup>3</sup>, Anand Mahadevan<sup>4</sup>, Edward A. Monaco III<sup>1</sup>

<sup>1</sup>Department of Neurosurgery, Geisinger Health System. 100 N. Academy Dr., Danville, PA 17821 USA

<sup>2</sup>Department of Pathology, Geisinger Health System. 100 N. Academy Dr., Danville, PA 17821 USA

<sup>3</sup>Department of Hematology and Oncology, Geisinger Health System. 100 N. Academy Dr., Danville, PA 17821 USA

<sup>4</sup>Department of Radiation Oncology, Geisinger



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## ABSTRACT

**Purpose.** There has been a proliferation of commercially available tumor molecular profiling services. However, there is a paucity of evidence as to whether these data result in treatment alterations or enrollment into clinical trials for neuro-oncology patients. This study analyses if increasing use of tumor profiling services has resulted in increased personal neuro-oncologic care with personalized targeted therapies.

**Methods.** We performed a retrospective chart review for all neuro-oncology patients at Geisinger Medical Center from 2016 to 2021 who underwent tumor profiling using commercial send-out testing. We analyzed factors including tumor pathology, actionable genes, treatment pre-tumor profiling, post-profiling, and survival after testing. The clinical action rate was based off these findings.

**Results.** From 2016 to 2021, 83 patients had tumor genetic and molecular profiling. Pathologies included glioblastoma (44.5%), metastases (10.8%), meningioma (9.63%), and others. There was increased testing from 2016 (n=1) to 2021 (n=28). In total, three patients (3.61%) had therapy offered based off NGS testing; these were adjudicated during analysis and did not result from the testing's recommendations but were extrapolations from specific mutations. None of the patients were enrolled in clinical trials based off their test results. The overall mean charges of testing in the five patients for whom our health plan had data were \$44,581.88 (range \$42,218.97-\$47,126.89).

**Conclusion.** Despite increased utilization of tumor profiling technologies in our patient cohort, we observed limited value in altering therapy. Selective testing for actionable alterations based on evidence and improved patient selection will be key to improve value of testing and make it more cost effective.

## Keywords:

Tumor genetics, precision medicine, molecular profiling, glioblastoma.

## Introduction

Although primary brain tumors make up 1.35% of cancer cases in the United States, they are considered the most lethal malignancies; glioblastomas (GBM) are the most aggressive type with a life expectancy of 12-18 months<sup>1</sup>. There have been many different methods discussed in the literature looking to improve GBM treatment including targeted delivery of chemotherapy through bypassing the blood brain barrier using nanoparticles and monoclonal antibodies, improvements in different radiotherapies for more accurate delivery, immunotherapies, cell/gene therapies using direct introduction of genetically modified bacteria to selectively destroy cancer cells, and many others<sup>2</sup>. While there are many potential applications being discussed and tested, there is no consensus on which treatment pathway is preferred and the existing therapeutic options remain limited. Recently, there has been an effort to progressively individualize therapy options for each patient's specific cancer. Next generation sequencing (NGS) is a burgeoning technology that is used to analyze patient's tumor genetic profile for possible germline or somatic mutations that may lead to potential therapeutic interventions<sup>3</sup>. Much discussion has taken place regarding the clinical utility of this testing in various fields including breast and gynecologic cancers<sup>4</sup>, advanced GI tumors<sup>5</sup>, neuro-oncology<sup>6-11</sup>, and many more. Our analysis focused on NGS testing of patients who suffer from neuro-oncologic diseases. While these services provide a genetic profile for each patient's tumor, there is a paucity of evidence in the literature as to whether these data result in treatment alterations or enrollment into clinical trials for neuro-oncology patients. We have empirically observed an increase in the utilization of this testing in neuro-oncology. As this type of testing can be costly, and may not be covered by health plans, we sought to discern if its increasing use resulted in clinicians personalizing neuro-oncologic care with targeted therapy. Our aim is to improve the utilization of this burgeoning

technology and make care for neuro-oncology patients as cost-effective as possible.

## Materials and Methods

### STUDY DESIGN AND SETTING

This study was conducted under the auspices of an Institutional Review Board (IRB) approval for retrospective evaluation of patients with neuro-oncology diagnoses. We performed a multi-institutional retrospective review of neuro-oncology patients who underwent send-out testing on their tumor tissue using a commercially available next-generation sequencing (NGS) laboratory, Caris Life Sciences, Irving, TX, USA. The study period ranged from January 2016 to October 2021.

### PATIENTS

Patients included in this study were those diagnosed with neuro-oncologic diseases and who had their tumor tissues evaluated using NGS. The electronic medical record (EMR) system was queried to collect available clinical information and testing results. A total of 87 neuro-oncology cases were identified for potential inclusion, with NGS testing completed in 83 cases. Demographic information, pathology data, NGS results, and treatments were extracted from the EMR. Overall survival post-NGS was defined as the time from the completion of testing to the last follow-up or death.

### TARGETED NEXT-GENERATION SEQUENCING

NGS was employed to identify genetic alterations in tumor tissues, potentially guiding therapeutic decisions. The sequencing focused on detecting actionable mutations that could influence treatment strategies. The average turnaround time for receiving NGS results was 13.2 days, with a range of 4 to 42 days. NGS testing was requested by treating physicians based on clinical judgment, often influenced by the aggressiveness of the tumor and previous treatment responses.

### DATA COLLECTION

Data collection encompassed patient demographics (age, sex), tumor characteristics (type, grade), NGS findings, and clinical outcomes. Specifically, information on tumor pathology, actionable genetic

alterations, and subsequent treatments were meticulously recorded. Pathological diagnoses were categorized, including glioblastoma, metastases, meningioma, and other neuro-oncologic entities.

#### STATISTICAL ANALYSIS

The primary endpoint was the clinical action rate, defined as a documented clinical decision in the EMR based on NGS results. This could include changes in therapy, enrollment in clinical trials, or other treatment modifications. Descriptive statistics were employed to summarize patient characteristics and NGS findings. The survival analysis was conducted using Kaplan-Meier methods to estimate overall survival post-NGS testing. Statistical analyses were performed using SPSS software (version XX; IBM Corp., Armonk, NY, USA)

pathological diagnoses included: 37 glioblastoma (44.5%), 9 metastases (10.8%), 8 meningioma (9.63%), 4 chordomas (4.82%), 3 anaplastic astrocytoma (3.61%). Table 1 shows the patient and tumor characteristics included in this study. This testing has been more frequently obtained on neuro-oncology patients at our institution over the last several years: 1 test in 2016, 3 in 2017, 18 in 2018, 13 in 2019, 24 in 2020, and 26 through October 2021 (Figure 1). The mean turn-around time for testing was 13.2 days (range 4 to 42 days). Next generation sequence testing identified a potential therapeutic target in 32 (38.6%) of the total cases.

## Results

#### PATIENT CHARACTERISTICS AND HISTOPATHOLOGICAL PROFILES

Eighty-three neuro-oncology patients had tumor tissue evaluated by CARIS NGS. The most frequent

Table 1: Patient demographics and tumor characteristics.

Sex		
Male		46
Female		37
Age at Report		
Mean		52.65
Median		54
Range		18 - 86
Tumor Type		
Glioblastoma		37
Other Glial Tumors		16
Metastasis		9
Meningioma		8
Chordoma		4
MPNST		2
Other		7
NGS Turnaround time		
Mean		13.2 Days (RANGE)
Refined Diagnosis		
None		

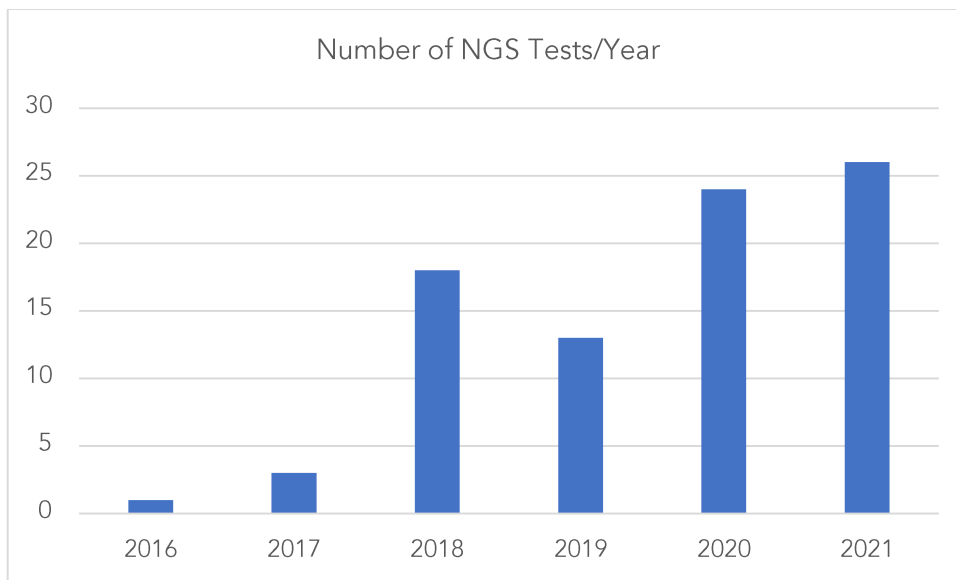


Figure 1: Number of Next Generation Sequencing tests per year. Abbreviations:

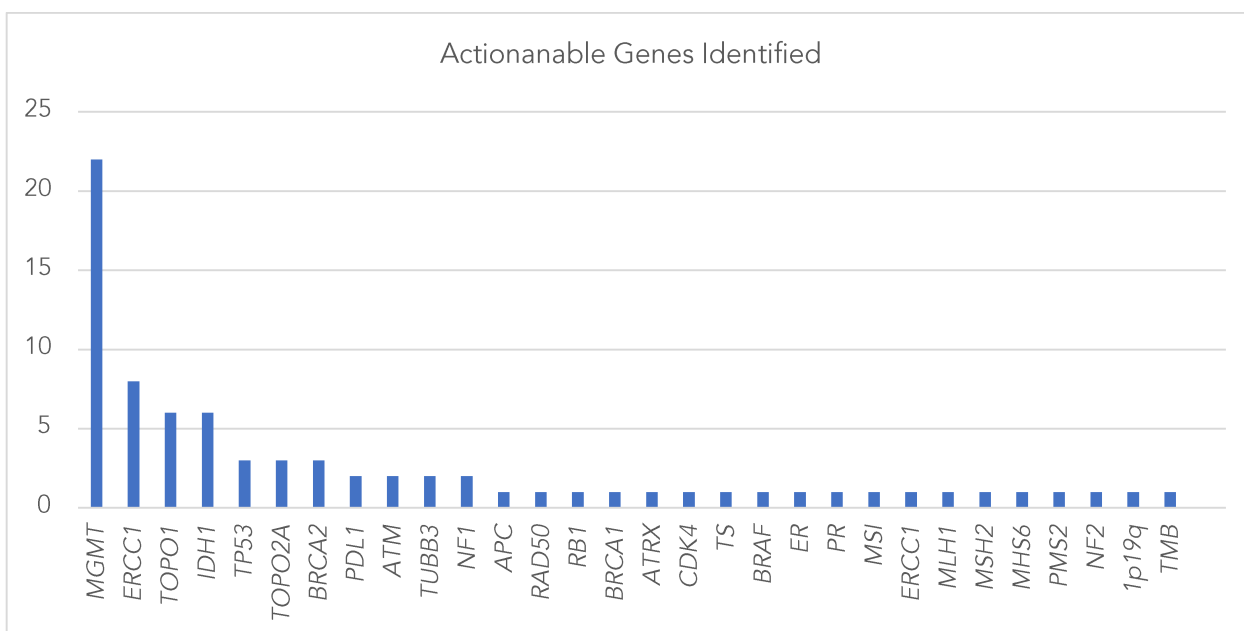


Figure 2: Frequency of actionable genes identified with next generation sequencing, N = 83 patients.

### GLIOBLASTOMA

Thirty-six of the patients for whom NGS testing was obtained harbored a diagnosis of GBM. Their mean age at the time of sequencing was 56 years (range 26-86). Eighteen patients were deceased at the time of data analysis. They demonstrated a median survival of 16.1 months (range 2.0 to 59.6 months). The median survival after NGS testing results was 4.71 months (range 0 to 37.6 months). Three patients died before NGS testing results became available. In 19 GBM patients (51.2%), NGS testing was performed within 3 months of the initial diagnosis with a median time from tumor specimen collection to testing results of 44 days (range 23 to 96 days). In the remaining patients,

testing was performed in a delayed fashion, often at the time of progression, with a median time from specimen collection to testing result of 8.2 months (range 1.1 to 88.9 months). Next generation sequence testing identified a potentially beneficial therapeutic target in 20 of 36 cases (57.1%). Temozolamide, the first line standard-of-care agent for glioblastoma, was the most identified therapeutic target with 11 (29.7%) of these cases, of which these patients were already taking. This recommendation was based on the presence of (O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation or isocitrate dehydrogenase 1 (*IDH1*) mutation. Platinum based agents were identified in six (16.2%) cases, and irinotecan was

noted in five (13.5%) on the basis of *ERCC1* and *TOPO1* mutations. Pembrolizumab was identified as potentially therapeutic in one (2.7%) patient on the basis of the mismatch repair status and tumor mutational burden (TMB). In the remaining 15 patients, no therapeutic target was identified. We observed no instances wherein a GBM patient's treatment was altered on the basis of the NGS testing results. In addition, there were no instances wherein a patient was enrolled in a clinical trial on the basis of the NGS testing.

#### OTHER GLIAL NEOPLASMS

Sixteen patients diagnosed with various other glial neoplasms had NGS testing obtained. These pathologic diagnoses included the following: anaplastic astrocytoma *IDH-WT* (n=4), diffuse astrocytoma *IDH1-MT* (3), anaplastic oligodendroglioma (2), and one each for grade 2 pleomorphic xanthoastrocytoma (PXA), low grade astrocytoma, pilocytic astrocytoma, PLNTY, low grade glioneuronal tumor, ganglioglioma, and grade 2 oligodendroglioma. All patients were alive at the time of data analysis. The median time from specimen collection to NGS testing date for these patients was 8.1 months (range 0.9 to 60.8 months). For these patients, therapeutic targets were noted in 8 (47%). In six instances, the therapeutic target identified was temozolomide. Dabrafenib and vemurafenib were identified as targets in the PXA harboring a *BRAF* mutation. Platinum based therapy was identified as potentially beneficial in a single case of anaplastic astrocytoma possessing an *ERCC1* mutation. For one anaplastic oligodendroglioma, lomustine, procarbazine, and vincristine were noted to be potentially beneficial on the basis of a 1p/19q co-deletion. Again, we observed no instances wherein a patient's treatment was altered by the results of NGS testing, nor were there any patients enrolled in a clinical trial.

#### METASTATIC TUMORS

Nine patients had a pathological diagnosis of metastatic brain or spine tumors, including the following histologies: non-small cell lung (3), breast

(2), and one each of small cell lung, endometrial adenocarcinoma, salivary duct, and cholangiocarcinoma (Table 1). Seven of the nine were deceased at the time of data analysis and one was lost to follow-up. The median survival of these patients was 53.4 months (range 11.4 to 112.9 months). Therapeutic targets were reported in 4 of the 9 cases (44.4%). DOXIL was identified in a patient who suffered from endometrial adenocarcinoma. Bicalutamide and leuprolide (AR) were identified as potentially therapeutic for a patient who suffered from salivary duct carcinoma. Pembrolizumab, atezolizumab, durvalibumab, and nivolumab were identified as therapeutic targets in a patient diagnosed with lung adenocarcinoma. One patient with an *ERCC1* and *TOP2A* mutations with metastatic small cell lung carcinoma where platinum and doxorubicin were identified as therapeutic. This potential therapy was adjudicated during analysis and was found not to result from the testing's recommendations but extrapolations from specific mutations. Again, there were no instances wherein a patient's treatment was altered on the basis of the NGS testing recommendations. No patients were enrolled in a clinical trial based on these results.

#### MENINGIOMAS

For patients diagnosed with meningioma, only one test revealed a potential therapeutic target: nivolumab. This was based on the PDL-1 overexpression status in an atypical meningioma.

#### OTHERS

No potentially therapeutic targets were identified for chordoma, malignant peripheral nerve sheath tumors or any of the more isolated pathological diagnoses.

#### COST OF TESTING

The overall mean charges of testing in the five patients for whom our health plan had data were \$44,581.88 (range \$42,218.97-\$47,126.89). The health plan's average outlay for this testing was \$12,554.94 (range \$3,916.37-\$29,619.16). In these five patients, there were no treatment changes prompted by testing.

## Discussion

The role of molecular characterization in central nervous system neoplasms is critical in our attempts to diagnose and prognosticate patients afflicted with brain and spinal cord tumors. Further, the past two decades have seen major progress in the development of NGS for the purposes of targeting therapy for these neoplasms. Currently, multiple groups have described effective workflows and developed advanced technologies that are designed to detect clinically-relevant mutations and biomarkers<sup>8</sup>. It remains unclear, however, even when potentially actionable mutations are found, whether patient care is ultimately guided by the findings. A recent meta-analysis of all cancer types, showed that approximately one in three patients saw changes to their treatment regimen based on NGS results<sup>12</sup>. These results have yet to be corroborated for brain tumors as a subgroup.

In our study, we followed 83 patients who underwent NGS testing. Our set included a range of pathologies including 37 GBM, 9 metastatic lesions, 8 meningiomas, 4 chordomas, and 3 anaplastic astrocytomas. Mean turnaround time for sample results was 13.2 days. Initial NGS test results appear promising with over 1/3 of patients demonstrating possible genetic targets for therapeutic intervention. Our results suggest that, while genomic sequencing of brain tumors can identify a multitude of theoretically targetable mutations, the ultimate downstream benefit may not be transmitted to patients.

Prior studies have demonstrated some clinical utility for brain tumor patients, in subsets of tumor types. Particularly, practical clinical impact was demonstrated for pediatric brain tumors in a recent single-institution report at a children's hospital<sup>6</sup>. This group found that more than half (55%) of children who underwent NGS experienced some change in management based on their results. However, only 24% of patients underwent a targeted treatment based on the NGS (the other patients underwent a refinement/revision of

diagnosis or were newly diagnosed with a syndrome). Considering that a much larger proportion (74%) of the cohort was found to have a theoretically actionable mutation, there remains a discrepancy between the NGS findings and downstream patient benefit. Furthermore, much of the study of the clinical utility of NGS for brain tumors is focused on pediatric pathology<sup>6,11</sup>. Given that pediatric brain tumors are known to display a wide spectrum of genetic abnormalities and the extensive literature surrounding molecular targeting of these tumors, the apparent usefulness of NGS in pediatric brain tumors may not apply to adult tumors<sup>13-15</sup>. As such, it is difficult to translate the findings from the current NGS literature to all brain tumors as a whole, warranting continued investigation of the applicability of NGS across the spectrum of brain neoplasms.

In our study, we found that average turnaround time was 13 days, which is generally consistent with prior studies. Turnaround time for NGS results is not consistently reported in the literature, but other studies of NGS for brain tumors have shown a wide range, with some averaging 8.7 days, and others nearly two weeks or more<sup>6,11</sup>. While most of our patients had results within two weeks, we did have a range wait times, sometimes in excess of a month, with three patients dying before their NGS resulted. Long wait times for results, particularly at institutions without the genomics support for high-throughput systems, risks delaying patient care, even if actionable results are obtained. As such, it is imperative that these times be reduced and that clinicians remain aware that treatment should not be delayed, as aggressive brain tumors grow significantly in volume within weeks<sup>16</sup>. Furthermore, long turnaround times risk invalidation of the sequencing results, given the rapid evolution seen in high-grade tumors<sup>17</sup>. At our institution, partially in response to results presented in this manuscript, we have switched to an entirely in-house genomics core for NGS, in hopes that costs and turnaround times are significantly reduced.

In our cohort, cost-to-payer data is available for a small subset of patients, and this averaged in

excess of \$19,000. In comparison, prior studies have demonstrated an average in excess of \$6,000 USD in per-patient costs, with costs markedly higher in the United States compared to all other countries<sup>18,19</sup>. The higher costs in our study are potentially reflective of our reliance on a third-party for genomics data, which is the case at other institutions<sup>20</sup>. Other analyses of NGS sequencing has estimated an average cost in excess of \$90,000 USD from initiation of testing to delivery of therapeutics<sup>21</sup>. Other cost-effective analysis models have demonstrated NGS sequencing to be remarkably cost-ineffective, although this data has not been focused on NGS for brain tumors<sup>22-24</sup>. As the number of targeted therapeutics continue to grow and genomics pipelines increase in effectiveness, the likelihood of improving cost-effectiveness, particularly by increasing quality-adjusted life-years is likely to increase. Multiple groups have demonstrated effective streamlining and clinical-laboratorial integration of in-house genomics cores, with successful clinical translation of results, but cost-effective analyses have not been specifically conducted<sup>7,11</sup>.

The landscape of genomics for brain tumors continues to evolve. The number of targetable mutations and the very definition of targetable continues to grow and expand. Even if clinical decisions are made and/or informed by NGS, the clinical significance of these changes need to be established. This is a particularly difficult task given the heterogeneity in clinical presentation, prior treatments and surgical intervention in most patient cohorts<sup>6,7,11</sup>. This clinical impact will need to be demonstrated clearly and consistently, particularly to garner medical community and payer support, which often display a degree of uncertainty towards these novel therapeutic targets<sup>25-27</sup>.

## Conclusion

Commercially available genetic and molecular technologies make tumor profiling widely accessible, and hold promise for personalized neuro-oncology treatment plans. Despite increased

utilization of such testing in our cohort, we observed limited value in altering patient management. Selective testing for actionable alterations based on evidence and improved patient selection will be key to improve value of testing and make it more cost effective.

## Conflict of Interest:

“The authors have no relevant financial or non-financial interests to disclose.”

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None.

## Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Kent Richter, Ali Tafreshi, and Edward Monaco. The first draft of the manuscript was written by Kent Richter, Ali Tafreshi, Alejandro Bugarini, and Edward Monaco, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.”

## Data Availability

“The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.”

## IRB Approval

This study fell under the auspices of an IRB approval for retrospective evaluation of patients with neuro-oncology diagnoses.

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