# Molecular Profiling in Neuro-Oncology: Where We Are, Where We're Heading, and How We Ensure Everyone Can Come Along

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Overview

**Advances in molecular profiling have led to improved understanding of glioma heterogeneity. Results have been used to inform diagnostic classification and targeted treatment strategies. Validation of these tests is necessary in the development of biomarkers that can aid in treatment decision, allowing for personalized medicine in neuro-oncologic diseases. Although not all populations have benefitted equally from awareness of and access to testing, opportunities arise regarding incorporating this testing into the standard of care for patients with glioma.**

## BACKGROUND

Over the last decade, there have been major advances in our ability to profile tumors molecularly with next-generation sequencing and DNA methylation analysis.[1,2] These techniques have significantly improved our understanding of the major molecular drivers in brain tumors and the identification of novel tumor types.[1,3,4] They provide the opportunity to improve the classification and diagnosis of brain tumors and identify potential targeted therapies. Nonetheless, to date, these advances have not translated into better outcomes for most patients.[5,6]

## 2021 WHO CLASSIFICATION OF CNS TUMORS

Undoubtedly the most important role of molecular profiling in brain tumors currently is the classification of these tumors. Beginning with the 2016 WHO CNS Tumor Classification update,[7] and expanded in the 2021 WHO CNS Tumor Classification,[8] molecular profiling now plays a crucial role in the diagnosis and classification of brain tumors (Fig 1).

Diffuse gliomas are now separated into adult-type and pediatric-type with different biology and molecular drivers.[8] Adult-type gliomas have been condensed into just three types (isocitrate dehydrogenase [*IDH*]–mutated astrocytomas and oligodendrogliomas, and *IDH* wild-type glioblastomas).[8] Glioblastomas now include not only tumors with the classical histologic findings of necrosis and microvascular proliferation but also tumors without these findings but with *TERT* promoter mutation, epidermal growth factor receptor (EGFR) amplification, or gain of chromosome 7 and loss of chromosome 10 (molecular glioblastomas).[8] For pediatric-type diffuse gliomas, there is differentiation into low-grade tumors, such as those with MAP kinase alterations, and high-grade gliomas with H3K27M alterations and infantile hemispheric gliomas, which are often associated with fusions, offering potential targets for therapies.[9]

Molecular classification of medulloblastomas also allows the identification of good prognostic groups with WNT alterations that may allow for reduction in radiotherapy dose and potential neurotoxicity and groups that have alterations in the sonic hedgehog pathway that may respond to smoothened inhibitors.[10] In contrast, those patients in other groups have a much poorer prognosis and require aggressive therapy.[8,10,11]

DNA methylation profiling enables quantitative interrogation of selected methylation sites across the genome, offering high-throughput capabilities.[2,12,13] It has improved the classification of brain tumors and allowed the identification of several previously unknown tumor types. Although it is currently not widely available, it offers the potential for a relatively cost-effective method to diagnose brain tumors, providing $O^6$-methylguanine–DNA methyltransferase (MGMT) methylation status and copy number information. Methylation of the MGMT promoter and silencing of the gene are predictive of improved response to alkylating chemotherapy (temozolomide and lomustine) in patients with glioblastoma.[14,15] MGMT promoter methylation status is being used increasingly to stratify patients in glioblastoma clinical trials and select patients without MGMT promoter methylation for trials omitting temozolomide, allowing the agent under investigation to be used at full dose or to avoid immunosuppression.[16]

The improved classification of CNS tumors with molecular profiling allows for better understanding of the

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**PRACTICAL APPLICATIONS**

- Molecular profiling plays a critical role in diagnosis, classification, and outcomes of brain tumors.
- The greatest advances have been seen in children, allowing targeted therapy for SEGA in tuberous sclerosis, low-grade glioma, and plexiform neurofibroma.
- Methylation of $O^6$-methylguanine–DNA methyltransferase promoter enzyme is predictive of improved response to alkylating chemotherapy in patients with glioblastoma and is being used to stratify patients in clinical trials.
- Developing a predictive biomarker for widespread use in patients with glioma requires validation.
- Improving access and awareness of advanced molecular testing will broaden understanding regarding the spectrum of diseases in patients with various elements of diversity.

prognosis and optimal therapy for patients.[9,17] It also allows more homogeneous populations of patients to be enrolled into clinical trials, facilitating the evaluation of novel therapies, and increases the potential for identifying more molecular targets for therapy. However, there is now a much greater requirement for neuropathology laboratories to have access to adequate molecular testing and to provide the results in a timely manner. There is also the need for payors to be educated on the importance of these tests and provide appropriate reimbursement.

## THERAPY ON THE BASIS OF MOLECULAR PROFILING

Although there has been major progress in understanding the molecular pathogenesis of brain tumors, these advances have only recently started to be translated into improved outcomes for patients, primarily in the pediatric population.

Therapy for systemic cancers has been effective with agents able to achieve therapeutic concentrations against well-validated therapeutic targets. For many brain tumors, targets are often not well-validated and there are uncertain ability of the agents to cross the blood-brain barrier (BBB) and achieve adequate concentrations in tumor and uncertain information regarding the ability of these agents to adequately inhibit the targeted pathways.[6] Other challenges to developing effective molecular therapies include the poorly predictive preclinical models, the limited number of agents under development that can effectively cross the BBB, redundancy of signaling pathways, tumor heterogeneity and plasticity of cellular states, the relative rarity of easy targets, such as *BRAFV600E* mutations and fusions, the poorly organized and funded infrastructure for early phase (phase I and surgical window of opportunity) clinical trials in neuro-oncology, the need for improved response criteria and trial design, and the relative lack of funding and interest from the pharmaceutical industry.[6]

Despite these challenges, there has been some recent progress (Table 1). In adults, the combination of dabrafenib (RAF inhibitor) and trametinib (MEK inhibitor) produced durable responses in 32% of *BRAFV600E*-mutated glioblastomas and 69% of lower-grade gliomas and contributed to the US Food and Drug Administration approval of the combination for all solid tumors in 2022.[18] Single-agent vemurafenib (BRAF inhibitor) produced a lower 25% objective response rate (ORR) and a 5.5-month median progression-free survival (PFS) in *BRAFV600E*-mutated gliomas.[19] Retrospective studies have also shown similar benefits.[36] In adults, durable response rates of 30% have been observed with larotrectinib for neurotrophic tyrosine receptor kinase fusion–positive brain tumors,[20] 20.7% with erdafitinib for high-grade gliomas with fibroblast growth factor receptor mutations or fusions,[21] and 20% with dordaviprone (ONC201), a dopamine receptor D2 inhibitor and ClpP agonist, in H3K27M-mutated diffuse midline gliomas.[22,23] In IDH-mutated gliomas, several IDH inhibitors have shown prolonged stabilization of disease and vorasidenib has shown response rates of up to 40%.[24-28,37,38]

However, the greatest advances have been seen in children. The first targeted therapy that received regulatory approval for brain tumors was the mammalian target of rapamycin inhibitor everolimus for subependymal giant cell astrocytoma associated with tuberous sclerosis.[29] A durable response rate of 35% was observed and associated with a reduction in seizure frequency. The combination of dabrafenib and trametinib has produced a response rate of 25% in children with recurrent low-grade gliomas with *BRAFV600E* mutations[30] and increased responses and prolonged progression-free survival compared with standard chemotherapy with newly diagnosed low-grade gliomas with these mutations (an ORR of 47% and a median PFS of 20.1 months with dabrafenib/trametinib *v* an ORR of 11% and a median PFS of 7.4 months with chemotherapy).[30] MEK inhibitors, such as selumetinib,[31,39] and type 2 RAF inhibitors, such as tovorafenib (day 101), also show high response rates in children with low-grade gliomas, including those with BRAF-KIAA fusions. Infants with hemispheric gliomas often have fusions, and responses have been seen with a variety of agents.[40] Dordaviprone (ONC201) has also shown activity in children with H3K27M-mutated midline gliomas,[32] and encouraging responses have been observed with GD2 CAR-T-cell therapy for these tumors.[33] Selumetinib has also shown encouraging activity for malignant plexiform neurofibromas.[34]



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**General Changes in Nomenclature**

Use of Arabic numerals (1, 2, 3, 4) rather than Roman numerals (I/II/III/IV)

*Not Otherwise Specified (NOS)* indicates that the molecular and/or immunohistochemical testing needed to precisely classify a particular CNS tumor by the new scheme is not available.

*Not Elsewhere Classified (NEC)* refers to cases in which advanced molecular testing was done, but still failed to classify the tumor.

**Adult-Type Diffuse Gliomas**

- Astrocytomas, IDH-mutant
- Oligodendrogliomas, IDH-mutant, 1p/19q codeleted
- Glioblastoma, IDH wild-type

**Pediatric-Type Diffuse Gliomas**

***Pediatric-Type Diffuse Low-Grade Gliomas***

- Diffuse astrocytomas, MYB- or MYB-L1–altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumor of the young
- Diffuse low-grade glioma, MAPK pathway–altered

***Pediatric-Type Diffuse High-Grade Gliomas***

- Diffuse midline gliomas, H3K27-altered
- Diffuse hemispheric gliomas, H3G34-mutant
- Diffuse pediatric-type high-grade glioma, H3 wild-type and IDH wild-type
- Infant-type hemispheric glioma

**Circumscribed Astrocytic Gliomas**

- Pilocytic astrocytoma
- High-grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma
- Chordoid glioma
- Astroblastoma, *MN1*–altered

**Glioneuronal and Neuronal Tumors**

- Ganglioglioma
- Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
- Dysembryoplastic neuroepithelial tumor
- Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
- Papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor
- Myxoid glioneuronal tumor
- Diffuse leptomeningeal glioneuronal tumor
- Gangliocytoma
- Multinodular and vacuolating neuronal tumor
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma

**Ependymal Tumors**

- Supratentorial ependymoma
- Supratentorial ependymoma, *ZFTA* fusion–positive
- Supratentorial ependymoma, *YAP1* fusion–positive
- Posterior fossa ependymoma
- Posterior fossa ependymoma, group PFA
- Posterior fossa ependymoma, group PFB
- Spinal ependymoma
- Spinal ependymoma, *MYCN*-amplified
- Myxopapillary ependymoma
- Subependymoma

**FIG 1.** Major changes on the basis of the 2021 WHO CNS Tumor Classification of Glial Tumors.[8,9] H3, histone H3; *IDH*, isocitrate dehydrogenase; MAPK, mitogen-activated protein kinase; *MN1*, MN1 proto-oncogene transcriptional regulator; *MYB*, MYB proto-oncogene transcription factor; *MYCN*, MYCN proto-oncogene, bHLH transcription factor; *YAP1*, yes1-associated transcriptional regulator; *ZFTA*, zinc finger translocation–associated.



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**TABLE 1.** Table Summarizing Molecular Targets Responding to Therapy

| Molecular Target | Agent | Activity (ORR) | Reference |
|---|---|---|---|
| Adults | | | |
| BRAFV600E | Vemurafenib | 25% | 19 |
| BRAFV600E | Dabrafenib/trametinib | 32% GBM; 69% LGG | 18 |
| NTRK | Larotrectinib | 30% | 20 |
| FGFR mutation/FGFRTACC fusion | Erdafitinib | 20.9% | 21 |
| H3K27M | Dordaviprone (ONC201) | 20% | 22,23 |
| IDH | Ivosidenib, vorasidenib<br>Olutasidenib, BAY 1436032<br>Safusidenib | 5%-40% | 24-28 |
| Children | | | |
| TSC1/2 | Everolimus | 35% | 29 |
| BRAFV600E | Dabrafenib/trametinib | 25%-47% | 30,35 |
| BRAF/KIAA fusion | Selumetinib | 35%-40% | 31 |
| BRAF/KIAA fusion | Tovorafenib | 64%[a] | |
| H3K27M | Dordaviprone (ONC201) | | 32 |
| H3K27M | GD2 CAR-T cell | 50% | 33 |
| NF1 | Selumetinib | 70% | 34 |

Abbreviations: CAR, chimeric antigen receptor; GBM, glioblastoma; LGG, low-grade glioma; ORR, objective response rate.
[a]Not yet published in peer review journal.

These recent examples of activity with targeted molecular therapies suggest that despite the concerns regarding tumor heterogeneity, plasticity of cellular states, and redundancy of signaling pathways, in small subsets of brain tumors, targeting of oncogenic drivers can be effective. Whether targeting of the more common molecular drivers involving the EGFR, the cyclin-dependent kinase (CDK) 4/6 pathway, and the phosphatidylinositol-3-kinase (PI3kinase) pathways will be effective remains to be seen. Trials with targeted therapies against these pathways, for example, abemaciclib for glioblastomas with CDKN2A/B loss, buparlisib for tumors with PI3K activation, and numerous agents against EGFR, have been ineffective. Paxalisib, a pI3 kinase inhibitor, did not graduate to stage 2 in GBM Agile, although the patients in that trial were not specifically selected for PI3 kinase pathway activation. Newer agents against EGFR directed at the molecular alterations specific for glioblastomas with good BBB penetration such as BDX1535 and ERAS-801 are in clinical trials. Whether they will be more effective remains to be determined. In addition, progress in evaluating sensitive and reliable blood and cerebrospinal fluid biomarkers will help with less invasive profiling of tumors and the selection and monitoring of molecular therapies.[41]

## ESTABLISHING PREDICTIVE BIOMARKERS IN NEURO-ONCOLOGY

Predictive biomarkers, also known as treatment selection biomarkers, typically represent some characteristics related to the study drug's mechanism of action. Successful identification and deployment of predictive biomarkers are crucial toward the goal of precision oncology as its central tenet lies in delivering the right cancer therapy to the right patients at the right time. However, to date, few molecular changes detected in brain tumors have risen to the level of being clinically useful. The reasons for the paucity of clinically useful biomarkers in neuro-oncology are multifaceted. In this section, we highlight several methodological challenges associated with identifying predictive biomarkers. Using examples in neuro-oncology, we first underscore the need for well-validated and reproducible biomarker assays for routine clinical use. Second, we illustrate some difficulties arising from evaluating the predictive value of a biomarker on the basis of data collected from previous randomized clinical trials (RCTs). Although these discussions are framed primarily around predictive biomarkers, many methodological principles apply generally to other types of biomarkers (diagnostic and prognostic biomarkers).

### Biomarker Assay Validity and Reproducibility

Uncertainty around the performance characteristics of the biomarker assay can pose significant challenges in clinical implementation. In a newly diagnosed glioblastoma, for example, *MGMT* promotor methylation status has emerged as a biomarker for prognosis and for predicting response to alkylating agents, such as temozolomide and



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lomustine.[14,42,43] Although *MGMT* status has been used in clinical trials for some time, the implementation of this biomarker in clinical practice is challenging. One reason is that there is currently no consensus regarding the best assay to evaluate *MGMT* methylation status. The use of different assay methods has led to discordant *MGMT* results in some patients, leading to ambiguous treatment recommendations.[44,45] A study by Lassman et al[46] analyzed the concordance of *MGMT* methylation results between local and central laboratories using tissue specimens collected from a randomized phase III trial RTOG 3508 and found that the interlaboratory concordance was only 61%. At present, several assays are in use to determine *MGMT* promoter methylation status in patient samples. A comprehensive review of the various methods is beyond the scope of this article; readers are referred to a review by Weller et al.[47]

Another considerable limitation is the lack of standard cutoff values for determining *MGMT* status from quantitative methods, such as methylation and expression assays. A group of investigators conducted an international survey regarding the use of *MGMT* assays in 25 countries. The survey results revealed that there is considerable variability with respect to the assays used and the cutoff values for *MGMT* methylation status.[48] Considering the potential of this biomarker in treatment decisions in clinical trials and routine practice for glioblastoma, there is a pressing need for an international consensus guideline to standardize the *MGMT* methylation assay and define a reliable cutoff for clinical deployment. Furthermore, appropriate quality measures need to be established to ensure comparable assay results across different laboratories.

### Challenges in Evaluating The Predictive Value of A Biomarker On The Basis of Completed Clinical Trials

Modern clinical trials frequently evaluate the predictive value of a biomarker for an experimental therapy using previously completed RCTs of the experimental therapy vs. the standard treatment, where the biomarker status is ascertained on patients with available biologic specimens but not used to direct therapies on the trial.[49-51] Simon et al[52] designated these types of biomarker studies as prospective-retrospective (P-R) studies to distinguish them from nonexperimental observational biomarker studies. A prime example of a prospective-retrospective predictive biomarker study is the one by Hegi et al, which examined *MGMT* promoter methylation status in a subset of patients with available tissue specimens and assay results in the practice setting trial EORTC/NCIC 22981/26981, which compared radiotherapy + temozolomide versus radiotherapy alone for newly diagnosed glioblastoma.[14,42] The investigators reported that there was a statistically significant survival benefit from temozolomide in the *MGMT*-methylated subgroup ($P$ = .007), but this benefit did not reach statistical significance in the *MGMT*-unmethylated subgroup ($P$ = .06). On the basis of these observations, they concluded that *patients with glioblastoma containing a methylated MGMT promoter benefited from temozolomide, whereas those who did not have a methylated MGMT promoter did not have such a benefit*.

It is important to note that in these retrospective evaluations of predictive biomarkers, the parent treatment trial is powered to discern a clinically meaningful treatment effect for all trial patients (regardless of their biomarker status). Consequently, the statistical power to detect treatment benefit from the experimental therapy in a biomarker-defined subgroup is limited because of the reduced sample size. This issue of low power is especially exacerbated in the biomarker subgroup that is not expected to derive benefit from the experimental therapy or to derive a much lesser degree of benefit, compared with the other biomarker subgroup. In a study by Hegi et al, the consequence of the reduced sample size and resultant uncertainty around the benefit from temozolomide were reflected in the wide confidence interval for the treatment hazard ratio in the *MGMT*-unmethylated subgroup (hazard ratio [HR], 0.69; 95% CI, 0.47 to 1.02). Of note, failure to demonstrate a statistically significant treatment benefit in a biomarker subgroup does not imply the lack of benefit in that subgroup since $P$ values are highly influenced by the sample size and number of observed events. Relatedly, achieving statistical significance in one biomarker subgroup but not in the other is not sufficient to establish the predictive value of a biomarker. As such, the data presented by Hegi et al do not lend conclusive evidence for *MGMT* methylation as a predictive biomarker for benefit from temozolomide in patients with glioblastoma. In fact, among *MGMT*-unmethylated patients, PFS was significantly improved with temozolomide (HR, 0.62; 95% CI, 0.42 to 0.92). With further clinical follow-up, a subsequent analysis reported a statistically significant survival benefit in *MGMT*-unmethylated patients (HR, 0.6; 95% CI, 0.4 to 0.8).[43]

This example underscores the challenges associated with establishing the predictive value of a biomarker using data from completed clinical trials. Retrospective evaluations of the predictive value of a biomarker frequently lack adequate statistical power to reliably discern a treatment effect, especially in the biomarker subgroup that is not expected to respond to the experimental therapy. In this setting, of critical relevance are the biomarker subgroup–specific treatment hazard ratio estimates and their confidence intervals, the width of which reflects the certainty that one should place around the estimated treatment benefit. Specifically, when the confidence interval around a treatment hazard ratio is too wide in a biomarker subgroup, it would be impossible to make a definitive conclusion about



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whether patients in that subgroup benefit from the experimental therapy. In turn, the clinical utility of the predictive biomarker cannot be confidently established. Possible solutions to this problem include pooling data from similar trials or increasing the clinical follow-up of the trial to obtain more events although the latter may be infeasible if the parent trial has been terminated. Furthermore, biologic insights into the biomarker and mechanism of action of the study agent from preclinical and clinical studies may increase confidence on the predictive value of the biomarker.

## LEVELING THE PLAYING FIELD: ADDRESSING RACIAL, GEOGRAPHIC, AND SOCIOECONOMIC DISPARITIES IN IMPLEMENTATION OF BRAIN TUMOR DIAGNOSTICS

Nearly universally fatal, there are more than 13,000 new cases of glioblastoma identified annually. Typically affecting men more than women age 55-65 years, aggressive multimodal treatment leads to an average survival of 2 years.[53] On the basis of SEER data, incidence of glioma is highest in non-Hispanic White (NHW) populations and has been associated with increased socioeconomic status.[54,55] Similar to other reports, Ostrom et al[54] found that NHW populations have reduced overall survival compared with other racial and ethnic groups after diagnosis of glioblastoma. Black patients, Hispanic patients, and patients with lower socioeconomic status have been found to have increased risk of non–glioblastoma-related mortality. Death from other cancer, cardiac, and cerebrovascular events is reported disproportionately in these populations.[56]

Limited reporting of race and ethnicity in glioblastoma-related clinical trials has led to an incomplete understanding of the impact of treatment and outcomes in varied populations.[57] Although it is believed that nearly 15% and 13% of patients with cancer are Black and Hispanic, these populations typically are under-represented in clinical trials at 6% collectively.[58] There are several challenges leading to poor enrollment in clinical trials, including stringent eligibility criteria, geographic distribution of access to trials, inefficient activation processes, limited consumer-friendly information, and an inadequate pipeline of novel therapies.[53] Barriers to clinical trial enrollment span the clinical care pathway from diagnosis to end of life. Issues of unconscious bias, cultural barriers, cost, healthy literacy, transportation, insurance, and patient/physician factors perpetuate these disparities including lack of advanced molecular testing on tumor tissue and limited pathologic interpretation.[59,60]

### Testing Disparities

Advanced molecular testing has provided deeper understanding as to the heterogeneity in high-grade glioma and is less likely to be offered to certain groups and often underutilized in clinical decision making.[61] While some patients are being offered testing up front to stratify clinical trial enrollment, others are using the results to determine treatment strategies after first or second recurrence. Understanding of promoter methylation status of MGMT is often an inclusion criterion in clinical trials, which aids in decision making regarding elderly and frail populations who may not tolerate multimodal treatment.[5] The importance of this nuance has reached the threshold to allow inclusion in National Comprehensive Cancer Network guidelines in the treatment of glioblastoma.[62]

Chukwueke et al found that patients with newly diagnosed glioblastoma who were from lower socioeconomic status, uninsured or insured through Medicaid, were less likely to receive MGMT testing.[63] Patients from these backgrounds are also noted to frequently present later in the course of disease with larger tumors, incomplete resection, and are less frequently recipients of multimodal therapy ultimately leading to reduction in survival.[64] Similarly, patients who were diagnosed at community hospitals were less likely to receive advanced testing and multimodal care. The authors note that despite the increasing incidence of testing across the United States, the populations with varied elements of diversity continued to experience disparity in testing frequency.[63] Data to direct the clinical management were also underutilized with undertreatment of populations that could have benefited from temozolomide.

### Opportunities for Improvement

Limitations in referral for advanced testing in diverse populations have led to an incomplete understanding in the spectrum of diseases. The US Food and Drug Administration published guidelines in 2020 to enhance clinical trial diversity including broadening eligibility criteria and adopting enrollment and retention practices that enhance inclusiveness.[65] Efforts to reduce disparities in diagnostics are multilayered, ranging from governmental and institutional policies to individual provider behavior and patient education. As testing becomes more widely available, increased coverage by insurers is essential. While patient assistance programs are available, the addition of this recommendation to National Comprehensive Cancer Network guidelines should lead to consideration of advanced testing becoming standard of care.[62] Patient education through advocacy groups and community engagement can help raise awareness among patients and caregivers regarding the relevance and importance of the additional information this testing provides.[59] In addition to provision of resource for advanced testing as part of the protocol, behavior modification in care teams to offer advanced testing to all patients is necessary to attempt to bridge this gap.



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## CONCLUSION

Advances in molecular profiling have introduced a growing number of biomarkers in neuro-oncology. Comprehensive characterization of molecular alterations in brain tumors has the potential to provide more accurate disease classification, risk stratification, and tailored treatments for individual patients. The future of molecular profiling in neuro-oncology, particularly concerning the utility of treatment selection biomarkers, will depend on the availability of robust biomarker assays and effective therapeutic options to allow tailored treatment choices for individual patients. Although a burgeoning field, opportunities remain for validation of testing and improved awareness and accessibility for widespread use. Failure to pursue molecular profiling not only contributes to disparate understanding of the spectrum of diseases and populations affected but also perpetuates disparities in treatment and outcome.


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