AmeriHealth Caritas
VIP Care Plus

Molecular analysis for treatment of primary brain tumors

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Policy contains: Astrocytoma; brain tumor; glioma; molecular testing; oligodendroglioma; glioblastoma; temozolomide

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Coverage policy

Molecular analysis of the following tumor markers may be clinically proven and, therefore, may be medically necessary for predicting treatment response in members with a primary brain tumor (Brat 2022; Gupta, 2017; National Comprehensive Cancer Network, 2023):

- Isocitrate dehydrogenase variants (IDH1 and IDH2) mutation testing for glioma.
- 1p19q co-deletion testing for oligodendroglioma.
- O6-methylguanine-deoxyribonucleic acid methyltransferase methylation (MGMT) for high grade III and IV gliomas.

Additional molecular analysis of the following tumor markers is clinically proven and, therefore, medically necessary to refine the diagnosis or prognosis in members with a primary brain tumor, if the information will impact treatment selection (Brat 2022; Gupta, 2017; National Comprehensive Cancer Network, 2023):

- Alpha-thalassemia intellectual disability syndrome X-linked (ATRX) mutation for glioma.
- Telomerase reverse transcriptase promoter mutations (TERT) mutation for glioma.

- C11orf95-RELA fusion (RELA fusion) for ependymoma.
- H3K27M and HIST1H3B mutation in diffuse midline gliomas of uncertain histology.
- Proto-oncogene B-Raf (BRAF) fusion for astrocytoma.
- BRAF V600E mutation in multiple glioma subtypes.
- Wingless activation [WNT-activated], sonic hedgehog activation [SHH-activated], and TP53 mutation testing for medulloblastoma subtyping.
- TP53 mutation testing for glioblastoma and IDH-mutant astrocytoma (Gupta, 2017).
- Focal amplification at chromosome region 19q13.42 (C19MC alteration) in embryonal tumor with multilayer rosettes (Gupta, 2017).
- Testing for chromosome 7 gain/chromosome 10 loss, EGFR amplification (for lower grade IDH-wildtype gliomas).
- CDKN2A/B deletion testing.
- H3 G34 mutation testing.
- MYB proto-oncogene (MYB) testing.
- FGFR1 testing.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

Other molecular testing may be reviewed on a case-by-case basis for medical necessity.

Molecular testing for the purpose of determining clinical trial eligibility is not medically necessary.

Alternative covered services

- Genetic testing.
- Nuclear medicine imaging.
- Radiographic imaging.
- Specialist consultation.

Background

The heterogeneity of brain tumors represents a significant clinical challenge to accurately diagnose, predict treatment efficacy, and create individualized treatment plans.

The term “glioma” describes a neuroepithelial tumor originating from the glial cells that surround and enrich neurons (American Cancer Society, 2020). Gliomas account for nearly one-third of all primary brain and central nervous system tumors. They comprise benign ependymoma and malignant forms of varied aggressiveness, such as astrocytoma (including glioblastoma) and oligodentroglioma. Other primary central nervous system tumors represent the location or originating cell type, such as benign meningioma, medulloblastoma, ganglioglioma, schwannoma, and craniopharyngioma.

The majority of gliomas occur sporadically, and less than 5% are associated with an underlying inherited syndrome (Davis, 2018). The only established risk factor for brain tumors is exposure to moderate to high doses of ionizing radiation, including medical irradiation for an original brain tumor.

The survival rate of patients with malignant central nervous system tumors depends on onset age, histologic and molecular diagnosis, and the tumor grade. Higher grade brain tumors are the most common type of primary brain cancer and occur more often in adults than children and in men than women (Davis, 2018). Yet, children are more likely than adults to survive these malignancies.

Primary brain tumors are characterized according to an updated World Health Organization (Louis, 2021) classification of central nervous system tumors based on histopathologic features and, more recently, molecular characteristics (Gupta, 2017). The histopathologic grading of brain tumors considers four morphologic criteria: cytological atypia, mitotic activity, microvascular proliferation (endothelial cell proliferation), and necrosis (Gupta, 2017). The grading ranges from Grade I tumors that do not meet any morphologic criteria, are slow growing and nonmalignant, and are associated with long-term survival, to Grade IV tumors that meet three or four of the morphologic criteria and are very aggressive and malignant tumors associated with poor survival.

Pathology laboratories use a range of molecular testing methods for brain tumor markers. They include immunohistochemical staining, direct sequencing, fluorescence in situ hybridization, chromosomal genomic hybridization, and next-generation sequencing. Since multiple molecular genetic abnormalities may need to be studied to diagnose various brain tumors, high-throughput genomic studies, such as next-generation sequencing, may be a more practical approach by rapidly replacing time-consuming and labor-intensive conventional methods.

First-line and salvage treatment options comprise surgery, radiation therapy, and chemotherapy, based on individual patient characteristics, tissue diagnosis, and selected molecular markers (American Cancer Society, 2020). Targeted therapies and immunological therapies are being explored within clinical trials. The range of prognostic features and treatment options requires interdisciplinary and individualized approaches of care.

As of March 2023, the following targeted treatments have been approved by the U.S. Food and Drug Administration for brain cancers (National Cancer Institute, 2023):

Brain Cancers:
Everolimus (Afinitor)
Bevacizumab (Avastin)
Belzutifan (Welireg)

Neuroblastomas:
Dinutuximab (Unituxin)
Naxitamab-gqgk (Danyelza)

Findings

Evaluation of brain tumors increasingly depends on molecular testing for accurate classification, prediction of biological behavior, and patient management. Central nervous system cancer guidelines utilize the World Health Organization 2016 classification system as the standard of care to improve diagnostic accuracy and impact treatment and care management. The revised classification system attempts to overcome the interobserver variability and prognostic imprecision of subjective histopathologic and radiographic assessment and surgical sampling by describing more homogenous and specific diseases, defining new genetically-defined diseases individually, and separating pediatric from adult tumors. Some molecular markers may also be predictive of treatment efficacy and toxicity and target patients who may or may not benefit from certain treatment types (National Comprehensive Cancer Network, 2023).

Integrating molecular testing presents new clinical challenges, as it requires time and increased resources needed to reach a conclusive diagnosis and development of a treatment plan. The complexity of testing choices presents the potential for practice variation, as some tests may not be readily available. Treatment algorithms provide guidance for optimizing diagnostic and management decisions, while limiting unnecessary treatments and resources (National Comprehensive Cancer Network, 2023).

Molecular markers have distinct indications related to the diagnosis and management of two categories: diffuse gliomas (astrocytic, oligodendroglial, and glioblastoma tumors), and embryonal tumors. Multiple independent studies have examined several molecular features in large populations of participants with grade II -IV tumors to identify subgroups of gliomas with distinct molecular profiles. The majority of grade II and III gliomas can be divided into three subtypes based on IDH mutation and 1p19q co-deletion status. Additional molecular testing may be warranted to refine the diagnosis and prognosis of specific tumor subtypes, but few have demonstrated an ability to predict treatment response or impact survival outcomes.

The following molecular tests are commonly used to guide treatment decisions toward therapy associated with a survival benefit (National Comprehensive Cancer Network, 2023):

- IDH1 and IDH2 mutation testing is required for the workup of glioma using immunohistochemistry or sequencing methods. Their presence indicates the tumor is at least a grade II diffusely infiltrative glioma and distinguishes lower-grade gliomas from primary glioblastoma. IDH1 and IDH2 mutations are associated with a survival benefit for patients treated with radiation or alkylating chemotherapy (e.g., temozolomide).
- 1p19q co-deletion testing is an essential molecular diagnostic for oligodendroglioma using fluorescence in situ hybridization, polymerase chain reaction, array-based genomic copy number testing, or next-generation sequencing methods. Its presence confers a favorable survival benefit and is predictive of response to alkylating chemotherapy and combination radiation-alkylating chemotherapy. 1p19q co-deletion testing is not necessary in tumors with IDH wild type. Tumors without an IDH mutation should not be regarded as 1p19q co-deleted.
- MGMT promoter methylation is an essential molecular diagnostic for all high grade III and IV gliomas using methylation-specific polymerase chain reaction, pyrosequencing, or array-based technologies. In high-grade gliomas, MGMT promoter methylation is associated with better outcomes and a higher likelihood of responding to alkylating chemotherapy such as temozolomide. Although no targeted agents have shown efficacy in treating glioblastoma, a detected driver mutation may direct patients toward a targeted therapy on a compassionate use basis and may expand clinical trial options.

Other molecular diagnostics may be recommended as clinically appropriate if the information will improve diagnosis or prognosis and guide treatment decisions, but there is insufficient evidence to support their ability to predict a treatment response. They include but are not limited to (Gupta, 2017; National Comprehensive Cancer Network, 2023):

- ATRX mutation testing — recommended using immunohistochemistry or sequencing. ATRX deficiency coupled with IDH mutation is typical of astrocytoma.
- TERT mutation — recommended but not required for glioma by sequencing the promotor region. Absence of TERT mutation coupled with IDH mutation indicates astrocytoma. TERT mutation coupled with IDH mutation and 1p19q co-deletion is characteristic of oligodendroglioma. TERT mutation is associated with reduced overall survival.
- H3K27M mutation testing in diffuse midline gliomas of uncertain histology. These mutations are adverse prognostic markers regardless of histologic appearance.
- BRAF fusion testing by ribonucleic acid sequencing or polymerase chain reaction or BRAF V600E mutation testing by sequencing in patients with low-grade glioma. Tumors with BRAF fusions tend to be indolent. Presence of BRAF V600E may identify candidates for BRAF inhibitors in clinical trials (e.g., vemurafenib in BRAF V600E mutant gliomas).
- RELA fusion testing by ribonucleic acid sequencing or break-apart fluorescence in situ hybridization. Fusion-positive ependymomas tend to be more aggressive and are a distinct class.

- Medulloblastoma molecular subtyping using nuclear immunoreactivity for beta-catenin, sequencing, fluorescence in situ hybridization, microarray, and immunohistochemistry methods. Medulloblastoma subtypes have markedly variable prognoses. Subtyping includes WNT-activated, SHH-activated, and TP53 mutation testing.
- Amplification of the C19MC region on chromosome 19 is noted in embryonal tumor with multilayered rosettes. The presence of a focal amplification at chromosome region 19q13.42 associated with an upregulation of the oncogenic micro ribonucleic acid cluster (Gupta, 2017).
- TP53 mutation contributes to the pathogenesis mainly of medulloblastoma, glioblastoma, and in 56% to 58% of IDH-mutant astrocytomas (Gupta, 2017).

In 2021, we updated the National Comprehensive Cancer Network guideline (2020, update of 2019) with no policy changes warranted.

In 2022, we updated the National Comprehensive Cancer Network guideline (2021). We also added several references on efficacy of targeted therapies for brain cancer. Very little research exists on the five such therapies approved by the Food and Drug Administration – beyond that of clinical trials – except for bevacizumab. One systematic review of 48 studies, 18 of which addressed bevacizumab, found little difference between treatment modes; median overall survival ranged between studies from 3.0 to 17.6 months (Fazzari, 2022).

In 2023, we updated the National Comprehensive Cancer Network guidelines to its most recent version (2022) and updated the World Health Organization classification of central nervous system tumors (Louis, 2021).

In 2024, we updated the National Comprehensive Cancer Network guidelines to its most recent version (2023). We also found a relevant 2022 joint guideline from the College of American Pathologists and others. The evidence suggests that molecular analysis, including testing for IDH, ATRX, TP53, and 1p/19q status, should be performed to classify diffuse gliomas in order to guide prognosis and clinical management (Brat, 2022). Specific recommendations include that IDH mutation testing should be done on all diffuse gliomas to diagnose relevant subtypes, ATRX testing should be performed on IDH-mutant gliomas to determine astrocytic lineage unless 1p/19q codeletion is present, and 1p/19q testing is essential in IDH-mutant gliomas to diagnose oligodendroglioma. For IDH wild-type lower grade gliomas, testing for whole chromosome 7 gain/whole chromosome 10 loss, EGFR amplification and TERT promoter mutations can suggest aggressive behavior corresponding to glioblastoma diagnosis. Ultimately, the integrated diagnoses formulated using histopathology and directed molecular testing provide critical information to determine optimal care for patients with diffuse gliomas.

We also added a review of 42 studies showing potential to use cerebrospinal fluid, rather than biopsy material, to detect mutations in pediatric brain tumor patients (Lehner, 2023). We added a systematic review/meta-analysis of 26 articles on the prognostic significance of various biomarkers in glioblastoma patients; the IDH1 mutation was associated with significantly improved survival, but the EGFR mutation was not (Sareen, 2022).

A network meta-analysis of 12 studies (n = 1,818) of elderly patients with glioblastoma found bevacizumab was associated with high rates of severe hematological and thromboembolic adverse events, and thus little justification exists for using this treatment in elderly patients other than in a clinical trial (Hanna, 2020).

A systematic review/meta-analysis of 13 studies (n = 272) of pediatric patients with brain cancer treated with bevacizumab plus irinotecan showed 41% had an objective response. Median progression-free survival and

overall survival were 6.47 and 11.9 months. The most common adverse events were gastrointestinal dysfunction (36.7%), leukopenia (33.6%), and hypertension (22.1%) (Xu, 2020).

In 2024, policy references updated. Policy changes were warranted as the result of changes in professional clinical guidelines.

References

On January 17, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “brain neoplasm” (MeSH) and “molecular biology” (MeSH). We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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4/2021: Policy references updated.

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