Medical Policy

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(See policy history boxes for previous effective dates)

Title: Genetic Testing — Malignant Gliomas Including MGMT Promoter Methylation

Description/Background

Testing for MGMT (O^6-methyl guanine methyl transferase) gene promoter methylation has been proposed as a method to predict which patients with malignant gliomas may benefit from the use of alkylating agent chemotherapy, such as temozolomide (TMZ). Malignant gliomas are often treated with combined therapy, including resection, chemotherapy and radiation. However, combined therapy may be too intensive in the elderly population, in whom these tumors are most commonly seen. A better understanding of the genetic diversity of these tumors has led to an effort to incorporate molecular findings into clinical practice to provide personalized treatment for individual patients, including possible single-agent therapy.

MALIGNANT GLIOMAS

Malignant gliomas are the most common primary brain cancer in adults, with approximately 13,000 new cases diagnosed per year in the United States.[1] Grading of brain tumors using the World Health Organization (WHO) histologic criteria corresponds to the degree of malignancy (aggressiveness), and ranges from WHO grade I (least aggressive) to grade IV (most aggressive). For malignant gliomas, anaplastic astrocytomas are considered to be grade III and glioblastoma multiforme (GBM) grade IV. Of these, GBM is the most common and most studied subtype.[1] Despite treatment advances, the prognosis for GBM remains poor, with only one-third of patients surviving one year and less than 5% surviving beyond 5 years.

In 2016, WHO revised its classification of tumors of the central nervous system (CNS) so that diffusely infiltrating gliomas are grouped based on genetic driver mutations.[2] Diffuse gliomas in the new classification include the former WHO grade II and III astrocytic tumors, grade II and III oligodendrogliomas, grade IV glioblastomas, and diffuse gliomas of childhood. Tumors with glioblastoma histology are grouped based on the presence of *IDH* variants.

Treatment

For high-grade malignant gliomas (anaplastic astrocytomas and GBM), standard treatment combines maximal possible surgical resection, postoperative radiation and chemotherapy.[2] Chemotherapy may include intraoperative placement of an implantable carmustine wafer. Temozolomide (TMZ) is an oral alkylating agent that is considered standard systemic chemotherapy for malignant gliomas. Response to TMZ has been associated with decreased O^6-methylguanine-DNA methyltransferase (MGMT) activity in tumor tissue because a methylated MGMT promoter leads to decreased MGMT levels, which enhances the effect of the alkylating agent.

TMZ is considered standard systemic chemotherapy for malignant gliomas in patients ages 70 or younger with good performance status and a methylated *MGMT* promoter.[3] This is based primarily on the results of a large, randomized multicenter trial (2005) that compared RT with or without TMZ in patients with GBM, which showed statistically significant better overall survival in the combination therapy group.[4] Adjuvant options mainly depend on the performance status of the patient.

Survival with GBM declines with increasing age. Options for patients with good performance status and age older than 70 years with methylated MGMT promoter may involve hypofractionated RT alone or TMZ alone. For patients with poor performance status, options include RT alone, chemotherapy alone, or palliative or best supportive care.

MGMT and Promoter Methylation

Gene methylation is a control mechanism that regulates gene expression. In malignancies, gene promoter regions can have abnormal or increased levels of methylation, which can block gene function, leading to decreased or absent levels of the protein encoded by the gene. MGMT is a DNA repair protein that causes resistance to the effect of alkylating chemotherapy by removing the alkylation of the O^6 position of guanine, the most cytotoxic lesion induced by alkylating chemotherapy agents.[5] Aberrant methylation of the MGMT gene promoter region leads to loss of MGMT protein expression, and reduced proficiency to repair DNA damage induced by alkylating chemotherapeutic agents, potentially making increasing tumor susceptibility to alkylating agent-based therapy. Approximately 40% to50% of GBMs have MGMT gene promoter methylation. Variants in *IDH1*, which occur at different frequencies across glioma tumor types, appear to mediate the effect of MGMT methylation status on glioma prognosis and treatment response.[6-14]

Immunohistochemistry can be used to measure MGMT protein levels. However, MGMT protein level assessment by immunohistochemistry has failed to correlate consistently with outcomes and has been associated with high interobserver variability in interpretation, even among expert neuropathologists. Additionally, many authors have failed to identify a correlation between MGMT promoter methylation assessed by polymerase chain reaction (PCR) and protein levels in glioma tissue measured by immunohistochemistry.[15] Other protein-based assays such as Western blot or MGMT enzyme activity assays require unfixed (fresh or frozen) material, which may not be available in the clinical setting.[16] DNA-based methods include multiplex ligation-dependent probe amplification and methylation-specific PCR (MSP). MSP is currently the most commonly used technique and is the only test shown to have predictive and prognostic value in phase 2 and 3 clinical trials.[15,17,18] However, MSP has been reported to be limited by the

adverse influence of formalin fixation and paraffin embedding on bisulfite modification, an essential step of the assay.[16,19] Additional studies have reported modifications of the MSP technique to overcome this problem, but no consensus on a specific protocol reliably yielding high-quality test results has been reached.[16,20]

IDH1/IDH2 Mutation

IDH1 and *IDH2* are metabolic enzymes. Specific mutations in genes encoding these enzymes lead to the aberrant production of D-2- hydroxyglutarate, an oncometabolite that causes epigenetic modifications in affected cells.[28] Diffusely infiltrative astrocytomas with *IDH* mutation are mostly grade 2–3. However, some develop the traditional grade 4 histologic features of necrosis and/or microvascular proliferation, which does suggest more aggressive behavior and worse prognosis, but still not as severe as *IDH* wild-type glioblastomas. *IDH* mutations are commonly associated with MGMT (O6-methylguanineDNA methyltransferase) promoter methylation. IDH mutations define WHO grade 2 and 3 astrocytomas and oligodendrogliomas, and grade 4 IDH-mutant astrocytomas. Their presence distinguishes lower-grade gliomas from glioblastomas, which are IDH wild-type. IDH1 or 2 mutations are associated with a survival benefit for patients treated with radiation or alkylating systemic therapy.

1p/19q Co-Deletion

1p19q codeletion stands for the combined loss of the short arm chromosome 1 (i.e. 1p) and the long arm of chromosome 19 (i.e. 19q) and is recognized as a genetic marker predictive of therapeutic response to both chemotherapy and combined chemoradiotherapy and overall longer survival in patients with diffuse gliomas, especially those with oligodendroglial components. 1p/19q testing is an essential part of molecular diagnostics for oligodendroglioma. The codeletion confers a favorable prognosis and is predictive of response to alkylating systemic therapy with or without RT.

Telomerase Reverse Transcriptase (*TERT*) Mutation

TERT promoter region is known to be mutated in different types of tumors. They occur frequently in *IDH* wild-type glioblastomas and *IDH* mutant, 1p/19q codeleted oligodendrogliomas. Absence of *TERT* promoter mutation, coupled with *IDH* mutation and lack of 1p/19q codeletion is indicative of astrocytoma. In the absence of an IDH mutation, TERT promoter mutation in diffusely infiltrative gliomas is associated with reduced overall survival compared to similar gliomas lacking TERT promoter mutation.

ATRX Mutation

ATRX mutation is caused by changes (mutations) in the ATRX gene. These mutations can lead to the production of an abnormal or non-functional ATRX protein. *ATRX* mutation can increase the risk of developing certain cancers, including gliomas, myelodysplastic syndromes and osteosarcoma. ATRX mutation testing is required for the workup of glioma. ATRX mutations in glioma are strongly associated with IDH mutations and are nearly always mutually exclusive with 1p/19q codeletion. ATRX deficiency, coupled with IDH mutation and TP53 mutation, is typical of astrocytoma.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the

Clinical Laboratory Improvement Amendments (CLIA). MGMT promoter methylation testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The analysis of MGMT Promoter Methylation, IDH1/IDH2 mutation testing, 1p/19q codeletion testing, *TERT* mutation testing and *ATRX* mutation testing in malignant gliomas is established. It may be considered a useful option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

MGMT Promoter Methylation
Methylation analysis of the O^6-methylguanine DNA methyltransferase (*MGMT*) gene promoter from glioma tumor tissue is established for individuals who meet the following criteria:

- They have a tumor type consistent with high-grade malignant glioma (e.g., glioblastoma multiforme, anaplastic astrocytoma); **and**
- Candidate for temozolomide therapy or radiation therapy; **and**
- Methylation results will be used to direct their therapy choices.

IDH1/IDH2
IDH mutation testing is required when:

- They have a tumor type consistent with malignant glioma;
- For diagnostic workup, staging, treatment selection and prognosis for glioma;

1p/19q Co-Deletion
1p/19q co-deletion is required for diagnosis and at the time of recurrent or progressive disease for:

- They have a tumor type consistent with malignant glioma;
- For diagnostic workup, staging, treatment selection and prognosis for glioma;

***TERT* Mutation**

- They have a tumor type consistent with malignant glioma;
- For diagnostic workup, staging, treatment selection and prognosis for glioma;

***ATRX* Mutation**

- They have a tumor type consistent with malignant glioma;
- For diagnostic workup, staging, treatment selection and prognosis for glioma;

Note: malignant gliomas include oligodendroglioma, astrocytoma, glioblastoma.

Exclusions:
MGMT promoter methylation analysis, IDH1/IDH2, 1p/19q codeletion, *TERT* and *ATRX* testing is experimental/investigational in situations that do not meet the above criteria.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81287	81120	81121	81345	81479*	88377

*NOC code used for 1p/19q codeletion and ATRX testing

Other codes (investigational, not medically necessary, etc.):

N/A	0481U

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

MGMT PROMOTER METHYLATION

Clinical Context and Test Purpose
The purpose of testing for O^6 -methylguanine-DNA methyltransferase (MGMT) gene promoter methylation in patients with high-grade gliomas is to inform a decision about treatment with temozolomide (TMZ), TMZ plus radiotherapy (RT), or other therapies.

The question addressed in this evidence review is: among patients with high-grade gliomas, does testing of tumor tissue for MGMT gene promoter methylation and associated decision making about adjuvant therapy lead to improved outcomes?

The following **PICOs** were used to select literature to inform this review.

Population
The relevant population(s) of interest are patients with glioblastoma, newly diagnosed or recurrent on therapy.

Interventions
The relevant intervention is evaluation of *MGMT* gene promoter methylation.

Comparators
Currently, clinical response to therapy is used to make decisions about therapy.

Outcomes
The ultimate outcome of interest is overall survival (OS). Progression-free survival (PFS) may be considered but has relatively limited use for a tumor such as glioblastoma, where long-term survival outcomes are uncommon. The general outcomes of interest are overall survival, disease-specific survival, test accuracy, and changes in disease status. Progression-free survival (PFS) and overall survival are expected to be short in persons with glioblastoma. Follow-up at 3, 6, and 12 months are reasonable time points to assess short term intervention outcomes. Overall survival outcomes over the course of 3 to 5 years would be reasonable.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There are 2 ways that MGMT methylation analysis may have clinical validity. The first is as a prognostic marker for survival from GBM. Pure prognostic markers, which predict outcome independent of treatment, may or may not have clinical value in terms of affecting treatment decisions. The second is as a predictive measure for response to chemotherapy, specifically TMZ. This second measure of clinical validity may be more clinically relevant, because it may lead to alterations in treatment decisions based on the expected response. Futile treatments might be avoided, or more effective alternatives might be substituted in patients with poor response to TMZ.

MGMT Promoter Methylation as a Prognostic Test

Systematic Reviews

Meta-analyses published in 2013 and 2014 have examined the association between MGMT promoter methylation status and survival outcomes.[21,22] Results are summarized in Table 1.

Yang et al (2014) systematically searched the literature through 2013 and included 50 studies (total N=6309; 5663 white, 646 Asian).[21] The quality of included studies was not assessed. Assay type was not reported, and treatments varied across studies, although most patients received TMZ plus radiotherapy (RT). Both progression-free survival (PFS) and OS were improved in patients with methylated MGMT compared with unmethylated MGMT; however, statistical heterogeneity was substantial for both outcomes (I^2>50%), suggesting inappropriateness of pooling. Similarly, observed differences across race (OS improved in both Asians and whites with methylated MGMT, but PFS improved in whites only) may be unreliable due to substantial statistical heterogeneity in the pooled results.

Chen et al (2013) conducted a systematic review and meta-analysis of MGMT promoter methylation and prognosis in GBM.[22] A PubMed search from January 2003 to November 2011 identified 24 studies that met inclusion criteria. Publication bias was not detected. Twenty-two studies reported on the relation between MGMT methylation status and OS, and 12 reported on PFS. OS and PFS rates significantly favored patients who received methylated MGMT. However, there was moderate-to-high heterogeneity in the studies included in the review for PFS and OS, respectively. Heterogeneity existed according to when studies were published, because of the inclusion in some studies of tumors with histology other than GBM (e.g., anaplastic gliomas); there was also variability across studies from one country to another, and in the chemotherapeutic agents used.

Table 1. Meta-Analyses of *MGMT* Methylation Status and Survival Outcomes

Study	Sample	DFS, Pooled HR (95% CI)	I^2	PFS, Pooled HR (95% CI)	I^2	OS, Pooled HR (95% CI)	I^2
Yang et al (2014)[21]	Overall	NR	NR	0.30 (0.13 to 0.72)[a]	98%	0.44 (0.37 to 0.52)[a]	61%
	Asian			0.13 (0.01 to 3.03)[a]	99%	0.56 (0.39 to 0.80)[a]	17%
	White			0.44 (0.36 to 0.54)[a]	32%	0.43 (0.35 to 0.51)[a]	65%
Chen et al (2013)[22]		NR	NR	0.43 (0.32 to 0.56)[a]	50%	0.48 (0.35 to 0.65)[a]	80%

CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; I^2: percentage of variance attributable to between-study heterogeneity; NR: not reported; OS: overall survival; PFS: progression-free survival.
[a] Random-effects model, methylated vs unmethylated.

MGMT Promoter Methylation as a Predictive Test for TMZ Response

Systematic Reviews

Yin et al (2014) published a systematic review and meta-analysis of patients 65 years of age or older with newly diagnosed GBM.[23] Five clinical trials and 8 observational studies were included (total N=1105 patients). Risk of bias, primarily selection bias, was low in trials and moderate-to-high in observational studies. Assay methods and treatments varied across studies. Publication bias was not detected. As shown in Table 2, PFS and OS improved in patients with methylated MGMT compared with unmethylated MGMT only in patients who received TMZ-containing chemotherapy regimens. PFS and OS also improved only in patients with methylated *MGMT* who received TMZ-containing chemotherapy regimens. However, statistical tests for interaction of treatment and *MGMT* methylation status were not conducted.

Table 2. Meta-Analysis of *MGMT* Methylation Status and Treatment Outcomes

Treatment	PFS, Pooled HR (95% CI)	I^2, %	OS, Pooled HR (95% CI)	I^2, %
By treatment, methylated vs unmethylated				
No temozolomide	0.97 (0.59 to 1.57)[a]	58	0.97 (0.77 to 1.21)[b]	3
Temozolomide	0.49 (0.40 to 0.60)[b]	15	0.49 (0.41 to 0.58)[b]	29
By methylation status, temozolomide-containing treatment vs radiotherapy				
Methylated tumors	0.35 (0.20 to 0.62)[b]	45	0.48 (0.36 to 0.65)[b]	17
Unmethylated tumors	1.08 (0.42 to 2.78)[a]	82	1.14 (0.90 to 1.44)[b]	8

Adapted from Yin et al (2014).[23]
CI: confidence interval; HR: hazard ratio; I^2: percentage of the variance attributable to between-study heterogeneity; *MGMT*: O^6-methylguanine-DNA methyltransferase; OS: overall survival; PFS: progression-free survival.
[a] Random-effects model.

Randomized Controlled Trials

Perry et al (2017) published the results of a trial designed to assess the benefit of adding TMZ to hypofractionated RT in patients 65 years of age and older.[24] The study characteristics, and results are summarized in Tables 3 and 4. The addition of TMZ resulted in longer median OS and PFS. There were no significant differences in global quality-of-life measure, and there was a low rate of high-grade adverse events in both arms. An exploratory analysis of outcomes based on MGMT status demonstrated the greatest benefit in patients with methylated MGMT receiving RT plus TMZ.

Table 3. Key RCT Characteristics for *MGMT* Promoter Methylation to Predict Treatment Response

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Perry et al (2017)[24]; NCT00482677	Canada, Germany, Netherlands, Australia, New Zealand, Japan	24	2007-2013	• ≥65 y • New diagnosis GBM (grade IV astrocytoma) • Not candidate for full course RT	RT alone[a] (n=281)	RT plus TMZ[b] (n=281)

BSA: body surface area; GBM: glioblastoma multiforme; *MGMT*: O^6-methylguanine-DNA methyltransferase; RT: radiotherapy; TMZ: temozolomide.
[a] Reduced intensity RT 40 gray in 15 daily fractions in 3 weeks.
[b] Dose of 75 mg/m^2 BSA per day for 21 consecutive days followed by adjuvant 150-200 mg/m^2 BSA 5 consecutive days of a 28-day cycle up to 12 cycles or disease progression.

Table 4. Key RCT Results for *MGMT* Promoter Methylation to Predict Treatment Response

Study	Median OS (95% CI), mo	Median PFS (95% CI), mo	Grade 0/1 Anemia, n (%)[a]	Grade 0/1 Neutropenia, N (%)[b]	Median Time to QOL Deterioration (95% CI), mo[b]
Perry et al (2017)[24]; NCT00482677	N=562	N=562			
RT alone (n=281)	7.6 (8.3 to 10.3)	3.9 (3.5 to 4.3)	252 (97.7) (n=258)	245 (98.4) (n=249)	12 (10 to 16) (n=241)
RT+TMZ (n=281)	9.3 (8.3 to 10.3)	5.3 (4.6 to 6.2)	247 (91.5) (n=270)	229 (81.61) (n=266)	12 (10 to 19) (n=237)
HR (95% CI); p	0.67 (0.56 to 0.80); <0.001	0.50 (0.41 to 0.60); <0.001	NR	NR	NR
	% Survival (95% CI)				
Exploratory analysis[c]					
Patients with unmethylated *MGMT*					
RT alone	3.8 (1.1 to 9.6)				
RT+TMZ	6.7 (2.7 to 13.10)				
Patients with methylated *MGMT*					
RT alone	4.1 (1.1 to 10.4)				
RT+TMZ	17.8 (10.5-26.7)				

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; *MGMT*: O^6-methylguanine-DNA methyltransferase; NR: not reported; OS: overall survival; PFS: progression-free survival; QOL: quality of life; QLQ-C30: Quality of Life Questionnaire Core 30; RT: radiotherapy; TMZ: temozolomide.
[a] Common Terminology Criteria for Adverse Events v3.0.
[b] EORTC QLQ-C30 Global domain with deterioration defined as a 10-point decrease.
[c] OS by treatment group and *MGMT* status. *MGMT* status obtained in 354 patients: 173 RT alone, 181 RT+TMZ.

Wick et al (2012) reported on the phase 3 NOA-08 trial, which enrolled patients between May 2005 and November 2009 who had de novo GBM (n=331) or anaplastic astrocytoma (n=40) that was histologically confirmed after biopsy or resection.[18] Patients were enrolled from 23 university centers across Germany and Switzerland and had to be older than 65 years of age with a Karnofsky Performance Status score of 60 or higher. Patients were randomized to RT alone (60.0 gray [Gy] administered over 6-7 weeks in 30 fractions) or to TMZ 100 mg/m^2 alone given in a 1-week on/1-week off schedule. Crossover from 1 treatment group to the other was allowed after disease progression. The primary end point was OS. The NOA-08 trial was designed as a noninferiority trial with a 25% noninferiority margin. Tumor response measured by magnetic resonance imaging was classified as complete response, partial response, stable disease, or progressive disease. MGMT promoter methylation analysis was assessed with 2 polymerase chain reaction assays. Minimum follow-up was 12 months (median follow-up from the start of the study, 25.2 months; range, 20.0 months to not reached). Seventy-six percent of patients in the TMZ group completed at least 4 chemotherapy cycles (8 weeks; median, 5 weeks; range, 0-20 weeks), and 84% of patients completed RT. Among patients in the TMZ and RT groups with observable disease progression (62% and 70%, respectively), salvage therapy was administered, which mainly comprised RT in the TMZ group and vice versa. Median OS was 8.6 months (95% CI, 7.3 to 10.2 months) in the TMZ group and 9.6 months (95% CI, 8.2 to 10.8 months) in the RT group (HR=1.09; 95% CI, 0.84 to 1.42; p=0.033 for noninferiority), indicating that TMZ was noninferior to RT.

Data on MGMT promoter methylation status was available for 56% of patients. In the TMZ group (n=195), 16% of patients had methylated MGMT promoter, 39% were unmethylated, and 45% were missing or inconclusive. Of the RT group (n=178), 24% had methylated MGMT, 33% were unmethylated, and 43% were missing or inconclusive. MGMT promoter methylation was associated with prolonged OS (median, 11.9 months for methylated [95% CI, 9.0 to not reached] vs 8.2 months for unmethylated [95% CI, 7.0 to 10.0 months]; HR=0.62; 95% CI, 0.42 to 0.91; p=0.014).

Table 5. Survival Outcomes in the 2012 NOA-8 Trial

Outcome Measures	Temozolomide (95% CI)	Radiotherapy (95% CI)
6-month overall survival	66.7% (60% to 73%)	71.7% (65 to 78.4)
1-year overall survival	34.4% (27.6% to 41.4%)	37.4% (30.1 to 44.7)
Median overall survival, mo	8.6 (7.3 to 10.2)	9.6 (8.2 to 10.8)
Event-free survival, mo	3.3 (3.2 to 4.1)	4.7 (4.2 to 5.2)
Methylated *MGMT*	8.4 (5.5 to 11.7)	4.6 (3.7 to 6.3)
Unmethylated *MGMT*	3.3 (3.0 to 3.5)	4.6 (3.7 to 6.3)
Subsample analysis		
Median overall survival, mo		
Methylated *MGMT*	11.9 (9.0 to not reached)	
Unmethylated *MGMT*	8.2 (7.0 to 10.0)	
1-year overall survival[a]		
Methylated *MGMT*	≈58%	≈45%
Unmethylated *MGMT*	≈30%	≈38%

Adapted from Wick et al (2012).[18]
CI: confidence interval; *MGMT*: O^6-methylguanine-DNA methyltransferase.
[a] Derived from the Kaplan-Meier curve.

This trial demonstrated that MGMT promoter methylation status is a predictor of response to TMZ, while there was little difference in response to RT by MGMT status.

In the 2012 Nordic phase 3 trial, GBM patients were randomized to single-agent TMZ, hypofractionated RT, or standard RT to assess survival, quality of life, and safety outcomes.[17]

Patients were recruited from 28 European centers between 2000 and 2009 and were eligible if age 60 years or older and with newly diagnosed GBM. Patients were randomized to TMZ (200 mg/m2 on days 1-5 every 28 days for 6 cycles), hypofractionated RT (34 Gy over 2 weeks), or standard RT (60 Gy over 6 weeks). Randomization lists were computer-generated and available only to oncology staff. The primary end point was OS. Baseline assessments comprised physical and neurologic examinations, blood counts, and administration of the EORTC Quality of Life Questionnaire Core 30. Patients were assessed at 6 weeks, 3 months, and 6 months after the start of therapy. Overall, 342 patients enrolled; 291 (85%) were randomized across the 3 treatment groups: TMZ (n=93), hypofractionated RT (n=98), and standard RT (n=100). Fifty-one additional patients from 4 centers that did not offer standard RT were randomized to TMZ (n=26) or hypofractionated RT (n=25) groups. In the 3-group randomization, 72% of patients in the standard RT group completed RT according to protocol vs 95% in the hypofractionated RT group. TMZ was started in 97% of patients assessed as part of the 3-group randomization; 86% received at least 2 cycles of chemotherapy and 34% completed all cycles. Second-line RT was given to 37% of TMZ patients, and 26% of RT groups received second-line chemotherapy. MGMT promoter methylation could be assessed in tumor tissue from 75% of the initial 342 enrollees.

Median OS was significantly longer with TMZ (83 months; 95% CI, 71 to 95 months) than with standard RT (60 months; 95% CI, 51 to 68 months; HR=0.70; 95% CI, 0.52 to 0.93, p=0.01), but not hypofractionated RT (75 months [95% CI, 65 to 86 months]; HR=0.85 [95% CI, 0.64 to 1.12]; p=0.24). For all patients who received TMZ or hypofractionated RT (n=242), OS was similar (84 months [95% CI, 73 to 94 months] vs 74 months [95% CI, 64 to 84 months]; HR=0.82; 95% CI, 0.63 to 1.06; p=0.12). Patients treated with TMZ who had tumor MGMT promoter methylation had significantly longer survival (9.7 months; 95% CI, 8.0 to 11.4 months) than those without MGMT promoter methylation (6.8 months; 95% CI, 5.9 to 7.7 months; HR=0.56; 95% CI, 0.34 to 0.93; p=0.02), but there was no difference between those with methylated and unmethylated MGMT promoter treated with RT (HR=0.97; 95% CI, 0.69 to 1.38; p=0.81; see Table 6).

Table 6. Overall Survival in the 2012 Nordic Phase 3 Trial

Methylation Status	Median Overall Survival (95% Confidence Interval), mo	
	Temozolomide	Radiotherapy
Methylated *MGMT*	9.7 (8.0 to 11.4)	8.2 (6.6 to 9.9)
Unmethylated *MGMT*	6.8 (5.9 to 7.7)	7.0 (5.7 to 8.3)

Adapted from Malmstrom et al (2012).[17]
MGMT: O^6-methylguanine-DNA methyltransferase.

In some randomized trials comparing different alkylating chemotherapy regimens, MGMT methylation status was not predictive of treatment response.[25,26] Gilbert et al (2013) conducted a phase 3 randomized controlled trial to compare 2 TMZ maintenance regimens after completion of RT (standard TMZ treatment: 150-200 mg/m2 days 1-5 of a 28-day cycle vs dose-dense TMZ treatment: 75-100 mg/m2 days 1-21 of a 28-day cycle).[25] Patients with newly diagnosed GBM were randomized 1:1 to standard (n=411) or dosedense TMZ (n=422), stratified by MGMT methylation status, as determined by methylation-specific polymerase chain reaction. A median number of cycles received was 3 in the standard TMZ group (37% received at least 6 cycles) and 4 in the dose-dense TMZ group (43% received at least 6 cycles). At a median follow-up of 31.9 months, no statistical between-group differences in PFS or OS were observed. MGMT methylation status was available for 762 (91%) patients. Tests of

interaction between MGMT methylation status and treatment were not statistically significant. However, this trial compared different TMZ regimens, which might explain the lack of interaction.

Similarly, Collins et al (2014) used 354 tumor samples from a previously conducted clinical trial and found that MGMT methylation status was not predictive of a benefit for TMZ vs. procarbazine, lomustine, plus vincristine or for 21-day TMZ vs. 5-day TMZ.[26] The BR12 trial enrolled patients with high-grade glioma who experienced a first relapse after RT. MGMT methylation, assessed by pyrosequencing, was analyzed successfully in tumor samples from 63% of patients enrolled in the original trial. However, the authors noted that interaction could not be ruled out due to the low statistical power of the study.

In 2005, the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada reported on a randomized, multicenter, phase 3 trial comparing RT alone with RT plus concomitant and adjuvant TMZ in patients who had newly diagnosed GBM.[4] A total of 573 patients from 85 centers were randomized. At a median follow-up of 28 months, 84% of patients had died. Median survival was 14.6 months (95% CI, 13.2 to 16.8 months) in the RT plus TMZ group and 12.1 months (95% CI, 11.2 to 13.0 months) in the RT alone group. Two-year survival was 26.5% (95% CI, 21.2% to 31.7%) with RT plus TMZ and 10.4% (95% CI, 6.8% to 14.1%) with RT alone.

Five-year follow-up data, reported by Stupp et al (2009), on the original trial showed that survival improved even in patients without MGMT promoter methylation when TMZ was added to RT, as summarized in Table 7.[27] This observation has led some to suggest that treatment of newly diagnosed GBM patients who are candidates for combination therapy should include RT and TMZ regardless of MGMT promoter status.[1] However, only patients with a methylated MGMT promoter benefited from TMZ in terms of PFS ($p<0.001$).

Table 7. Five-Year Results of the 2009 EORTC-NCIC Trial

Methylation Status	Median Overall Survival (95% Confidence Interval), mo	
	Radiotherapy Alone	Radiotherapy Plus TMZ Therapy
Methylated *MGMT*	15.3 (13.0 to 20.9)	23.4 (18.6 to 32.8)
Unmethylated *MGMT*	11.8 (10.0 to 14.4)	12.6 (11.6 to 14.4)

Adapted from Stupp et al (2009).[27] EORTC: European Organization for Research and Treatment of Cancer; MGMT: O^6 -methylguanine-DNA methyltransferase; NCIC: National Cancer Institute of Canada; TMZ: temozolomide.

Section Summary: Clinically Valid

As a prognostic marker in GBM, *MGMT* promoter methylation has been shown to be associated with improved survival. As a predictive marker for response to alkylating chemotherapy, randomized trials and 1 meta-analysis have suggested a positive effect of *MGMT* promoter methylation and improved survival in patients with GBM treated with TMZ.[17,18] However, these studies had high rates of crossover between treatment arms, heterogeneity of treatment completion rates, and, in 1 study, only approximately half of patients had their tumors tested for promoter methylation and correlated with survival. One 2009 RCT, which assessed TMZ combined with RT, showed apparent survival benefits compared to RT alone in patients with and without *MGMT* promoter methylation[32]; however, patients without *MGMT* methylation showed less improvement than those with *MGMT* methylation. Studies have consistently suggested that *MGMT* methylation identifies patients who are more likely to benefit from TMZ.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Direct evidence on the clinical utility of testing for MGMT promoter methylation is lacking.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Although studies are consistent with lower treatment response to TMZ among patients with unmethylated MGMT, studies have still suggested some treatment benefit with TMZ. TMZ plus RT remains the standard of care for most patients. TMZ is associated with a modest increase in hematologic adverse events compared with RT alone. Counseling about risks and benefits in a patient with comorbidities may result in a choice to avoid TMZ when that patient is less likely to benefit from the treatment.

***IDH1/IDH2* Mutation**
The fifth edition of the WHO classification of CNS tumors was published in 2021. In this newest classification, adult diffuse gliomas are subsumed within a super category of gliomas and glioneuronal tumors and are split into three subtypes: 1) IDH-mutant astrocytoma; 2) oligodendroglioma, 1p/19q-codeleted and IDH-mutant; and 3) glioblastoma, IDH wild-type. WHO grades are now further specified for select CNS tumors, including diffuse gliomas. Specifically, IDH-mutant astrocytoma can be grade 2, 3, or 4. Oligodendroglioma (1p/19q-codeleted and IDH-mutant) can be grade 2 or 3. Glioblastoma, IDH wild-type, can only be grade 4. This updated classification further takes into account the importance of molecular data for accurately diagnosing CNS tumors.[29,30]

Multiple independent studies on gliomas have conducted genome-wide analyses evaluating an array of molecular features, including DNA copy number, DNA methylation, and mutations, in large populations of patients with grade 2–4 tumors. Unsupervised clustering analyses, an unbiased method for identifying molecularly similar tumors, have been used to identify subgroups of gliomas with distinct molecular profiles. Remarkably, further analysis has shown that these molecular subgroups could be distinguished based on only a handful of molecular features, including IDH mutation and 1p/19q codeletion, biomarkers independently verified by numerous studies as hallmarks for distinguishing molecular subgroups in grade 2–3 gliomas.[31-35] The unsupervised clustering analysis published by the Cancer Genome Atlas Research Network supports the idea that the majority of grade 2–3 tumors can be divided into three molecular subtypes: 1) mutation of IDH with 1p/19q codeletion; 2) IDH-mutant with no 1p/19q codeletion; and 3) no mutation of IDH (i.e., IDH wild-type). Multiple studies have shown that the 1p/19q codeletion is strongly associated with IDH mutations, such that true whole-arm 1p/19q codeletion in IDH wild-type tumors is extremely rare.[31,36-38] In a tumor that is equivocal, the presence of an IDH mutation indicates at least a grade 2 diffusely infiltrative glioma. Some

IDH-mutant diffusely infiltrative astrocytomas develop the traditional grade 4 histologic features of necrosis and/or microvascular proliferation, which suggest more aggressive behavior and worse prognosis, but still not as severe as IDH wild-type glioblastoma. Such tumors are now referred to as astrocytoma, IDH-mutant, WHO grade 4, to distinguish them from IDH wild-type glioblastoma.[39,40] Grade 1 non-infiltrative gliomas do not have IDH mutations.

Numerous large studies of patients with brain tumors have determined that, among WHO grade 2–3 gliomas, 1p/19q codeletion correlates with greatly improved progression-free survival (PFS) and overall survival (OS).[33,36,41] Likewise, the presence of an IDH mutation is a strong favorable prognostic marker for OS in grade 2–3 gliomas. Analyses within single treatment arms showed that the IDH status is prognostic for outcome across a variety of postoperative adjuvant options.

MGMT promoter methylation is associated with better survival outcomes in patients with high-grade glioma and is a predictive factor for response to treatment with alkylating chemotherapy such as TMZ or lomustine.[42] IDH mutations are commonly associated with MGMT promoter methylation.[32] Tumors with H3K27M mutations are far less likely to be MGMT promoter methylated and are associated with even worse prognosis than IDH wild-type glioblastomas. Patients whose hemispheric high-grade gliomas have relatively higher rates of MGMT promoter methylation than midline gliomas, and do not have a worse prognosis than other IDH wild-type glioblastomas.[43,44]

Based on studies showing that IDH status is associated with better prognosis in patients with grade 2–3 glioma,[37,44,45] the NCCN panel recommends IDH mutation testing in patients with glioma. Immunohistochemistry (IHC) can detect the most common (canonical) IDH mutation, IDH1 R132H. However, sequencing must be done to detect non-canonical IDH1 mutations (e.g., IDH1 R132C) and IDH2 mutations. Since ATRX and IDH mutations frequently co-occur, a lack of ATRX immunostaining, coupled with negative R132H immunostaining for IDH1 in a glioma, should trigger screening for such non-canonical IDH mutations.[46]

SUMMARY OF EVIDENCE

For individuals who have high-grade glioma(s) who receive O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation testing, the evidence includes cohort studies of prognosis, studies nested within randomized trials, and treatment trials that selected subjects based on *MGMT* methylation status. Relevant outcomes include overall survival, disease-specific survival, test accuracy, and changes in disease status. There are no studies directly evaluating whether use of *MGMT* methylation testing improves patient outcomes. *MGMT* status is consistently associated with outcomes of glioma patients. Data from randomized controlled trials have shown that *MGMT* promoter methylation is predictive for response to alkylating chemotherapeutic agents such as temozolomide (TMZ). The response rate and overall survival with the use of TMZ are higher in patients who have *MGMT* promoter methylation. While TMZ offers some benefit regardless of *MGMT* methylation status, studies have consistently suggested that *MGMT* methylation identifies patients who are more likely to benefit from TMZ. TMZ is associated with morbidity, and, with counseling about risks and benefits, a patient who is less likely to benefit from the treatment might choose to avoid TMZ. Clinical input indicated that measuring *MGMT* promoter methylation improves health outcomes by predicting treatment response to TMZ in patients with high-grade gliomas. This input supports a chain of evidence for the use of *MGMT* promoter methylation in this setting. The

evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who receive IDH1/IDH2 testing multiple studies have shown molecular profiling of WHO grade II and III gliomas distinguishes biologically distinct tumor groups and provides prognostically relevant information beyond histological classification as well as IDH1/2 mutation. Studies show that IDH1/IDH2 mutations were associated with longer survival as well as response to temozolomide treatment. IDH mutation appears to be a marker of positive prognosis and chemosensitivity in low grade gliomas. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who receive 1p/19q codeletion, TERT and ATRX testing, the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06186440	Cisplatin Plus Temozolomide Compared with Temozolomide in Patients with MGMT Promotor Unmethylated Glioblastoma (Glioblastoma)	60	Jan 2025 (not yet recruiting)
NCT05694416	Etoposide Plus Cisplatin Compared with Temozolomide in Patients with Glioblastoma	60	Jan 2025 (not yet recruiting)
NCT03643549	Bortezomib and Temozolomide in Recurrent Grade-4 Glioma Unmethylated MGMT Promoter (BORTEM-17) (BORTEM-17)	63	Dec 2025
NCT03011671	Study of Acetazolamide with Temozolomide in Adults with Newly Diagnosed or Recurrent Malignant Glioma	60	Oct 2026
NCT06419946	Lomustine in Addition to Standard of Care in Patients with MGMT Methylated Glioblastoma	200	Dec 2031
NCT06388733	A Study Comparing Niraparib with Temozolomide in Adult Participants with Newly diagnosed, MGMT Unmethylated Glioblastoma	450	Mar 2028
Unpublished			
NCT00482677	A randomized phase III study of Temozolomide and short course radiation versus short course radiation alone in the treatment of newly diagnosed glioblastoma multiforme in elderly patients	562	Mar 2016 (completed)
NCT02152982a	A phase II/III randomized trial of Veliparib or placebo in combination with adjuvant Temozolomide in newly diagnosed glioblastoma with MGMT promoter hypermethylation	447	Dec 2024

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT

In 2017, clinical input was sought to help determine whether, in current practice, testing of *MGMT* methylation status is used to determine whether treatment with temozolomide (TMZ) will be used for patients with malignant glioma.

RESPONDENTS

Clinical input was provided by the Association for Molecular Pathology (AMP) as well as the following clinicians identified by an associated medical specialty society or clinical health system:

- Daniel J. Brat, MD, PhD, Pathology and Lab Medicine, Emory University School of Medicine (American Society of Clinical Oncology [ASCO])
- Anonymous, FACMG, Clinical Molecular Genetics, Clinical Cytogenetics
- Anonymous, FACMG, Clinical Molecular Genetics, Clinical Cytogenetics
- Sameek Roychowdhury, MD, PhD, FACMG, Medical Oncology, The Ohio State University
- Anonymous, Medical Oncology (Cancer Treatment Centers of America [CTCA])
- Anonymous, Medical Oncology, Eastern Regional Medical Center (CTCA)
- Frank Senecal, MD, Medical Oncology, Northwest Medical Specialties (Catholic Health Initiatives [CHI])

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by the specialty society is attributed to the individual physician and is not a statement from the specialty society. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by the specialty society or clinical health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

CLINICAL INPUT RESPONSES

Regarding the use of MGMT testing in patients with malignant glioma for prediction of treatment response to alkylating agent chemotherapy, such as temozolomide:

Respondent	Identified by	Confidence Level that Evidence Supports Improved Health Outcomes (Low – Intermediate – High)					Confidence Level that Clinical Use is in Accordance with Generally Accepted Medical Practice (Low – Intermediate – High)				
		1	2	3	4	5	1	2	3	4	5
Association for Molecular Pathology (AMP)						■					■
Daniel J Brat, MD, PhD Pathology and Lab Medicine	ASCO				■					■	
Anonymous - FACMG Clinical Molecular Genetics, Clinical Cytogenetics					■					■	
Anonymous - FACMG Clinical Molecular Genetics, Clinical Cytogenetics					■					■	
Sameek Roychowdhury, MD, PhD, FACMG Medical Oncology						■					■
Anonymous Medical Oncology	CTCA	■									■
Anonymous Medical Oncology	CTCA				■						■
Frank Senecal, MD Medical Oncology	CHI					■					■

Additional Comments

AMP noted “that there is sufficient evidence to support MGMT testing all glioma patients with a post treatment imaging study suggesting progression/pseudo-progression.” The rationale for this position was that “retrospective determination of MGMT promoter methylation status in the pre-treated, original biopsies can be critical in the distinction of this post-treatment effect in patients with imaging consistent with progression/pseudo-progression to ensure that effective therapies are not inappropriately terminated under the false assumption of disease progression (versus the alternative diagnosis of transient good prognosis pseudo-progression).”

Regarding test performance and reliability for *MGMT* methylation, both the methylation-specific polymerase chain reaction method and the multiplex ligation-dependent probe amplification method were rated with intermediate to higher confidence ratings. AMP noted that pyrosequencing and methylation sensitive restriction enzyme polymerase chain reaction are 2 other methods rated with high confidence. Protein-based assays (i.e., immunohistochemistry, Western blot) were generally rated with lower to intermediate confidence ratings.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines on central nervous system cancers (v.3.2024)[3] support several treatment options based on the presence of methylated O^6-methylguanine DNA methyltransferase (MGMT) promoter. NCCN has a Category 1 recommendation for the utility of methylated, unmethylated and indeterminate status for the selection of therapy with temozolomide with or without standard radiation therapy and/or

alternating electric field therapy in patients with good performance status (KPS> 60) in all patients (< and > 70 years of age).

***IDH1/IDH2* Testing**
IDH1 and *IDH2* are metabolic enzymes. Specific mutations in genes encoding these enzymes lead to the aberrant production of D-2- hydroxyglutarate, an oncometabolite that causes epigenetic modifications in affected cells. Diffusely infiltrative astrocytomas with *IDH* mutation are mostly grade 2–3. However, some develop the traditional grade 4 histologic features of necrosis and/or microvascular proliferation, which does suggest more aggressive behavior and worse prognosis, but still not as severe as *IDH* wild-type glioblastomas. *IDH* mutations are commonly associated with MGMT (O6-methylguanineDNA methyltransferase) promoter methylation. Recommendation: IDH mutation testing is required for the workup of all gliomas.

1p/19q Codeletion Testing
NCCN recommendation: 1p/19q testing is an essential part of molecular diagnostics for oligodendroglioma.

***TERT* Testing**
NCCN recommendation: *TERT* promoter mutation testing is recommended for the workup of gliomas.

***ATRX* Testing**
NCCN recommendation: *ATRX* mutation testing is required for the workup of glioma.

Government Regulations
National/Local:
There is no national coverage determination for this test.

Local Coverage Determination.
LCD (L37001), MolDX: MGMT Promoter Methylation Analysis. Effective for services performed on or after 08/31/23.

This policy provides limited coverage for methylation analysis for hypermethylation of the O^6 methylguanine DNA methyltransferase (MGMT) gene promoter. MGMT methylation analysis testing is considered to be reasonable and necessary for adult patients when the following criteria are met:

- Tumor type is high-grade malignant glioma (e.g., glioblastoma multiforme (GBM), anaplastic astrocytoma) **and**
- Patients are able to tolerate temozolomide therapy or radiation therapy, **and**
- The physician will use the of MGMT testing results to decide between radiation therapy and chemotherapy alone as 1st line adjuvant treatment, or between temozolomide and other chemotherapy for 1st line adjuvant treatment.

Note: This assessment is predicated on the assumption that therapy is considered beneficial for the specific patient.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are

updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.

Related Policies

N/A

References

1. Holdhoff M, Ye X, Blakeley JO et al. Use of personalized molecular biomarkers in the clinical care of adults with glioblastomas. J Neurooncol 2012; 110(2):279-85. PMID: 22930388
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. Jun 2016;131(6):803-820. PMID 27157931
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed January 2025.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. Mar 10, 2005;352(10):987-996. PMID 15758009
5. Weller M, Stupp R, Hegi ME, et al. Personalized care in neuro-oncology coming of age: why we need MGMT and 1p/19q testing for malignant glioma patients in clinical practice. Neuro Oncol. Sep 2012;14 Suppl 4: iv100-108. PMID 23095825
6. Chamberlain MC. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. Neurology. Jun 10, 2014;82(23):2147-2148. PMID 24912510
7. Kalkan R, Atli EI, Ozdemir M, et al. IDH1 mutations is prognostic marker for primary glioblastoma multiforme but MGMT hypermethylation is not prognostic for primary glioblastoma multiforme. Gene. Oct 14, 2014;554(1):81-86. PMID 25455102
8. Minniti G, Scaringi C, Arcella A, et al. IDH1 mutation and MGMT methylation status predict survival in patients with anaplastic astrocytoma treated with temozolomide-based chemoradiotherapy. J Neurooncol. Jun 2014;118(2):377-383. PMID 24748470
9. Molenaar RJ, Verbaan D, Lamba S, et al. The combination of IDH1 mutations and MGMT methylation status predicts survival in glioblastoma better than either IDH1 or MGMT alone. Neuro Oncol. Sep 2014;16(9):1263- 1273. PMID 24510240
10. Myung JK, Cho HJ, Kim H, et al. Prognosis of glioblastoma with oligodendroglioma component is associated with the IDH1 mutation and MGMT methylation status. Transl Oncol. Dec 2014;7(6):712-719. PMID 25500080
11. Takahashi Y, Nakamura H, Makino K, et al. Prognostic value of isocitrate dehydrogenase 1, O^6-methylguanineDNA methyltransferase promoter methylation, and 1p19q co-deletion in Japanese malignant glioma patients. World J Surg Oncol. Oct 25, 2013; 11:284. PMID 24160898
12. Wick W, Weller M, van den Bent M, et al. MGMT testing—the challenges for biomarker-based glioma treatment. Nat Rev Neurol. Jul 2014;10(7):372-385. PMID 24912512
13. Wick W, Meisner C, Hentschel B, et al. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. Neurology. Oct 22, 2013;81(17):1515-1522. PMID 24068788

14. Wiestler B, Capper D, Hovestadt V, et al. Assessing CpG island methylator phenotype, 1p/19q codeletion, and MGMT promoter methylation from epigenome-wide data in the biomarker cohort of the NOA-04 trial. Neuro Oncol. Dec 2014;16(12):1630-1638. PMID 25028501
15. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nat Rev Neurol. Jan 2010;6(1):39-51. PMID 19997073
16. Berghoff AS, Preusser M. Clinical neuropathology practice guide 06-2012: MGMT testing in elderly glioblastoma patients—yes, but how? Clin Neuropathol. Nov-Dec 2012;31(6):405-408. PMID 23083460
17. Malmstrom A, Gronberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic Randomized, phase 3 trial. Lancet Oncol. Sep 2012;13(9):916-926. PMID 22877848
18. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol. Jul 2012;13(7):707-715. PMID 22578793
19. Preusser M, Elezi L, Hainfellner JA. Reliability and reproducibility of PCR-based testing of O6-methylguanineDNA methyltransferase gene (MGMT) promoter methylation status in formalin-fixed and paraffin-embedded neurosurgical biopsy specimens. Clin Neuropathol. Nov-Dec 2008;27(6):388-390. PMID 19130735
20. Pulverer W, Hofner M, Preusser M, et al. A simple quantitative diagnostic alternative for MGMT DNA-methylation testing on RCL2 fixed paraffin embedded tumors using restriction coupled qPCR. Clin Neuropathol. Jan-Feb 2014;33(1):50-60. PMID 23993306
21. Yang H, Wei D, Yang K, et al. The prognosis of MGMT promoter methylation in glioblastoma patients of different race: a meta-analysis. Neurochem Res. Dec 2014;39(12):2277-2287. PMID 25230908
22. Chen Y, Hu F, Zhou Y, et al. MGMT promoter methylation and glioblastoma prognosis: a systematic review and meta-analysis. Arch Med Res. May 2013;44(4):281-290. PMID 23608672
23. Yin AA, Zhang LH, Cheng JX, et al. The predictive but not prognostic value of MGMT promoter methylation status in elderly glioblastoma patients: a meta-analysis. PloS One. Jan 2014;9(1): e85102. PMID 24454798
24. Perry JR, Laperriere N, O'Callaghan CJ, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med. Mar 16, 2017;376(11):1027-1037. PMID 28296618
25. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. Nov 10, 2013;31(32):4085-4091. PMID 24101040
26. Collins VP, Ichimura K, Di Y, et al. Prognostic and predictive markers in recurrent high-grade glioma; results from the BR12 randomised trial. Acta Neuropathol Commun. Jun 2014; 2:68. PMID 24952577
27. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTCNCIC trial. Lancet Oncol. May 2009;10(5):459-466. PMID 19269895
28. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV." Acta Neuropathol 2018; 136:805-810.

29. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. Aug 2021;23(8): 1231-1251.
30. Gritsch S, Batchelor T, Castro LN. Diagnostic, therapeutic, and prognostic implications of the 2021 WHO classification of tumors of the central nervous system. Cancer. Jan 2022;128(1): 47-58.
31. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. Feb 2009;360(8): 765-773.
32. Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH and TERT promoter mutations in tumors. N Engl J Med. Jun 2015;372(26): 2499-2508.
33. Weller M, Weber R, Willscher E, et al. Molecular classification of diffuse cerebral WHO grade II/III gliomas using genome and transciptome wide profiling improves stratification of prognostically distinct patient groups. Acta Neuropathol. May 2015;129(5): 679-693.
34. Baumert B, Hegi M, Van den Bent M, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma: randomized, open-label, phase 3 intergroup study. Lancet Oncol. Nov 2016; 17(11):1521-1532.
35. Neumann J, Dorostkar M, Korshunov A, et al. Distinct histomorphology in molecular subgroups of glioblastomas in young patients. J Neuropathol Exp Neurol. May 2016;75(5):408-414.
36. Houillier C, Wang X, Kaloshi G, et al. IDH1 and IDH2 mutations predict longer survival and response to temozolomide in low grade gliomas. Neurology. Oct 2010;75(17):1560-1566.
37. Dubbink H, Atmodimedjo P, Kros J, et al. Molecular classification of anaplastic oligodendroglioma using NGS: a report of the prospective randomized EORTC brain tomor group 26951 phase III trial. Neuro Oncol. Mar 2016;18(3):388-400.
38. Labussiere M, Idbaih A, Wang X, et al. All the 1p19q codeleted gliomas are mutated on IDH1 or IDH2. Neurology. Jun 2010;74(23):1886-1890.
39. Brat D, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for diffuse astrocytic glioma, IDH wild type, with molecular features of glioblastoma, WHO grade IV. Acta Neuropathol. Nov 2018; 136(5):805-810.
40. Brat D, Aldape K, Colman H, et al. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH mutant astrocytomas. Act Neuropathol. Mar 2020; 139(3): 603-608.
41. Cairncross JG, Wang M, Jenkins RB, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol. Mar 2014;32(8): 783-790.
42. Kristensen BW, Ackley LP, Peterson JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol. Aug 2019;30(8): 1265-1278.
43. Sturm D, Witt H, Hovestdt V, et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell. Oct 2012; 22(4): 425-437.
44. Jiang H, Cui Y, Wang J, et al. Impact of epidemiological characteristics of supratentorial gliomas in adults brought about by the 2016 WHO classification of tumors of the central nervous system. Oncotarget. Mar 2017;8(12): 20354-20361.
45. Chang S, Zhang P, Cairncross J, et al. Phase III randomized study of radiation and temozolomide versus radiation and nitrosourea therapy for anaplastic astrocytoma: results of NRG oncology RTOG 9813. Neuro Oncol. Feb 2017; 19(2): 252-258.
46. Reuss DE, Sahm F, Schrimpf D, et al. ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an integrated diagnostic approach for adult astrocytoma, oliogodendrolglioma, and glioblastoma. Acta Neuropathol. Jan 2015; 129(1): 133-146.

47. Blue Cross Blue Shield Association. Analysis of MGMT Promoter Methylation in Malignant Gliomas. Medical Policy Reference Manual. Policy #2.04.113, Issue 1:2017, original policy date 1/19/14, last updated May 2018. Archived July 2019.
48. HAYES GTE Report. Methylguanine-DNA Methyltransferase (*MGMT*) Gene Methylation for Glioblastoma Multiforme (GBM) (Various Manufacturers). Lansdale, PA: HAYES, Inc. January 29, 2015, Archived July 2017. Outdated.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/14	2/18/14	2/28/14	Joint policy established
11/1/15	8/24/15	9/14/15	Routine maintenance
9/1/16	6/21/16	6/21/16	Routine maintenance. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance. References 33, 36-38 added. No change in policy status.
5/1/18	2/20/18	2/20/18	Code update added codes 81120 and 81121 as E/I. Effective 1/1/18. Policy status change from E/I to established with criteria. Added IDH1/IDH2 testing to MPS as E/I.
5/1/19	2/19/19		Rationale reformatted, added reference #24. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance. No change in policy status.
5/1/23	3/29/23		MPS changed to reflect coverage for IDH1/2 when indicated per NCCN guidelines. Added to rationale addressing IDH, added references 29-46. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)
5/1/25	2/18/25		Added code 0481U as EST. Routine policy maintenance, no change in status. Vendor managed: N/A (ds)
7/1/25	4/15/25		Added 1p/19q, TERT and ATRX testing as established to MPS. Added codes 81345, 81479, 88377 as established and 0481U as E/I to policy as established. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING - MALIGNANT GLIOMAS INCLUDING MGMT PROMOTER METHYLATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy guidelines
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A