
Medical Policy



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Title: Genetic Testing - Analysis of MGMT Promoter Methylation in Malignant Gliomas

Description/Background

Testing for MGMT (O⁶-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 17,000 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 O⁶-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 O⁶ 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% to 50% 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}

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 safety and effectiveness of the analysis of MGMT Promoter Methylation in malignant gliomas is established. It may be considered a useful option when indicated.

The analysis of IDH1/IDH2 mutations for prognostic value is experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Methylation analysis of the O⁶-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.

MGMT promoter methylation analysis is **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

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

81120

81121

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 O⁶-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.

Patients

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*: O⁶-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	<ul style="list-style-type: none"> • ≥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*: O⁶-methylguanine-DNA methyltransferase; RT: radiotherapy; TMZ: temozolomide.

^aReduced intensity RT 40 gray in 15 daily fractions in 3 weeks.

^bDose of 75 mg/m² BSA per day for 21 consecutive days followed by adjuvant 150-200 mg/m² 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 <i>MGMT</i>					
RT alone	3.8 (1.1 to 9.6)				
RT+TMZ	6.7 (2.7 to 13.10)				
Patients with methylated <i>MGMT</i>					
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*: O⁶-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.

^aCommon Terminology Criteria for Adverse Events v3.0.

^bEORTC QLQ-C30 Global domain with deterioration defined as a 10-point decrease.

^cOS 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/m² 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: O⁶-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: O⁶-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 <i>MGMT</i>	15.3 (13.0 to 20.9)	23.4 (18.6 to 32.8)
Unmethylated <i>MGMT</i>	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: O⁶-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 methylation³²; 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.

SUMMARY OF EVIDENCE

For individuals who have high-grade glioma(s) who receive O⁶-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.

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			
NCT02152982 ^a	A phase II/III randomized trial of Veliparib or placebo in combination with adjuvant Temozolomide in newly diagnosed glioblastoma with <i>MGMT</i> promoter hypermethylation	440	Jun 2022
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)

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

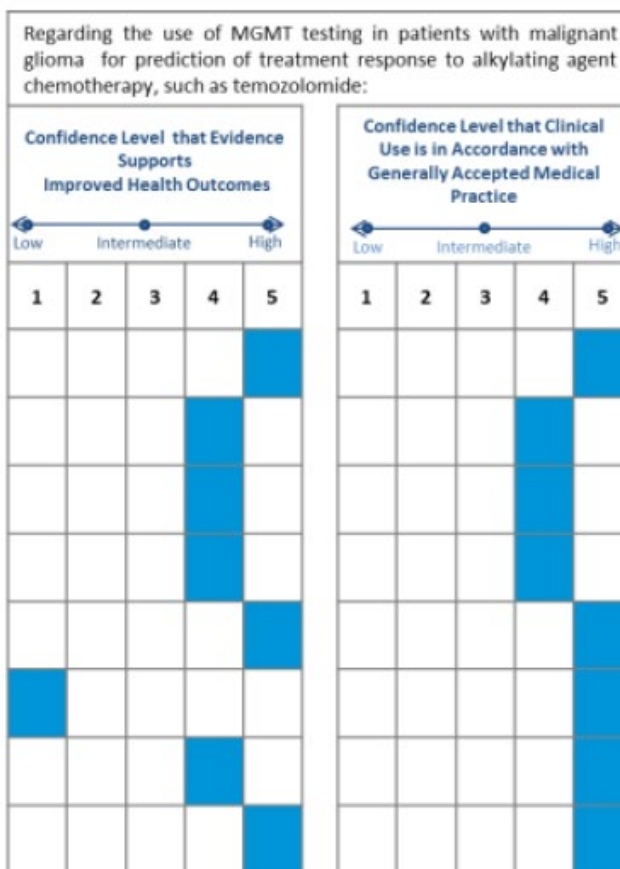
Clinical input was provided by the Association for Molecular Pathology (AMP) as well as the following clinicians identified by an associated medical specialty society or clinical health system:

- 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

Respondent	Identified by
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.2.2021)³ support several treatment options based on the presence of methylated O⁶-methylguanineDNA 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).

Government Regulations

National/Local:

There is no national coverage determination for this test.

Local Coverage Determination.

LCD (L37001), MoIDX: MGMT Promoter Methylation Analysis. effective for services performed on or after 10/14/2021.

This policy provides limited coverage for methylation analysis for hypermethylation of the O⁶ 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

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, 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.
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.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING - ANALYSIS OF MGMT PROMOTER METHYLATION IN
MALIGNANT GLIOMAS

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