2.04.113	Analysis of *MGMT* Promoter Methylation in Malignant Gliomas		
Original Policy Date:	2.0 Medicine	**Effective Date:**	September 1, 2018
Section:	April 30, 2015	**Page:**	Page 1 of 23

Policy Statement

Methylation analysis of the O^6-methylguanine DNA methyltransferase (*MGMT*) gene promoter from glioma tumor tissue may be considered **medically necessary** for individuals who meet **all** of the following criteria:

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

MGMT promoter methylation analysis is considered **investigational** in situations that do not meet the above criteria.

Policy Guidelines

Coding

There is a specific CPT code for this testing:

- **81287**: *MGMT (0-6-methylguanine-DNA methyltransferase)* (e.g., glioblastoma multiforme), methylation analysis

Description

Testing for O^6-methylguanine-DNA methyltransferase (*MGMT*) 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 radiotherapy. However, combined therapy may be too intense in the elderly population, in whom these tumors are most commonly seen.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *MGMT* promoter methylation testing is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background

Malignant Gliomas

Malignant gliomas are the most common primary brain cancer in adults, with approximately 17,000 new cases diagnosed annually in the United States.[1] Until 2016, brain tumors were graded using histologic criteria corresponding to the degree of malignancy, ranging from World Health Organization 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 1 year and less than 5% surviving beyond 5 years.

In 2016, World Health Organization revised its classification of tumors of the central nervous system so that diffusely infiltrating gliomas are grouped based on genetic driver mutations.[2] Diffuse gliomas in the new classification include the former World Health Organization 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 radiotherapy (RT), and chemotherapy.[3] Chemotherapy may include intraoperative placement of an implantable carmustine wafer. Temozolomide (TMZ) is an oral alkylating agent. Response to TMZ has been associated with decreased O^6-methylguanine-DNA methyltransferase (*MGMT*) activity in tumor tissue (see MGMT and Promoter Methylation section below) 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, reported by Stupp et al (2005), that compared RT with or without TMZ in patients with GBM; this trial 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 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 increasing tumor susceptibility to alkylating agent-based chemotherapy. Approximately 40% to 50% of GBMs have *MGMT* gene promoter methylation. Variants in *IDH1* (isocitrate dehydrogenase 1), 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 have failed to identify a correlation between *MGMT* promoter methylation assessed by polymerase chain reaction 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 polymerase chain reaction (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]

Literature Review
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 PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients with glioblastoma multiforme (GBM), newly diagnosed or recurrent on therapy.

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

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

Outcomes
The outcome of interest is overall survival (OS). Progression-free survival (PFS) may be considered but has a relatively limited use for a tumor such as a glioblastoma, where long-term survival outcomes are uncommon.

Timing
Survival outcomes over the course of 3 to 5 years would be reasonable.

Setting
Patients would be treated in the inpatient and outpatient oncology setting.

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 patients; 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 RT. Both PFS and OS 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) might 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 meeting inclusion criteria. Publication bias was not detected. Twenty-two studies reported on the relation between *MGMT* methylation status and OS, and 12 reported on the relation between *MGMT* methylation status and 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 analyses for PFS and OS. Heterogeneity existed for study publication

dates and tumor histology other than GBM (e.g., anaplastic gliomas); there was also variability across studies from 1 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 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 rates 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 between 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.
[b] Fixed-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).

Survival rates from the NOA-8 trial are summarized in Table 5.

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/m^2 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/m^2 days 1-5 of a 28-day cycle vs dose-dense TMZ treatment: 75-100 mg/m^2 days 1-21 of a 28-day cycle).[25] Patients with newly diagnosed GBM were randomized 1:1 to standard (n=411) or dose-dense 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 a 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 one, only approximately half of patients had their tumors tested for promoter methylation and correlated with survival. One 2009 RCT, which assessed TMZ plus RT, showed apparent survival benefits compared with RT alone in patients with and without *MGMT* promoter methylation[27]; however, patients without *MGMT* methylation showed less improvement than those with *MGMT* methylation. A 2017 RCT confirmed these findings in an elderly population receiving shorter course RT. 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 *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. While there are no studies directly evaluating whether the 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 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 combined with radiotherapy remains the standard of care for most patients. TMZ is associated with a modest increase in hematologic adverse events compared with radiotherapy 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical Input

Objective

In 2017, clinical input was sought from Blue Cross Blue Shield Association to help determine whether, in current practice, testing of O^6-methylguanine-DNA methyltransferase (*MGMT*) methylation status is used to determine whether treatment with temozolomide will be used for patients with malignant glioma.

Respondents

Clinical input was provided by the Association for Molecular Pathology 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 or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the clinical input process provide a review, input, and feedback on topics being evaluated. However, participation in the clinical input process by a special society and/or physician member designated by the specialty society or health system does not imply an endorsement or explicit agreement with the Opinion published by Blue Cross Blue Shield Association or Blue Shield of California.

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) 1	2	3	4	5	Confidence Level that Clinical Use is in Accordance with Generally Accepted Medical Practice (Low / Intermediate / High) 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

Association for Molecular Pathology 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. Association for Molecular Pathology 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.

See Appendices 1 and 2 for details of the clinical input.

Supplemental Information

Practice Guidelines and Position Statements

Current National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2018)[3] support several treatment options based on the presence of methylated O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter. In patients over age 70 with good performance status and methylated *MGMT* promoter, the use of hypofractionated brain radiotherapy, plus concurrent and adjuvant temozolomide is a category 1 recommendation.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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			
NCT02209948	Clinical Trial Phase IIB Randomized, Multicenter, of Continuation or Non Continuation with 6 Cycles of Temozolomide after the First 6 Cycles of Standard First-line Treatment in Patients with Glioblastoma	160	Jun 2018
NCT02152982[a]	A Phase II/III Randomized Trial of Veliparib or Placebo in Combination with Adjuvant Temozolomide in Newly Diagnosed Glioblastoma with MGMT Promoter Hypermethylation	440	Jun 2022

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

Appendix

Appendix 1. Clinical Input Respondents
Appendix Table 1. Respondent Profile

Specialty Society			
No.	**Name of Organization**	**Clinical Specialty**	
1	Association for Molecular Pathology	Molecular Pathology	

Physician					
No.	**Name**	**Degree**	**Name of Organization**	**Clinical Specialty**	**Board Certification and Fellowship Training**
Identified by American Society of Clinical Oncology					
2	Brat, Daniel, J.	MD, PhD	Emory University School of Medicine	Pathology and Lab medicine	Anatomic pathology, Neuropathology
Identified by American College of Medical Genetics & Genomics					
3	Anonymous	MS, PhD, FACMG		Clinical molecular genetics, Clinical cytogenetics	ABMGG
4	Anonymous	MD		Clinical molecular genetics, Clinical cytogenetics	ABMG certified in clinical cytogenetics and clinical molecular genetics
5	Roychowdhury, Sameek	MD, PhD	The Ohio State University	Medical oncology	ABIM Internal medicine and Medical oncology
Identified by Cancer Treatment Centers of America					
6	Anonymous	DO	Cancer Treatment Centers of America	Medical oncology	Medical Oncology
7	Anonymous	MD	Eastern Regional Medical Center	Medical oncology	Internal medicine, Medical oncology

	Specialty Society				
Identified by Catholic Health Initiatives					
8	Senecal, Frank	MD	Northwest Medical Specialties	Medical oncology	Hematology, Oncology

ABIM: American Board of Internal Medicine; ABMG: American Board of Medical Genetics.

Appendix Table 2. Respondent Conflict of Interest Disclosure

	1. Research support related to the topic where clinical input is being sought		**2. Positions, paid or unpaid, related to the topic where clinical input is being sought**		**3. Reportable, more than $1000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought**		**4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought**	
No.	**Yes/ No**	**Explanation**	**Yes/ No**	**Explanation**	**Yes/No**	**Explanation**	**Yes/No**	**Explanation**
Association for Molecular Pathology								
1	No		No		No		No	
Identified by American Society of Clinical Oncology								
2	No		No		No		No	
Identified by American College of Medical Genetics & Genomics								
3	No		No		No		No	
4	No		No		No		No	
5	No		No		No		No	
Identified by Cancer Treatment Centers of America								
6	No		No		No		No	
7	No		No		No		No	
Identified by Catholic Health Initiatives								
8	No		No		No		No	

Individual physician respondents answered at the individual level. Specialty society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the society level response.

Appendix 2. Clinical Input Responses

Objective

Clinical input is sought to help determine whether, in current practice, testing of *MGMT* methylation status is used to determine whether treatment with temozolomide will be used for patients with malignant glioma.

Responses

1. With regard to use of *MGMT* testing in patients with malignant glioma for prediction of treatment response to alkylating agent chemotherapy, such as temozolomide,
   a. Please use the 1 to 5 scale, outlined below to indicate your level of confidence that there is adequate evidence demonstrating that this use will improve health outcomes.

No.	**Low Confidence**		**Intermediate Confidence**		**High Confidence**
	1	**2**	**3**	**4**	**5**
Association for Molecular Pathology					
1					X
Identified by American Society of Clinical Oncology					
2				X	
Identified by American College of Medical Genetics & Genomics					
3				X	
4				X	
5					X

No.	Low Confidence		Intermediate Confidence		High Confidence
Identified by Cancer Treatment Centers of America					
6	X				
7				X	
Identified by Catholic Health Initiatives					
8					X

b. Please use the 1 to 5 scale, outlined below to indicate your level of confidence that this clinical use is in accordance with generally accepted medical practice.

No.	Low Confidence		Intermediate Confidence		High Confidence
	1	**2**	**3**	**4**	**5**
Association for Molecular Pathology					
1					X
Identified by American Society of Clinical Oncology					
2				X	
Identified by American College of Medical Genetics & Genomics					
3				X	
4				X	
5					X
Identified by Cancer Treatment Centers of America					
6					X
7					X
Identified by Catholic Health Initiatives					
8					X

2. The following questions relate to test performance and reliability:
   a. Please use the 1 to 5 scale, outlined below to indicate your level of confidence in the methylation-specific polymerase chain reaction method.

No.	Low Confidence		Intermediate Confidence		High Confidence
	1	**2**	**3**	**4**	**5**
Association for Molecular Pathology					
1					X
Identified by American Society of Clinical Oncology					
2				X	
Identified by American College of Medical Genetics & Genomics					
3					X
4				X	
5					X
Identified by Cancer Treatment Centers of America					
6					X
7				X	
Identified by Catholic Health Initiatives					
8			X		

   b. Please use the 1 to 5 scale, outlined below to indicate your level of confidence in the multiplex ligation–dependent probe amplification method.

No.	Low Confidence		Intermediate Confidence		High Confidence
	1	**2**	**3**	**4**	**5**
Association for Molecular Pathology					
1					X
Identified by American Society of Clinical Oncology					
2				X	
Identified by American College of Medical Genetics & Genomics					
3					X
4			X		

No.	Low Confidence		Intermediate Confidence		High Confidence
5					X
Identified by Cancer Treatment Centers of America					
6					X
7			X		
Identified by Catholic Health Initiatives					
8				X	

c. Please use the 1 to 5 scale, outlined below to indicate your level of confidence in protein-based assays (i.e., immunohistochemistry, Western blot).

No.	Low Confidence		Intermediate Confidence		High Confidence
	1	**2**	**3**	**4**	**5**
Association for Molecular Pathology					
1	X				
Identified by American Society of Clinical Oncology					
2	X				
Identified by American College of Medical Genetics & Genomics					
3			X		
4		X			
5			X		
Identified by Cancer Treatment Centers of America					
6					X
7		X			
Identified by Catholic Health Initiatives					
8		X			

3. Additional comments and/or any citations supporting your clinical input on the clinical use of MGMT testing in guiding the treatment in patients with malignant glioma.

No.	Additional Comments
Association for Molecular Pathology	
1	Additional Considerations for Question 2: With regards to question 2, we would like to point out the use of pyrosequencing as another valid and reliable method for MGMT methylation and therefore included below additional considerations for question 2. Please use the 1 to 5 scale outlined below to indicate your level of confidence in pyrosequencing: 5 - High Confidence Please use the 1 to 5 scale outlined below to indicate your level of confidence in Methylation-sensitive restriction enzyme-PCR (MSRE-PCR): 5 - High Confidence AMP has low confidence in protein-based assays to detect MGMT methylation. The concern about IHC is well-founded and is based on the biology of the MGMT protein. MGMT is a "suicide enzyme" and protein levels won't necessarily correlate with gene expression. However, with regard to specific molecular testing methods (RNA expression and DNA methylation patterns), it is the responsibility of laboratories to ensure that there is concordance between their testing methodology results and what is considered "gold standard" through good clinical laboratory practices, which is regulated by CMS, under CLIA. Also, various molecular testing platforms for MGMT testing exist and it is likely we did not list all the viable methods above. We recommend that BCBSA not rate specific assays and leave method determination up to the laboratory. AMP plans to follow-up with Evidence Street staff to discuss this in more detail. Additional comments to support AMP's clinical input on the use of MGMT testing in guiding the treatment in patients with malignant glioma AMP does not agree with the interpretation of the NCCN guidelines in the Evidence Summary. In those patients with MGMT promoter methylation, a temozolomide containing regimen is essentially mandated (category 1) whereas in unmethylated cases there are additional therapeutic options that may include temozolomide with the caveat that benefit is lower in patients whose tumors lack MGMT promoter methylation (footnote "s"). Also, in patients with poor performance status, the clinician may consider temozolomide monotherapy (footnote "t"). Therefore, AMP considers these recommendations as standard of care, has high confidence that there is adequate

No.	Additional Comments
	evidence demonstrating that MGMT methylation testing to guide treatment, that its clinical use is in accordance with generally accepted medical practice and, therefore, recommend that BCBSA reconsider their conclusion that the evidence is insufficient to determine the effects of the technology on health outcomes. The summary of evidence section on page 10 states that "there are no studies directly evaluating whether the use of MGMT methylation testing improves patient outcomes." We would like to point out that the kind of evidence traditionally used for medical interventions including pharmaceuticals and medical procedures - that is randomized controlled trials evaluating directly whether the use of an intervention improves patient outcomes - is not valid for laboratory testing. By definition laboratory tests do not directly affect the course of a patient. Rather the testing provides information or data about the patient to a provider whose subsequent decision making, including decisions about interventions, may improve a patient's outcome. Thus, the direct measurement of an "improved outcome" is inappropriate for laboratory testing. The outcomes are dependent on clinical decisions that occur downstream from the test result. We believe this to be a fundamental concept that must be understood appropriately when evaluating evidence for potential coverage policy for laboratory testing and encourage BSBCA to incorporate the concept into its decision making. Fundamentally, it should result in an expanding of the concept of clinical benefit of laboratory testing beyond "drug selection." AMP plans to follow-up with Evidence Street staff to discuss appropriate evidence criteria for molecular laboratory diagnostics and the necessity of incorporating them into future evidence reviews of lab tests. MGMT Testing for Glioma Patients with Pseudo-progression: The neuro-oncology community has recently come to recognize the concept of pseudo-progression in the treatment course of high grade gliomas. In particular, pseudo-progression is defined as apparent post-treatment radiographically-identified disease progression followed by subsequent improvement or stabilization without any additional treatment. Pseudo-progression is a transient phenomenon that likely represents a local tissue reaction to the therapy, and has actually been correlated with improved overall survival (Hygino da Cruz LC Jr, Rodriguez I, Domingues RC, et al. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR Am J Neuroradiol. 2011 Dec; 32(11):1978-85. PMID: 21393407). Pseudo-progression is, therefore, a radiographic mimic of true tumor-specific disease progression and its distinction is thus critical, given that the best treatment option for pseudo-progression is to continue the current therapy, while a different glioma therapy is the best treatment option for true disease progression. Current radiographic imaging methods cannot distinguish (Hygino da Cruz et al. 2011) these two disparate diagnoses with radically different treatment ramifications, and a brain biopsy is the classic option to distinguish these two conditions. However, it has recently been determined that gliomas with MGMT promoter methylation have a significantly higher prevalence of pseudo-progression than non- methylated tumors (Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol. 2008 May 1; 26(13):2192-7. PMID: 18445844). In this study, 91% of patients whose original biopsies demonstrated methylated MGMT had pseudo-progression (versus 41% of patients without methylated MGMT, P =.0002), and were best managed by continuing the current therapy. The 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). It is also critical in true recurrence/tumor progression that these new biopsies of treated tumors be retested for MGMT methylation status as methylation of MGMT in tumor cells renders these cells sensitive to alkylating chemotherapy. Often, but not always, recurrent tumors will exhibit altered methylation status with significant implications for therapeutic decision making (Brandes AA, Franceschi E, Tosoni A, et al. O(6)-methylguanine DNA-methyltransferase methylation status can change between first surgery for newly diagnosed glioblastoma and second surgery for recurrence: clinical implications. Neuro Oncol. 2010 Mar; 12(3):283-8. PMID: 20167816).

No.	Additional Comments
	We therefore determine that there is sufficient evidence to support MGMT testing all glioma patients with a post-treatment imaging study suggesting progression/pseudo-progression.
Identified by American Society of Clinical Oncology	
2	It is true that there is variation in the testing of MGMT and that a standard approach to testing, interpreting, reporting and clinical decisions based on this testing. This is especially true in the indeterminate or intermediate category. However, the results reported as Methylated or Unmethylated have clear clinical meaning that is used to guide therapy by neuro-oncologists. Some neuro-oncologists will treat patients with malignant glioma with temozolomide regardless of MGMT status. However, this is not universally true. Some clinicians do not think it is justified to administer temozolomide to a patient with an unmethylated high grade glioma. In addition, as noted, there are many clinical factors that may come into consideration when considering treatment, including the performance status and age, in addition to MGMT status. However, the conclusion that MGMT testing has low clinical validity or utility is not supported by the evidence provided or by commonly held clinical practice. There is not enough consideration given to potential side effects of treating patients who have high grade gliomas that are unmethylated.
Identified by American College of Medical Genetics & Genomics	
3	No response
4	• MGMT testing—the challenges for biomarker-based glioma treatment by Wolfgang Wick, et al. (Wick W, Weller M, van den Bent M, et al. MGMT testing--the challenges for biomarker-based glioma treatment. Nat Rev Neurol. 2014 Jul; 10(7):372-85. PMID: 24912512). • Park CK, Kim J, Yim SY, et al. Usefulness of MS-MLPA for detection of MGMT promoter methylation in the evaluation of pseudoprogression in glioblastoma patients. Neuro Oncol. 2011 Feb; 13(2):195-202. PMID: 21075779.
5	In clinical practice, assessment of MGMT methylation is considered standard and is a board question, with biomarker implications that are both prognostic and predictive. • Is there Analytic Validity for lab tests? Yes. See references. This is offered by multiple labs with an accurate and precise assay. • Is there Clinical Validity with marker status? Yes, clinical outcomes with methylation have implications on whether TMZ therapy has value or not. When TMZ does not have value, other therapy options should be considered (Trial). • Is there Clinical Utility with marker status? Yes. Patients with poor outcomes with TMZ could skip it, and should be considered/offered other therapies in clinical trials. In another example, elderly or frail patients would/could skip TMZ if there is low benefit (This is from NCCN guideline). On my review of the report and literature, I found the reports assessment of Clinical Validity and Utility discordant, on page 9. "uncertain whether testing for MGMT promoter methylation can identify patients who do not benefit from TMZ" and "studies are consistent with lower treatment response to TMZ among patients with unmethylated MGMT."
Identified by Cancer Treatment Centers of America	
6	MGMT does not change management for upfront treatment with glioblastoma, however it may change how I interpret MRI findings or how often I would do imaging. In lower grade glioma, it helps me to determine if I should give radiation, temodar alone, or both.
7	It is clear that MGMT methylation status has general prognostic and some predictive value in response, primarily to Temozolamide (TMZ), when compared to standard EBRT. It is also apparent that TMZ does have some clinical utility in patients that are MGMT negative. The evaluation of MGMT methylation status has become standard practice in guiding therapeutic decisions especially in the older population or patients with poor performance status patients with GBM who are at increased risk of toxicity to standard initial combination therapy with EBRT / TMZ. A concern I have found in assessing the role of MGMT methylation is the method used to do the analysis. I am not very familiar with the specifics of all the testing methods but the most common appears to be the methylation-specific PCR (MSP) which does not appear to be ideal for the reasons noted analysis that was sent to me for review. Despite the limitations of this method it is commonly used and has been validated in some randomized clinical trials.

No.	Additional Comments
Identified by Catholic Health Initiatives	
8	No response

4. Is there any evidence missing from the attached draft review of evidence?

No.	Yes/No	Citations of Missing Evidence
Association for Molecular Pathology		
1	Yes	MGMT Analytical Method Detection: • Berghoff AS, Hainfellner JA, Marosi C, et al. Assessing MGMT methylation status and its current impact on treatment in glioblastoma. CNS Oncol. 2015; 4(1):47-52. PMID: 25586425. • Cankovic M, Nikiforova MN, Snuderl M, et al. The role of MGMT testing in clinical practice: a report of the Association for Molecular Pathology. J Mol Diagn. 2013 Sep; 15(5):539-55. PMID: 23871769. • Lattanzio L, Borgognone M, Mocellini C, et al. MGMT promoter methylation and glioblastoma: a comparison of analytical methods and of tumor specimens. Int J Biol Markers. 2015 May 26; 30(2):e208-16. PMID: 25588856. • National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: central nervous system cancers. Version 1.2016. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf (page 61) • 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. 2014 Jan-Feb; 33(1):50-60. PMID: 23993306. (cited in the summary but AMP suggest you reassess this article as evidence for use of the MSRE-PCR method). MGMT Testing for Glioma Patients with Pseudo-progression: • Hygino da Cruz LC Jr, Rodriguez I, Domingues RC, et al. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR Am J Neuroradiol. 2011 Dec; 32(11):1978-85. PMID: 21393407. • Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol. 2008 May 1; 26(13):2192-7. PMID: 18445844. • Brandes AA, Franceschi E, Tosoni A, et al. O(6)-methylguanine DNA-methyltransferase methylation status can change between first surgery for newly diagnosed glioblastoma and second surgery for recurrence: clinical implications. Neuro Oncol. 2010 Mar; 12(3):283-8. PMID: 20167816. Additional Supplemental Evidence to Consider: The evidence summary lists pertinent supplemental information (page 10) including any practice guidelines and position statements, USPSTF, Medicare National Coverage, or any ongoing and unpublished clinical trials. However, the evidence summary does not list any Medicare local coverage determinations (LCDs) on MGMT promoter methylation in malignant gliomas. There are currently LCDs for MGMT Promoter Methylation Analysis under Medicare Administrative Contractors CGS (L36113), Noridian (L36188 and L36192), and Palmetto (L35974). Each LCD provides limited coverage for methylation analysis for hypermethylation of the MGMT gene promoter. AMP supports the rationale used and decision to cover MGMT promoter methylation analysis under limited circumstances. We suggest BCBSA assess the evidence used by the MACs. See question 4 for more information. Local Coverage Determinations on MGMT: • Palmetto (L35974) • Noridian (L36188) • Noridian (L36192) • CGS (L36113)
Identified by American Society of Clinical Oncology		
2	No	The evidence provided is very thorough. However, the interpretation and conclusions of the guidance do not seem supported by the evidence provided. There is good evidence that patients with MGMT promoter methylation benefit from temozolomide. The evidence for a benefit of temozolomide in patients with unmethylated promoter is not as strong. There is evidence that MGMT testing provides prognostic and predictive information to treating physicians that is currently used in making complex treatment decisions. While some physicians may administer temozolomide to patients with

No.	Yes/No	Citations of Missing Evidence
		unmethylated GBMs, this is not universal and the decision making takes into account the potential side effects, performance status and age of the patient.
Identified by American College of Medical Genetics & Genomics		
3	No	
4		The draft review is quite comprehensive. However, I disagree with the conclusion based on the evidence. The test does have clinical utility, i.e., prognostic and predictive, for at least some of the patients with malignant gliomas based on the available evidence. There will always be differences on treatment responses to a specific therapy among different individuals, especially when only one biomarker is measured.
5	Yes	Xie H, Tubbs R, Yang B. Detection of MGMT promoter methylation in glioblastoma using pyrosequencing. Int J Clin Exp Pathol. 2015 Jan 1; 8(1):636-42. PMID: 25755756. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4348884/ "Recent clinical trials on patients with glioblastoma revealed that O6-Methylguanine-DNA methyltransferase (MGMT) methylation status significantly predicts patient's response to alkylating agents. In this study, we sought to develop and validate a quantitative MGMT methylation assay using pyrosequencing on glioblastoma. We quantified promoter methylation of MGMT using pyrosequencing on paraffin-embedded fine needle aspiration biopsy tissues from 43 glioblastoma. Using a 10% cutoff, MGMT methylation was identified in 37% cases of glioblastoma and 0% of the non-neoplastic epileptic tissue. Methylation of any individual CpG island in MGMT promoter ranged between 33% and 95%, with a mean of 65%. By a serial dilution of genomic DNA of a homogenously methylated cancer cell line with an unmethylated cell line, the analytical sensitivity is at 5% for pyrosequencing to detect MGMT methylation. The minimal amount of genomic DNA required is 100 ng (approximately 3,000 cells) in small fine needle biopsy specimens. Compared with methylation-specific PCR, pyrosequencing is comparably sensitive, relatively specific, and also provides quantitative information for each CpG methylation." Quillien V, Lavenu A, Ducray F, et al. Validation of the high-performance of pyrosequencing for clinical MGMT testing on a cohort of glioblastoma patients from a prospective dedicated multicentric trial. Oncotarget. 2016 Sep 20; 7(38):61916-61929. PMID: 27542245. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308700/ "Background The goal of this prospective multicentric trial was to validate a technique that allowed for MGMT promoter methylation analysis in routine clinical practice. Methods The MGMT status of 139 glioblastoma patients, whom had received standard first line treatment, was determined using pyrosequencing (PSQ) and a semi-quantitative Methylation-specific PCR (sqMS-PCR) method, using both frozen and formalin-fixed paraffin-embedded FFPE samples. Eight participating centers locally performed the analysis, including external quality controls. Results There was a strong correlation between results from FFPE and frozen samples. With cut-offs of 12% and 13%, 98% and 91% of samples were identically classified with PSQ and sqMS-PCR respectively. In 12% of cases frozen samples were excluded because they had a low percentage of tumor cells. In 5-6% of cases the analysis was not feasible on FFPE samples. The optimized risk cut-offs were higher in both techniques when using FFPE samples, in comparison to frozen samples. For sqMS-PCR, we validated a cut-off between 13-15% to dichotomize patients. For PSQ, patients with a low level of methylation (<= 8%) had a median progression-free survival under 9 months, as compared with more than 15.5 months for those with a level above 12%. For intermediate values (9-12%), more discordant results between FFPE and frozen samples were observed and there was not a clear benefit of temozolomide treatment, which indicated a "grey zone"." Vlassenbroeck I, Califice S, Diserens AC, et al. Validation of real-time methylation-specific PCR to determine O6-methylguanine-DNA methyltransferase gene promoter methylation in glioma. J Mol Diagn. 2008 Jul; 10(4):332-7. PMID: 18556773. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2438202/ "Epigenetic silencing of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) by promoter methylation predicts successful alkylating

No.	Yes/No	Citations of Missing Evidence
		agent therapy, such as with temozolomide, in glioblastoma patients. Stratified therapy assignment of patients in prospective clinical trials according to tumor MGMT status requires a standardized diagnostic test, suitable for high-throughput analysis of small amounts of formalin-fixed, paraffin-embedded tumor tissue. A direct, real-time methylation-specific PCR (MSP) assay was developed to determine methylation status of the MGMT gene promoter. Assay specificity was obtained by selective amplification of methylated DNA sequences of sodium bisulfite-modified DNA. The copy number of the methylated MGMT promoter, normalized to the β-actin gene, provides a quantitative test result. We analyzed 134 clinical glioma samples, comparing the new test with the previously validated nested gel-based MSP assay, which yields a binary readout. A cut-off value for the MGMT methylation status was suggested by fitting a bimodal normal mixture model to the real-time results, supporting the hypothesis that there are two distinct populations within the test samples. Comparison of the tests showed high concordance of the results (82/91 [90%]; Cohen's kappa = 0.80; 95% confidence interval, 0.82–0.95). The direct, real-time MSP assay was highly reproducible (Pearson correlation 0.996) and showed valid test results for 93% (125/134) of samples compared with 75% (94/125) for the nested, gel-based MSP assay. This high-throughput test provides an important pharmacogenomic tool for individualized management of alkylating agent chemotherapy."
Identified by Cancer Treatment Centers of America		
6	No	
7	Yes	I was able to identify a testing method that was reported by Switzeny OJ, et al (Switzeny OJ, Christmann M, Renovanz M, et al. MGMT promoter methylation determined by HRM in comparison to MSP and pyrosequencing for predicting high-grade glioma response. Clin Epigenetics. 2016 May 5; 8:49. PMID: 27158275).
Identified by Catholic Health Initiatives		
8	No	

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. Nov 2012;110(2):279-285. 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 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed April 20, 2018.
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, O6-methylguanine-DNA 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 randomised, 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-methylguanine-DNA 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 randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. May 2009;10(5):459-466. PMID 19269895
28. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.113 (May 2018).

Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Diagnosis and cancer stage
  - Previous treatment plan(s) and response(s)
  - Current treatment plan
  - Clinical justification for analysis testing

Post Service

- Analysis testing results

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	81287	MGMT (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme), methylation analysis
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
04/30/2015	BCBSA Medical Policy adoption	Medical Policy Committee
04/01/2016	Policy revision without position change	Medical Policy Committee
12/01/2017	Policy revision with position change	Medical Policy Committee
09/01/2018	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.