Analysis of MGMT Promoter Methylation in Malignant Gliomas

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. 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.

Background

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

The 2016 National Comprehensive Cancer Network (NCCN) guidelines and most published studies continue to report the older WHO grades.

Treatment of Gliomas

For high-grade malignant gliomas (anaplastic astrocytomas and GBM), standard treatment combines maximal possible surgical resection, postoperative radiation and chemotherapy. 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.
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TMZ is considered standard systemic chemotherapy for malignant gliomas in patients ages 70 or younger with good performance status and a methylated MGMT promoter. 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. Adjuvant options mainly depend on the performance status of the patient.

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. The 2016 NCCN guidelines for first-line adjuvant treatment of anaplastic gliomas and glioblastomas, depending on age, performance status, and promoter status.

**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 for by the gene. O\(^{6}\)-methylguanine-methyltransferase (MGMT) is a DNA repair protein that causes resistance to the effect of alkylating chemotherapy by removing the alklylation of the O\(^{6}\) position of guanine, the most cytotoxic lesion induced by an alkylating chemotherapy agent. 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 the tumor more susceptible 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.

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 (PCR) and protein levels in glioma tissue measured by immunohistochemistry. 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. 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. 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. 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.

**Regulatory Status**

No U.S. Food and Drug Administration–cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

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Policy
Analysis of MGMT Promoter Methylation in Malignant Gliomas

BCBSNC will provide coverage for methylation analysis of the O-6 methylguanine DNA methyltransferase (MGMT) gene promoter when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When Analysis of MGMT Promoter Methylation in Malignant Gliomas is covered**

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

- tumor type is consistent with high-grade malignant glioma (eg, glioblastoma multiforme, anaplastic astrocytoma); AND
- candidate for temozolomide therapy or radiation therapy; AND
- methylation results will be used to direct their therapy choices.

**When Analysis of MGMT Promoter Methylation in Malignant Gliomas is not covered**

Methylation analysis of the O-6-methylguanine DNA methyltransferase (MGMT) gene promoter is **considered investigational** when the above criteria are not met.

**Policy Guidelines**

For individuals who have high-grade gliomas who receive MGMT promoter methylation testing, the evidence includes studies of analytic validity, cohort studies of prognosis, studies nested within randomized trials, and treatment trials that selected subjects based on MGMT methylation status. Relevant outcomes are 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 (RCTs) show that MGMT promoter methylation is predictive for response to alkylating chemotherapeutic agents like 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 highgrade 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.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative
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Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81287

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Senior Medical Director – 2/2014


Specialty Matched Consultant Advisory Panel 4/2017


Senior Medical Director review 5/2017

Policy Implementation/Update Information


2/24/15 Reference added. (lpr)

5/26/15 Specialty Matched Consultant Advisory Panel review 4/29/2015. No change to policy. (lpr)

2/29/16 Updated Policy Guidelines section. Reference added. No change to policy intent. (lpr)

5/31/16 Specialty Matched Consultant Advisory Panel review 4/27/2016. No change to policy statement. (lpr)
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5/26/17 Updated Description and Policy Guidelines sections. Specialty Matched Consultant Advisory Panel review 4/26/2017. Reference added. No change to policy statement. (lpr)

6/30/17 Under “When Covered” section: added coverage criteria for analysis of MGMT methylation testing for patients with high-grade gliomas. Updated Description and Policy Guidelines sections. Reference added. Senior Medical Director review 5/2017. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.