Medical Policy

Analysis of MGMT Promoter Methylation in Malignant Gliomas

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Policy Number: 587
BCBSA Reference Number: 2.04.113
NCD/LCD: Local Coverage Determination (LCD): MolDX: MGMT Promoter Methylation Analysis (L35974)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

MGMT promoter methylation testing for prognostic value or as a predictive biomarker for response to treatment with alkylating agents is INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): MolDX: MGMT Promoter Methylation Analysis (L35974)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.
Outpatient

<table>
<thead>
<tr>
<th>Service Type</th>
<th>Coverage Status</th>
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<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
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<td>Medicare HMO Blue℠</td>
<td>No</td>
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<tr>
<td>Medicare PPO Blue℠</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO and Indemnity:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81287</td>
<td>MGMT (0-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis</td>
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**Description**

Testing for 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. 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.

**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.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 1 year and less than 5% surviving beyond 5 years.²

**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 that is considered standard systemic chemotherapy for malignant gliomas. This is based primarily on a large, randomized multicenter trial that compared radiation therapy (RT) with or without TMZ in patients with GBM, with statistically significant better overall survival in the combined therapy group.³ Adjuvant options mainly depend on the performance status (PS) of the patient, and patients with...
good PS are further stratified by age. Elderly and/or frail patients may not be candidates for combined therapy, nor may intensive therapy be seen as justifiable given the short survival associated with GBM.

For patients with good PS who are age 70 years or younger, RT plus concurrent and adjuvant TMZ is recommended. Options for patients with good PS and age older than 70 years are the same as for those younger than 70, alternatively treatment options for elderly patients may involve hypofractionated RT alone or TMZ alone. For patients with poor PS, options include RT alone, chemotherapy alone, or palliative/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 that are encoded for by the gene. O6-methylguanine-methyltransferase (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 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.

Commercially available testing for MGMT promoter methylation
MGMT promoter methylation testing is available from several commercial laboratories and academic centers, and typically involves methylation-specific polymerase chain reaction (PCR) technology. Laboratories that offer this test include Mayo Clinic, Cleveland Clinic, Henry Ford Health System, OHSU Knight Diagnostic Laboratories, University of Wisconsin, University of Pittsburgh, Stanford University, University of North Carolina, LabCorp and Caris Life Sciences.

Summary
The analytic validity of testing for MGMT promoter methylation status has not been established, nor is it clear which testing method is optimal in terms of reproducibility. There is some evidence of clinical validity for the test. Several studies have suggested that MGMT gene promoter methylation in glioblastoma multiforme (GBM) tumor cells is associated with an improved prognosis. However, the utility of the prognostic information from MGMT promoter methylation status in clinical decision-making is unclear.

Data from RCTs supports that MGMT promoter methylation also serves as a predictive marker for response to alkylating chemotherapeutic agents like temozolomide (TMZ). RCTs have shown a greater response rate to and overall survival with the use of TMZ in patients with GBMs that have MGMT promoter methylation. However, it has also been demonstrated that, in patients without MGMT promoter methylation, TMZ may offer some survival benefit. It has not been established that the determination of MGMT promoter methylation status will alter clinical decision-making, and as a result it is not possible to determine the impact of MGMT testing on health outcomes.

Therefore, MGMT promoter methylation testing for prognostic value or as a predictive biomarker for response to treatment with alkylating agents is considered investigational.

Policy History

<table>
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<tr>
<td>12/2015</td>
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<td>3/2015</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References


7. 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):12631273. PMID 24510240


