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**

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

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

**Medicare HMO Blue\(^{SM}\) and Medicare PPO Blue\(^{SM}\) 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](https://www.cms.gov).
Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

<table>
<thead>
<tr>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
</tr>
</tbody>
</table>

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 above **medical necessity criteria MUST be met** for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if **medical necessity criteria** are met:

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C71.0</td>
<td>Malignant neoplasm of cerebrum, except lobes and ventricles</td>
</tr>
<tr>
<td>C71.1</td>
<td>Malignant neoplasm of frontal lobe</td>
</tr>
<tr>
<td>C71.2</td>
<td>Malignant neoplasm of temporal lobe</td>
</tr>
<tr>
<td>C71.3</td>
<td>Malignant neoplasm of parietal lobe</td>
</tr>
<tr>
<td>C71.4</td>
<td>Malignant neoplasm of occipital lobe</td>
</tr>
<tr>
<td>C71.5</td>
<td>Malignant neoplasm of cerebral ventricle</td>
</tr>
<tr>
<td>C71.6</td>
<td>Malignant neoplasm of cerebellum</td>
</tr>
<tr>
<td>C71.7</td>
<td>Malignant neoplasm of brain stem</td>
</tr>
<tr>
<td>C71.8</td>
<td>Malignant neoplasm of overlapping sites of brain</td>
</tr>
<tr>
<td>C71.9</td>
<td>Malignant neoplasm of brain, unspecified</td>
</tr>
</tbody>
</table>
**Description**

**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 O6-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 O6 position of guanine, the most cytotoxic lesion induced by alkylating chemotherapy agents.⁵ Aberrant methylation of the MGMT gene promoter region leads to loss of MGMT protein expression and reduced proficiency to repair DNA damage induced by alkylating chemotherapeutic agents, potentially 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16,20}

**Summary**

Testing for O6-methylguanine-DNA methyltransferase (\textit{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.

For individuals who have high-grade glioma(s) who receive \textit{MGMT} promoter methylation testing, the evidence includes cohort studies of prognosis, studies nested within randomized trials, and treatment trials that selected subjects based on \textit{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 \textit{MGMT} methylation testing improves patient outcomes, \textit{MGMT} status is consistently associated with outcomes of glioma patients. Data from randomized controlled trials have shown that \textit{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 \textit{MGMT} promoter methylation. While TMZ offers some benefit regardless of \textit{MGMT} methylation status, studies have consistently suggested that \textit{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 obtained in 2017 supports that the following indication provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice.

- Use of methylation analysis of \textit{MGMT} gene promoter from glioma tumor tissue for individuals who meet the following criteria:
  - Have a tumor type consistent with high-grade malignant glioma (eg, glioblastoma multiforme, anaplastic astrocytoma); and
  - Candidate for TMZ therapy or radiotherapy; and
  - Methylation results will be used to direct therapy choices.

Thus, the above indication may be considered medically necessary considering the suggestive evidence and clinical input support.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>7/2018</td>
<td>BCBSA National medical policy review. Minor edit to the first policy statement; statements otherwise unchanged. 7/1/2018</td>
</tr>
<tr>
<td>2/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
</tbody>
</table>
**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


