Medical Policy

Analysis of *MGMT* Promoter Methylation in Malignant Gliomas

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- Policy: Medicare
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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 (e.g., glioblastoma multiforme, anaplastic astrocytoma); and
- Candidate for temozolomide therapy or radiation therapy; and
- Methylation results will be used to direct their therapy choices.

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

**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
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.

<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 BlueSM</td>
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<tr>
<td>Medicare PPO BlueSM</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:

CPT Codes

<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:

ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM 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>
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. Until 2016, brain tumors were graded using histologic criteria corresponding to the degree of malignancy, ranging from World Health Organization (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, 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 oligodendrogliomas, 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

For high-grade malignant gliomas (anaplastic astrocytomas and GBM), standard treatment combines maximal possible surgical resection, postoperative radiotherapy (RT), 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 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. 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, are summarized in Table 1.

Table 1. 2016 NCCN Guidelines for Adjuvant Treatment for Anaplastic Gliomas and Glioblastomas

<table>
<thead>
<tr>
<th>Age</th>
<th>Performance Status</th>
<th>MGMT Promoter Status</th>
<th>Adjuvant Treatment Options</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70 y</td>
<td>Good (KPS≥60)</td>
<td>Methylated</td>
<td>Standard brain RT + concurrent TMZ and adjuvant TMZ + alternating electric field therapy OR Standard brain RT + concurrent TMZ and adjuvant TMZ</td>
<td>2A</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unmethylated or indeterminate</td>
<td></td>
<td>Standard brain RT + concurrent TMZ and adjuvant TMZ + alternating electric field therapy OR Standard brain RT + concurrent TMZ and adjuvant TMZ</td>
<td>2A</td>
</tr>
<tr>
<td></td>
<td>Poor (KPS&lt;60)</td>
<td></td>
<td>Standard or hypofractionated brain RT OR TMZ (if tumor is MGMT promoter methylated)</td>
<td>2A</td>
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<tr>
<td></td>
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### 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, 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.\(^16,20\)

### Summary

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.

For individuals who have high-grade glioma(s) 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 include overall survival, disease-specific survival, test accuracy, and changes in disease status. There are no studies directly evaluating whether use of MGMT methylation testing improves patient outcomes. MGMT status is consistently associated with outcomes of glioma patients. Data from randomized controlled trials have shown that MGMT promoter methylation is predictive for response to alkylating chemotherapeutic agents such as temozolomide (TMZ). The response rate and overall survival with the use of TMZ are higher in patients who have MGMT promoter methylation. While TMZ offers some benefit regardless of MGMT methylation status, studies have consistently suggested that MGMT methylation identifies patients who are more likely to benefit from TMZ. TMZ is associated with morbidity, and, with counseling about risks and benefits, a patient who is less likely to benefit from the treatment might choose to avoid TMZ. Clinical input indicated that measuring MGMT promoter methylation improves health outcomes by predicting treatment response to TMZ in patients with 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.

Policy History

<table>
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<tr>
<td>12/2015</td>
<td>Added coding language.</td>
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<tr>
<td>3/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</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