MGMT Testing for Malignant Glioma
Alkylation Agent Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
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<td>MGMT Promoter Methylation Analysis</td>
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What is MGMT

Definition

MGMT is the O6-methylguanine- DNA methyltransferase gene, which encodes an essential DNA repair enzyme. MGMT expression in tumors causes resistance to DNA-alkylating drugs. MGMT repairs the damage produced by these DNA cross linking agents.¹

- Gene methylation is a control mechanism that regulates gene expression. If the MGMT gene is hypermethylated, its expression is absent (“turned off”) or reduced (“turned down”). With less MGMT DNA repair protein present, the tumor is typically more responsive to alkylating drugs.²
- Glioblastoma is a common and aggressive brain tumor that is often treated with alkylating drugs.² Temozolomide is a standard systemic chemotherapy shown to be effective for malignant gliomas.²
- About 40-50% of glioblastoma tumors exhibit MGMT hypermethylation, leading to increased chemosensitivity.³,⁴
- Treatment of gliomas often includes resection, radiation, and chemotherapy. For frail or elderly patients, combined treatment may not be tolerated; therefore, treatment with a single agent (radiation therapy or chemotherapy) or chemotherapy with deferred radiation therapy may be considered.¹

Test information

- MGMT promoter methylation testing is performed on paraffin embedded tumor tissue. Quantitative methylation-sensitive PCR or pyrosequencing is used to determine MGMT gene promoter methylation levels.
Guidelines and evidence

- The National Comprehensive Cancer Network (NCCN, 2018) states:
  - “MGMT promoter methylation is an essential part of molecular diagnostics for all high grade gliomas (grade III and IV).”
  - “MGMT promoter methylation is particularly useful in treatment decisions for elderly patients with high grade gliomas (grades III-IV).”
  - “Patients with glioblastoma that are not MGMT promoter methylated derive less benefit from treatment with temozolomide compared to those whose tumors are methylated.”

- In September 2012, Alberta Health Services published a Clinical Practice Guideline on Glioblastoma. It concluded:
  - “Determination of MGMT promoter methylation status may assist in determination of prognosis.”
  - “…whenever possible, determination of MGMT promoter methylation status should be conducted, as it may assist in determination of prognosis.”

- An analysis of epigenetic promoter methylation of the MGMT gene in 206 patients with glioblastoma demonstrated:
  - Significantly improved median survival for those with a methylated MGMT promoter—21.7 months for those treated with temozolomide compared to 15.3 months for those treated with radiotherapy alone (p=0.007).
  - Marginally improved median survival for those without a methylated MGMT promoter—12.7 months for those treated with temozolomide versus 11.8 months for those treated with radiotherapy alone (p=0.06).
  - MGMT promoter methylation was an independent prognostic factor for favorable response to any glioblastoma treatment (HR=0.45, 95% CI 0.32 – 0.61; p<0.001).

Criteria

- Testing criteria:
  - Diagnosis of glioblastoma (or gliosarcoma), and
  - Adjuvant temozolomide chemotherapy is being considered, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.
References


