FEP 2.04.113 Analysis of MGMT Promoter Methylation in Malignant Gliomas

Effective Date: July 15, 2017  Related Policies: None

Analysis of MGMT Promoter Methylation in Malignant Gliomas

Description
Testing for MGMT (O6-methylguanine-DNA methyltransferase) 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.

FDA REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). MGMT promoter methylation testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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

• Have a tumor type consistent with high-grade malignant glioma (e.g., glioblastoma multiforme [GBM], anaplastic astrocytoma); and

• Able to tolerate temozolomide therapy or radiation therapy; and

• Methylation results will be used to direct therapy choices.

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

BENEFIT APPLICATION
Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).
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RATIONALE

Summary of Evidence
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 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). 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 consistently suggest 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 temozolomide. Clinical input indicated that measuring MGMT promoter methylation is improves health outcomes for predicting treatment response to alkylating chemotherapy in patients with high grade gliomas. This input supports the development of indirect evidence for the use of MGMT methylation in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
Current National Comprehensive Cancer Network guidelines for central nervous system tumors (v.1.2016) show several treatment options based on presence of methylated MGMT promoter. In patients over age 70 with good performance status and methylated MGMT promoter, temozolomide (TMZ) alone is listed as an additional treatment option. However, the remaining combination treatment options including those with TMZ are identical to those with unmethylated MGMT promoter. In patients over age 70 with poor performance status, TMZ alone is an option if the MGMT promoter is methylated. In patients under age 70 with good performance status, if the MGMT promoter is unmethylated, brain radiotherapy alone is a treatment option. However, combination treatments that include TMZ are also options for these patients. In patients under age 70 with poor performance status, TMZ alone is an option if the MGMT promoter is methylated. It is noted that for treatment recommendations that include TMZ, clinical benefit is likely to be lower in patients whose tumors lack MGMT promoter methylation. All of these recommendations were category 2A recommendations.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

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9. 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):1263-1273. PMID 24512512


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POLICY HISTORY

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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>June 2017</td>
<td>Revise Policy</td>
<td>Policy updated with results of clinical input; literature review through December 10, 2016, and updated with studies based on clinical input; references 2, 3, and 27 added. Policy statement revised to include medically necessary statement for MGMT methylation testing for patients with high grade gliomas with criteria.</td>
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