Analysis of MGMT Promoter Methylation

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DESCRIPTION

Testing for O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation has been proposed as a method to predict which individuals with a high-grade (grades III and IV) glioblastoma (gliomas) may benefit from the use of an alkylating chemotherapy agent, such as temozolomide (TMZ). Tumors which emerge from glial cells are called gliomas/glioblastomas and are classified into four main grades based on laboratory characteristics of the tumor. Both grade III and IV are known as high-grade and typically have a worse prognosis when compared to low-grade gliomas/ glioblastomas. Despite advancements in treatment the survival rate of individuals with high-grade gliomas/glioblastomas remains poor.

Glioblastomas (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 commonly seen.

Individuals with high-grade glioma typically present with subacute neurological signs and symptoms that progress over days to weeks and vary according to the location of the

tumor within the brain. Magnetic resonance imaging (MRI) of the brain provides confirmatory evidence of a mass lesion, but a tissue diagnosis is ultimately required to distinguish high-grade gliomas from other primary and metastatic brain tumors.

The presenting signs and symptoms of high-grade gliomas are dependent upon the location and size of the lesion and are similar to those produced by other primary and metastatic brain tumors. Individuals typically present with progressive neurological symptoms that evolve over the course of days to week. Among individuals with high-grade gliomas, the most common presenting symptoms include the following:

- Headache (50 to 60 percent)
- Focal neurologic symptoms such as memory loss, motor weakness, visual symptoms, language deficit, and cognitive and personality changes (10 to 40 percent)
- Seizures (20 to 50 percent)

Gliomas are diagnosed based on results of neurological examination, brain imaging (e.g., MRI, CT), and tissue (histological) diagnosis (biopsy). Although, imaging is useful in distinguishing high-grade from low-grade glioma, grading is established based on both histology and molecular characteristics. Histological diagnosis can be accomplished either at the time of surgical resection or by a more limited biopsy. A biopsy alone is used in situations where the lesion is not amendable to resection, a meaningful amount of tumor tissue cannot be removed, or the individual's overall clinical condition will not permit surgery.

High-grade gliomas (defined by WHO grade III and IV gliomas) are the most common type of brain cancer, accounting for more than half of all malignant primary tumors of the CNS. Whereas the prognosis for glioblastoma (grade IV glioma) is grim (5-year survival rates between 1% to 19%, depending on age), outcomes for anaplastic gliomas (grade III gliomas) are typically better, depending on the molecular features of the tumor. Challenges regarding treatment of glioblastoma include the inability of most systemic therapy agents to penetrate the blood-brain barrier (BBB) and heterogeneity among genetic drivers. The NCCN recommendations (CNS Cancers Version 2.2021) for high-grade glioma is neurosurgical input regarding the feasibility of maximal safe resection. For first-line treatment of high-grade glioma, the NCCN guidelines recommend maximal safe resection whenever possible. Adjuvant therapy includes radiation therapy (RT) which is generally recommended after maximal safe resection of the high-grade glioma to improve local control and survival with or without chemotherapy including PCV or TMZ (the use of TMZ is considered based on the tumors MGMT methylation status).

Based on current NCCN guideline CNS Cancers Version 2.2021 grade III-IV gliomas should undergo testing for MGMT promoter methylation status, since MGMT promoter methylated tumors typically respond better to alkylating chemotherapy, compared to unmethylated tumors. According to the current NCCN guideline MGMT promoter methylation testing has the following prognostic value:

- MGMT promoter methylation is strongly associated with IDH mutations and genome-wide epigenetic changes (G-CIMP phenotype).
- MGMT promoter methylation confers a survival advantage in glioblastoma and is used for risk stratification in clinical trials.
- MGMT promoter methylation is particularly useful in treatment decisions for elderly individuals with high-grade gliomas (grades 3 and 4).
- Patients with glioblastoma that are not MGMT promoter methylated derive less benefit from treatment with TMZ compared those whose tumors are methylated.

For individuals who have high-grade glioma/glioblastoma who receive MGMT promoter methylation testing, the evidence includes cohort studies of prognosis, studies nested within randomized trials, and treatment trials that selected subjects based on MGMT methylation status. Data from randomized controlled trials have shown that the presence of MGMT promoter methylation in high-grade gliomas/glioblastomas (grade III and IV) is predictive for response to alkylating chemotherapeutic agents such as TMZ. The presence of MGMT promoter methylation in high-grade glioma/glioblastoma is both a prognostic marker and a predictive one of response to treatment with alkylating agents.

Summary of Evidence
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. An analysis of epigenetic promoter methylation of the MGMT gene in 206 individuals 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; $p<0.001$).

The evidence is sufficient to determine that the technology results in meaningful improvement in net health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)
- **Central Nervous System (CNS) Cancers (Version 2.2021)**
  - **Principles of Brain Tumor Pathology Molecular Markers:** The following molecular markers are often used by neuropathologists to facilitate characterization of gliomas and/or by neuro-oncologists to guide treatment decisions:
    - **Prognostic value**:

- MGMT promoter methylation is strongly associated with IDH mutations and genome-wide epigenetic changes (G-CMIP phenotype).
- MGMT promoter methylation congers a survival advantage in glioblastoma and is used for risk stratification in clinical trials.
- MGMT prompter methylation is particularly useful in treatment decision for elderly patients with high-grade gliomas (grades 3-4).
- Patients with glioblastoma that are not MGMT promoter methylated derive less benefit from treatment with TMZ compared to those whose tumors are methylated. (*Accessed May 2022*)

- **MGMT Promoter Methylation**
  - Recommendation: MGMT promoter methylation is an essential part of molecular diagnostics for all high-grade gliomas (grade 3 and 4).
  - Description: MGMT is a DNA repair enzyme that reverse the DNA damage caused by alkylating agents, resulting in tumor resistance to TMZ and nitrosourea-based chemotherapy. Methylation of the MGMT promoter silences MGMT, making the tumor more sensitive to treatment with alkylating agents.
  - Detection: There are multiple ways to test for MGMT promoter methylation, including methylation-specific PCR, methylation-specific high-resolution melting, pyrosequencing, and droplet-digital PCR. One study suggested that pyrosequencing is the best prognostic stratifier among GMBs treated with TMZ. However, qMS-PCR remains the assay that has had the most validation in clinical trials. (Accessed May 2022)

- **Gliomas**
  The NCCN Guidelines for CNS Cancers include recommendations for management of the following gliomas:
  - Grade I: Pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, and subependymal giant cell astrocytoma
  - Grade II: Diffuse astrocytomas and oligodendrogliomas
  - Grade III: Anaplastic astrocytomas and oligodendroglioma
  - Grade IV: Glioblastoma (*Accessed May 2022*)

- **Molecular Profiling for Gliomas**
  - Integrated histopathologic and molecular characterization of gliomas should be standard practice. Molecular/genetic characterization complements standard histologic analysis providing additional diagnostic and prognostic information that improves diagnostic accuracy and aids in treatment selection. (*Accessed May 2022*)

- **Updated Classification of Gliomas Based on Histology and Molecular Features**
  - The WHO classification for grade II-III gliomas was revised as follows:

1) oligodendrogliomas are now defined as tumors that have 1p19q codeletion and IDH mutation (unless molecular data are not available and cannot be obtained, in which case designation can be based on histology with appropriate caveats);
2) anaplastic gliomas were further subdivided according to IDH mutation status;
3) oligoastrocytoma is no longer a valid designation unless molecular data (1p19q codeletion and IDH mutation status) are not available and cannot be obtained. Such tumors should be described as oligoastrosytoma, not otherwise specified (NOS) to indicated that the characterization of the tumor is incomplete. Very rare cases of concurrent, spatially distinct oligodendroglioma (1p19q codeleted) and astrocytoma (1p19q intact) components in the same tumor may also be labeled oligoastrocytoma.

It is important to note that correlations between the molecularly defined 2016 WHO categories the histology- based 2007 WHO categories are limited and vary across studies. Thus, the change from 2007 WHO to 2016 WHO reclassified a significant proportion of gliomas.

Multiple independent studies on gliomas have conducted genome-wide analyses evaluating an array of molecular features (e.g., DNA copy number, DNA methylation, protein expression) in large populations of patients with grade II-IV tumors. Unsupervised clustering analyses, an unbiased method for identifying molecularly similar tumors, have been used to identify subgroups of gliomas with distinct molecular profiles. Remarkable, further analysis has shown that these molecular subgroups could be distinguished based on only a handful of molecular features, including mutation of IDH1/2 and 1p or 19q; and 3) no mutation of IDH1 or IDH2 (IDH wild type; IDH-wt). Multiple studies have shown that the 1p19q codeletion is strongly associated with IDH mutations, such that true whole-arm 1p19q codeletion in IDH-wt tumors is extremely rare. In a tumor that is equivocal, the presence of an IDH mutation indicates at least a grade II diffusely infiltrative glioma. Grade I non-infiltrative gliomas do not have IDH mutations.

Other mutations commonly detected in gliomas can have diagnostic and prognostic value, such as those involving the histone chaperone protein, ATRX, which is most often found in grade II-III gliomas and secondary glioblastomas. ATRX mutation is robustly associated with IDH mutations, and this combination strongly suggestive of astrocytoma. In contrast, ATRX mutation is nearly always mutually exclusive with 1p19q codeletion. Therefore, a glioma that has loss of normal ATRX immunostaining is unlikely to be an oligodendroglioma. Mutations in the promoter region of the telomerase reverse transcriptase (TERT) gene

occur frequenting in glioblastomas and oligodendrogliomas. TERT promoter mutations in gliomas are associated with 1p19q codeletion and IDH mutations in oligodendrogliomas. Interestingly, they are also highly characteristic of IDH-wt and ATRX wild-type glioblastomas, especially those that contain amplification of epidermal growth factor receptor (EGFR). H3K27M mutations in the histone encoding H3F3A gene are mostly found in diffuse midline gliomas in both children and adults. Patients with these H3K27M mutated gliomas tend to have a very poor prognosis regardless of histologic appearance, so they are classified as WHO grade IV.

Analyses of large database have also suggested a number of other molecular markers as being potential characteristic/prognostic features of specific subgroups. Molecular features suggested as markers for subtyping grade II-III gliomas include mutations NOTCH1, CIC, and FUBP1; mutation in TP53 and/or over expression of aberrant TP53; PTEN loss or promotor methylation; amplification of EGFR; and chromosome 7 gain, chromosome 10 loss. Due to variability in results across studies, many of these molecular markers are not widely used to subclassify gliomas, although the 2020 version of the WHO classification of CNS tumors will include CDKN2A/B homozygous deletion as evidence of grade 4 status in IDH mutant astrocytomas, as indicated by a recent consensus statement. (*Accessed May 2022*)

- **Prognostic Relevance of Molecular Subgroups in Glioma**
  - Numerous large studies of patents with brain tumors have determined that, among grade II-III gliomas, 1p19q codeletion correlates with greatly improved progression-free survival (PFS) and overall survival (OS). Likewise, the presence of an IDH mutation is a strong -favorable prognostic markers for OS in grade II-III gliomas. Analysis within single treatment arms shows that the IDH status is prognostic for outcome across a variety of postoperative adjuvant options. For example, in the NOA-04 phase III randomized trial in newly diagnosed anaplastic gliomas, IDH mutation is associated with improved PFS, longer time to treatment failure (TTF), and extended OS in each of the three treatment arms: standard RT (n=160); combination therapy with procarbazine lomustine, and vincristine (PCV; RT upon progression; n=78); and temozolomide (TMZ, RT upon progression; n=80).

    Multiple independent studies have shown that subdividing gliomas by molecular subtype, especially IDH1/2 and 1p19q status, yields greater prognostic separation than subdivision based on histology (as defined by WHO 2007). These include very large studies covering multiple grades and histology-based subtypes of gliomas, as well as smaller studies limited to 1 to 2 grades or histologic subtypes. Multiple studies have also shown that, among patients with grade II – III gliomas, the IDH-mut plus 1pq19 codeletion; the

IDH-wt group has the worst prognosis. Analyses within single treatment arms have confirmed this trend in prognosis across a variety of postoperative adjuvant treatment options. TERT mutations in patients with high-grade IDH-wt tumors are associated with shorter OS, compared to IDH-wt tumors without TERT Mutation. However, a multivariate analysis of data from 291 patients with IDH-mut+1p19q-codelted oligodendrogliomas showed that absence of TERT mutation was associated with worse OS, compared to patients with TERT-mut oligodendrogliomas (HR, 2.72;95% CI, 1.05-7.04; P=.04).

MGMT (O-6 methylguanine -DNA methyltransferase is a DNA repair enzyme that can cause resistance to DNA-alkylating drugs. MGMT promoter methylation is associated with better survival outcomes in patients with high-grade glioma and is predictive factor for response to treatment with alkylating chemotherapy such as TMZ or lomustine, even in older adult patients. Tumors with H3K27M mutations are far less likely to be MGMT promoter methylated and are associated with worse prognosis. Patients whose glioblastomas contain H3F3A G34 mutations, however, may have relatively higher rates of MGMT promoter methylation, and do not have a worse prognosis than other IDH-wt glioblastomas.

Most pilocytic astrocytomas in pediatric patients contain BRAF fusions or, less commonly, BRAF V600E mutations, especially those arising in the posterior fossa; such tumors are rarely high grade. BRAF fusion is associated with better prognosis in pediatric low-grade astrocytoma. The likelihood of a BRAF fusion in a pilocytic astrocytoma decreases with age. The BRAF V600E mutation is present in most pleomorphic xanthoastrocytomas, though it has been also found in some other pediatric low-grade gliomas, such as gangliogliomas and dysembryoplastic neuroepithelial tumors as well as a small proportion of glioblastomas (especially epitheloid glioblastoma). (*Accessed May 2022*)

- **NCCN Molecular Testing Recommendations for Glioma**
  - Recommendations for molecular testing of glioma tumors are provided in the Principles of Brain Tumor Pathology section in the algorithm. Based on studies showing that IDH status is associated with better prognosis in patients with grade II-III glioma, the panel recommends IDH mutation testing in patients with glioma. Immunohistochemistry can detect the most common IDH mutation, which is IDH1 R132H. However, sequencing must be done to detect the less common IDH1 mutations (e.g., IDH1 r132C) and IDH2. This sequencing should be done in the proper clinical context (e.g., younger patients with non-enhancing gliomas). Patients with oligodendroglioma should also undergo 1p19q testing. However, since 1p19q codeletion is strongly associated with IDH mutation, 1p19q testing is not necessary in tumors that are definitely IDH-wt, and tumors without an IDH mutation

should not be regarded as 1p19q codeleted, even when results suggest otherwise. Mutation testing for ATRX and TERT are also recommended, given the diagnostic value in these mutations. Screening for H3K27M mutations (H3F3A and HIST1H3B) sequencing preferred) and BRAF fusion and/or mutation testing may be carried out as clinically indicated.

Grade III-IV gliomas should undergo testing for MGMT promoter methylation status, since MGMT promoter methylated tumors typically respond better to alkylating chemotherapy, compared to unmethylated tumors. To date, there are no targeted agents that have shown improvement in OS in the treatment of blastoma. Nevertheless, molecular testing of glioblastomas is still encouraged by the panel, as patients with a detected driver mutation may be treated with targeted therapy on a compassionate basis, and these tests improve diagnostic accuracy and prognostic stratification. Detection of genetic or epigenetic alterations could also expand clinical trial options for a brain tumor patient.
(*Accessed May 2022*)

- **MGMT Promoter Methylated Glioblastoma**
  - The presence of MGMT promoter methylation in glioblastoma is both a prognostic marker and a predictive one of response to treatment with alkylating agents. In the small (N=31), single-arm phase II UKT-03 trial, postoperative RT and TMZ combined with lomustine in patients with newly diagnosed glioblastoma resulted in a median OS of 34.3 months, which compared favorably to the historical control data of 23.4 months in patients with MGMT promoter methylated tumors who were treated with RT and TMZ in the EORTC-NIC trial. Based on this improvement in survival with combination alkylating agents in patients with MGMT promoter methylated glioblastoma, the phase III CeTeG/NOA-09 trial randomized patients with newly diagnosed MGMT promoter methylated glioblastoma (aged 18-70 and KPS $\geq$ 70) to treatment with RT and lomustine + TMZ or RT and TMZ alone. Analysis of the modified intent-to-treat population (N=129) showed that OS was significantly improved in the TMZ= lomsutine arm (59% vs 51%, respectively), but the study was too small to adequately define the toxicity profile of the RT with TMZ + lomustine. Analysis of health-related quality of life showed no significant difference between the study arms. (*Accessed May 2022*)

National Institute for Health and Clinical Excellence (NICE)
(Updated 2021) NICE published guidance in 2018 for *Brain Tumors (Primary) and Brain Metastases in over 16s* which noted the following information:

- Test all high-grade glioma specimens for MGMT promoter methylation.
- Offer radiotherapy using 40 Gy in 15 fractions with concomitant and up to 12 cycles of adjuvant temozolomide for people aged around 70 or over who have:
  - a Karnofsky performance status of 70 or more and

    - a newly diagnosed grade IV glioma (glioblastoma) with MGMT methylation
- Consider radiotherapy using 40 Gy in 15 fractions with concomitant and up to 12 cycles of adjuvant temozolomide for people aged around 70 or over who have:
    - a Karnofsky performance status of 70 or more and
    - a newly diagnosed grade IV glioma (glioblastoma) without MGMT methylation or for which methylation status is unavailable.
- For people with an initial diagnosis of grade IV glioma (glioblastoma) not covered in previous recommendations, consider the treatment options of:
    - radiotherapy using 60 Gy in 30 fractions with concurrent and up to 6 cycles of adjuvant temozolomide
    - radiotherapy alone using 60 Gy in 30 fractions
    - hypofractionated radiotherapy
    - up to 6 cycles of temozolomide alone if the tumor has MGMT methylation and the
    - person is aged around 70 or over
    - best supportive care alone
- The individual with the anaplastic oligodendroglioma should agree to the treatment plan of PCV chemotherapy and radiotherapy as discussed by the provider to include the potential advantages and disadvantages of each option with them.

How the recommendations might affect practice
For younger individuals with a grade IV glioma and a good performance status, a course of radiotherapy with concurrent and adjuvant temozolomide is standard care However, for people aged around 70 and over, particularly those with a glioma with methylated MGMT, the use of concurrent and adjuvant temozolomide with 15 fractions of radiotherapy is a change of practice that will probably result in more people being treated. This is a relatively small group of people, and so the recommendation is unlikely to have a significant resource impact.
(*Accessed May 2022*)

Regulatory Status
No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

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.

PRIOR APPROVAL

Not applicable

POLICY

Medically Necessary
MGMT (O-6-methylguanine DNA methyltransferase) promoter methylation testing may be considered **medically necessary** for individuals meeting **all of the following** criteria:

- Diagnosed with high-grade (grade III or IV) * glioma/glioblastoma; **and**
- Adjuvant temozolomide (temodar) chemotherapy, is being considered **and**
- Testing is being performed prior to initiation of the temozolimide (temodar) therapy to assess tumor sensitivity to this alkylating agent.

Investigational
MGMT (O-6- methylguanine DNA methyltransferase) promoter methylation testing is considered **investigational** when the criteria above are not met and for all other indications, because the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Policy Guidelines

NCCN Guidelines for CNS Cancers (Version 2.2021):

- Grade I: Pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, and subependymal giant cell astrocytoma
- Grade II: Diffuse astrocytomas and oligodendrogliomas
- Grade III: Anaplastic astrocytomas and oligodendroglioma
- Grade IV: Glioblastoma

(2016) World Health Organization (WHO) Classification of Diffuse Gliomas
In this new classification, the diffuse gliomas include the WHO grade II and grade III astrocytic tumors, the grade II and III oligodendrogliomas, the grade IV glioblastomas.

Astrocytic Tumors: Diffuse Gliomas	
Tumor Classification	**Tumor Grade**
Diffuse astrocytoma, IDH-mutant	II
Diffuse astrocytoma, IDH-wildtype	II
Anaplastic astrocytoma, IDH-mutant	III
Anaplastic astrocytoma, IDH-wildtype	III
Glioblastoma, IDH-mutant	IV
Glioblastoma, IDH-wildtype	IV
Glioblastoma, NOS	IV

Midline diffuse glioma, H3 K27M-mutant	IV
Oligodendroglial Tumors	
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Oligodendroglioma, NOS	II
Oligoastrocytoma, NOS	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Anaplastic oligodendroglioma, NOS	III
Anaplastic oligoastrocytoma, NOS	III

World Health Organization (WHO) Classification of Other Astrocytic Tumors

Other Astrocytic Tumors	
Tumor Classification	**Tumor Grade**
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81287 MGMT (O-6-methylguanine-DNA methyltranferase) (eg, glioblastoma multiforme), promoter methylation analysis

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POLICY HISTORY		
Date	**Reason**	**Action**
June 2022	Annual Review	Policy Revised
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Revised
June 2019	Annual Review	Policy Renewed
June 2018		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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