Molecular Analysis for Gliomas AHS - M2139

Description of Procedure or Service

Glioma refers to tumors resulting from metaplastic transformation of glial tissue of the nervous system. Tumors have historically been classified by the retained histologic features of the three types of glial cells; astrocytes, oligodendrocytes, and ependymal cells. Tumors of each type can vary widely in aggressiveness, response to treatment and prognosis (Louis, Schiff, & Batchelor, 2018).

Molecular genetic features were added to histopathologic appearance in the current WHO classification to yield more biologically homogeneous and narrowly defined diagnostic entities for greater diagnostic accuracy, improved patient management, more accurate determinations of prognosis, and better treatment response (Louis et al., 2016).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for molecular analysis for gliomas when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Molecular Analysis for Gliomas is covered

The use of the following tests for the prognosis of malignant gliomas is considered medically necessary:

a. MGMT promoter methylation testing;
b. IDH1 and IDH2 testing for prognosis of malignant gliomas;
c. ATRX mutation testing via EITHER immunohistochemistry OR gene sequencing;
d. Genetic sequencing of TERT;
e. H3F3A gene sequencing for suspected midline gliomas;
f. BRAF fusion and mutation testing, including BRAF V600E common variant;

Reimbursement is allowed for RELA fusion testing using either RNA sequencing analysis (RNA-Seq) or fluorescent in situ hybridization (FISH)
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Reimbursement is allowed for testing for the co-deletion of 1p and 19q by either fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) for the characterization of gliomas and/or to guide treatment decisions;

Reimbursement is allowed for ATRX mutation testing via immunohistochemistry

**When Molecular Analysis for Gliomas is not covered**

Reimbursement is not allowed for ATRX mutation co-testing using BOTH immunohistochemistry and gene sequencing

H3F3A testing using a K27M histone antibody for the prognosis of malignant gliomas is considered investigational.

**Policy Guidelines**

An estimated 78,980 new cases (23,830 malignant and 55,150 non-malignant) of brain and other CNS tumors are expected to be diagnosed in the United States in 2018. 3,560 of these cases are expected to be in children (Ostrom et al., 2017). The five year survival rate is only 34.9% (SEER, 2016).

Studies over the past two decades have clarified the genetic basis of tumorigenesis in the common and some rarer brain tumor entities (Louis et al., 2016), and identified clinically relevant molecular genetic characterizations which complement standard histologic analysis providing additional diagnostic and prognostic information that can improve diagnostic accuracy, influence treatment selection and survival (NCCN, 2018). Molecular /genetic characterization does not replace standard histologic assessment, but rather serves as a complimentary approach (NCCN, 2018).

**Isocitrate dehydrogenase (IDH1/2) mutations**

IDH 1 and 2 are metabolic enzymes which oxidize isocitrate to alpha-keoglutarate and are important in the mitigation of cellular oxidative damage (Horbinski, 2013b). Mutations in genes encoding these enzymes leads to the aberrant production of D-2 hydroxyglutarate (Dang et al., 2009), an oncometabolite that causes epigenetic modifications in affected cells (Horbinski, 2013b).

IDH mutations are a defining feature of WHO grade II and III astrocytomas and oligodendrogliomas (Louis et al., 2016). Their presence distinguishes lower grade gliomas from primary glioblastomas, which are IDH wild type. IDH mutations are commonly associated with MGMT promoter methylation and associated with a relatively favorable prognosis (Brat et al., 2015; Eckel-Passow et al., 2015).

**O-6-methylguanine-DNA methyltransferase (MGMT) methylation**

MGMT is a DNA repair enzyme that reverses the DNA damage caused by alkylating agents, resulting in tumor resistance to temozolomide and nitrosourea-based chemotherapy. Methylation of the MGMT promoter silences MGMT making the tumor more sensitive to treatment with alkylating agents (Esteller et al., 2000; Gusyatiner & Hegi, 2018).

MGMT promoter methylation is strongly associated with IDH mutation and genome wide epigenetic change (Eckel-Passow et al., 2015), and with longer survival in patients with glioblastoma who receive alkylating agents (Hegi et al., 2005; Zhao, Wang, Song, Zha, & Li, 2016). MGMT promoter methylation is particularly useful in treatment decisions for elderly patients with high grade gliomas (Malmstrom et al., 2012; Wick et al., 2012; Wick et al., 2014).

**Codeletion of 1p and 19q**

This codeletion represents an unbalanced translocation (1;19)(q10;p10) leading to whole arm deletion of 1p and 19q (Jenkins et al., 2006).

Codeletion of 1p and 19q a defining feature of oligodendrogial tumors, strongly associated with oligodendrogial histology, and helps confirm the oligodendrogial character of tumors with equivocal or
mixed histologic features (Brat et al., 2015; Burger et al., 2001; Eckel-Passow et al., 2015). Combined loss involving chromosomes 1p and 19q is significantly associated with both favorable therapeutic response and longer recurrence-free survival after chemotherapy (Cairncross et al., 1998).

**Alpha-thalassemia/mental retardation syndrome X-linked (ATRX) mutations**

Mutations in the chromatin regulator gene, ATRX, enable alternative lengthening of telomeres (Abedalthagafi et al., 2013).

ATRX mutations in glioma are strongly associated with IDH and TP53 mutations and are nearly always mutually exclusive with 1p19q codeletion (Reuss et al., 2015). ATRX deficiency, coupled with IDH mutation, is typical of astrocytoma (Brat et al., 2015).

**Tumor protein 53 (TP53) mutation**

TP53 is essential for regulating cell division and preventing tumor formation (Parikh et al., 2014). Missense mutations in the TP53 gene are present in the clear majority of IDH-mutant astrocytomas (Brat et al., 2015). Immunopositivity for mutant p53 is not entirely sensitive or specific for TP 53 mutation, however, and loss of ATRX expression may be a more reliable marker of astrocytic differentiation (Louis et al., 2018).

**Telomerase reverse transcriptase (TERT) mutations**

TERT encodes the catalytic active site of telomerase, the enzyme responsible for maintaining telomere length in dividing cells. TERT mutations in its noncoding promoter region cause increased expression of the TERT protein and are one of the major mechanisms of telomerase activation in gliomas (Arita et al., 2013). TERT mutations are strongly associated with 1p19q codeletion and are found in most glioblastomas. TERT mutation in combination with IDH mutation and 1p19q codeletion is characteristic of oligodendroglioma. Absence of TERT mutation, coupled with IDH mutation, designates astrocytoma (Eckel-Passow et al., 2015). In terms of survival, mutation in the TERT promoter is generally unfavorable in the absence of IDH mutation and favorable in the presence of IDH mutation and 1p19q codeletion. TERT promoter mutation is associated with an older age of the patient at presentation, regardless of whether IDH mutation is present (Eckel-Passow et al., 2015).

**Histone (H3FA) mutations**

A lysine to methionine substitution in the H3F3A gene (H3K27M) is the most common histone mutation in brain tumors and inhibits the trimethylation of H3.3 histone (Sturm et al., 2012) arresting cells in a primitive state refractory to differentiation induction (Weinberg, Allis, & Lu, 2017). G34R/G34V mutations are more common in cortical gliomas in children (Schwartzentruber et al., 2012). H3FA mutations can be useful in the diagnosis of infiltrative glioma (Sturm et al., 2012). The K27M mutation is an adverse prognostic marker in children and adults (Meyronet et al., 2017). The G34 mutation does not appear to have any prognostic significance once the diagnosis of a glioblastoma has been established (Sturm et al., 2012).

**B-Raf proto-oncogene (BRAF) mutations**

BRAF is a serine-threonine protein kinase involved in cell survival, proliferation, and differentiation (Davies et al., 2002). Activating mutations in BRAF, most often V600E have been discovered in most pediatric and some adult gliomas (Chappe et al., 2013; Horbinski, 2013a) including approximately 80% of pleomorphic xanthoastrocytomas, 20% of gangliogiomas, 10% of pilocytic astrocytomas and occasionally diffuse gliomas (Chi et al., 2013). Tandem duplication of chromosome 7q34 resulting in an activating fusion of the BRAF and KIAA1549 genes occur in 60-80% of pilocytic astrocytoma (Jones et al., 2008).

The presence of a BRAF fusion is reliable evidence that the tumor is a pilocytic astrocytoma, and predicts better clinical outcome (Hawkins et al., 2011). BRAF mutation is more complicated, as it can occur in a variety of tumors and requires integration with histology. Tumors with BRAF mutations may respond to BRAF inhibitors, however in pediatric gliomas, BRAFV600E indicates poor prognosis when treated with current adjuvant therapy, especially in combination with CDKN2A mutation (Lasaletta et al., 2017).
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**v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA, p65, NFκB3) fusion**

Fusion between the C11orf95 and RELA genes defines approximately 70 percent of all childhood supratentorial ependymomas (Louis et al., 2018). These fusions are associated with increased NFκB signaling and poor outcome (Malgulwar et al., 2018).

**Next generation sequencing (NGS) panels**

Nikiforova et al (2016) validated GlioSeq, a commercial NGS panel, GlioSeq with a panel of 30 genes in 54 patients with CNS tumors against fluorescence in-situ hybridization, Sanger sequencing, and reverse transcription PCR. GlioSeq correctly identified 71/71 (100%) genetic alterations known to be present by conventional techniques. The assay sensitivity was 3%-5% of mutant alleles for SNVs and 1%-5% for gene fusions.

Zacher et al (2017) developed a panel of 20 genes that allowed for molecular classification of 121 gliomas. They conclude that gene panel NGS as a promising diagnostic technique that may facilitate integrated histological and molecular glioma classification.

Rmikissoon et al (2017) used OncoPanel and OncoCopy to identify targetable alterations in tumors towards establishing best practices in routine clinical pediatric oncology. They analyzed 117 samples analyzed by OncoPanel, 146 by OncoCopy, and 60 tumors subjected to both methodologies. OncoPanel revealed clinically relevant alterations in 56% of patients (44 cancer mutations and 20 rearrangements), including BRAF alterations that directed the use of targeted inhibitors. Rearrangements in MYB-QKI, MYBL1, BRAF, and FGFR1 were also detected. Furthermore, while copy number profiles differed across histologies, the combined use of OncoPanel and OncoCopy identified subgroup-specific alterations in 89% (17/19) of medulloblastomas.

**State and Federal Regulations, as applicable**

No diagnostic tests have been specifically approved for use in detecting mutations in gliomas.

Other tests are laboratory developed tests (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes:  81120, 81121, 81210, 81287, 81345, 81479, 88341, 88342, 88374, 88377*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**

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Horbinski, C. (2013a). To BRAF or not to BRAF: is that even a question anymore? J Neuropathol Exp Neurol, 72(1), 2-7. doi:10.1097/NEN.0b013e318279f3db
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https://www.nccn.org/professionals/physician_gls/default.aspx


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Medical Director review 4/2020

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for molecular analysis for gliomas when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
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12/31/19 Reviewed by Avalon 3rd Quarter 2019 CAB. Under Billing/Coding section: CPT codes 88364, 88365 removed and 88374, 88377 added. Medical Director review 11/2019. (lpr)

5/12/20 Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.