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, 2020).

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).

Related Policies:
Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy AHS-M2109

***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 and HIST1H3B gene sequencing for suspected midline gliomas;
f. BRAF fusion and mutation testing, including BRAF V600E common variant;
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Reimbursement is allowed for RELA fusion testing using either RNA sequencing analysis (RNA-Seq) or fluorescent in situ hybridization (FISH)
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 86,970 new cases (26,170 malignant and 60,800 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., 2018. 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, 2020).

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 alkylation 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 alkylation 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 alkylation 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 oligodendroglial tumors, strongly associated with oligodendroglial histology, and helps confirm the oligodendroglial 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 is a switch/sucrose helicase that assists with H3.3 chromatin deposition in telomeric regions. Disruption of this gene leads to the alternative lengthening of telomeres stated above and is thought to represent an early event in gliomagenesis (Batchelor, 2020).

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., 2019).

**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 1p/19q 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). A similar mutation to H3K27M may also occur in the HIST1H3B/C gene, which encodes the histone H3.1 variant. However, the mutation at HIST1H3B/C is about one third as common as H3F3A and often confers a better prognosis than its H3F3A counterpart (Louis et al., 2019).

**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 gangliogliomas, 10% of pilocytic astrocytomas and occasionally diffuse
gliomas (Chi et al., 2013). Tandem duplication of chromosome 7q34 resulting in an activating fusion of the \textit{BRAF} and \textit{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 (Lassaletta et al., 2017).

\textbf{v-rel avian reticuloendotheliosis viral oncogene homolog A (\textit{RELA}, p65, \textit{NFKB3}) fusion}

Fusion between the \textit{C11orf95} and \textit{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). Normally, NfkB is an inactive transcription factor in the cytoplasm. When its inhibitor degrades, it activates transcription of certain genes, \textit{RELA} among them (NCBI, 2011).

New research supports the hypothesis that the status of \textit{RELA} fusion and p53 overexpression are significantly associated with the prognosis of supratentorial extraventricular ependymomas (Wang et al., 2019).

\textbf{New Tests}

Assessment of gliomas is incredibly difficult, and new methods of molecular analyses for gliomas are consistently being developed. For example, Miller et al. (2019) devised a liquid-biopsy based method to evaluate cerebrospinal fluid from 42 (of 85) patients. The genomic profile developed from the cerebrospinal fluid (CSF) samples closely matched established profiles, such as the characteristic 1p/19q codeletion and \textit{IDH1/2} mutations. The authors stated that the ability to monitor the glioma genome in real time could be useful in management of this condition (Miller et al., 2019). Other researchers report that “A cerebrospinal fluid ct-DNA liquid biopsy approach may virtually support all the stages of glioma management, from facilitating molecular diagnosis when surgery is not feasible, to monitoring tumor response, identifying early recurrence, tracking longitudinal genomic evolution, providing a new molecular characterization at recurrence and allowing patient selection for targeted therapies” (Simonelli et al., 2020).

\textbf{Clinical Validity and Utility}

Nikiforova et al. (2016) validated GlioSeq, a commercial next generation sequencing (NGS) panel of 30 genes, in 54 patients with CNS tumors against fluorescence in-situ hybridization (FISH), Sanger sequencing, and reverse transcription polymerase chain reaction (PCR). GlioSeq correctly identified 71/71 (100%) genetic alterations known to be present by conventional techniques. The assay sensitivity was 3%-5% for mutant alleles of single nucleotide variants (SNVs), and 1%-5% for gene fusions. Likewise, Zacher et al. (2017) developed an NGS panel of 20 genes that allowed for molecular classification of 121 gliomas. The researchers conclude that gene panel NGS is a promising diagnostic technique that may facilitate integrated histological and molecular glioma classification.

Ramkissoon et al. (2017) used OncoPanel and OncoCopy to identify targetable alterations in tumors for the establishment of best practices in routine clinical pediatric oncology. They analyzed 117 samples by OncoPanel and 146 by OncoCopy; further, 60 tumors were subjected to both methodologies. OncoPanel revealed clinically relevant alterations in 56% of patients (44 cancer mutations and 20 rearrangements), including \textit{BRAF} alterations that directed the use of targeted inhibitors. Rearrangements in \textit{MYB-QKI}, \textit{MYBL1}, \textit{BRAF}, and \textit{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.

Ryall et al. (2016) evaluated the prognostic impact of H3K27M and MAPK pathway aberrations in 64 gliomas (44 low grade, 22 high grade). Tumors are designated as low-grade if the cells are well differentiated, are less aggressive overall, and suggest a better prognosis for the patient. Five low grade gliomas contained the \textit{H3F3A/HIST1H3B K27M (H3K27M)} mutation, and 11 high grade gliomas...
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contained the $H3K27M$ mutation. Survival analysis evaluated the median survival at 9.12 years for wildtype H3 patients compared to 1.02 years for patients with the $H3K27M$ mutation. MAPK pathway mutations (through $BRAF$ or $FGFR1$ mutation) were associated with long-term survival in absence of $H3K27M$ mutations. Further, $H3K27M$ status and high-grade histology were found to be the most significant independent predictors of poor overall survival with hazard ratios of 6.945 and 7.721 respectively. MAPK pathway activation was considered to be a predictor of “favourable patient outcome,” but dependent on other factors (Ryall et al., 2016).

Houdova Megova et al. (2017) evaluated the prognostic value of the $IDH1/2$ mutation in glioblastomas. A total of 37 $IDH$ mutations were examined and studied. The authors found that $IDH1$ mutations were positively associated with $MGMT$ methylation (odds ratio [OR]: 3.08), 1p/19q co-loss (OR: 8.85), and negatively associated with $EGFR$ amplification. IDH-mutant patients had an overall survival of 25 months compared to only 9 months for IDH-wildtype gliomas (Houdova Megova et al., 2017).

Johnson et al. (2017) performed comprehensive genomic profiling of 282 pediatric gliomas: 157 high-grade and 125 low-grade. The investigators used a 315 gene panel and calculated the tumor mutational burden (TMB). In low grade gliomas, $BRAF$ was the most frequent mutation found (48%), followed by $FGFR$ missense (17.6%), $NF1$ loss of function (8.8%), and $TP53$ (5.6%). Rearrangements were found in 35% of low-grade gliomas. In high-grade gliomas, $TP53$ was the most frequent mutation found (49%), followed by $H3F3A$ (37.6%), $ATRX$ (24.2%), $NF1$ (22.2%), and $PDGFRA$ (21.7%). $H3F3A$ mutations were found to be the K28M variant. Approximately 6% of the high-grade gliomas were found have a TMB of >20 mutations/Mb (“hypermutated”) (Johnson et al., 2017).

Back et al. (2020) studied the pattern of failure in anaplastic glioma (AG) patients with an $IDH1/2$ mutation. A total of 156 patients participated in the study, with data collected from 2008 to 2014; the median follow-up time was 5.1 years. Of all 156 patients, 75% were found to have an $IDH1$ or $IDH2$ mutation. The authors concluded that “patients with $IDH$-mutated AG have improved outcomes”; however, this population also had a greater number of distant relapses approximately two years after intensity-modulated radiation therapy compared to individuals with $IDH$ wild type mutations (Back et al., 2020).

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN, 2019, 2020)

The NCCN published Clinical Practice Guidelines in Oncology (2020) for Central Nervous System Cancers which recommend:

- $IDH1$ and $IDH2$ mutation
  Recommendation: $IDH$ mutation testing is required for the workup of glioma.
  “The most common $IDH1$ mutation (R132H) is reliably screened by mutation specific immunohistochemistry, which is recommended for all glioma patients. If the R132H immunostain result is negative, in the appropriate clinical context, sequencing of $IDH1$ and $IDH2$ is highly recommended to detect less common $IDH1$ and $IDH2$ mutations. Prior to age 55 years, sequencing of $IDH1$ and $IDH2$ is required if the R132H immunostain result is negative. Standard sequencing methods include Sanger sequencing, pyrosequencing, and next-generation sequencing, and should be performed on formalin fixed, paraffin embedded tissue (NCCN, 2020).”

- $MGMT$ promoter methylation
  Recommendation: $MGMT$ promoter methylation is an essential part of molecular diagnostics for all high-grade gliomas (grade III and IV). The NCCN also notes that “$MGMT$ promoter methylation is strongly associated with IDH mutations and other genome-wide epigenetic changes (G-CIMP phenotype)” (NCCN, 2019, 2020).
  “Methylation of the $MGMT$ promoter is detectable by methylation specific PCR, pyrosequencing, or array-based technologies (NCCN, 2019, 2020).”

- Codeletion of 1p and 19q
  Recommendation: 1p19q testing is an essential part of molecular diagnostics for oligodendroglioma.
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“The codeletion of 1p and 19q is detectable by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR). Additional methods, including array based genomic copy number testing and next generation sequencing may also be employed… IDH mutated gliomas that do not show loss of ATRX (for example, by IHC) should be strongly considered for 1p19q testing even if not clearly oligodendrogial by histology. Conversely, IDH1 wild type gliomas do not contain true whole-arm 1p19q codeletion. Therefore, 1p19q testing is unnecessary if a glioma is not IDH-mutant, and a glioma should not be regarded as 1p19q codeleted without an accompanying IDH mutation, regardless of the test results (NCCN, 2019, 2020).”

**ATRX mutation**

“Recommendation: ATRX mutation testing is strongly recommended but not required for glioma.”

“ATRX mutations can be detected by IHC for wild-type ATRX (loss of wild type expression) and/or sequencing. ATRX mutations in glioma are strongly associated with IDH mutations, and are nearly always mutually exclusive with 1p/19q codeletion. ATRX deficiency, coupled with IDH mutation, is typical of astrocytoma. A lack of ATRX immunostaining in glioblastoma should trigger IDH1/2 sequencing if IDH1 R132H immunostaining is negative, due to frequent co-occurrence of ATRX and IDH mutations (NCCN, 2020).”

**TERT mutation**

“Recommendation: TERT mutation testing is recommended but not required for gliomas. TERT mutation can be detected by sequencing of the promoter region (NCCN, 2019, 2020).”

**H3F3A and HIST1H3B mutation**

“Recommendation: H3F3A and HIST1H3B mutation testing is recommended in the appropriate clinical context.”

“Although a K27M histone antibody is available, it is not 100% specific and interpretation can be difficult for non-experts. Therefore, screening by H3F3A and HIST1H3B sequencing is a viable alternative and preferred approach, especially since it will also detect mutations in G34 (NCCN, 2020).”

“Histone mutations most commonly occur in pediatric midline gliomas (eg, diffuse intrinsic pontine gliomas [DIPG]), although midline gliomas in adults can also contain histone modifications. Their presence can be considered solid evidence of an infiltrative glioma, which is often helpful in small biopsies of midline lesions that may not be fully diagnostic with light microscopy or do not fully resemble infiltrative gliomas. The K27M gliomas typically do not have MGMT promoter methylation, and the mutation is an adverse prognostic marker in children and adults. The G34 mutation does not appear to have any prognostic significance once the diagnosis of a glioblastoma has been established (NCCN, 2020).”

**BRAF mutation**

“Recommendation: BRAF fusion and/or mutation testing is recommended in the appropriate clinical context.”

“BRAF V600E is best detected by sequencing, and BRAF fusions can be detected with RNA-Seq or other PCR-based breakpoint methods that capture the main 16-9, 15-9, and 16-11 breakpoints between BRAF and its main fusion partner, KIAA1549. FISH is too unreliable to detect BRAF fusions” (NCCN, 2019, 2020).

“The presence of a BRAF fusion is reliable evidence that the tumor is a pilocytic astrocytoma, provided the histology is compatible. BRAF V600E is more complicated, as it can occur in a variety of tumors over all four WHO grades and requires integration with histology. Tumors with BRAF fusions tend to be indolent, with occasional recurrence but only rare progression to lethality. BRAF V600E tumors show a much greater range of outcomes and need to be considered in context with other mutations and clinicopathologic findings (eg, CDKN2A/B deletion) (NCCN, 2020).”

**RELA fusion**

“Recommendation: RELA fusion testing is recommended in the appropriate clinical context.”

“The most common RELA fusion partner is C11orf95. This can be detected with RNAsEq or a break apart FISH probe set. Detection of RELA fusion is not required for the diagnosis of ependymoma, as this entity is still diagnosed by light microscopy. RELA fusion-positive ependymomas are now a distinct entity in the WHO classification of CAN tumors, as this subset of ependymomas tends to be far more aggressive than other supratentorial ependymomas (NCCN, 2020).”

**Miscellaneous**
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Other markers have been suggested for various uses in evaluating gliomas. For example, other markers for subtyping grade II-III gliomas include assessment of PTEN, TP53, NOTCH1, CIC, FUBP1, EGFR, chromosome 7 gain, and chromosome 10 loss. However, these markers are not currently widely accepted as markers for gliomas.

Finally, the NCCN states there are no identified targeted agents with demonstrated efficacy in glioblastoma (NCCN, 2019, 2020).

National Institute for Health and Care Excellence (NICE, 2018)
NICE recommends the following molecular markers for investigation of gliomas: IDH1/2 mutations, ATRX mutations, 1p/19q co-deletion, histone H3.3 K27M, BRAF mutation, and MGMT promoter methylation (for prognosis). NICE also notes that testing IDH wild type gliomas for TERT promoter mutations may be considered (NICE, 2018).

European Society for Medical Oncology (ESMO, 2014)
The ESMO has published clinical practice guidelines for the diagnosis, treatment, and follow-up of high-grade gliomas. They state that MGMT promoter methylation status, IDH1/2 mutation status, and 1p/19q codeletions are “commonly determined” for assessment of gliomas (ESMO, 2014).

World Health Organization (WHO) (Wen & Huse, 2016)
In 2016, the WHO published guidelines on the classification of central nervous system tumors. These WHO guidelines, for the first time, incorporated molecular testing in the diagnosis of gliomas and medulloblastomas. The following key points were given by the WHO regarding molecular testing:

- “IDH1 R132H, which accounts for approximately 90% of IDH mutations, can be detected immunohistochemically. If this testing is negative, sequencing of IDH1 and IDH2 is necessary to ensure that no other IDH mutations are present.
- Given the importance of IDH mutational status in the diagnosis or gliomas, at a minimum, it will be important that most institutions have the capacity to both stain tumor specimens for IDH1 R132H by immunohistochemistry and, ideally, sequence those tumors that are negative for both IDH1 and IDH2 mutations” (Wen & Huse, 2016).

State and Federal Regulations

No diagnostic tests have been specifically approved for use in detecting mutations in gliomas as of July 29, 2020. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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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Medical Director review 4/2020

Medical Director review 10/2020


Medical Director review 3/2021

**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)

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Under “When Covered” section added gene HIST1H3B to item e. Updated references and policy guidelines section. Literature review and Medical Director review 10/2020. (lpr)

4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)

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