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Release date: January 10, 2023; Expiration date: January 10, 2024

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Central Nervous System Cancers
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Central Nervous System Cancers

Disclosure of Relevant Financial Relationships

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Jane Portnow, MD, Panel Vice Chair, has disclosed receiving grant/research support from Agios, Inc., Bayer HealthCare, Celularity, Incyte Corporation, and Novocure; and serving as a scientific advisor for IN8bio, Inc.
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Central Nervous System Cancers, Version 2.2022

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Central Nervous System (CNS) Cancers focus on management of the following adult CNS cancers: glioma (WHO grade 1, WHO grade 2–3 oligodendroglioma [1p19q codeleted, *IDH*-mutant], WHO grade 2–4 *IDH*-mutant astrocytoma, WHO grade 4 glioblastoma), intracranial and spinal ependymomas, medulloblastoma, limited and extensive brain metastases, leptomeningeal metastases, non–AIDS-related primary CNS lymphomas, metastatic spine tumors, meningiomas, and primary spinal cord tumors. The information contained in the algorithms and principles of management sections in the NCCN Guidelines for CNS Cancers are designed to help clinicians navigate through the complex management of patients with CNS tumors. Several important principles guide surgical management and treatment with radiotherapy and systemic therapy for adults with brain tumors. The NCCN CNS Cancers Panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. These NCCN Guidelines Insights summarize the panel's most recent recommendations regarding molecular profiling of gliomas.

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*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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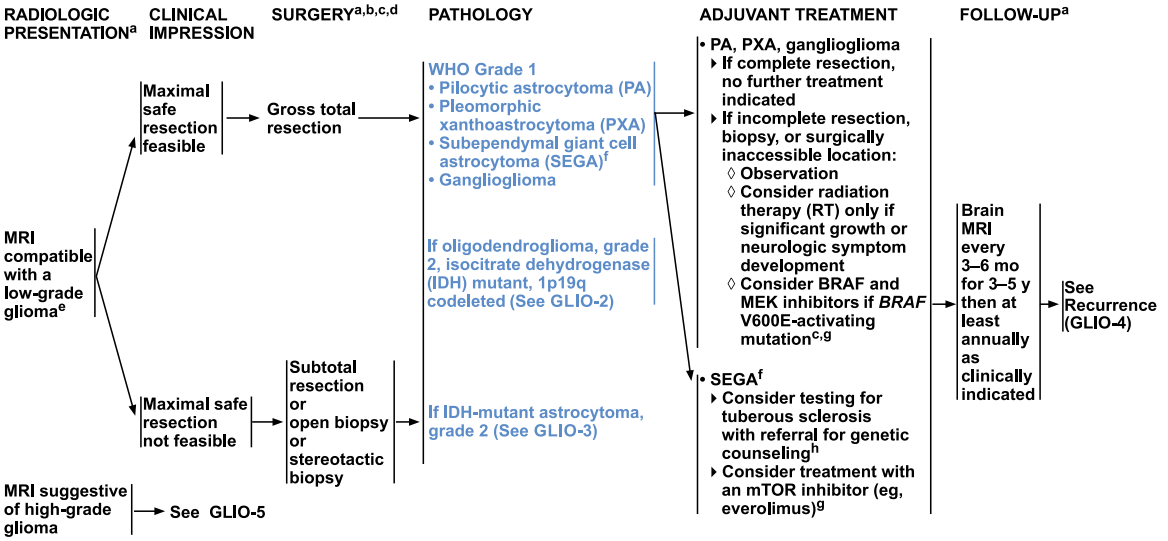


[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] See Principles of Brain Tumor Surgery (BRAIN-B).
[c] For recommended molecular diagnostics, see Principles of Brain Tumor Pathology (BRAIN-F).
[d] Postoperative brain MRI within 48 hours after surgery.
[e] Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[f] The need to treat SEGAs or other findings in the appropriate tuberous sclerosis patient population should be determined by the patient's symptoms and/or change on serial radiologic studies. Referral to a neurofibromatosis or specialty center is recommended.
[g] See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[h] See Principles of Cancer Risk Assessment and Counseling (BRAIN-G).

GLIO-1

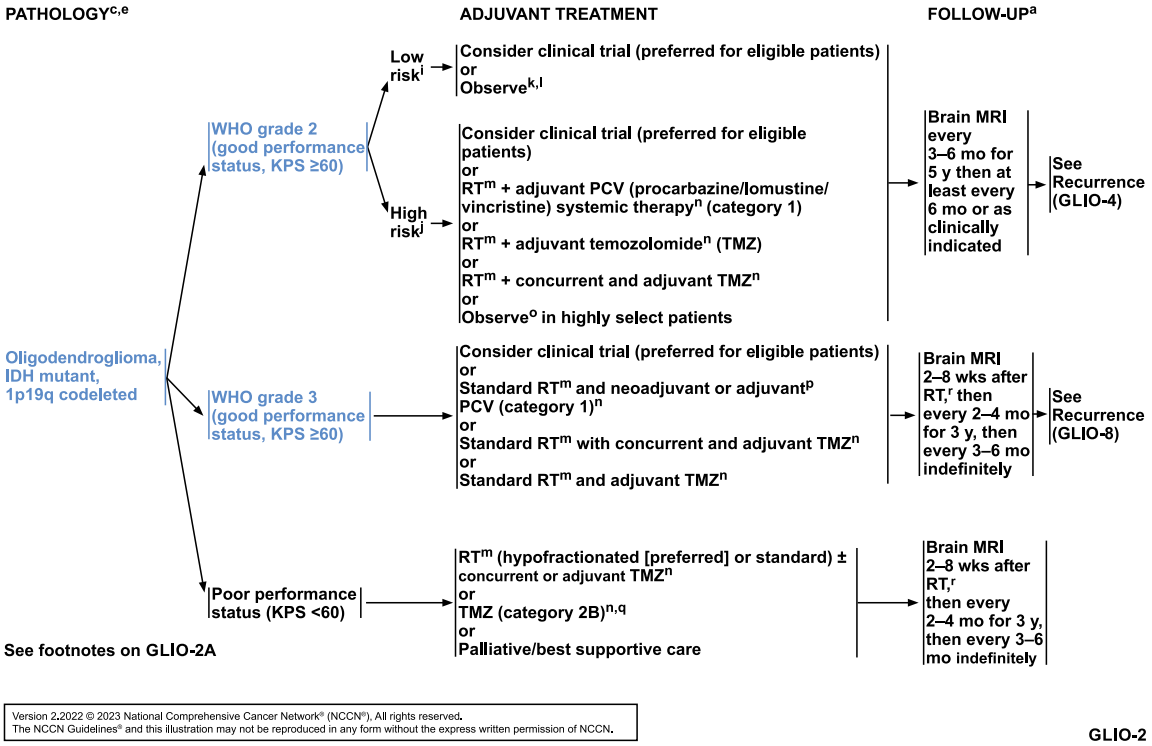
Overview

Integrated histopathologic and molecular characterization of gliomas, as per WHO classification,[1] should be an essential part of practice. Molecular/genetic characterization complements standard histologic analysis, improves diagnostic accuracy, provides prognostic information, and aids in treatment selection and clinical trial enrollment. Histopathologic and molecular analysis of central nervous system (CNS) tumors is limited by interobserver discrepancies and surgical sampling that do not always capture all relevant diagnostic features in morphologically heterogeneous tumors. It is important to note, however, that most of the studies describing molecular patterns and outcomes were based on large retrospective cohorts, and many of the seminal brain tumor clinical trials were not based on those molecular patterns. Without full incorporation of molecular profiling, precision medicine for brain tumors will not be fully realized.

Updated Classification of Gliomas Based on Histology and Molecular Features

In 2016, the WHO classification for grade 2–3 gliomas was revised as follows: (1) oligodendrogliomas were gliomas that had whole-arm 1p/19q codeletion and *IDH1* or *IDH2* (together referred to as "*IDH*") mutation (unless molecular data were not available and could not be obtained, in which case designation was based on histology with appropriate caveats); (2) anaplastic gliomas were further subdivided according to *IDH* mutation status; (3) oligoastrocytoma was no longer a valid designation unless molecular data (1p/19q codeletion and *IDH* mutation status) were not available and could not be obtained.[2] Such tumors were described as "oligoastrocytoma, not otherwise specified" to indicate that the characterization of the tumor was incomplete. Very rare cases of concurrent, spatially distinct oligodendroglioma (1p/19q codeleted) and astrocytoma (1p/19q intact) components in the same tumor could also be labeled oligoastrocytoma.[2] Correlations between the molecularly defined 2016 WHO categories and the histology-based 2007 WHO categories were limited and varied across studies.[3–6] Thus, the change from 2007 WHO to 2016 WHO reclassified a large proportion of gliomas.

The fifth edition of the WHO classification of CNS tumors was published in 2021.[1,7] In this newest classification, "adult-type diffuse gliomas" are subsumed within a supercategory of gliomas and glioneuronal tumors, and are split into 3 subtypes: (1) *IDH*-mutant astrocytoma; (2) oligodendroglioma, 1p/19q-codeleted and *IDH*-mutant; (3) glioblastoma, *IDH*-wild-type. WHO grades are now further specified for select CNS tumors, including diffuse gliomas. Specifically, *IDH*-mutant astrocytoma can be grade 2, 3, or 4. Oligodendroglioma, 1p/19q-codeleted and *IDH*-mutant, can be grade 2 or 3. Glioblastoma, *IDH*-wild-type, can only be grade 4. This updated classification further emphasizes the importance of molecular data for accurately diagnosing CNS



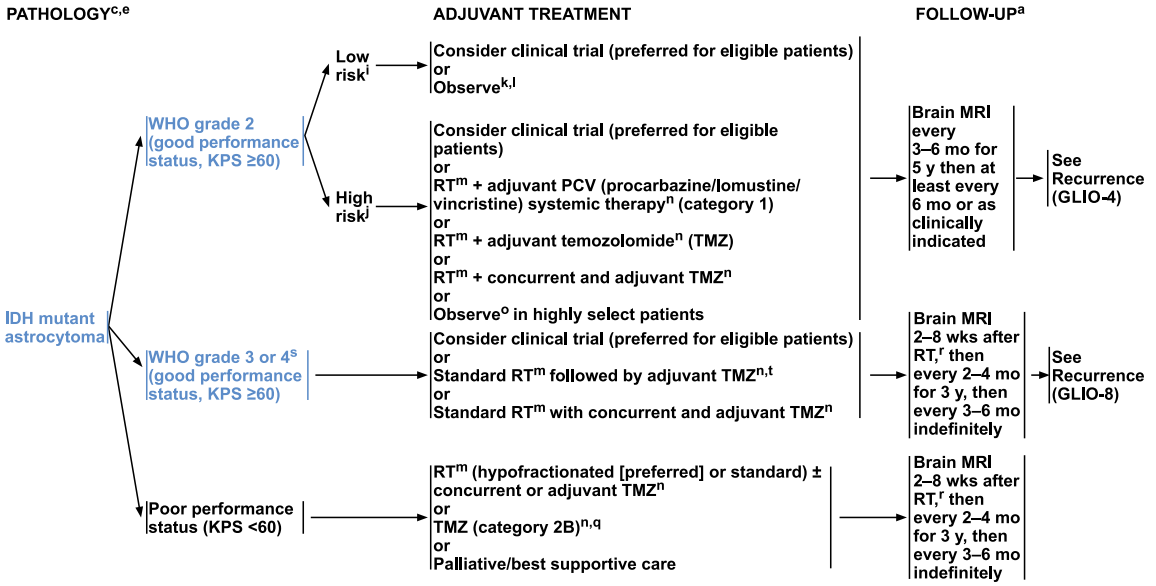
GLIO-2

tumors (see GLIO-1, GLIO-2, GLIO-3, and GLIO-5, pages 14–17).[1]

Multiple independent studies on gliomas have conducted genome-wide analyses evaluating an array of molecular features, including DNA copy number, DNA methylation, and mutations, in large populations of patients with grade 2–4 tumors.[5,8,9] Unsupervised clustering analyses, an unbiased method for binning molecularly similar tumors, have been used to identify subgroups of gliomas with distinct molecular profiles.[5,8,9] Further studies have shown that these molecular subgroups can be distinguished based on only a handful of molecular features, including *IDH* mutation and 1p/19q codeletion, biomarkers independently verified by numerous studies as hallmarks for distinguishing molecular subgroups in grade 2–3 gliomas.[3–6,9–15] The unsupervised clustering analysis published by The Cancer Genome Atlas Research Network supports the idea that the majority of grade 2–3 tumors can be divided into 3 molecular subtypes: (1) mutation of *IDH* with 1p/19q codeletion; (2) *IDH*-mutant with no 1p/19q codeletion; and (3) no mutation of *IDH* (ie, *IDH*-wild-type).[5] Multiple studies have shown that 1p/19q codeletion is strongly associated with *IDH* mutations, such that true whole-arm 1p/19q codeletion in *IDH*-wild-type tumors is extremely rare.[3,4,12,16,17] In a tissue biopsy that is equivocal for glioma, the presence of an *IDH* mutation indicates at least a grade 2 diffusely infiltrative glioma.[18] Some *IDH*-mutant diffusely infiltrative astrocytomas develop the traditional grade 4 histologic features of necrosis and/or microvascular proliferation, which suggest more aggressive behavior and worse prognosis, but are still not as severe as *IDH*-wild-type glioblastoma. Such tumors are now referred to as astrocytoma, *IDH*-mutant, WHO grade 4, to distinguish them from *IDH*-wild-type glioblastoma.[19,20] Grade 1 noninfiltrative gliomas do not have *IDH* mutations.[18]

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 2–3 gliomas and secondary glioblastomas.[21,22] *ATRX* mutation is robustly associated with *IDH* mutations, and this combination, along with *TP53* mutations, is diagnostic of astrocytoma.[23] In contrast, *ATRX* mutation is nearly always mutually exclusive with 1p/19q codeletion, and is uncommon in *IDH*-wild-type glioblastoma. Because loss of normal nuclear ATRX immunostaining is a fairly reliable indicator of an *ATRX* mutation, an *IDH*-mutant glioma that has loss of normal nuclear ATRX immunostaining is much more likely to be an astrocytoma than an oligodendroglioma.

Mutations in the promoter region of the telomerase reverse transcription (*TERT*) gene occur frequently in *IDH*-wild-type glioblastomas and *IDH*-mutant, 1p/19q codeleted oligodendrogliomas.[24,25] Absence of *TERT* promoter mutation, coupled with *IDH* mutation and lack of 1p/19q



See footnotes on GLIO-3A

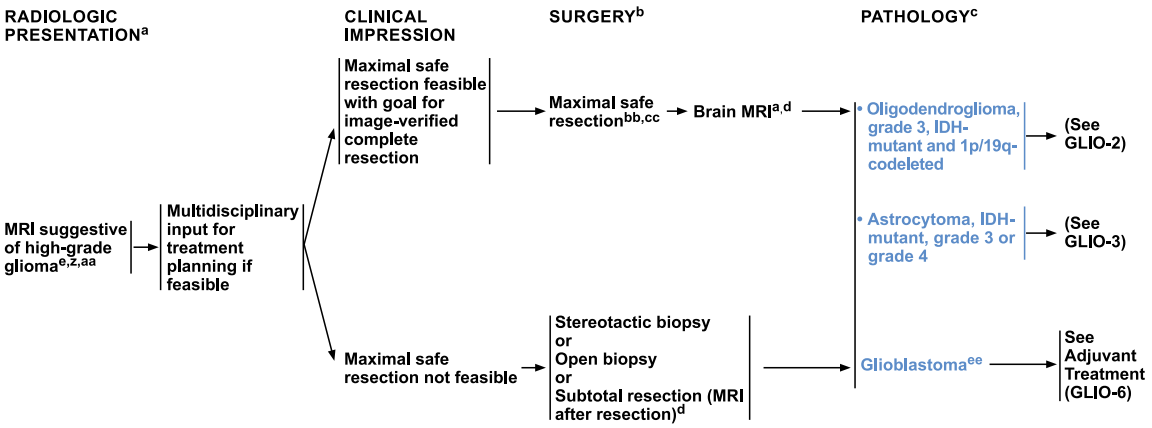
GLIO-3

codeletion, is indicative of astrocytoma. Some *IDH*–wild-type diffusely infiltrative astrocytomas lack the histologic features of glioblastoma (necrosis and/or microvascular proliferation) but have ≥1 molecular hallmarks of glioblastoma, including the following: *EGFR* amplification; gain of chromosome 7 and loss of chromosome 10; and *TERT* promoter mutation. In such cases, the tumor can still be diagnosed as glioblastoma, *IDH*-wild-type, WHO grade 4. These tumors have similar clinical outcomes as typical histologic grade 4 *IDH*-wild-type glioblastomas, so they may be managed accordingly.[18,20] The 2021 updated WHO classification of CNS tumors also now includes *CDKN2A/B* homozygous deletion as evidence of grade 4 status in *IDH*-mutant astrocytomas, even if such astrocytomas lack necrosis and/or microvascular proliferation.[1,19,26–29]

H3K27M mutations in the histone-encoding *H3-3A* gene are mostly found in diffuse midline gliomas in both children and adults.[30] Patients with these H3K27M-mutated gliomas tend to have a very poor prognosis regardless of histologic appearance, so they are classified as WHO grade 4; however, some patients seem to fare better than a grade 4 diagnosis would imply, so there remains some controversy regarding this issue.[30–32] Another variant in *H3-3A*, resulting in a G34V (or R) mutation in histone 3.3, is characteristic of some diffusely infiltrative gliomas arising not in the midline, but in the cerebral hemispheres. These gliomas tend to occur in children and younger adults and are *IDH*-wild-type, but still have mutations in *ATRX* and *TP53*. Thus, the fifth edition of the WHO classification calls these tumors "diffuse hemispheric glioma, H3.3 G34-mutant, WHO grade 4."[1] H3K27M immunopositivity is associated with loss of histone trimethylation immunostaining in diffuse midline gliomas.[33–37] The presence of a histone mutation 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 and/or do not clearly look like infiltrative gliomas.[30,38] Both kinds of *H3-3A*–mutant gliomas are now subsumed by the 2021 WHO classification under "pediatric-type diffuse high grade gliomas," even if such tumors arise in adults.[1,7] None of the histone-driven gliomas are called glioblastomas anymore, because that term is now reserved exclusively for *IDH*-wild-type gliomas meeting the criteria discussed earlier.

Prognostic Relevance of Molecular Subgroups in Glioma

Numerous large studies of patients with brain tumors have determined that, among WHO grade 2–3 gliomas, 1p/19q codeletion correlates with greatly improved progression-free survival (PFS) and overall survival (OS).[4,9,10,39–41] Likewise, the presence of an *IDH* mutation is a strong favorable prognostic marker for OS in grade 2–3 gliomas.[5,12] Analyses within single-treatment arms showed that the *IDH* status is prognostic for outcome across a variety of postoperative adjuvant options. For example, in the NOA-04 phase III



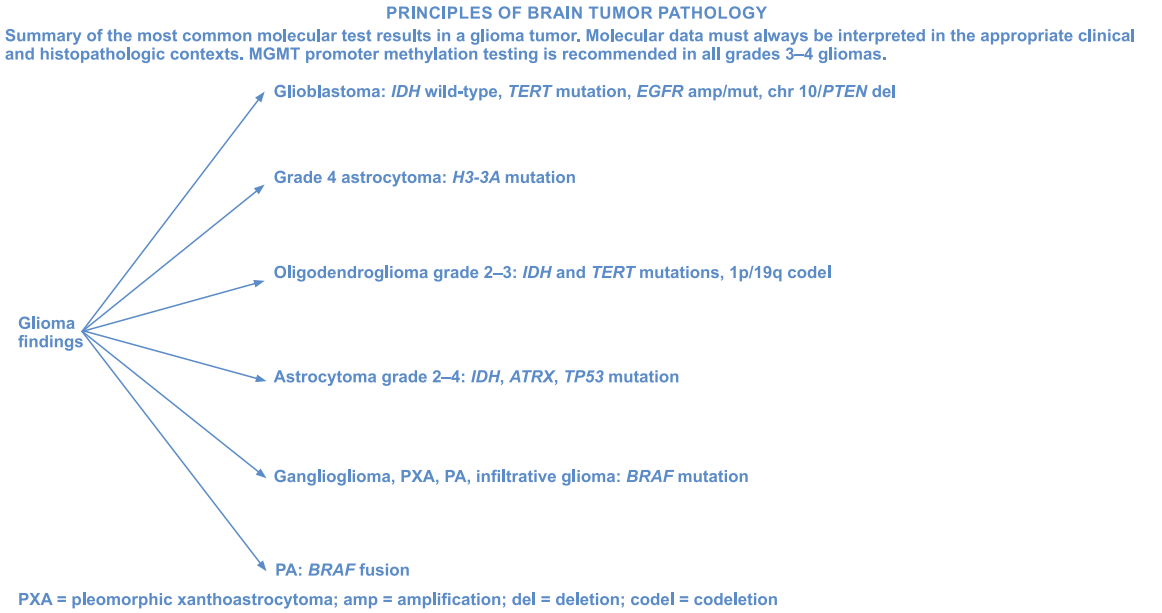
[a] See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] See Principles of Brain Tumor Surgery (BRAIN-B).
[c] See Principles of Brain Tumor Pathology (BRAIN-F).
[d] Postoperative brain MRI within 48 hours after surgery.
[e] Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-E).
[z] This pathway includes the classification of grade 3 astrocytoma, IDH-mutant; grade 3 oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and other rare grade 3 gliomas.
[aa] Biopsy prior to administration of steroids if MRI compatible with CNS lymphoma.
[bb] If frozen section diagnosis supports high-grade glioma.
[cc] Consider carmustine (BCNU) wafer implant during maximal safe resection (category 2B). Treatment with carmustine wafer may impact enrollment in adjuvant clinical trials.
[ee] This pathway also includes gliosarcoma.

GLIO-5

randomized trial, *IDH* mutation was associated with improved PFS, longer time to treatment failure, and extended OS in each of the 3 treatment arms: standard radiotherapy (RT; n=160); combination therapy with procarbazine/lomustine/vincristine (RT upon progression; n=78); and temozolomide (RT upon progression; n=80).[40]

Multiple independent studies, covering multiple grades and histology-based subtypes of gliomas,[5,9,39] as well as smaller studies limited to 1 to 2 grades or histologic subtypes,[4,42–44] have consistently supported the subdivision of gliomas by molecular subtype (eg, by *IDH* and 1p/19q status) as recommended by the WHO 2021 CNS tumor classification, because this yields greater prognostic separation than subdivision by histology alone. Multiple studies have shown that, among patients with grade 2–3 gliomas, the *IDH*-mutant plus 1p/19q-codeletion group (ie, oligodendroglioma) has the best prognosis, followed by *IDH*-mutant without 1p/19q codeletion (ie, astrocytoma), and the *IDH*-wild-type group (ie, glioblastoma) has the worst prognosis.[4–6,39–41] Analyses within single-treatment arms have confirmed this trend in prognosis across a variety of postoperative adjuvant treatment options.[4,40,41,44] *TERT* promoter mutations in patients with high-grade *IDH*-wild-type glioma are associated with shorter OS, compared with *IDH*-wild-type tumors without a *TERT* promoter mutation.[6,25,45] However, a multivariable analysis of data from 291 patients with *IDH*-mutant, 1p/19q-codeleted oligodendrogliomas showed that absence of a *TERT* promoter mutation was associated with worse OS, compared with those with *TERT* promoter–mutant oligodendrogliomas (hazard ratio, 2.72; 95% CI, 1.05–7.04; *P*=.04).[46] An analysis of an older database, which included 271 patients with WHO grade 2 gliomas that were diagnosed according to the 2007 WHO classification, showed that *IDH*-mutant gliomas were associated with increased OS and better response to temozolomide than *IDH*-wild-type gliomas.[4]

MGMT (O-6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that can confer resistance to DNA-alkylating drugs.[47] Gene suppression via *MGMT* promoter methylation is associated with better survival outcomes in patients with high-grade glioma, and is a predictive factor for response to treatment with alkylating chemotherapy, such as temozolomide or lomustine,[31,48–50] even in older adults.[51,52] *IDH* mutations are commonly associated with *MGMT* promoter methylation.[6] Tumors with H3K27M mutations are far less likely to be *MGMT* promoter methylated.[30] and are associated with even worse prognosis than *IDH*-wild-type glioblastomas.[38,53] Patients whose hemispheric high-grade gliomas contain *H3-3A* G34 mutations, however, have relatively higher rates of *MGMT* promoter methylation than H3K27M diffuse midline gliomas, and do not have a worse prognosis than patients with other *IDH*-wild-type glioblastomas.[38,54]



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BRAF fusion and/or mutation testing are clinically indicated in patients with low-grade glioma. Most WHO grade 1 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.[55] *BRAF* fusion is associated with better prognosis in pediatric low-grade astrocytoma.[55–57] The likelihood of a *BRAF* fusion in a pilocytic astrocytoma decreases with age.[55] *BRAF* V600E is present in 60% to 80% of pleomorphic xanthoastrocytomas, though it has also been found in many other low-grade gliomas, such as gangliogliomas and dysembryoplastic neuroepithelial tumors,[31,55,58] as well as <5% of glioblastomas (especially epithelioid glioblastoma).[59] Pediatric low-grade gliomas with *BRAF* fusions tend to be indolent with occasional recurrence, but only rarely do they progress to cause death.[56,57,60] Retrospective studies have shown that *BRAF* V600E may be associated with increased risk of progression in pediatric low-grade gliomas,[61] but one study found that this association did not meet the threshold for statistical significance (n=198; *P*=.07).[57] Some studies have shown that tumors with a *BRAF* V600E mutation may respond to BRAF inhibitors such as vemurafenib,[62–64] but ongoing trials will further clarify targeted treatment options in the presence of a *BRAF* fusion or V600E mutation (eg, ClinicalTrials.gov identifiers: NCT03224767, NCT03430947).

NCCN Molecular Testing Recommendations for Glioma

Recommendations for molecular testing of glioma tumors are provided in "Principles of Brain Tumor Pathology" (see BRAIN-F 6 of 10, above). Based on studies showing that *IDH* status is associated with better prognosis in patients with grade 2–3 glioma,[16,39,40,65] the panel recommends *IDH* mutation testing in patients with glioma. Immunohistochemistry can detect the most common (canonical) *IDH* mutation, *IDH1* R132H. However, sequencing must be performed to detect noncanonical *IDH1* mutations (eg, *IDH1* R132C) and *IDH2* mutations. Because *ATRX* and *IDH* mutations frequently co-occur, a lack of *ATRX* immunostaining, coupled with negative R132H immunostaining for *IDH1* in a glioma, should trigger screening for such noncanonical *IDH* mutations.[23] Loss of nuclear ATRX via immunostaining should trigger reflex sequencing to confirm an *ATRX* mutation. Sequencing is also recommended in patients aged <55 years with negative immunohistochemistry for *IDH1* R132H, regardless of *ATRX* immunostaining.

Testing for 1p/19q codeletion is essential for the diagnosis of oligodendroglioma. A very common method to do this is by fluorescence in situ hybridization (FISH), but FISH only targets regions near the telomeric ends of 1p and 19q. Thus, FISH is vulnerable to misinterpreting short segmental deletions as whole-arm codeletion.[66–68] When possible, whole genomic copy number scanning,

either by genomic copy number variation assay or DNA methylation profiling, is preferred for assessing 1p/19q status. Furthermore, because true whole-arm 1p/19q codeletion is essentially nonexistent in the absence of an *IDH* mutation,[16,17,69] 1p/19q testing is not necessary in tumors that are definitely *IDH*-wild-type, and tumors without an *IDH* mutation should not be regarded as truly 1p/19q-codeleted, even when results suggest otherwise. Mutation testing for *ATRX* and *TERT* promoter are also recommended, given the diagnostic value of these mutations.[21,23–25] *IDH*-mutated gliomas that do not show loss of nuclear ATRX immunostaining should be strongly considered for 1p/19q testing, even if not clearly oligodendroglial by histology. *H3A* and *HIST1H3B* sequencing and *BRAF* fusion and/or mutation testing may be performed as clinically indicated. A K27M histone-specific antibody is available, but it can be difficult to interpret.[70]

Grade 3–4 gliomas should undergo testing for *MGMT* promoter methylation, because *MGMT* promoter methylated tumors typically respond better to alkylating chemotherapy compared with unmethylated tumors.[48,51,52,71] There are several accepted methods for testing *MGMT* promoter methylation. Methylation-specific PCR has had the most validation in clinical trials,[72] but a 2012 study including 100 patients with glioblastoma treated with temozolomide suggested that pyrosequencing may be the best prognostic stratifier.[73] Molecular testing of glioblastomas is encouraged by the panel, because patients with a detected driver mutation (eg, *BRAF* V600E mutation or *NTRK* fusion) may be treated with a targeted therapy, and these tests improve diagnostic accuracy and prognostic stratification. Detection of genetic or epigenetic alterations could also expand clinical trial options for a patient with a CNS tumor.

In summary, in order for patients to receive appropriate care and prognostic information, molecular and genetic testing of gliomas is warranted.

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