**Template for Reporting Results of Biomarker Testing of Specimens From Patients With Tumors of the Central Nervous System**

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For the Members of the Cancer Biomarker Reporting Committee, College of American Pathologists

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CAP CNS Biomarker Template Revision History

**Version Code**

The definition of the version code can be found at www.cap.org/cancerprotocols.

**Version:** CNS\_Biomarkers 1.0.0.0

**Summary of Changes**

This is a new template.

CNS Biomarker Reporting Template

Template web posting date: December 2014

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient’s medical record and thus readily available to the treating clinical team.

**CENTRAL NERVOUS SYSTEM (CNS)**

**Select a single response unless otherwise indicated.**

***Note:*** *Use of this template is optional.*

**+ RESULTS**

**+ GLIOMAS**

**+ *IDH1/2* Mutation**

+ \_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ IDH1 R132H Immunohistochemistry**

+ \_\_\_ Positive

+ \_\_\_ Negative

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ 1p/19q Deletion**

+ \_\_\_ 1p/19q co-deletion

+ \_\_\_ 1p only deleted

+ \_\_\_ 19q only deleted

+ \_\_\_ Polysomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Monosomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ None detected

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *TP53* Mutation**

+ \_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *ATRX* Mutation**

+ \_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ ATRX Immunohistochemistry**

+ \_\_\_ Loss of nuclear expression

+ \_\_\_ Intact nuclear expression

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *EGFR* Amplification**

+ \_\_\_ Present

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+10q23 *(PTEN* Locus)Deletion**

+ \_\_\_ Deletion identified

+ \_\_\_ Polysomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Monosomy (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ None detected

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *PTEN* Mutation**

+ \_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *MGMT* Promoter Methylation**

+ \_\_\_ Present

 *If laboratory reports by level:*

+ \_\_\_ Low level

 + \_\_\_ High level

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *BRAF* Mutation**

+ \_\_\_ *BRAF* V600E (c.1799T>A) mutation present

+ \_\_\_ Other *BRAF* mutation present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ BRAF V600E Immunohistochemistry**

+ \_\_\_ Positive

+ \_\_\_ Negative

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *BRAF* Rearrangement**

+ \_\_\_ Present

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Ki-67**

+ Percentage of positive nuclei: \_\_\_\_ %

**+ EMBRYONAL TUMORS**

**+ Nuclear Beta-Catenin Immunohistochemistry**

+ \_\_\_ Positive (nuclear staining in at least 50% of tumor cells)

+ \_\_\_ Negative (no staining or nuclear staining in <50% of tumor cells)

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Monosomy 6**

+ \_\_\_ Present

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ GAB1 Immunohistochemistry**

+ \_\_\_ Positive

+ \_\_\_ Negative

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *MYC* Amplification**

+ \_\_\_ Present

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *MYCN* Amplification**

+ \_\_\_ Present

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Isochromosome 17 (i17q)**

+ \_\_\_ Present

+ \_\_\_ Absent

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ INI1 (BAF47) Immunohistochemistry**

+ \_\_\_ Loss of nuclear expression

+ \_\_\_ Intact nuclear expression

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *SMARCB1/INI1/HNSF5* Mutation**

+ \_\_\_ Present (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Absent (*SMARCB1/INI1/HNSF5*)

+ \_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ METHODS**

**+ GLIOMAS**

**+ *IDH1/2* Mutational Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ Direct Sanger sequencing

+ \_\_\_ Pyrosequencing

+ \_\_\_ Polymerase chain reaction (PCR), allele-specific hybridization

+ \_\_\_ Real-time PCR

+ \_\_\_ High-throughput next-generation sequencing

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Immunohistochemistry for IDH1 R132H**

+ Primary Antibody

+ \_\_\_ H09

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ 1p/19q Deletion Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Loss of heterozygosity

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *TP53* Mutational Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ Direct Sanger sequencing

+ \_\_\_ Pyrosequencing

+ \_\_\_ PCR, allele-specific hybridization

+ \_\_\_ Real-time PCR

+ \_\_\_ High-throughput next-generation sequencing

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *ATRX* Mutational Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ Direct Sanger sequencing

+ \_\_\_ Pyrosequencing

+ \_\_\_ PCR, allele-specific hybridization

+ \_\_\_ Real-time PCR

+ \_\_\_ High-throughput next-generation sequencing

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Immunohistochemistry for ATRX**

+ Primary Antibody

+ Specify: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *EGFR* Amplification Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Chromosome 10q23 (*PTEN* Locus) Deletion Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Loss of heterozygosity

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *PTEN* Mutational Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ Direct Sanger sequencing

+ \_\_\_ Pyrosequencing

+ \_\_\_ PCR, allele-specific hybridization

+ \_\_\_ Real-time PCR

+ \_\_\_ High-throughput next-generation sequencing

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *MGMT* Promoter Methylation**

+ Testing Method (select all that apply)

+ \_\_\_ Methylation-specific PCR

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *BRAF* V600E Mutational Analysis**

+ Mutations Assessed (select all that apply)

+ \_\_\_ V600E

+ \_\_\_ Any mutation in exon 15

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ Testing Method (select all that apply)

+ \_\_\_ Direct Sanger sequencing

+ \_\_\_ Pyrosequencing

+ \_\_\_ PCR, allele-specific hybridization

+ \_\_\_ Real-time PCR

+ \_\_\_ High-throughput next-generation sequencing

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Immunohistochemistry for BRAF V600E**

+ Primary Antibody

+ \_\_\_ VE1

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *BRAF* Rearrangement Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Real-time PCR

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Immunohistochemistry for Ki-67**

+ Primary Antibody

+ \_\_\_ MIB1

+ \_\_\_ SP6

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ EMBRYONAL TUMORS**

**+ Immunohistochemistry for Beta-Catenin**

+ Primary Antibody

+ \_\_\_ E-5

+ \_\_\_ 14

+ \_\_\_ Beta-catenin-1

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Monosomy 6 Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Immunohistochemistry for GAB1**

+ Primary Antibody

+ Specify: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *MYC* Amplification Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *MYCN* Amplification Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Isochromosome 17 (i17q) Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ In situ hybridization

+ \_\_\_ Cytogenomic microarray (CMA)

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Immunohistochemistry for INI1 (BAF47)**

+ Primary Antibody

+ \_\_\_ MRQ-27

+ \_\_\_ 25/BAF47

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ *SMARCB1/INI1/HNSF5* Mutational Analysis**

+ Testing Method (select all that apply)

+ \_\_\_ Direct Sanger sequencing

+ \_\_\_ Pyrosequencing

+ \_\_\_ PCR, allele-specific hybridization

+ \_\_\_ Real-time PCR

+ \_\_\_ High-throughput next-generation sequencing

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Comments:**

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Explanatory Notes**

The diagnosis of central nervous system (CNS) tumors increasingly relies on molecular genetic applications to aid in classification, offer prognostic value, and predict response to therapy.[1-6](#_ENREF_1) These applications may assess genetic losses, amplifications, translocations, mutations, or the expression levels of specific gene transcripts or proteins. Molecular diagnostics is quickly transitioning from testing for one biomarker at a time to a panel-based approach and whole genome analysis. Frequently employed methods for genetic testing are gene sequencing, fluorescence in situ hybridization (FISH), and cytogenomic microarray (CMA). In some cases, immunohistochemistry can be used as a surrogate for genetic analysis when the marker gene is consistently overexpressed or underexpressed**.** This template for reporting results of biomarker testing for CNS tumors represents a common framework for the reporting of molecular findings relevant to these diseases and does not advocate their specific application.

**GLIOMAS**

**Isocitrate Dehydrogenase (IDH)**

Isocitrate dehydrogenase (IDH) is an enzyme that exists in 5 isoforms, each of which catalyzes the reaction of isocitrate to α-ketoglutarate.[7](#_ENREF_7) The finding of mutations in *IDH1* and *IDH2* in diffuse gliomas has dramatically changed the practice of neuropathology and neurooncology. Mutations in *IDH1* are frequent (70%-80%) in World Health Organization (WHO) grade II and III astrocytomas, oligodendrogliomas, and oligoastrocytomas, as well as glioblastomas (GBMs; WHO grade IV) that have progressed from these lower grade neoplasms (secondary GBMs).[8](#_ENREF_8) Mutations in *IDH2* have also been detected in these same tumor types, but much less frequently. *IDH* mutations are infrequent in de novo GBMs. The mutant forms of *IDH1* and *IDH2* lead to the production of the oncometabolite 2-hydroxyglutarate, which inhibits the function of numerous α-ketoglutarate–dependent enzymes.[9](#_ENREF_9) Inhibition of the family of histone demethylases and the TET family of 5-methylcytosine hydroxylases has profound effect on the epigenetic status of mutated cells and leads directly to a hypermethylator phenotype that has been referred to as the CpG island methylator phenotype (G-CIMP).[10](#_ENREF_10) The finding of *IDH* mutations in an infiltrating glioma is associated with substantially improved prognosis, grade for grade. Indeed, *IDH* mutant GBMs, WHO grade IV, are associated with longer survivals than *IDH* wild-type anaplastic astrocytomas, WHO grade III. Over 90% of *IDH1* mutations in diffuse gliomas occur at a specific site and are characterized by a base exchange of guanine to adenine within codon 132, resulting in an amino acid change from arginine to histidine (R132H). Because of this consistent protein alteration, a monoclonal antibody has been developed to the mutant protein, allowing its use in paraffin-embedded specimens (mIDH1R132H).[11](#_ENREF_11) The ability of the antibody to detect a small number of cells as mutant may make this method more sensitive than sequencing for identifying *R132H* mutant gliomas. However, mutations in *IDH2* and other mutations in *IDH1* will not be detected using immunohistochemistry with this antibody.

**1p/19q**

One of the best studied relationships between genetic alterations and glioma histology is the strong association of allelic losses on chromosomes 1p and 19q and the oligodendroglioma phenotype.[12](#_ENREF_12),[13](#_ENREF_13) Approximately 60% to 80% of oligodendroglial neoplasms demonstrate combined 1p and 19q losses, and those oligodendrogliomas that are morphologically classic have even higher frequencies.[14](#_ENREF_14) Most studies have indicated that combined losses of 1p and 19q are specific to oligodendrogliomas, with only few astrocytomas and a small subset of oligoastrocytomas harboring these alterations. Those oligodendrogliomas with 1p/19q loss show enhanced response to chemotherapy and are associated with prolonged survival. Co-deletion of 1p/19q occurs by an unbalanced translocation after which only one copy of the short arm of chromosome 1 and one copy of the long arm of chromosome 19 remain and der(1;19) (q10;p10) is produced.[15](#_ENREF_15) Solitary losses of 1p or 19q are also occasionally noted within an infiltrating glioma, but are not as strongly linked to the oligodendroglioma histology and are not predictive of enhanced response to therapy or prolonged survival.[13](#_ENREF_13) Polysomy of 1p, 19q or both is also noted in a subset of oligodendrogliomas and has been associated with a poor prognosis, independent of deletion status.[16](#_ENREF_16), [17](#_ENREF_17) Co-deletion of 1p/19q is highly associated with the *IDH1* mutation, with over 80% of 1p/19q co-deleted oligodendrogliomas also carrying the *IDH1* mutation.[18](#_ENREF_18) Oligodendrogliomas of grades II and III that have 1p/19q co-deletion also have a high frequency of *TERT* promoter mutations, *CIC* mutations on the remaining chromosome 1p allele and *FUBP1* mutation on the remaining 19q allele.[18](#_ENREF_18),[19](#_ENREF_19)

**TP53**

Mutations of *TP53* are found in over 60% to 80% of infiltrative astrocytomas, anaplastic astrocytomas and secondary GBMs, yet are rare in oligodendrogliomas.[8](#_ENREF_8),[20](#_ENREF_20),[21](#_ENREF_21) The vast majority of diffuse astrocytomas that have *IDH* mutations also harbor a *TP53* mutation.[22](#_ENREF_22) In one study, 80% of anaplastic astrocytomas and GBMs that had an *IDH1* or *IDH2* mutation also carried a *TP53* mutation. Conversely, *TP53* mutations were identified in only 18% of high-grade astrocytomas that lacked an *IDH1* or *IDH2* mutation.[8](#_ENREF_8) Thus, there is a strong association between *IDH1* mutation and *TP53* mutation in diffuse astrocytomas, and this combination of mutations is helpful in distinguishing astrocytomas from oligodendroglimas. Immunohistochemical reactivity for the p53 protein is often used as a marker for astrocytic differentiation in diffuse gliomas, since the mutant protein is degraded more slowly and accumulates in the nucleus of tumor cells. This immunostain reacts with both the normal and mutant forms of p53 and therefore is not entirely specific for *TP53* mutations.[23](#_ENREF_23)

**ATRX**

*IDH1* mutation and *TP53* mutation in infiltrating gliomas are strongly associated with inactivating alterations in *Alpha Thalassemia/Mental Retardation Syndrome X-linked* (*ATRX*), a gene that encodes a protein involved in chromatin remodeling.[22](#_ENREF_22),[24](#_ENREF_24) *ATRX* mutations are a marker of astrocytic lineage among the *IDH* mutant gliomas and are mutually exclusive with 1p/19q codeletion. Mutations are most frequent in grade II (67%) and grade III (73%) astrocytomas and secondary GBMs (57%), while they are uncommon in primary GBMs and oligodendrogliomas. Nearly all diffuse gliomas with *IDH* and *ATRX* mutations also harbor *TP53* mutation and are associated with the alternative lengthening of telomeres (ALT) phenotype.[24](#_ENREF_24) Immunohistochemistry for ATRX demonstrates a loss of protein expression in neoplastic cells that harbor inactivating mutations, while expression is retained in nonneoplastic cells within the sample (eg, endothelial cells).[25](#_ENREF_25),[26](#_ENREF_26)

**EGFR**

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase, whose ligands include EGF and TGF-α. *EGFR* is the most frequently amplified oncogene in astrocytic tumors, being amplified in over 40% of all GBMs and less frequently in anaplastic astrocytomas (5%-10%).[27](#_ENREF_27) *EGFR* amplification is much more frequent in de novo (primary) GBMs than in secondary GBMs.[28](#_ENREF_28) Approximately one-half of those GBMs with *EGFR* amplification also have specific *EGFR* mutations (the *vIII* mutant), which produce a truncated transmembrane receptor with constitutive activity. Both *EGFR* amplification and the *EGFRvIII* mutant are mutually exclusive with *IDH* mutations. *EGFR* amplification is specific to those gliomas that are astrocytic in differentiation and of higher grade, such as anaplastic astrocytoma, WHO grade III, and GBM, WHO grade IV.[29](#_ENREF_29) This molecular finding can be useful in distinguishing the morphologically similar small cell GBM, which harbor the amplification, from anaplastic oligodendrogliomas, which does not.[30](#_ENREF_30)

**PTEN and LOH Chromosome 10**

Loss of the entire chromosome (monosomy), deletions, and copy neutral loss of heterozygosity (LOH) of chromosome 10 occurs in 60% to 95% of GBMs and less frequently in grade II or III diffuse astrocytomas.[28](#_ENREF_28) Loss of large regions at 10p, 10q23 and 10q25-26 loci, or loss of an entire copy of chromosome 10 are the most frequent genetic alterations in GBMs.[1](#_ENREF_1) Loss of the long arm, which occurs more frequently than the short arm in GBMs, occurs equally in primary and secondary GBMs. The *PTEN* gene at 10q23.3 has been most strongly implicated as a glioma-related tumor suppressor on chromosome 10q, with *PTEN* mutations identified in about 25% of GBMs and less frequently in anaplastic astrocytomas, WHO grade III.[29](#_ENREF_29) *PTEN* mutations are more common in primary GBMs than secondary GBMs. Losses on chromosome 10 and mutations in *PTEN* are considered to be specific for astrocytic differentiation and are rare in oligodendrogliomas. They are also markers of high-grade progression and aggressive clinical behavior in astrocytomas.[4](#_ENREF_4),[31](#_ENREF_31) The clinical significance of polysomy involving chromosome 10 is not fully understood.

**MGMT**

The current standard therapy for GBM includes radiation and chemotherapy with temozolomide, which acts by crosslinking DNA by alkylating multiple sites including the O6 position of guanine.[32](#_ENREF_32) DNA crosslinking at the O6 position of guanine is reversed by the DNA repair enzyme MGMT (O6-methylguanine-DNA methyltransferase). Thus, low levels of MGMT expression by GBM cells would be expected to be associated with an enhanced response to alkylating agents. The expression level of MGMT is determined in large part by the methylation status of the gene’s promoter. This “epigenetic silencing” of *MGMT* occurs in 40% to 50% of GBMs and can be assessed by its promoter methylation status on PCR-based tests of genomic DNA. Some laboratories report the promoter methylation status as “low level” and “high level,” or indicate that “partial methylation” is present, yet the clinical implications of this distinction are not fully understood. Most investigations have shown that epigenetic gene silencing of *MGMT* is a strong predictor of prolonged survival, independent of other clinical factors or treatment.[33](#_ENREF_33) It has also been demonstrated that *MGMT* promoter methylation is associated with prolonged progression-free and overall survival in patients with GBM treated with chemotherapy and radiation therapy. [33](#_ENREF_33), [34](#_ENREF_34)

***BRAF***

Genomic alterations involving *BRAF* are common in sporadic cases of pilocytic astrocytoma and result in the downstream activation of the ERK/MAPK pathway.[2](#_ENREF_2) *BRAF* activation in pilocytic astrocytoma occurs most commonly through a gene fusion between *KIAA1549* and *BRAF*, producing a fusion protein that lacks the BRAF regulatory domain and demonstrates constitutive activity.[35](#_ENREF_35) This fusion is seen in the majority of cerebellar and midline pilocytic astrocytomas, but is present at lower frequency in cerebral tumors.[36](#_ENREF_36) Cerebral hemispheric pilocytic astrocytomas are more likely to harbor activating *BRAF* V600E point mutations. Other genomic alterations in pilocytic astrocytomas include other *BRAF* gene fusions, *RAF1* rearrangements, and *RAS* mutations, but these are less common. Given the role of neurofibromatosis 1 (NF1) deficiency in activating the ERK/MAPK pathway, *BRAF* genomic alterations are uncommon in pilocytic astrocytoma associated with NF1. *BRAF* point mutations (V600E) are also observed in other low-grade gliomas and glioneuronal neoplasms, including approximately two-thirds of pleomorphic xanthoastrocytomas (PXAs) and lower percentages of ganglioglioma, desmoplastic infantile ganglioglioma (DIG), and dysembryoplastic neuroepithelial tumor (DNT).[37](#_ENREF_37) While these tumor types are most frequently encountered in children, they are also occasionally seen in adults and have similar *BRAF* mutations. Although less common, diffusely infiltrative gliomas including GBM, particularly the epithelioid variant, may also demonstrate the V600E mutation.[27](#_ENREF_27),[38-40](#_ENREF_38) More recently, *BRAF* mutations have been identified in papillary craniopharyngiomas.[41](#_ENREF_41)

**Ki-67**

The most reliable and technically feasible marker of proliferation for gliomas is Ki-67, a nuclear antigen expressed in cells actively engaged in the cell cycle but not expressed in the resting phase, G0.[5](#_ENREF_5) Results are expressed as a percentage of positive staining tumor cell nuclei (Ki-67 labeling index). Numerous investigations have demonstrated a positive correlation between Ki-67 indices and histologic grade for astrocytomas, oligodendrogliomas, and oligoastrocytomas.[42](#_ENREF_42),[43](#_ENREF_43) Among grade II and III diffuse gliomas, the Ki-67 index provides prognostic value, as there is a strong inverse relation with survival on multivariate analysis.[42](#_ENREF_42) In contrast, investigations of Ki-67 proliferation on patient outcome for GBM, WHO grade IV, have consistently concluded that it does not provide prognostic value in this set of tumors.[44](#_ENREF_44) One potential shortcoming of Ki-67 as a marker is the high degree of variability in tissue processing, immunohistochemical staining, and quantization techniques between laboratories, making it difficult to standardize proliferation indices.[45](#_ENREF_45) Large variations in proliferation rates within a single tumor may also be noted. Nonetheless, when interpreted uniformly within a given laboratory, the Ki-67 proliferation index provides prognostic value to clinicians and can be helpful in histologically borderline cases, such as those that are at the grade II to III and III to IV border. A high labeling index in this setting may indicate a more aggressive neoplasm.

**EMBRYONAL TUMORS**

**Medulloblastoma Markers**

Medulloblastomas are primitive embryonal neoplasms of the cerebellum, generally arising in childhood, whose molecular genetic alterations have now been well defined. Four subgroups have been described based on gene expression profiles: wingless (WNT), sonic hedgehog (SHH), "group 3," and "group 4."[3](#_ENREF_3), [46](#_ENREF_46) WNT medulloblastomas display monosomy 6 and most also show nuclear accumulation of the WNT pathway protein beta-catenin, the latter serving as a useful immunohistochemical screen for this group.[47](#_ENREF_47) Medulloblastomas with >50% nuclear staining for beta-catenin have been shown to have WNT pathway activation, *CTNNB1* mutations, and monosomy 6, whereas those with only focal nuclear staining do not.[48](#_ENREF_48) The overall survivals for WNT pathway medulloblastomas are dramatically longer than those of the other subtypes, and clinical practices are changing in light of this.[49](#_ENREF_49) SHH medulloblastomas often show a nodular/desmoplastic histology and are associated with a better prognosis in younger children and infants. 9q deletion is characteristic of the SHH group, and *MYCN* amplifications are occasionally noted. GAB1 is expressed in the cytoplasm of nearly all SHH medulloblastomas but not in other groups and can be detected immunohistochemically, making it a valuable SHH-group marker.[47](#_ENREF_47) Targeted therapies directed at this subgroup have been established and are entering clinical practice.[50](#_ENREF_50),[51](#_ENREF_51) Group 3 has the worst overall prognosis and contains the vast majority of *MYC* amplified tumors. *MYC* and *MYCN* amplification are strong negative prognostic factors, although they occur in only a small percentage of cases.[49](#_ENREF_49) Approximately 30% to 40% of all medulloblastomas have i(17q), making it the most common genetic defect. Those tumors with i(17q) have a worse prognosis than those that don’t. Among the genetic markers for medulloblastoma, monosomy 6 (or nuclear beta-catenin immunoreactivity), GAB1 expression, *MYC* or *MYCN* amplification, and i(17q) appear to be the most reliable and carry the strongest prognostic and therapeutic implications.

**INI1**

The atypical teratoid/rhabdoid tumor (AT/RT) is a clinically aggressive embryonal tumor of infancy that occurs in the posterior fossa and cerebral hemispheres.[6](#_ENREF_6) The tumor is characterized by deletions and mutations of *SMARCB1/INI1* (*HSNF5*) (22q11.2).[52](#_ENREF_52),[53](#_ENREF_53) Immunohistochemical evaluation of AT/RT for the INI1 protein (using the BAF47 antibody) shows a loss of labeling in tumor cell nuclei, but retention of nuclear labeling in nonneoplastic cells, such as endothelial cells. The recognition of AT/RT is important for clinical management, since AT/RTs have morphologic overlap with medulloblastoma, CNS primitive neuroectodermal tumor (PNET), choroid plexus carcinoma, GBM, and other malignant tumors of childhood.[54](#_ENREF_54) The diagnosis of AT/RT and the finding of *SMARCB1/INI1* loss or mutation also carry potential implications for inheritance. These tumors are often a component of the rhabdoid tumor predisposition syndrome (RTPS), characterized by germline mutations of *SMARCB1/INI1* and manifested by a marked predisposition to the development of malignant rhabdoid tumors of infancy and early childhood.[52](#_ENREF_52),[55](#_ENREF_55) Up to one-third of AT/RTs arise in the setting of RTPS, and the majority of these occur within the first year of life.[56](#_ENREF_56) The diagnosis of RTPS is established with certainty by sequencing of *SMARCB1/INI1* on tissue representing the patient’s germline. Because of the risk associated with the RTPS, the germline status of *SMARCB1/INI1* is typically assessed for each new case of AT/RT.

**References**

1. Nikiforova MN, Hamilton RL. Molecular diagnostics of gliomas. *Arch Pathol Lab Med*. 2011;135(5):558-568.

2. Rodriguez FJ, Lim KS, Bowers D, Eberhart CG. Pathological and molecular advances in pediatric low-grade astrocytoma. *Annu Rev Pathol*. 2013;8:361-379.

3. Northcott PA, Jones DT, Kool M, et al. Medulloblastomics: the end of the beginning. *Nat Rev Cancer.* 2012;12(12):818-834.

4. Bourne TD, Schiff D. Update on molecular findings, management and outcome in low-grade gliomas. *Nat Rev Neurol*. 2010;6(12):695-701.

5. Brat DJ, Prayson RA, Ryken TC, Olson JJ. Diagnosis of malignant glioma: role of neuropathology. *J Neurooncol.* 2008;89(3):287-311.

6. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *WHO Classification of Tumours of the Central Nervous System.* 4th ed. Lyon, France: IARC Press; 2007.

7. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008;321(5897):1807-1812.

8. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360(8):765-773.

9. Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature*. 2012;483(7390):479-483.

10. Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell.* 2010;17(5):510-522.

11. Capper D, Weissert S, Balss J, et al. Characterization of R132H mutation-specific IDH1 antibody binding in brain tumors. *Brain Pathol.* 2010;20(1):245-254.

12. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst*. 1998;90(19):1473-1479.

13. Smith JS, Perry A, Borell TJ, et al. Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. *J Clin Oncol.* 2000;18(3):636-645.

14. Burger PC, Minn AY, Smith JS, et al. Losses of chromosomal arms 1p and 19q in the diagnosis of oligodendroglioma. A study of paraffin-embedded sections. *Mod Pathol.* 2001;14(9):842-853.

15. Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. *Cancer Res*. 2006;66(20):9852-9861.

16. Wiens AL, Cheng L, Bertsch EC, Johnson KA, Zhang S, Hattab EM. Polysomy of chromosomes 1 and/or 19 is common and associated with less favorable clinical outcome in oligodendrogliomas: fluorescent in situ hybridization analysis of 84 consecutive cases. *J Neuropathol Exp Neurol*. 2012;71(7):618-624.

17. Snuderl M, Eichler AF, Ligon KL, et al. Polysomy for chromosomes 1 and 19 predicts earlier recurrence in anaplastic oligodendrogliomas with concurrent 1p/19q loss. *Clin Cancer Res.* 2009;15(20):6430-6437.

18. Yip S, Butterfield YS, Morozova O, et al. Concurrent CIC mutations, IDH mutations, and 1p/19q loss distinguish oligodendrogliomas from other cancers. *J Pathol.* 2012;226(1):7-16.

19. Killela PJ, Reitman ZJ, Jiao Y, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proc Natl Acad Sci U S A*. 2013;110(15):6021-6026.

20. Okamoto Y, Di Patre PL, Burkhard C, et al. Population-based study on incidence, survival rates, and genetic alterations of low-grade diffuse astrocytomas and oligodendrogliomas. *Acta Neuropathol.* 2004;108(1):49-56.

21. Watanabe T, Nobusawa S, Kleihues P, Ohgaki H. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathol.* 2009;174(4):1149-1153.

22. Liu XY, Gerges N, Korshunov A, et al. Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. *Acta Neuropathol.* 2012;124(5):615-625.

23. Kurtkaya-Yapicier O, Scheithauer BW, Hebrink D, James CD. p53 in nonneoplastic central nervous system lesions: an immunohistochemical and genetic sequencing study. *Neurosurgery*. 2002;51(5):1246-1254; discussion 1254-1255.

24. Jiao Y, Killela PJ, Reitman ZJ, et al. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. *Oncotarget*. 2012;3(7):709-722.

25. Wiestler B, Capper D, Holland-Letz T, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. *Acta Neuropathol*. 2013;126(3):443-451.

26. Nguyen DN, Heaphy CM, de Wilde RF, et al. Molecular and morphologic correlates of the alternative lengthening of telomeres phenotype in high-grade astrocytomas. *Brain Pathol.* 2013;23(3):237-243.

27. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155(2):462-477.

28. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol.* 2007;170(5):1445-1453.

29. Smith JS, Tachibana I, Passe SM, et al. PTEN mutation, EGFR amplification, and outcome in patients with anaplastic astrocytoma and glioblastoma multiforme. *J Natl Cancer Inst*. 2001;93(16):1246-1256.

30. Perry A, Aldape KD, George DH, Burger PC. Small cell astrocytoma: an aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma. *Cancer*. 2004;101(10):2318-2326.

31. Rasheed BK, Stenzel TT, McLendon RE, et al. PTEN gene mutations are seen in high-grade but not in low-grade gliomas. *Cancer Res*. 1997;57(19):4187–4190.

32. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.

33. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997-1003.

34. Rivera AL, Pelloski CE, Gilbert MR, et al. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. *Neuro Oncol*. 2010;12(2):116-121.

35. Pfister S, Janzarik WG, Remke M, et al. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. *J Clin Invest.* 2008;118(5):1739-1749.

36. Horbinski C. To BRAF or not to BRAF: is that even a question anymore? *J Neuropathol Exp Neurol.* 2013;72(1):2-7.

37. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* 2011;121(3):397-405.

38. Chi AS, Batchelor TT, Yang D, et al. BRAF V600E mutation identifies a subset of low-grade diffusely infiltrating gliomas in adults. *J Clin Oncol*. 2013;31(14):e233-236.

39. Dahiya S, Emnett RJ, Haydon DH, et al. BRAF-V600E mutation in pediatric and adult glioblastoma. *Neuro Oncol.* 2013;16(2):318-319.

40. Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, Foreman NK. Epithelioid GBMs show a high percentage of BRAF V600E mutation. *Am J Surg Pathol.* 2013;37(5):685-698.

41. Larkin SJ, Preda V, Karavitaki N, Grossman A, Ansorge O. BRAF V600E mutations are characteristic for papillary craniopharyngioma and may coexist with CTNNB1-mutated adamantinomatous craniopharyngioma. *Acta Neuropathol.* 2014;127(6):927-929.

42. Giannini C, Scheithauer BW, Burger PC, et al. Cellular proliferation in pilocytic and diffuse astrocytomas. *J Neuropathol Exp Neurol.* 1999;58(1):46-53.

43. Coons SW, Johnson PC. MIB-1/Ki-67 labelling index predicts patient survival for oligodendroglial tumors. *J Neuropathol Exp Neurol.* 1995;(54):440.

44. Moskowitz SI, Jin T, Prayson RA. Role of MIB1 in predicting survival in patients with glioblastomas. *J Neurooncol.* 2006;76(2):193-200.

45. Marie D, Liu Y, Moore SA, et al. Interobserver variability associated with the MIB-1 labeling index: high levels suggest limited prognostic usefulness for patients with primary brain tumors. *Cancer*. 2001;92(10):2720-2726.

46. Northcott PA, Korshunov A, Pfister SM, Taylor MD. The clinical implications of medulloblastoma subgroups. *Nat Rev Neurol.* 2012;8(6):340-351.

47. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol.* 2011;121(3):381-396.

48. Fattet S, Haberler C, Legoix P, et al. Beta-catenin status in paediatric medulloblastomas: correlation of immunohistochemical expression with mutational status, genetic profiles, and clinical characteristics. *J Pathol.* 2009;218(1):86-94.

49. Pfister S, Remke M, Benner A, et al. Outcome prediction in pediatric medulloblastoma based on DNA copy-number aberrations of chromosomes 6q and 17q and the MYC and MYCN loci. *J Clin Oncol*. 2009;27(10):1627-1636.

50. Rudin CM, Hann CL, Laterra J, et al. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. *N Engl J Med.* 2009;361(12):1173-1178.

51. Macdonald TJ, Aguilera D, Castellino RC. The rationale for targeted therapies in medulloblastoma. *Neuro Oncol*. 2014;16(1):9-20.

52. Biegel JA. Molecular genetics of atypical teratoid/rhabdoid tumor. *Neurosurg Focus*. 2006;20(1):E11.

53. Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res.* 1999;59(1):74-79.

54. Judkins AR, Mauger J, Ht A, Rorke LB, Biegel JA. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. *Am J Surg Pathol.* 2004;28(5):644-650.

55. Biegel JA, Fogelgren B, Wainwright LM, Zhou JY, Bevan H. Rorke LB. Germline INI1 mutation in a patient with a central nervous system atypical teratoid tumour and renal rhabdoid tumour. *Genes Chromosomes Cancer.* 2000;28(1):31–37.

56. Bourdeaut F, Lequin D, Brugieres L, et al. Frequent hSNF5/INI1 germline mutations in patients with rhabdoid tumor. *Clin Cancer Res.* 2011;17(1):31-38.