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ONCOLOGY: *Molecular Biomarkers in Tumors of the Central Nervous System*

Samples to test: Primary or recurrent tumors; formalin-fixed paraffin-embedded tissue (FFPE)

Biomarker	Alteration/ Alternative terms	Indications	Significance	Common methods
IDH1 ***IDH2***	*IDH1*: Mutations in codon R132 *IDH2*: Mutations in codons R140, R172	Diagnosis Prognosis	Diagnostic biomarker of astrocytoma, *IDH*-mutant and oligodendroglioma, *IDH*-mutant and 1p/19q co-deleted. Associated with improved prognosis except when the tumor also has a homozygous deletion of *CDKN2A/B* (negative prognosis).	NGS, Sanger sequencing, genotyping, PCR-based assays, IHC
1p/19q co-deletion	Deletion	Diagnosis Prognosis	1p/19q whole-arm co-deletion is a diagnostic molecular biomarker of oligodendroglioma and is associated with improved prognosis.	FISH, array, NGS
BRAF	Mutations (particularly V600E); fusions	V600E mutations are therapeutic Fusions such as *BRAF::KIAA1549* are diagnostic	Seen in a variety of tumors, such as pleomorphic xanthoastrocytoma; ganglioglioma; pilocytic astrocytoma; diffuse low-grade glioma, MAPK pathway-altered. V600E mutations are targetable; fusions can be used in diagnosis (e.g., *KIAA1549::BRAF*) and are potentially targetable.	NGS, Sanger sequencing, genotyping, PCR-based assays, IHC, RT-PCR, AMP
***H3-3A* (previously *H3F3A*)** ***H3C2* (previously *HIST1H3B*)**	Alterations in codons K28 (K27) or G35 (G34)	Diagnosis Prognosis	Diagnostic molecular biomarker of diffuse midline glioma, H3 K28M (K27M)-altered; and diffuse hemispheric glioma, H3 G35 (G34)-mutant. H3 K28M (K27M) in adult patients and in supratentorial tumors confer better prognosis than in children with this alteration.	NGS, Sanger sequencing, genotyping, PCR-based assays, IHC
TERT	Promoter mutation	Prognosis	Presence confers WHO Grade 4 designation in diffuse astrocytoma, *IDH*-wildtype (glioblastoma). Present in almost all oligodendrogliomas, *IDH*-mutant and 1p/19q co-deleted.	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
MGMT	Promoter methylation	Prognosis Therapeutic	Associated with more favorable prognosis and response to temozolomide in patients with glioblastoma, IDH-wildtype.	Methylation-specific PCR-based assays, bisulfite real-time bisulfite sequencing
ATRX	Loss of function mutations; loss of protein expression	Diagnosis	Diagnostic molecular biomarker for astrocytoma, *IDH*-mutant. Associated with *IDH1* and *IDH2* mutations. Typically, mutually exclusive with 1p/19q co-deletion. Supportive diagnostic biomarker for diffuse hemispheric glioma, H3 G34-mutant, and high-grade astrocytoma with piloid features.	NGS, pyrosequencing, Sanger sequencing, IHC
***ZFTA* (previously *C11orf95*)**	Fusion	Diagnosis Prognosis	Diagnostic molecular biomarker for supratentorial ependymoma, *ZFTA* fusion-positive. *ZFTA* fusion-positive ependymomas tend to show more aggressive behavior.	NGS, RT-PCR, AMP, FISH
EGFR **chromosome 7** **chromosome 10**	*EGFR* amplification Gain of chromosome 7 Loss of chromosome 10	Diagnosis	If an *IDH*-wildtype diffuse astrocytic glioma of histologic grade 2 or 3 has any one of the following three molecular alterations, it can be classified as a glioblastoma: *EGFR* amplification, *TERT* promoter mutation, gain of chromosome 7 with loss of chromosome 10.	FISH, array, NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays

Abbreviations: NGS: next-generation sequencing; IHC: immunohistochemistry; FISH: fluorescence *in situ* hybridization; AMP: anchored multiplex PCR; RT-PCR: reverse transcription-polymerase chain reaction.

Where to test: Testing should be performed in the laboratories that are certified under clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

***References*: 1.** Louis DN, *et al.* (Eds). WHO Classification of Tumours of the Central Nervous System. Vol 1. 4th ed. Geneva, Switzerland: World Health Organization; 2016. **2.** Louis DN, *et al.* cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathology 2020:30(4):844-856. **3.** van den Bent MJ, *et al*. Primary brain tumours in adults. Lancet 2023:402(10412):1564-79. **4.** Louis DN, *et al*. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncology 2021:23(8):1231-51.

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