Molecular In My Pocket…

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

Molecular Biomarkers in Tumors of the Central Nervous System

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

Biomarker	Specific alterations Alternative terms	Indications	Result interpretation significance	Assays Techniques
IDH1 ***IDH2***	*IDH1*: Mutations in codon R132 *IDH2*: Mutations in codons R140, R172	Diagnosis Prognosis	Can be seen in astrocytoma, glioblastoma, oligodendroglioma. Associated with improved prognosis except when the tumor also has a homozygous deletion of *CDKN2A/B*	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays, IHC
1p/19q co-deletion	Deletion	Diagnosis Prognosis	Co-deletion of 1p/19q is seen in oligodendrogliomas and is associated with improved prognosis.	FISH, array, NGS
BRAF	Mutations in codon V600; fusions	V600 mutations are therapeutic: Fusions such as *BRAF-KIAA1549* are more diagnostic	Seen in tumors such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma. Activating mutations or fusions are potentially targetable.	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays, IHC, RT-PCR, AMP
H3F3A ***HIST1H3B***	Mutations in codon K27, G34	Diagnosis	Seen in diffuse midline glioma, H3 K27M-mutant G34 mutations can be seen in pediatric cortical gliomas	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays, IHC
TERT	Promoter mutation	Prognosis	Associated with less favorable prognosis in IDH-wild type astrocytomas and present in almost all oligodendrogliomas.	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
MGMT	Promoter methylation	Therapeutic	Associated with response to temozolomide	Methylation-specific PCR, bisulfite real-time PCR, bisulfite sequencing
ATRX	Loss of function mutations	Diagnosis	Associated with the presence of *IDH1* or *IDH2* mutations. Typically mutually exclusive with 1p/19q co-deletion	NGS, pyrosequencing, Sanger sequencing, IHC
RELA	Fusion	Diagnosis Prognosis	RELA-fusion positive ependymomas (usually supratentorial) tend to show more aggressive behavior.	RT-PCR, AMP, FISH
EGFR **chromosome 7** **chromosome 10**	*EGFR* amplification Gain of chromosome7 Loss of chromosome 10	Diagnosis	If a histologic grade 2 or 3, IDH-wildtype astrocytoma has any one of the following three molecular alterations, then is classified as a glioblastoma: *EGFR* amplification, *TERT* promoter mutation, or combined gain of chromosome 7 and loss of chromosome 10.	FISH, array, NGS

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-Ultrecht meeting on future CNS tumor classification and grading. Brain Pathology 2020:30 (4):844-856.

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