

# DIFFUSE GLIOMAS – DIAGNOSTIC APPROACH AND ANCILLARY TESTS FOR CLASSIFICATION

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## Case-Based Questions (please see page 3 for answers)

1.	You receive a left parietal lobe tumor resection from a 21-year-old man. Morphologically, the tumor is a diffusely infiltrative glioma with numerous mitotic figures. Immunohistochemistry shows: GFAP positive, P53 positive, ATRX lost, IDH1 p.R132H negative. Which of the following alteration is most likely to be present?
a.	BRAF p.V600E
b.	H3.3 p.G34R
c.	H3.3 p.K27M
d.	NF1 mutation
e.	PDGFRA p.K385L
2.	You receive a resection of a left temporal lobe tumor from a 39-year-old woman. Morphologically, the tumor is a diffusely infiltrative glioma without discernable mitotic activity, necrosis or microvascular proliferation. Tumor harbors <i>IDH2</i> p.R172M and <i>TERT</i> promoter mutations. What is the most likely immunophenotype of this tumor?
a.	IDH1 R132H+ / ATRX-lost / H3 K27M- / H3 G34R-
b.	IDH1 R132H+ / ATRX-retained / H3 K27M- / H3 G34R-
c.	IDH1 R132H- / ATRX-lost / H3 K27M+ / H3 G34R-
d.	IDH1 R132H- / ATRX-retained / H3K27M- / H3 G34R-
e.	IDH1 R132H- / ATRX-lost / H3K27M- / H3 G34R+
3.	You receive a partial resection of a left insular tumor from a 55-year-old woman. Morphologically, the tumor is a diffusely infiltrative glioma composed of atypical cells with irregular hyperchromatic nuclei and shows numerous mitotic figures. No necrosis or microvascular proliferation is identified. Immunohistochemistry shows: IDH1R132H negative, ATRX retained, p53 positive in 50% of the cells. Which one of the molecular alterations below supports the diagnosis of grade 4 glioma?
a.	<i>CDKN2A</i> homozygous deletion
b.	<i>EGFR</i> amplification
c.	Monosomy 7 and 10
d.	<i>PTEN</i> truncating mutation
e.	<i>TERT</i> truncating mutation

**Scroll to Page 3 for Answers**

Question 1: Correct answer and rationale: B

H3.3 p.G34R. In anaplastic astrocytomas or GBMs of the adolescent/ young adult population, an important differential diagnosis to consider in an IDH wildtype tumor is an H3.3 p.G34R mutation. Similar to IDH mutant astrocytomas, these will have loss of ATRX expression and will be diffusely P53 positive.

Question 2: Correct answer and rationale: D

The tumor harbors a noncanonical IDH mutation involving IDH2 gene. Therefore immunohistochemical stain specific for IDH1 R132H mutation is expected to be negative. Tumor also harbors a TERT promoter mutation, and among IDH-mutant gliomas, those with TERT promoter mutations are typically oligodendrogliomas. ATRX alterations are often seen in astrocytomas and almost always mutually exclusive with TERT promoter mutations. Given the expected wildtype ATRX in this tumor, ATRX stain is expected to show retained nuclear expression. Histone mutations are mutually exclusive with IDH mutations, and therefore mutation specific stains for histone mutations are expected to be negative.

Question 3: Correct answer and rationale: B

According to cIMPACT-NOW update 3 recommendations, diffusely infiltrating IDH-wildtype astrocytomas with the molecular alteration listed below should be classified as “Diffuse astrocytic glioma, IDH-wildtype with molecular features of glioblastoma, WHO grade IV” given diffuse astrocytomas with these molecular alterations show outcomes similar to glioblastoma, diagnosed based on the presence of necrosis and/or microvascular proliferation.

TERT promoter mutation **OR**

EGFR amplification **OR**

Trisomy 7 **and** monosomy 10