NF1-Associated Nervous System Tumors

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

1.	A patient is followed in neurofibromatosis clinic for increased burden of plexiform neurofibromas affecting deep nerves. A right brachial plexus lesion shows increased FDG uptake on PET scan, prompting a diagnostic biopsy. The biopsy reveals a hypercellular proliferation of spindled cells but no definite cytologic atypia, loss of neurofibroma architecture, mitotic figures, or necrosis is seen in the limited sample. What molecular alteration is considered an early marker of higher-grade transformation in NF1-associated nerve sheath tumors?	
	a.	ATRX inactivating mutation
	b.	CDKN2A homozygous deletion
	c.	Large-scale chromosome arm gains and losses
	d.	SUZ12 and EED mutations

2.	A 42-year-old patient with NF1 is found to have cerebral hemispheric glioma. Sequencing studies reveal two inactivating NF1 mutations, an inactivating ATRX mutation, and CDKN2A homozygous deletion. Based on these results, what is the most appropriate next step?	
	a.	Array comparative genomic hybridization (aCHG) to confirm CDKN2A homozygous deletion and assess for other copy number alterations
	b.	DNA methylation profiling to confirm the diagnosis
	c.	Fusion panel to assess for presence of BRAF::KIAA1549
	d.	No additional testing is needed

3.	A patient with NF1 presents with decreased visual acuity. Imaging demonstrates expansion of the left optic nerve. A pilocytic astrocytoma is suspected. NF1-associated pilocytic astrocytoma typically arise in which of the below groups?	
	a.	Adult patients
	b.	Elderly patients
	c.	Neonates
	d.	Pediatric patients

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Correct Answers and Rationales

Question 1 Correct Answer and Rationale: **B. CDKN2A homozygous deletion**

Rationale: To date, studies have revealed CDKN2A homozygous deletion as one of the earlier events in "malignant transformation" of plexiform neurofibromas. The presence of CDKN2A homozygous deletion can be used to support a diagnosis of "atypical neurofibromatous neoplasm of uncertain biologic potential" or ANNUBP.

Question 2 Correct Answer and Rationale: **B. DNA methylation profiling to confirm the diagnosis**

Rationale: The constellation of MAPK alteration (NF1 in this case), ATRX inactivation, and CDKN2A homozygous deletion raise suspicion for a "high-grade astrocytoma with piloid features" or HGAP. While the mutation pattern is consistent, current WHO guidelines require confirmation with DNA methylation testing to render this specific diagnosis.

Question 3 Correct Answer and Rationale: **D. Pediatric patients**

Rationale: NF1-associated pilocytic astrocytoma predominantly occur in children, but can present at any age.