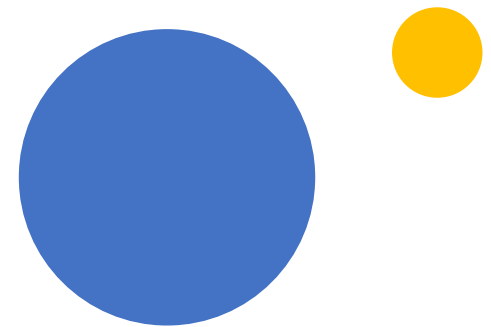
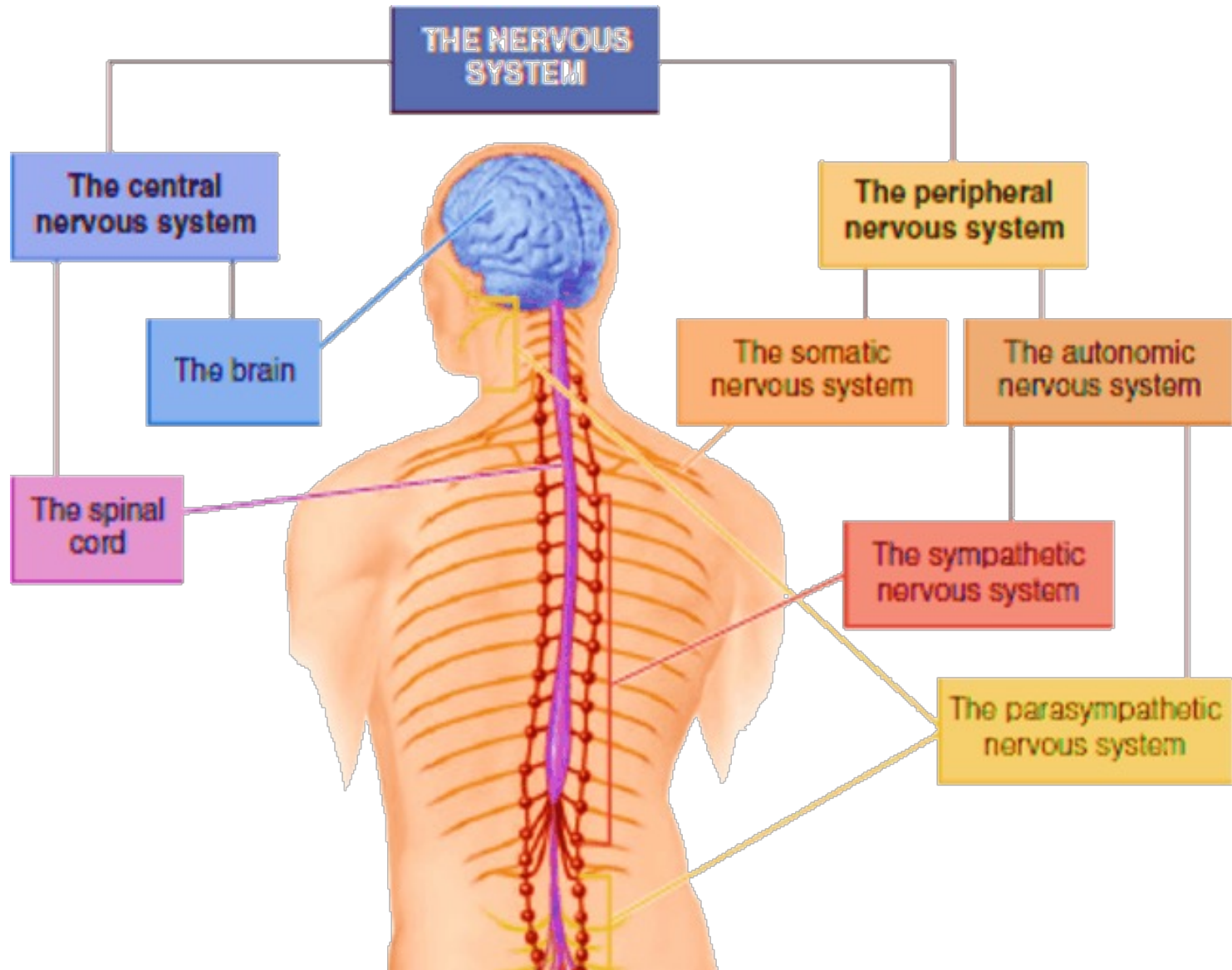


Α' Παιδιατρική Κλινική,
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών
Πανεπιστημιακή Ογκολογική/ Αιματολογική Μονάδα
Μαρία Φιλιππίδου

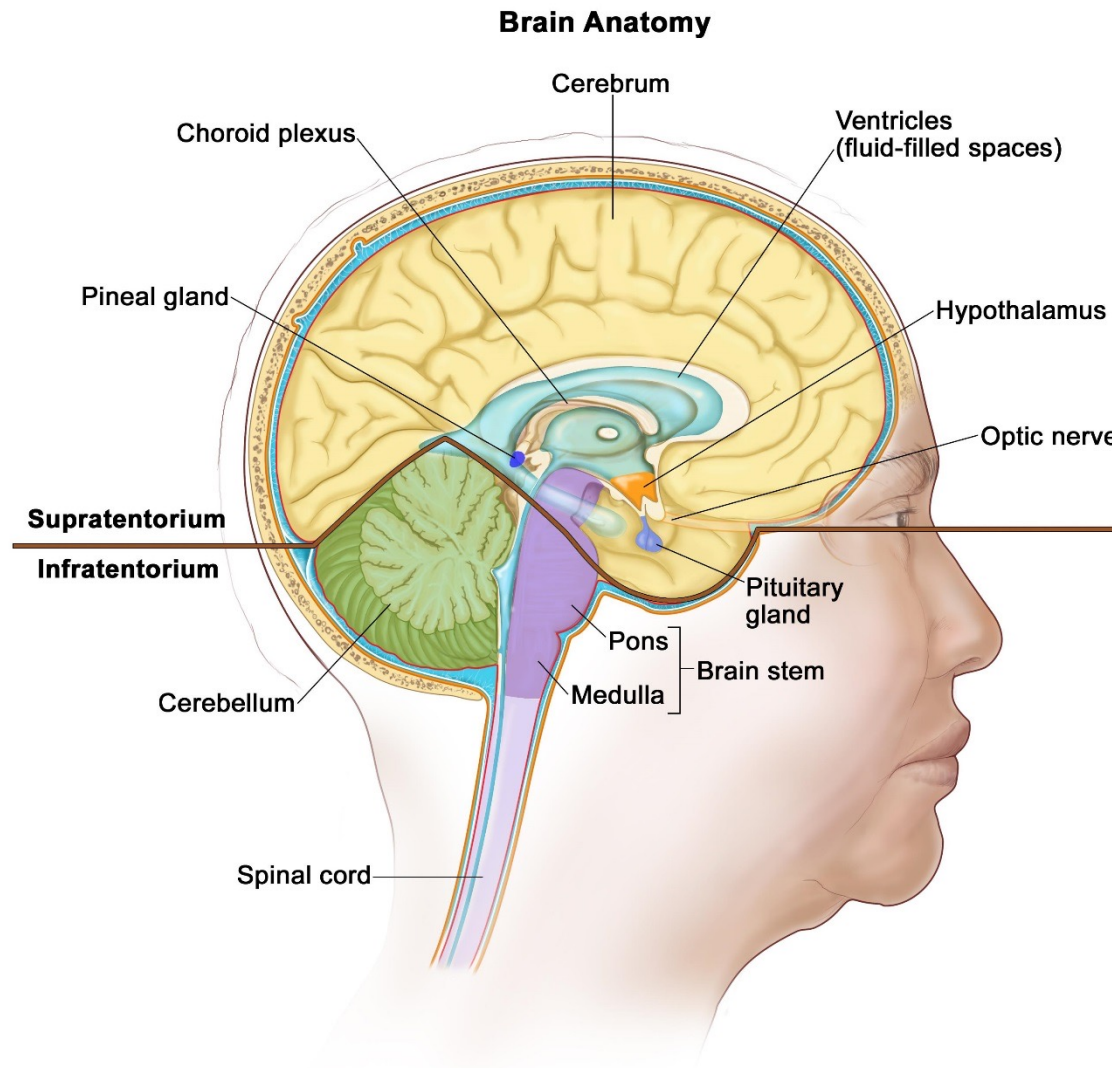
CNS TUMORS - CLASSIFICATION



Το νευρικό σύστημα



Location

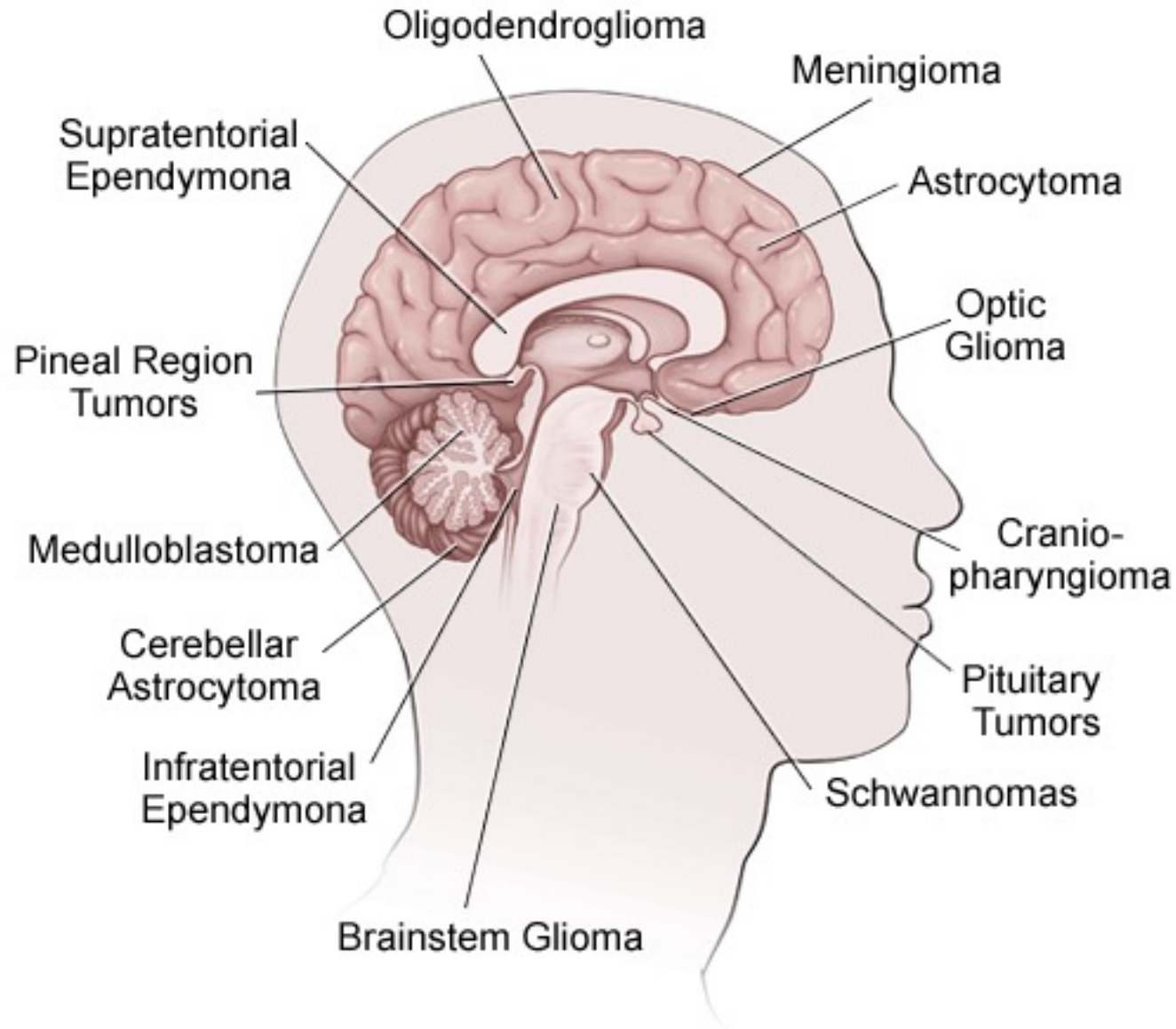


Supratentorial tumors

Infratentorial tumors

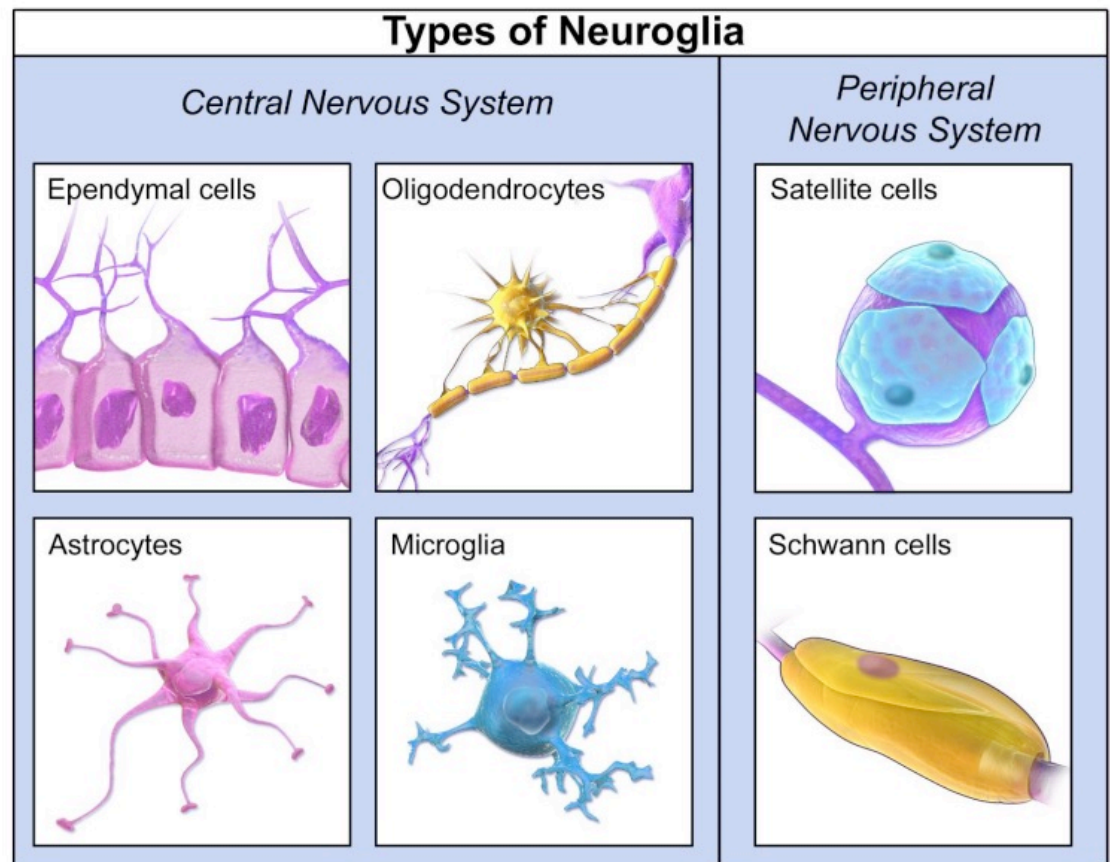
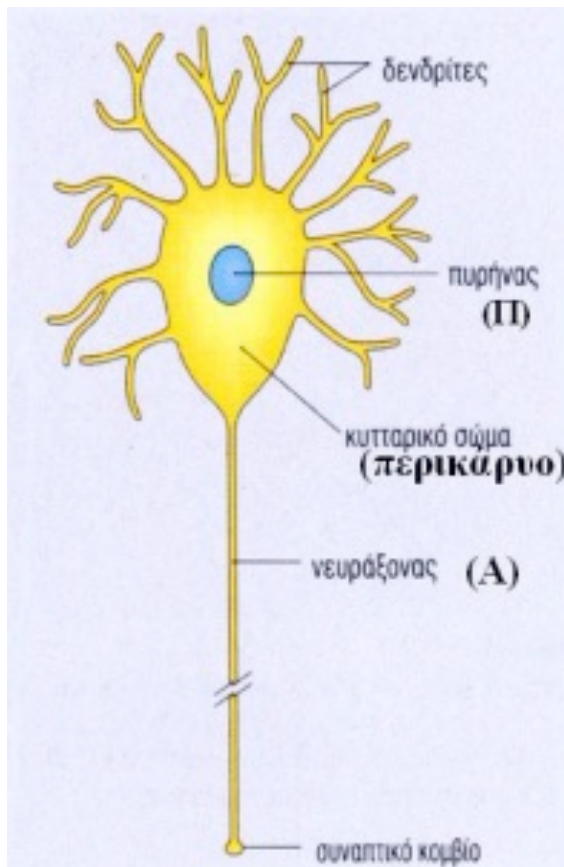
CNS tumors

Location



Histology

The nervous system consists mainly of neurons ($\sim 2 \times 10^{10}$) and neuroglial cells ($\sim 8 \times 10^{10}$)



Histology

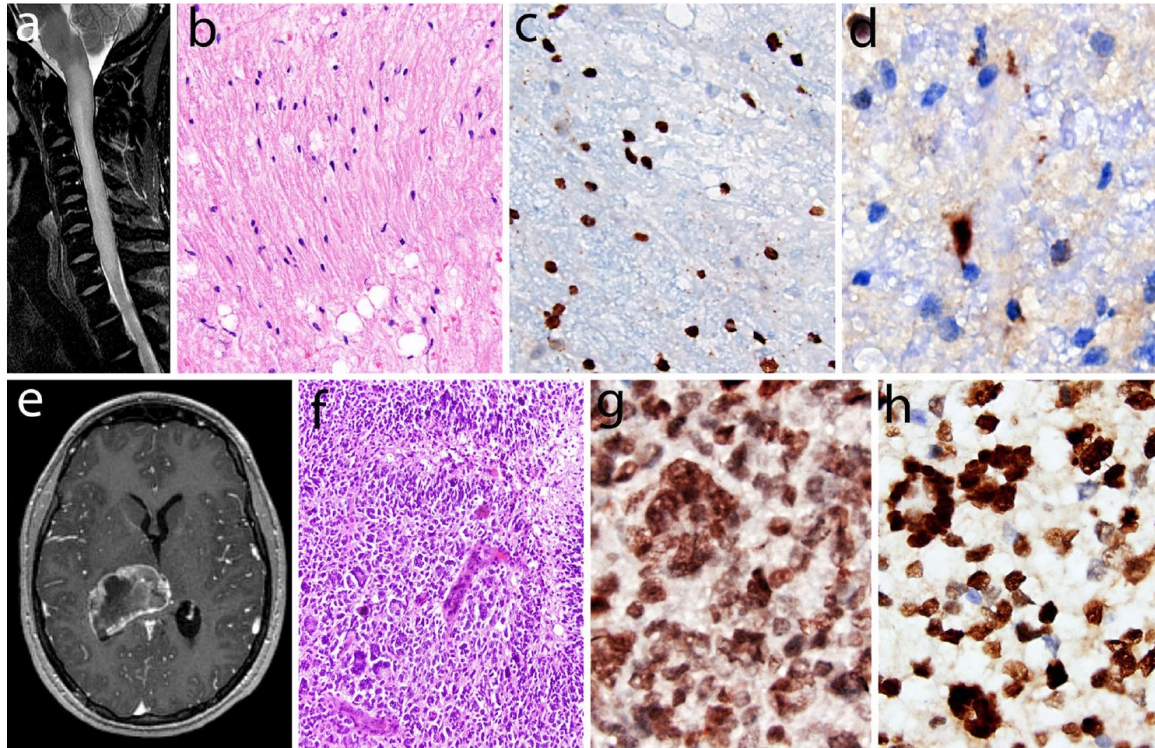


Fig. 4 Diffuse midline gliomas, H3 K27M-mutant. These tumors most often involve the brain stem (especially pons), spinal cord (**a–d**), and thalamus (**e–f**) in children and young adults. The morphologic spectrum varies widely, as in these two examples. This spinal lesion presented as a non-enhancing intramedullary mass with expansion and signal abnormalities on T2-weighted MRI (**a**). There was only minimal hypercellularity and cytologic atypia (**b**), but tumor cells

strongly expressed the H3 K27M-mutant protein (**c**) and also showed loss of ATRX expression (**d**). In contrast, the thalamic example showed a rim-enhancing mass on post-contrast T1 MRI (**e**) and histology demonstrated classic features of glioblastoma with prominent multinucleated giant cells (**f**). In addition to H3 K27M-mutant protein expression (**g**), there was strong p53 staining (**h**)

Histology

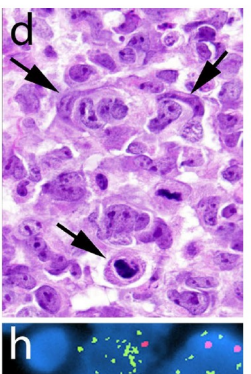
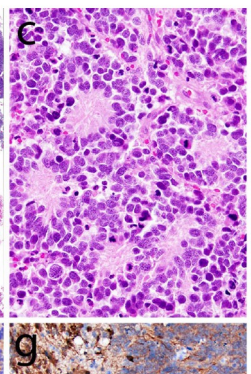
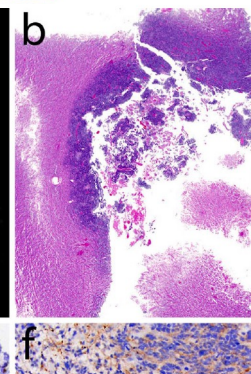
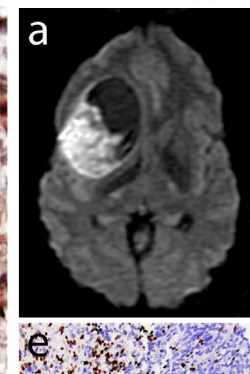
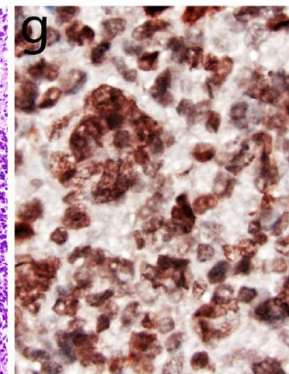
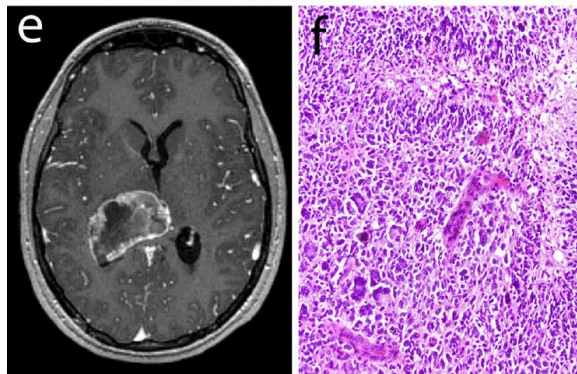
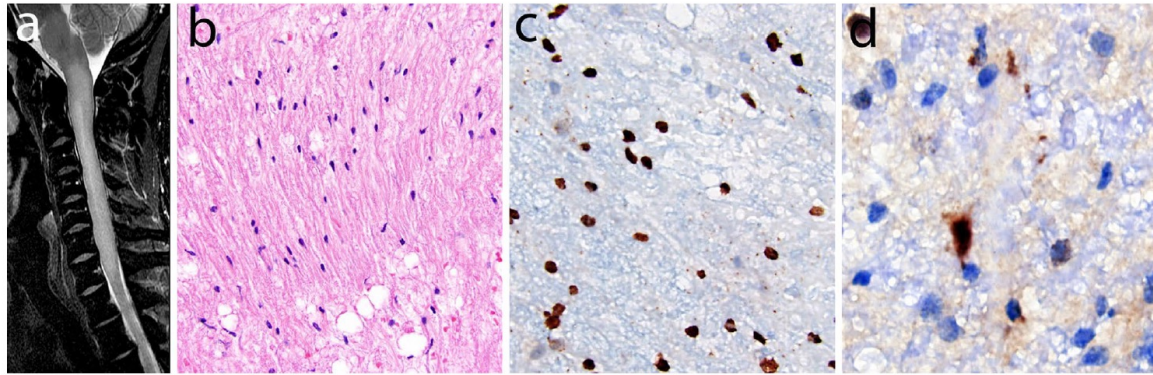


Fig. 4 Diffuse midline gliomas, H3 K27M-mutant. These tumors most often involve the brain stem (especially pons), spinal cord (a–d), and thalamus (e–f) in children and young adults. The morphologic spectrum varies widely, as in these two examples. This spinal lesion presented as a non-enhancing intramedullary mass with expansion and signal abnormalities on T2-weighted MRI (a). There was only minimal hypercellularity and cytologic atypia (b), but tumor cells

strongly expressed the H3 K27M-mutant (c). Loss of ATRX expression (d) showed a rim-enhancing mass on T2-weighted MRI (e). The morphology demonstrated classic features of diffuse midline glioma, including multinucleated giant cells (f). Immunohistochemistry for p53 (g), there was strong

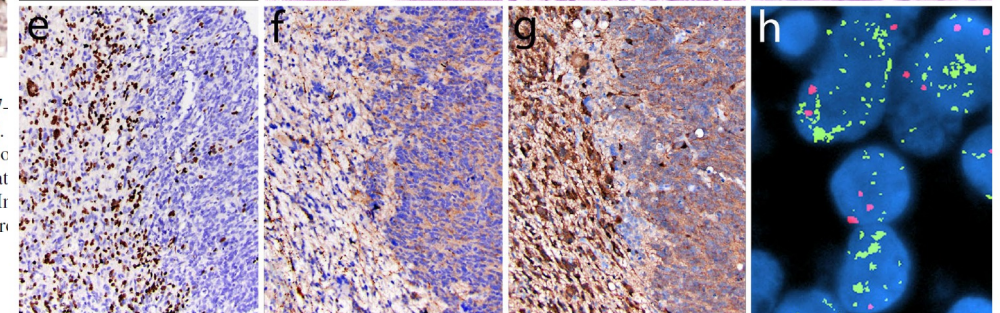
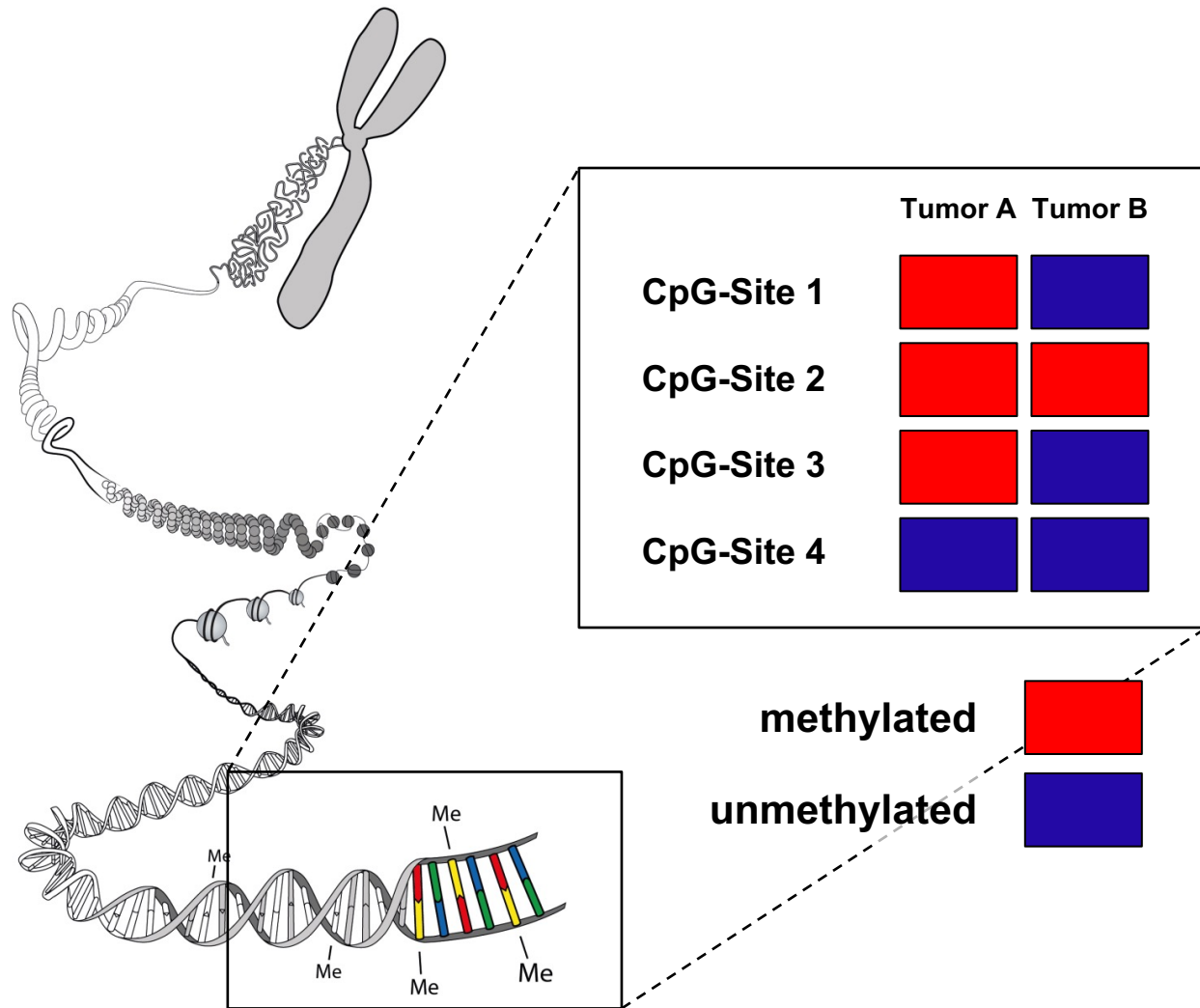


Fig. 3 Glioblastomas with primitive neuronal components (GBM-PNC; b and e–g show the astrocytic component on the left and the primitive neuronal component on the right). In this GBM-PNC, the imaging was essentially identical to that of conventional GBM, including a rim-enhancing mass; however, the markedly restricted diffusion on this DWI MR image highlights the more cellular primitive component (a). The primitive clone in this GBM-PNC is evident as a highly cellular nodule within an otherwise classic diffuse astrocytoma (b). Well-formed Homer Wright rosettes were seen in the primitive portion of this GBM-PNC (c). Large cell/anaplastic features (similar to those of medulloblastoma) are seen in a subset of

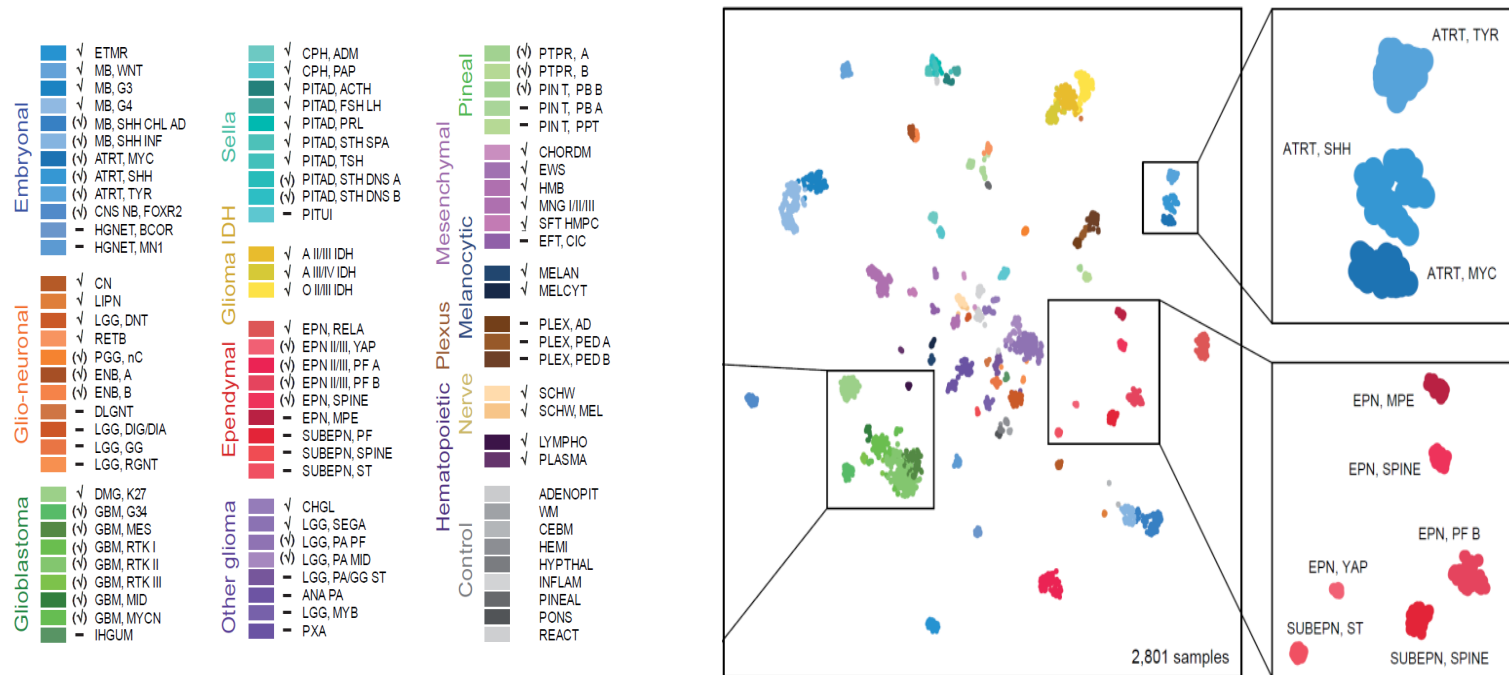
GBM-PNC; note the increased cell size, vesicular chromatin, macronucleoli, and cell–cell wrapping (arrows) in this case (d). The primitive component typically displays loss of glial marker expression, including GFAP (not shown) and OLIG2 (e), along with gain of neuronal features, such as synaptophysin positivity (f; note also staining of Homer Wright rosettes). A subset of cases demonstrates features of secondary glioblastoma, including IDH1 R132H mutant protein expression (g). FISH revealed MYCN gene amplification limited to the primitive foci of this GBM-PNC (h; centromere 2 signals in red and MYCN signals in green)

Molecular Profiling of DNA Methylation Patterns

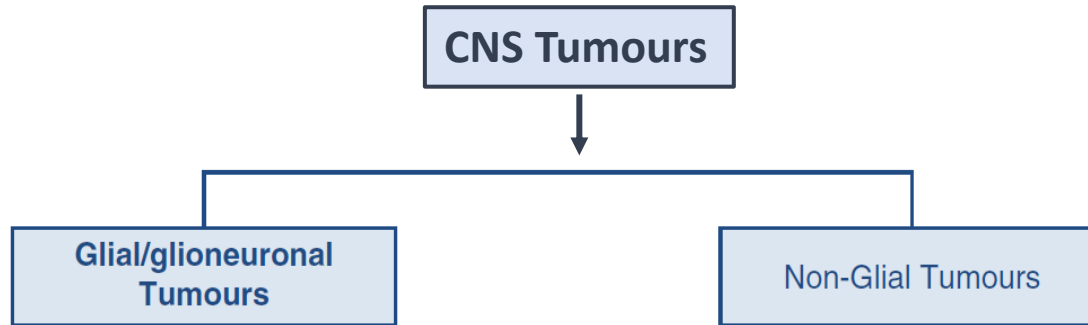


Classification of CNS Tumors based on DNA Methylation Profile

Development of a large, high-quality tumor set with good annotation



CNS tumor methylation classes and control tissue methylation classes of the reference cohort



CNS Tumours



Glial/glioneuronal Tumours

Non-Glial Tumours

Low-grade gliomas

High-grade gliomas

Ependymomas

Pilocytic astrocytoma BRAF dupl

Ganglioglioma BRAFV600Emut

Angiocentric Glioma (MYB/MYBL1)

DNET (FGFR mut/fusion)

Diffuse leptomeningeal glioneuronal tumor (BRAF dupl, 1p and/or19q del.)

Desmoplastic infantile astrocytoma and ganglioglioma

Subependymal giant cell astrocytoma (TSC1/2 germline mut)

LGG, NOS

Midline glioma H3K27 mut

GBM-IDH mut

GBM-(ped)RTK1/RTK2

GBM-MES

GBM-MYCN

GBM-H3.3G34 mut

Anaplastic astro. with piloid features* (NF1/FGFR1/BRAF, CDKN2A del)

Pleomorphic Xanthoastrocytoma* (BRAFV600E, CDKN2A del)

Supratentorial subependymoma

ST-EPN-YAP1

ST-EPN-RELA

Posterior fossa subependymoma

PF-EPN-A

PF-EPN-B

Spinal subependymoma

Spinal myxopapillary ependymoma

Spinal ependymoma (NF2 mut)

Low Grade Gliomas (LGG)

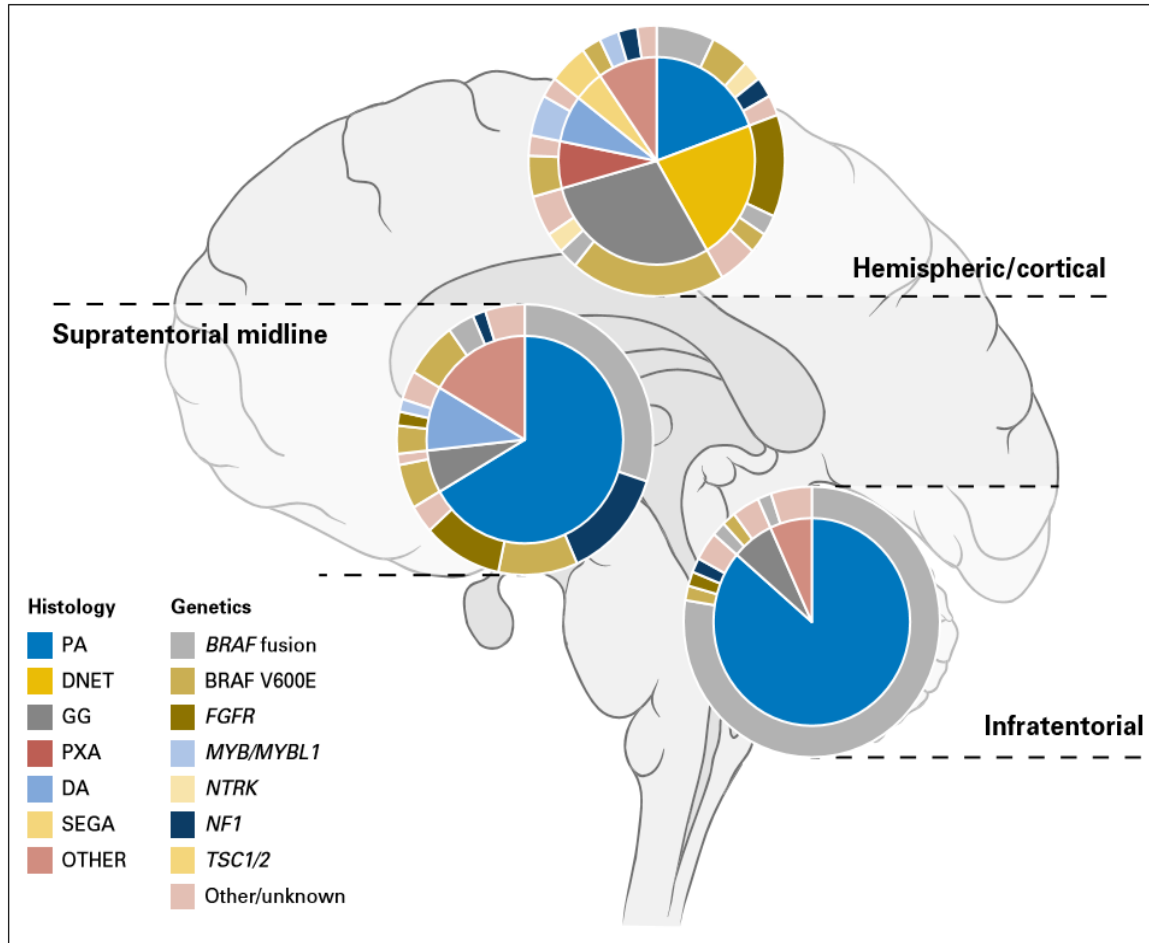


Fig 1. Distribution of pediatric low-grade glioma histologies and molecular genetic alterations by anatomic tumor location. Inner pie charts represent relative frequencies of the most common pediatric low-grade glioma histologic entities represented by colors as indicated. Outer rings represent the most common molecular genetic alterations associated with each histologic entity in a given location. Original data from the German Cancer Research Center in Heidelberg aligned with published data from other studies.^{1,2,6,8,12,13,16-21} DA, diffuse astrocytoma; DNET, dysembryoplastic neuroepithelial tumor; GG, ganglioglioma; PA, pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma; SEGA, subependymal giant cell astrocytoma.

High Grade Gliomas (HGG)

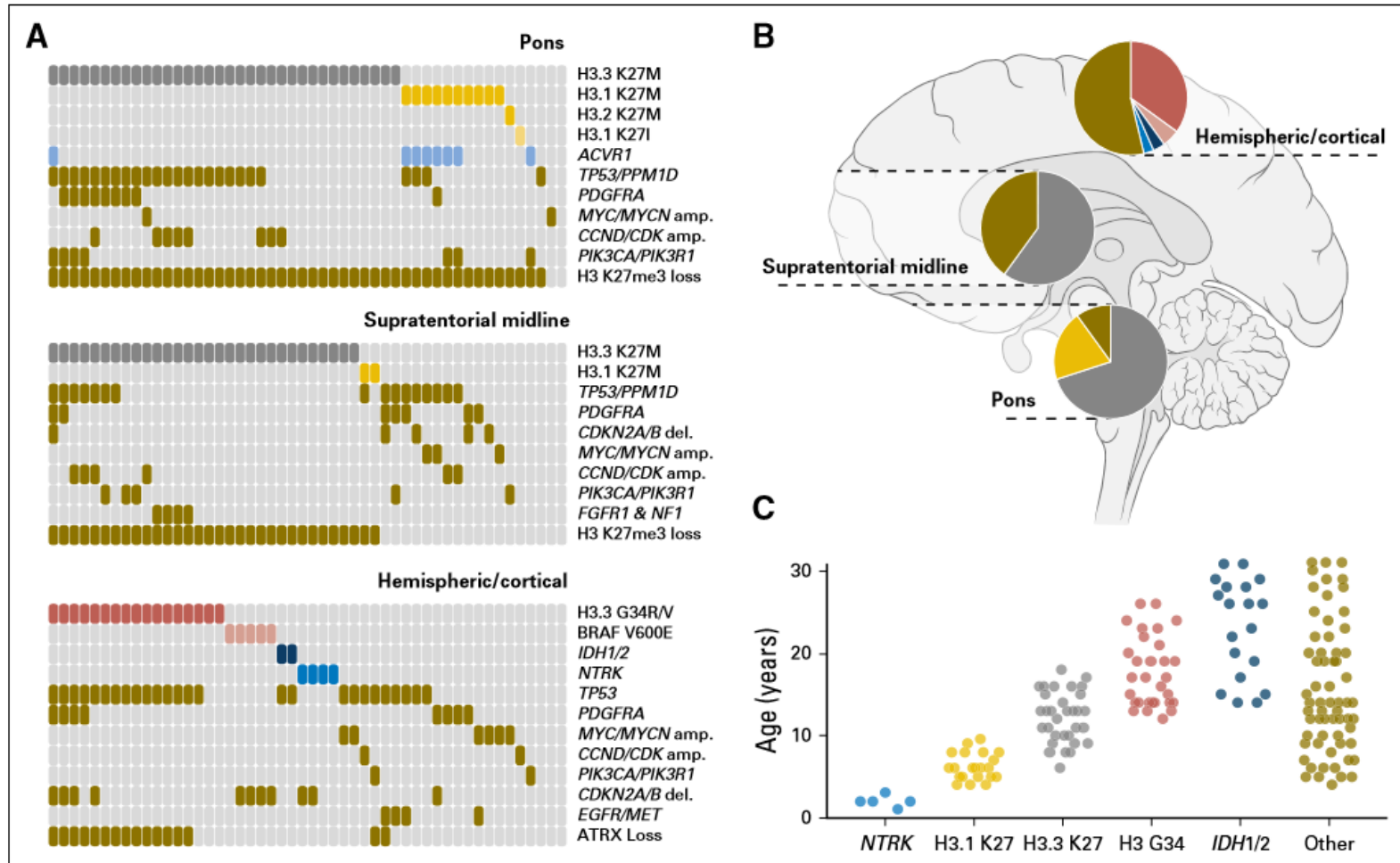
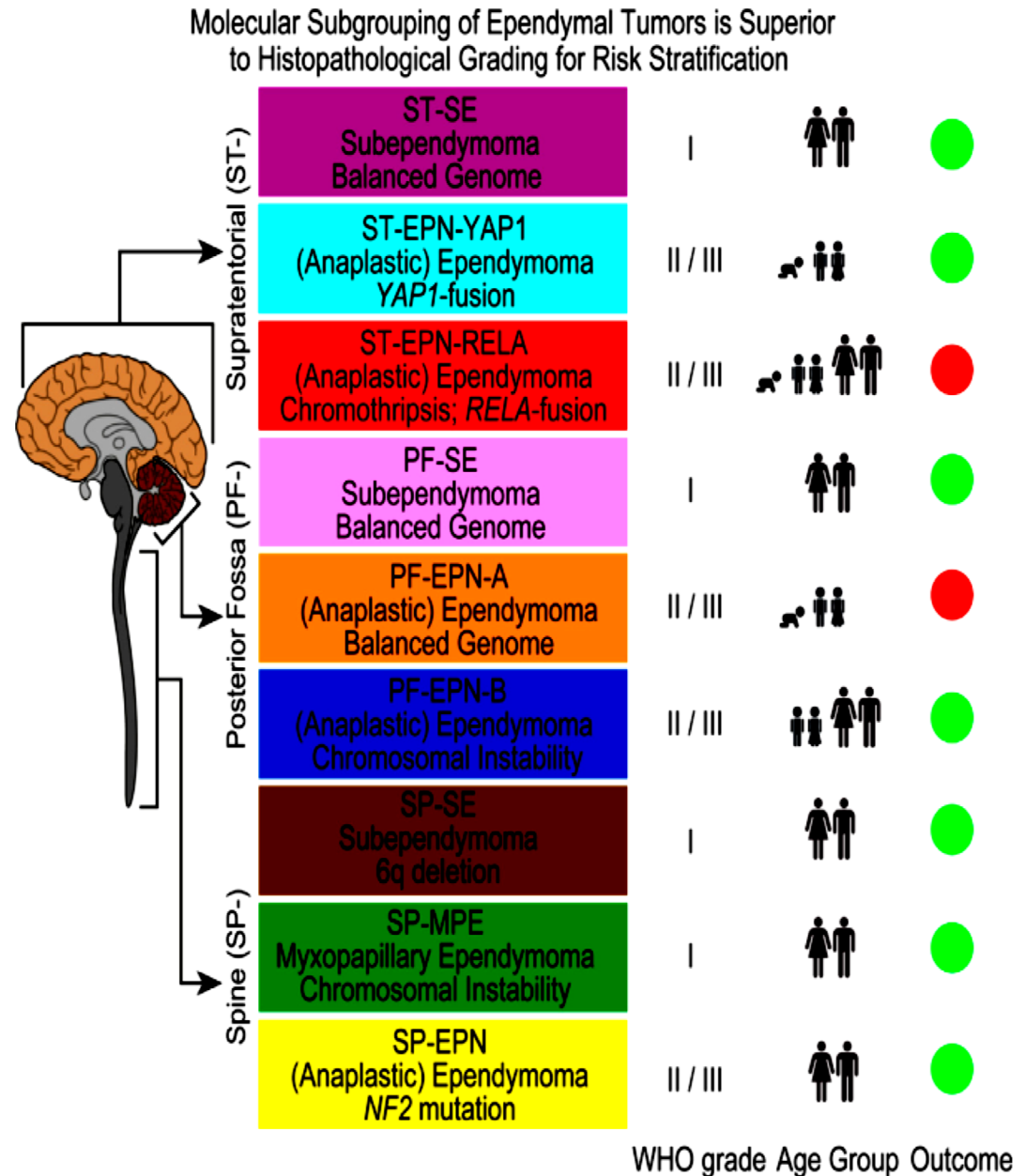
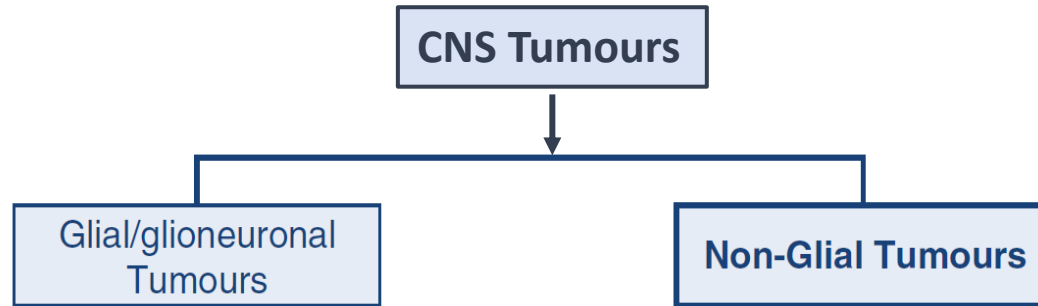


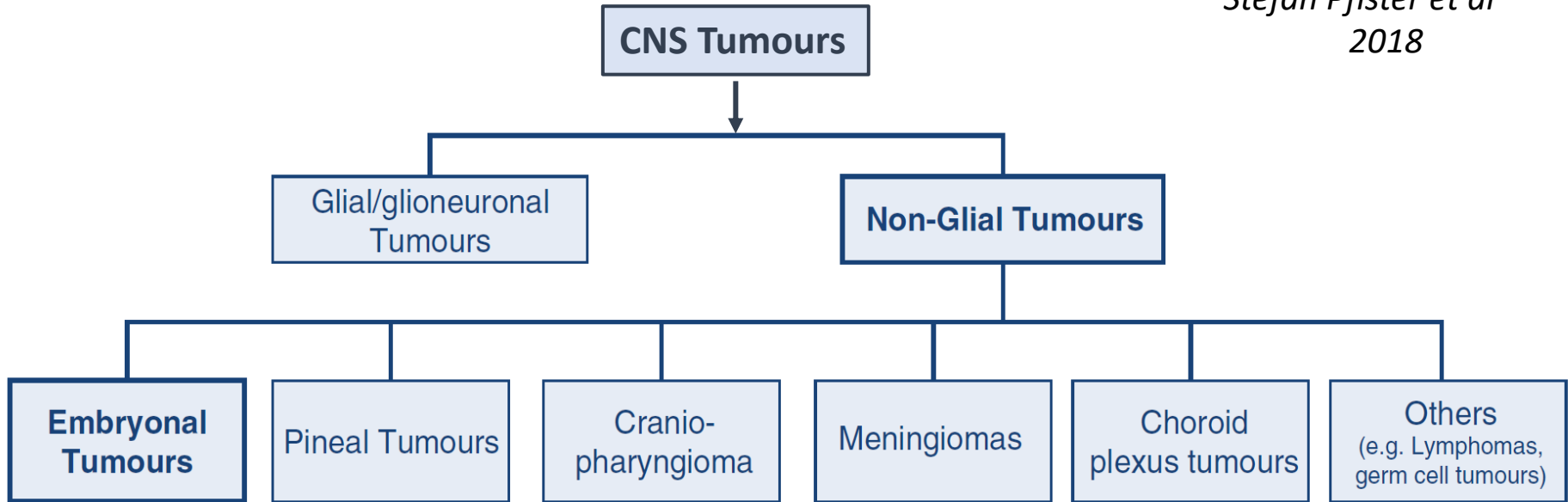
Fig 2. Molecular patterns and clinical features of pediatric high-grade glioma subgroups. (A) Oncoprints schematically depicting selected common molecular alterations in pediatric high-grade gliomas by anatomic location. Colored boxes indicate alterations being present. (B) Pie charts representing relative frequencies of common pediatric high-grade glioma molecular alterations represented by colors corresponding to (A) and (C). (C) Age distribution of common pediatric high-grade glioma molecular alterations in children and young adults (age younger than 30 years). Original data from the German Cancer Research Center in Heidelberg aligned with published data from other studies.^{2,39-46,48,49,52-55,63-65} amp., amplification; del., deletion.

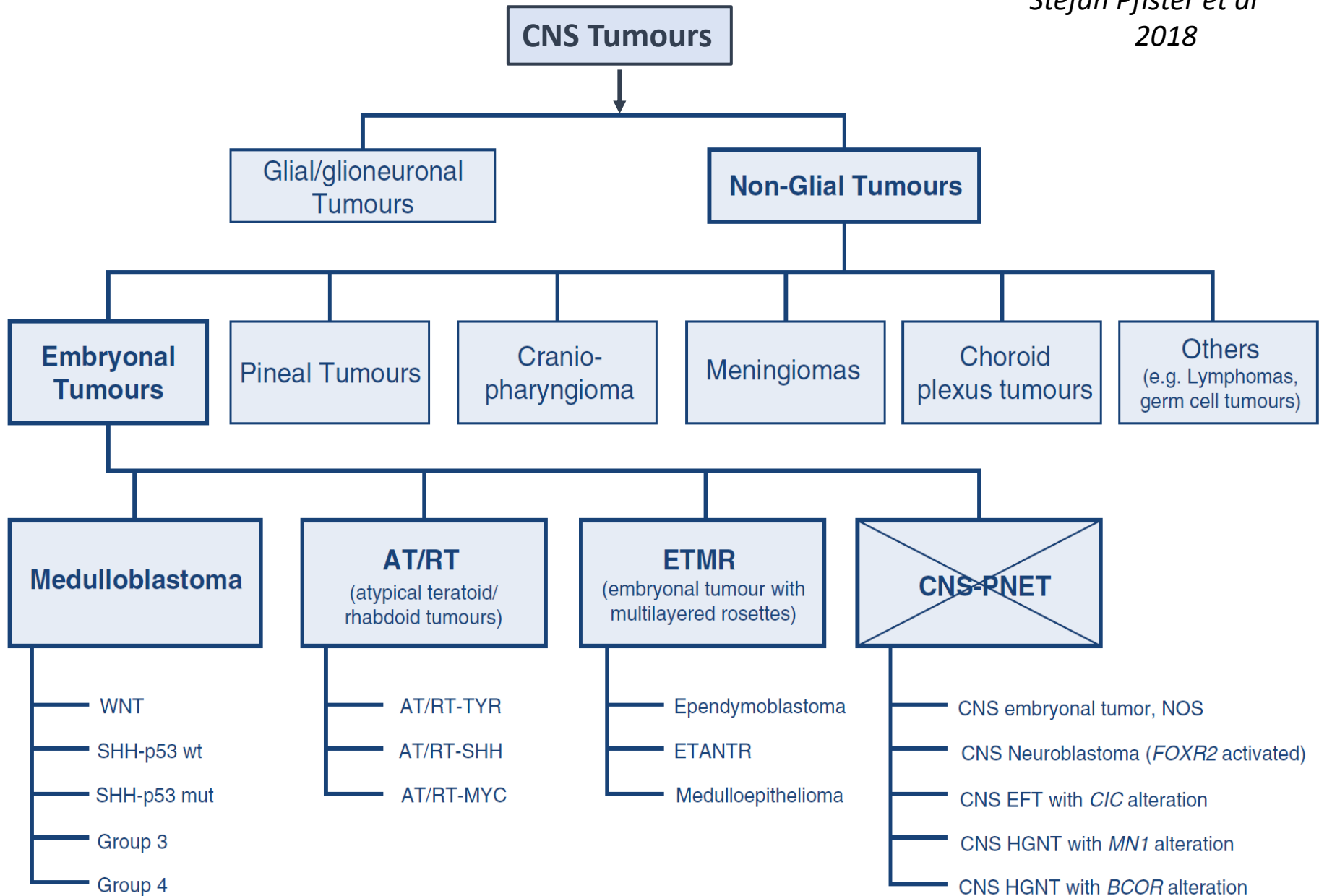
Ependymomas

- DNA methylation profiling of ependymomas identifies 9 molecular subgroups, 3 in each anatomical compartment of the CNS
- YAP1 and RELA fusions characterize two distinct groups of supratentorial ependymoma
- Patients with PFA or supratentorial RELA-positive ependymoma show dismal prognosis

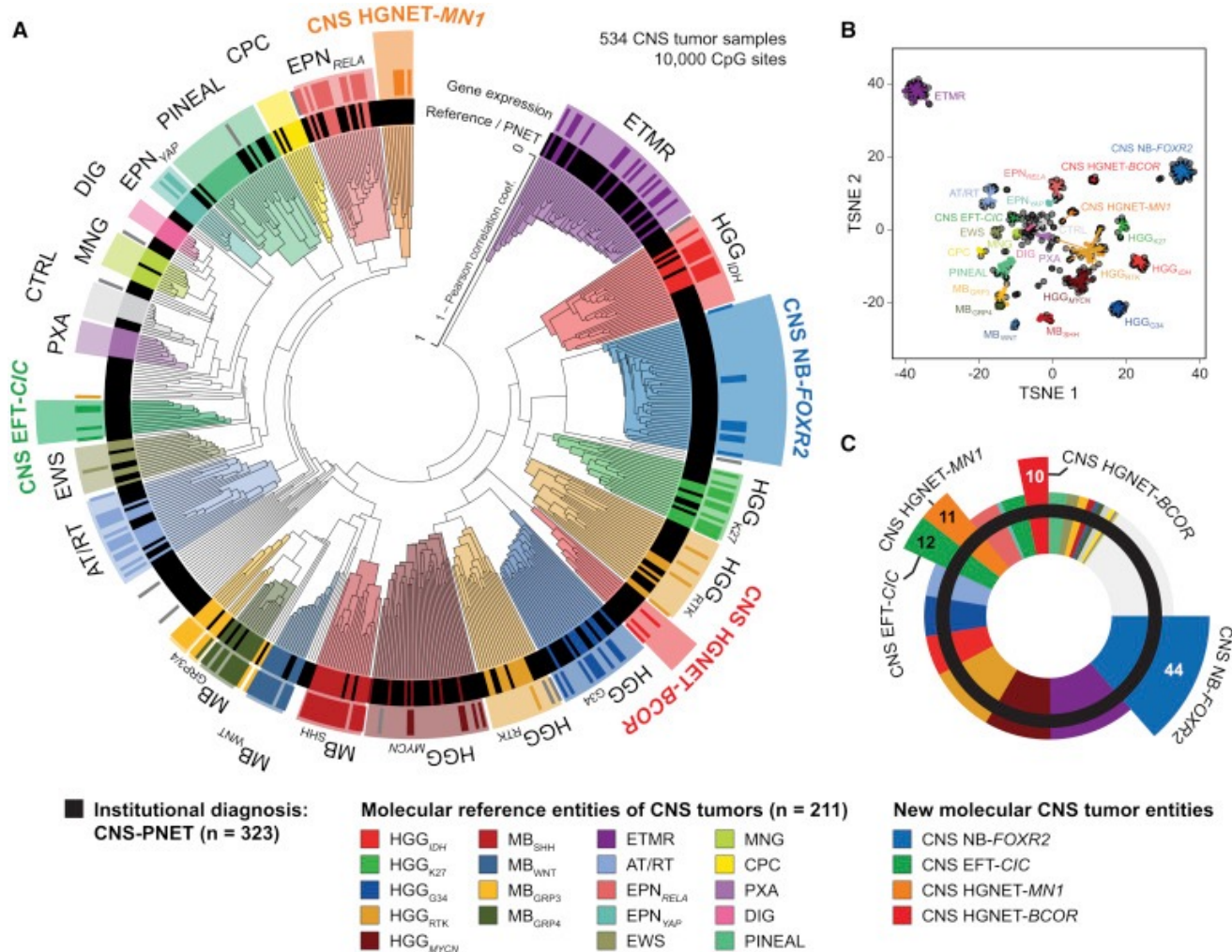




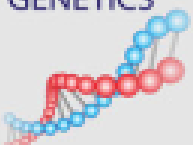




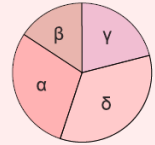
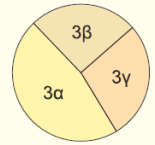
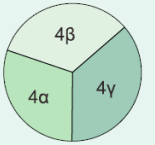
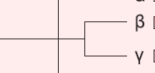
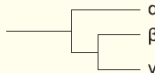
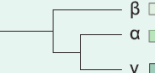
WHO 2016 : No CNS-PNETs anymore!



Embryonal Tumors-Medulloblastoma (2012)

Molecular Subgroups of Medulloblastoma				
CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C
DEMOGRAPHICS				
Age Group:   	  	  	  	  
Gender: ♀ ♂	♂ ♂ : ♀ ♀	♂ ♂ : ♀ ♀	♂ ♂ : ♀	♂ ♂ : ♀
CLINICAL FEATURES				
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate
GENETICS				
	 CTNNB1 mutation	 PTCH1/SMO/SUFU mutation GLI2 amplification MYCN amplification	 i17q MYC amplification	 i17q CDK6 amplification MYCN amplification
GENE EXPRESSION				
	WNT signaling MYC +	SHH signaling MYCN +	Photoreceptor/GABAergic MYC +++	Neuronal/Glutamatergic minimal MYC / MYCN

Embryonal Tumors-Medulloblastoma (2017)

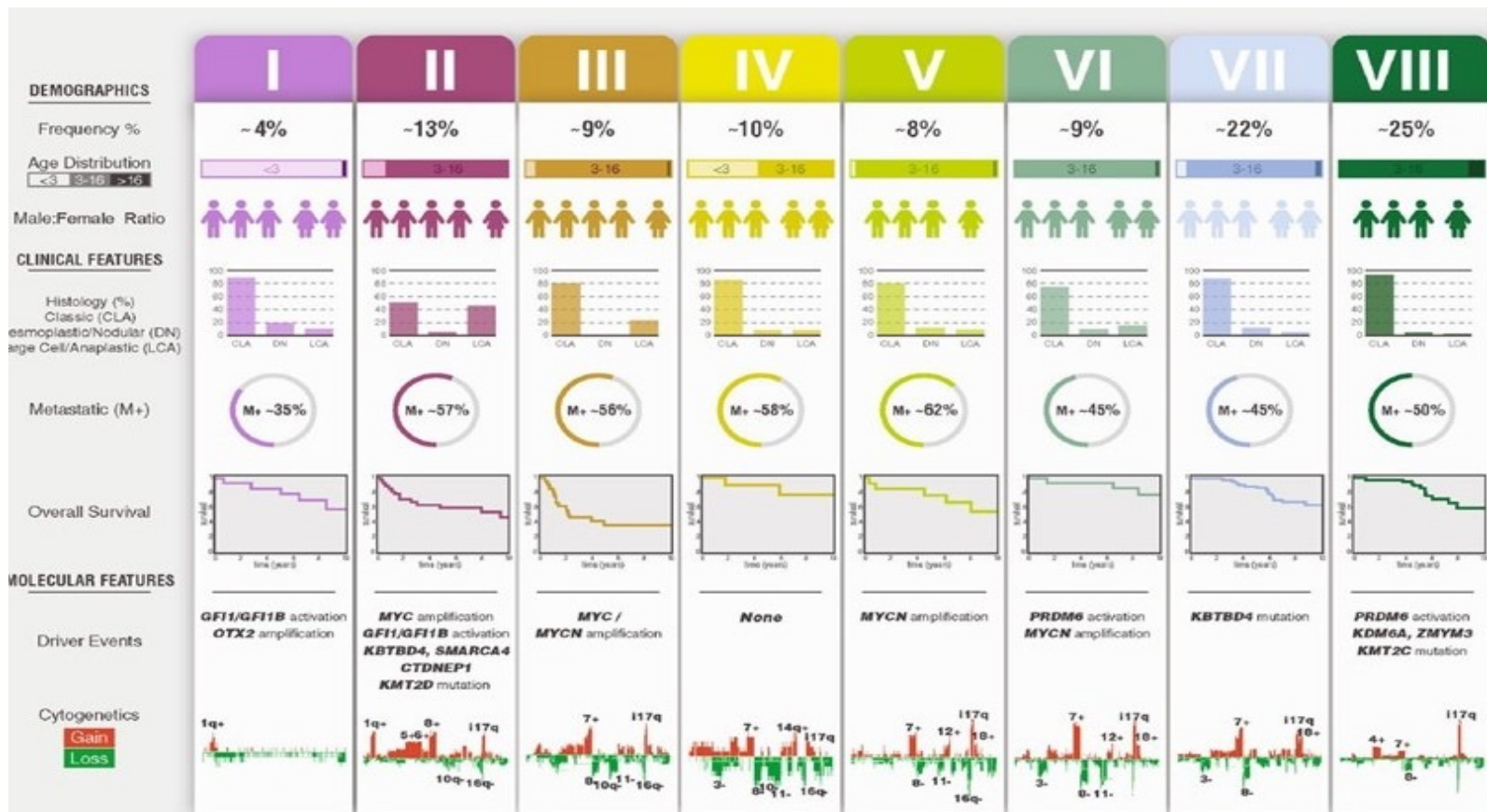
Subgroup		WNT		SHH				Group 3			Group 4		
Subtype		WNT α	WNT β	SHH α	SHH β	SHH γ	SHH δ	Group 3 α	Group 3 β	Group 3 γ	Group 4 α	Group 4 β	Group 4 γ
Subtype proportion													
Subtype relationship													
Clinical data	Age	 		 				 	 	 	 	 	
	Histology			LCA Desmoplastic	Desmoplastic	MBEN Desmoplastic	Desmoplastic						
	Metastases	8.6%	21.4%	20%	33%	8.9%	9.4%	43.4%	20%	39.4%	40%	40.7%	38.7%
	Survival at 5 years	97%	100%	69.8%	67.3%	88%	88.5%	66.2%	55.8%	41.9%	66.8%	75.4%	82.5%
Copy number	Broad	6 ⁻		9q ⁻ , 10q ⁻ , 17p ⁻		Balanced genome		7 ⁺ , 8 ⁻ , 10 ⁻ , 11 ⁻ , i17q		8 ⁺ , i17q	7q ⁺ , 8p ⁻ , i17q	i17q	7q ⁺ , 8p ⁻ , i17q (less)
	Focal			MYCN amp, GLI2 amp, YAP1 amp	PTEN loss		10q22 ⁻ , 11q23.3 ⁻		OTX2 gain, DDX31 loss	MYC amp	MYCN amp, CDK6 amp	SNCAIP dup	CDK6 amp
Other events				TP53 mutations			TERT promoter mutations		High GF11/1B expression				

Age (years):  0-3  >3-10  >10-17  >17

Embryonal Tumors-Medulloblastoma (2019)

➤ Second-generation molecular subgrouping of medulloblastoma: an international meta-analysis of Group 3 and Group 4 subtypes

Sharma T, Schwalbe EC, Williamson D, Sill M, Hovestadt V, Mynarek M, Rutkowski S, Robinson GW, Gajjar A, Cavalli F, Ramaswamy V, Taylor MD, Lindsey JC, Hill RM, Jäger N, Korshunov A, Hicks D, Bailey S, Kool M, Chavez L, Northcott PA, Pfister SM, Clifford SC. *Acta Neuropathol*.



WHO Classification of Tumors of CNS (2016)

Diffuse astrocytic and oligodendroglial tumours					
Diffuse astrocytoma, IDH-mutant	9400/3				
Gemistocytic astrocytoma, IDH-mutant	9411/3				
<i>Diffuse astrocytoma, IDH-wildtype</i>	9400/3				
Diffuse astrocytoma, NOS	9400/3				
Anaplastic astrocytoma, IDH-mutant	9401/3				
<i>Anaplastic astrocytoma, IDH-wildtype</i>	9401/3				
Anaplastic astrocytoma, NOS	9401/3				
Glioblastoma, IDH-wildtype	9440/3				
Giant cell glioblastoma	9441/3				
Gliosarcoma	9442/3				
<i>Epithelioid glioblastoma</i>	9440/3				
Glioblastoma, IDH-mutant	9445/3*				
Glioblastoma, NOS	9440/3				
Diffuse midline glioma, H3 K27M-mutant	9385/3*				
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3				
Oligodendroglioma, NOS	9450/3				
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3				
<i>Anaplastic oligodendroglioma, NOS</i>	9451/3				
<i>Oligoastrocytoma, NOS</i>	9382/3				
<i>Anaplastic oligoastrocytoma, NOS</i>	9382/3				
Other astrocytic tumours					
Pilocytic astrocytoma	9421/1				
Piloxyoid astrocytoma	9425/3				
Subependymal giant cell astrocytoma	9384/1				
Pleomorphic xanthoastrocytoma	9424/3				
Anaplastic pleomorphic xanthoastrocytoma	9424/3				
Ependymal tumours					
Subependymoma	9383/1				
Myxopapillary ependymoma	9394/1				
Ependymoma	9391/3				
Papillary ependymoma	9393/3				
Clear cell ependymoma	9391/3				
Tanycytic ependymoma	9391/3				
Ependymoma, <i>RELA</i> fusion-positive	9396/3*				
Anaplastic ependymoma	9392/3				
Other gliomas					
Chordoid glioma of the third ventricle	9444/1				
Angiocentric glioma	9431/1				
Astroblastoma	9430/3				
Choroid plexus tumours					
Choroid plexus papilloma	9390/0				
Atypical choroid plexus papilloma	9390/1				
Choroid plexus carcinoma	9390/3				
Neuronal and mixed neuronal-glial tumours					
Dysembryoplastic neuroepithelial tumour	9413/0				
Gangliocytoma	9492/0				
Ganglioglioma	9505/1				
Anaplastic ganglioglioma	9505/3				
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0				
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1				
Papillary glioneuronal tumour	9509/1				
Rosette-forming glioneuronal tumour	9509/1				
<i>Diffuse leptomeningeal glioneuronal tumour</i>					
Central neurocytoma	9506/1				
Extraventricular neurocytoma	9506/1				
Cerebellar liponeurocytoma	9506/1				
Paraganglioma	8693/1				
Tumours of the pineal region					
Pineocytoma	9361/1				
Pineal parenchymal tumour of intermediate differentiation	9362/3				
Pineoblastoma	9362/3				
Papillary tumour of the pineal region	9395/3				
Embryonal tumours					
Medulloblastomas, genetically defined					
Medulloblastoma, WNT-activated	9475/3*				
Medulloblastoma, SHH-activated and TP53-mutant	9476/3*				
Medulloblastoma, SHH-activated and TP53-wildtype	9471/3				
Medulloblastoma, non-WNT/non-SHH	9477/3*				
<i>Medulloblastoma, group 3</i>					
<i>Medulloblastoma, group 4</i>					
Medulloblastomas, histologically defined					
Medulloblastoma, classic	9470/3				
Medulloblastoma, desmoplastic/nodular	9471/3				
Medulloblastoma with extensive nodularity	9471/3				
Medulloblastoma, large cell / anaplastic	9474/3				
Medulloblastoma, NOS	9470/3				
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*				
<i>Embryonal tumour with multilayered rosettes, NOS</i>	9478/3				
Medulloepithelioma	9501/3				
CNS neuroblastoma	9500/3				
CNS ganglioneuroblastoma	9490/3				
CNS embryonal tumour, NOS	9473/3				
Atypical teratoid/rhabdoid tumour	9508/3				
<i>CNS embryonal tumour with rhabdoid features</i>	9508/3				
Tumours of the cranial and paraspinal nerves					
Schwannoma	9560/0				
Cellular schwannoma	9560/0				
Plexiform schwannoma	9560/0				
Melanotic schwannoma	9560/1				
Neurofibroma	9540/0				
Atypical neurofibroma	9540/0				
Plexiform neurofibroma	9550/0				
Perineurioma	9571/0				
Hybrid nerve sheath tumours					
Malignant peripheral nerve sheath tumour	9540/3				
Epithelioid MPNST	9540/3				
MPNST with perineurial differentiation	9540/3				
Meningiomas					
Meningioma	9530/0				
Meningothelial meningioma	9531/0				
Fibrous meningioma	9532/0				
Transitional meningioma	9537/0				
Psammomatous meningioma	9533/0				
Angiomatous meningioma	9534/0				
Microcystic meningioma	9530/0				
Secretory meningioma	9530/0				
Lymphoplasmacyte-rich meningioma	9530/0				
Metaplastic meningioma	9530/0				
Chordoid meningioma	9538/1				
Clear cell meningioma	9538/1				
Atypical meningioma	9539/1				
Papillary meningioma	9538/3				
Rhabdoid meningioma	9538/3				
Anaplastic (malignant) meningioma	9530/3				
Mesenchymal, non-meningothelial tumours					
Solitary fibrous tumour / haemangiopericytoma**					
Grade 1	8815/0				
Grade 2	8815/1				
Grade 3	8815/3				
Haemangioblastoma	9161/1				
Haemangioma	9120/0				
Epithelioid haemangiopericytoma	9133/3				
Angiosarcoma	9120/3				
Kaposi sarcoma	9140/3				
Ewing sarcoma / PNET	9364/3				
Lipoma	8850/0				
Angiolipoma	8861/0				
Hibernoma	8880/0				
Liposarcoma	8850/3				
Desmoid-type fibromatosis	8821/1				
Myofibroblastoma	8825/0				
Inflammatory myofibroblastic tumour	8825/1				
Benign fibrous histiocytoma	8830/0				
Fibrosarcoma	8810/3				
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3				
Leiomyoma	8890/0				
Leiomyosarcoma	8890/3				
Rhabdomyoma	8900/0				
Rhabdomyosarcoma	8900/3				
Chondroma	9220/0				
Chondrosarcoma	9220/3				
Osteoma	9180/0				
Osteochondroma	9210/0				
Osteosarcoma	9180/3				
Melanocytic tumours					
Meningeal melanocytosis	8728/0				
Meningeal melanocytoma	8728/1				
Meningeal melanoma	8720/3				
Meningeal melanomatosis	8728/3				
Lymphomas					
Diffuse large B-cell lymphoma of the CNS	9680/3				
Immunodeficiency-associated CNS lymphomas					
AIDS-related diffuse large B-cell lymphoma					
EBV-positive diffuse large B-cell lymphoma, NOS					
Lymphomatoid granulomatosis	9766/1				
Intravascular large B-cell lymphoma	9712/3				
Low-grade B-cell lymphomas of the CNS					
T-cell and NK/T-cell lymphomas of the CNS					
Anaplastic large cell lymphoma, ALK-positive	9714/3				
Anaplastic large cell lymphoma, ALK-negative	9702/3				
MALT lymphoma of the dura	9699/3				
Histiocytic tumours					
Langerhans cell histiocytosis	9751/3				
Erdheim-Chester disease	9750/1				
Rosai-Dorfman disease					
Juvenile xanthogranuloma					
Histiocytic sarcoma	9755/3				
Germ cell tumours					
Germinoma	9064/3				
Embryonal carcinoma	9070/3				
Yolk sac tumour	9071/3				
Choriocarcinoma	9100/3				
Teratoma	9080/1				
Mature teratoma	9080/0				
Immature teratoma	9080/3				
Teratoma with malignant transformation	9084/3				
Mixed germ cell tumour	9085/3				
Tumours of the sellar region					
Craniopharyngioma	9350/1				
Adamantinomatous craniopharyngioma	9351/1				
Papillary craniopharyngioma	9352/1				
Granular cell tumour of the sellar region	9582/0				
Pituitaryoma	9432/1				
Spindle cell oncocytoma	8290/0				
Metastatic tumours					
The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded 0 for benign tumours; 1 for unspecified, borderline, or uncertain behaviour; 2 for carcinoma in situ and grade III intraepithelial neoplasia; and 3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. *These new codes were approved by the IARC/WHO Committee for ICD-O. <i>Italics:</i> Provisional tumour entities. **Grading according to the 2013 WHO Classification of Tumours of Soft Tissue and Bone.					

Grading

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III

Other astrocytic tumours

Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

Ependymal tumours

Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, <i>RELA</i> fusion-positive	II or III
Anaplastic ependymoma	III

Other gliomas

Angiocentric glioma	I
Chordoid glioma of third ventricle	II

Choroid plexus tumours

Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III

Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I

Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II

Tumours of the pineal region

Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III

Embryonal tumours

Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV

Tumours of the cranial and paraspinal nerves

Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV

Meningiomas

Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III

Mesenchymal, non-meningothelial tumours

Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I

Tumours of the sellar region

Craniopharyngioma	I
Granular cell tumour	I
Pituitary tumour	I
Spindle cell oncocytoma	I

Grading

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III

Other astrocytic tumours

Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

Ependymal tumours

Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, <i>RELA</i> fusion-positive	II or III
Anaplastic ependymoma	III

Other gliomas

Angiocentric glioma	I
Chordoid glioma of third ventricle	II

Choroid plexus tumours

Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III

Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I

Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II

Tumours of the pineal region

Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III

Embryonal tumours

Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV

Tumours of the cranial and paraspinal nerves

Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV

Meningiomas

Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III

Mesenchymal, non-meningothelial tumours

Solitary fibrous tumour / hemangiopericytoma	I
Haemangioblastoma	I

Tumours of the

Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

I-II Low Grade
III-IV High Grade

WHO CLASSIFICATION 2021

Integrated and layered diagnosis

- Localization of tumor
- Histopathological classification
- CNS WHO grade
- Molecular Information



final diagnosis

Cerebrum	
Integrated diagnosis	Supratentorial ependymoma, NOS
Histopathological classification	Ependymoma
CNS WHO grade	3
Molecular Information	Derivatives extracted from FFPE tissue were of insufficient quality for sequencing and insufficient tissue remained for FISH studies

WHO CLASSIFICATION 2021: SPECIFIC CHANGES

Gliomas, glioneuronal tumours, and neuronal tumours

2.1:	Gliomas, glioneuronal tumours, and neuronal tumours
2.1.1:	Adult-type diffuse gliomas
2.1.1.1:	Astrocytoma, IDH-mutant
2.1.1.2:	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
2.1.1.3:	Glioblastoma, IDH-wildtype
2.1.5:	Paediatric-type diffuse low-grade gliomas
2.1.4.1:	Diffuse astrocytoma, MYB- or MYBL1-altered
2.1.4.2:	Angiocentric glioma
2.1.3.5:	Polymorphous low-grade neuroepithelial tumour of the young
2.1.5.1:	Diffuse low-grade glioma, MAPK pathway-altered
2.1.2:	Paediatric-type diffuse high-grade gliomas
2.1.2.1:	Diffuse midline glioma, H3K27-altered
2.1.2.2:	Diffuse hemispheric glioma, H3G34-mutant
2.1.2.3:	Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
2.1.2.4:	Infant-type hemispheric glioma
2.1.3:	Circumscribed astrocytic gliomas
2.1.3.1:	Pilocytic astrocytoma
2.1.3.2:	High-grade astrocytoma with piloid features
2.1.3.3:	Pleomorphic xanthoastrocytoma
2.2.0.4:	Subependymal giant cell astrocytoma
2.2.0.1:	Chordoid glioma
2.2.0.2:	Astroblastoma, MN1-altered
2.1.4:	Glioneuronal and neuronal tumours
2.1.3.7:	Ganglioglioma
2.2.0.8:	Gangliocytoma
2.1.3.9:	Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
2.1.3.10:	Dysembryoplastic neuroepithelial tumour
	Diffuse glioneuronal tumour with oligodendroglioma-like features and

Major restructuring of diffuse gliomas

- Incorporation of distinct pediatric-type vs adult-type entities
- Additional molecularly defined entities

Ependymal tumours

2.3.0.2:	Supratentorial ependymoma
2.3.0.3:	Supratentorial ependymoma, ZFTA fusion-pc
2.3.0.4:	Supratentorial ependymoma, YAP1 fusion-pc
2.3.0.5:	Posterior fossa ependymoma
2.3.0.6:	Posterior fossa group A (PFA) ependymoma
2.3.0.7:	Posterior fossa group B (PFB) ependymoma
2.3.0.8:	Spinal ependymoma
2.3.0.9:	Spinal ependymoma, MYCN-amplified
2.3.0.10:	Myxopapillary ependymoma
2.3.0.11:	Subependymoma

Restructuring of ependymomas to recognize distinct location-based and molecular entities

Choroid plexus tumours

3.0.0.1:	Choroid plexus papilloma
3.0.0.2:	Atypical choroid plexus papilloma
3.0.0.3:	Choroid plexus carcinoma

Medulloblastoma

4.1.1:	Medulloblastomas, molecularly defined
4.1.1.1:	Medulloblastoma, WNT-activated
4.1.1.3:	Medulloblastoma, SHH-activated and TP53-wildtype
4.1.1.2:	Medulloblastoma, SHH-activated and TP53-mutant
4.1.1.4:	Medulloblastoma, non-WNT/non-SHH
4.1.2:	Medulloblastomas, histologically defined
4.1.2.1:	Medulloblastoma, histologically defined

Other CNS embryonal tumours

4.2.0.2:	Atypical teratoid/rhabdoid tumour
2.2.0.10:	Cribiform neuroepithelial tumour
4.2.0.3:	Embryonal tumour with multilayered rosettes
4.2.0.6:	CNS neuroblastoma, FOXR2-activated
4.2.0.7:	CNS tumour with BCOR internal tandem duplication
4.2.0.8:	CNS embryonal tumour NOS

Pineal tumours

5.0.0.1:	Pineocytoma
5.0.0.2:	Pineal parenchymal tumour NOS
5.0.0.4:	Papillary pinealoma
5.0.0.5:	Desmoplastic pinealoma

Additional molecularly-defined embryonal tumors