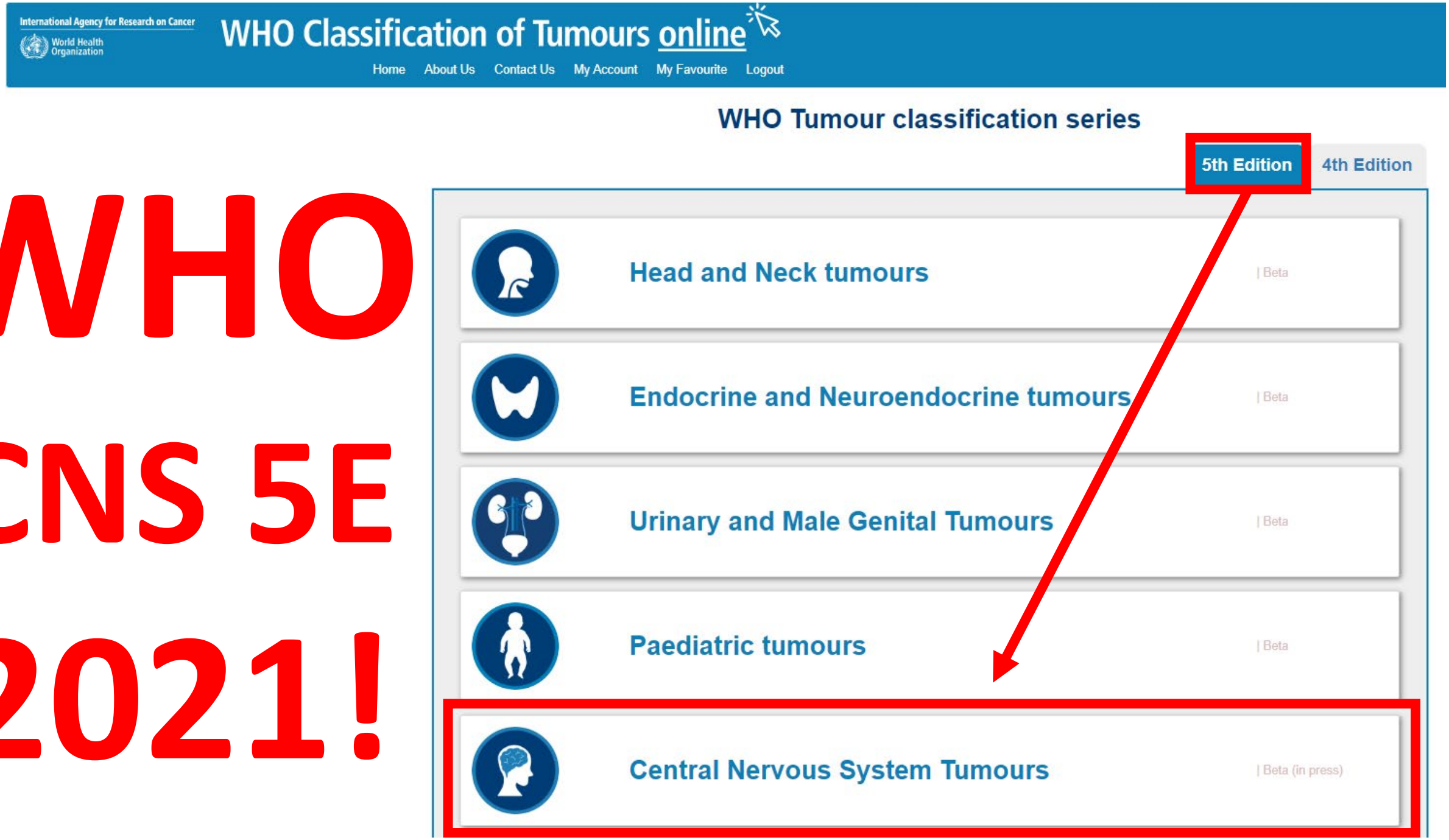
The BIG NEWS for 2022

WHO CNS 5E 2021!



// Gliomas, glioneuronal tumours, and neuronal tumours

Epidermal growth factor receptor

The receptor tyrosine kinase (RTK) EGFR (HER1) is frequently altered in IDH-wildtype glioblastoma. Overall, about 60% of tumours show evidence of *EGFR* amplification, mutation, rearrangement, or altered splicing { 24120142 }. The most frequent of these alterations is *EGFR* amplification { 1374522 }, which occurs in about 40% of all IDH-wildtype glioblastomas { 24120142 ; 30187121 } and in as many as 60% of glioblastomas in the DNA methylation group RTK2, but only in about 25% of RTK1 and mesenchymal glioblastomas { 23079654 ; 30187121 }. In the majority of cases, *EGFR* amplifications are associated with a second *EGFR* alteration, such as extracellular domain mutations or in-frame intragenic deletions encoding either *EGFRvIII* or other alternative transcripts { 24120142 ; 7622287 ; 2236070 }. *EGFR* gene fusions are discussed below.

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Review > Mutat Res. 1992 May;276(3):299-306. doi: 10.1016/0165-1110(92)90016-3.

Amplified cellular oncogenes in neoplasms of the human central nervous system

Affiliations + expand

PMID: 1374522 DOI: 10.1016/0165-1110(92)90016-3

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MUTREV 00323

Amplified cellular oncogenes in neoplasms of the human central nervous system

Gregory N. Fuller and Sandra H. Bigner

Department of Pathology, Duke University Medical Center, Durham, NC 27710 (U.S.A.)

(Accepted 12 December 1991)

Summary

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Vol. 87, pp. 4207–4211, June 1990
Medical Sciences

Anti-synthetic peptide antibody reacting at the fusion junction of deletion–mutant epidermal growth factor receptors in human glioblastoma

(protooncogene/c-*erbB*/peptide immunization/brain tumor)

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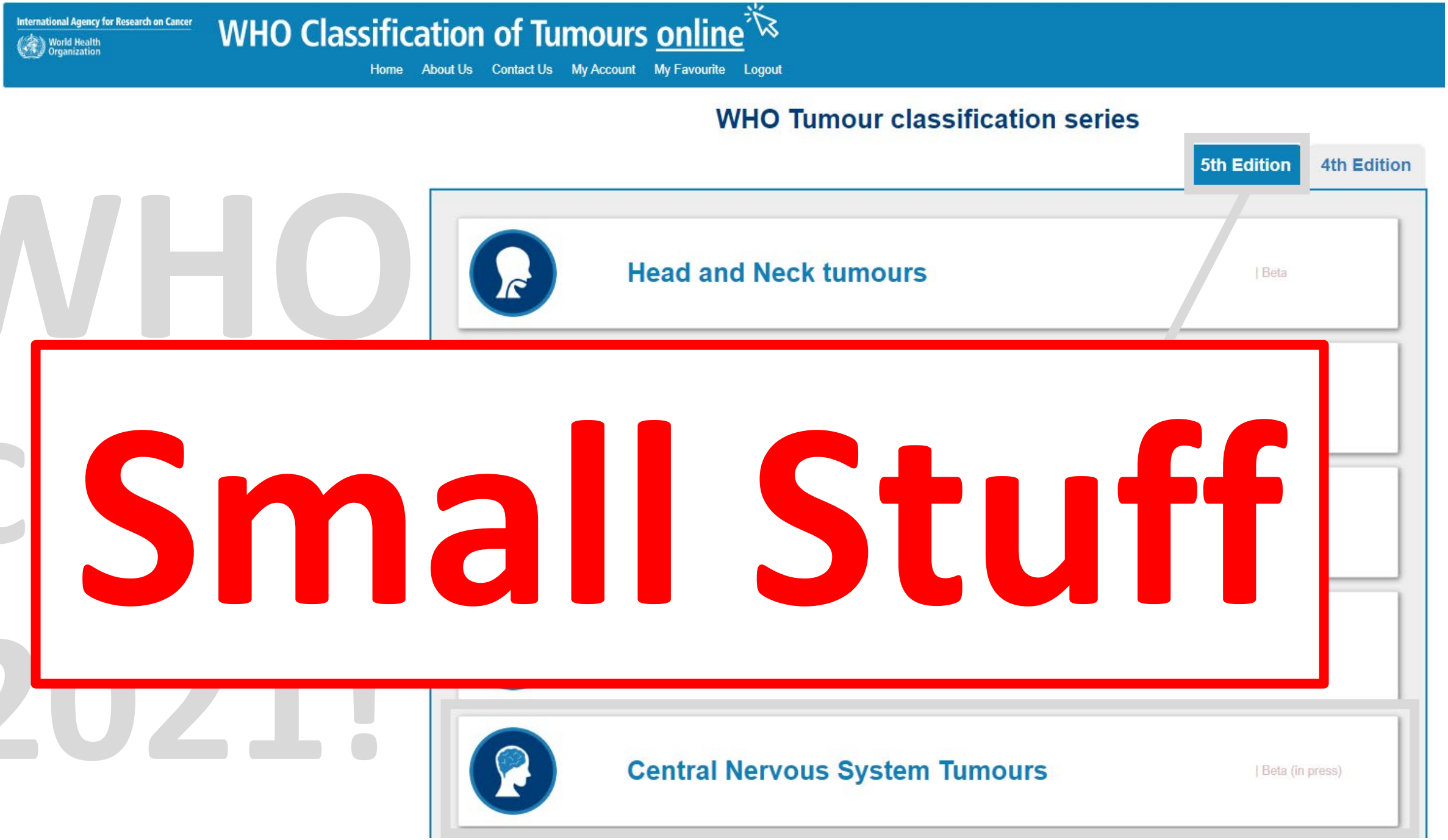
International Agency for Research on Cancer
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Home
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Logout
WHO Tumour classification series
5th Edition
4th Edition
Head and Neck tumours
Beta
Central Nervous System Tumours
Beta (in press)
WHO
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2021!
Small Stuff

WHO CNS 5 (WHO 2021)

- **WHO Grade vs CNS WHO Grade**

WHO CNS 5 (WHO 2021)

- ~~WHO Grade~~ vs **CNS WHO Grade**

WHO CNS 5 (WHO 2021)

- ~~WHO Grade~~ vs **CNS WHO Grade**
- **I, II, III, IV vs 1, 2, 3, 4**

WHO CNS 5 (WHO 2021)

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WHO CNS 5 (WHO 2021)

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- **Pit Adenoma vs PitNET**

WHO CNS 5 (WHO 2021)

- ~~WHO Grade~~ vs **CNS WHO Grade**
- ~~I, II, III, IV~~ vs **1, 2, 3, 4**
- **Pit Adenoma vs PitNET**

Pituitary adenoma / pituitary neuroendocrine tumour

Definition

Pituitary adenoma / pituitary neuroendocrine tumour (PitNET) is a clonal neoplastic proliferation of anterior pituitary hormone–producing cells.

ICD-O coding

8272/3 Pituitary adenoma / pituitary neuroendocrine tumour (PitNET)

ICD-11 coding

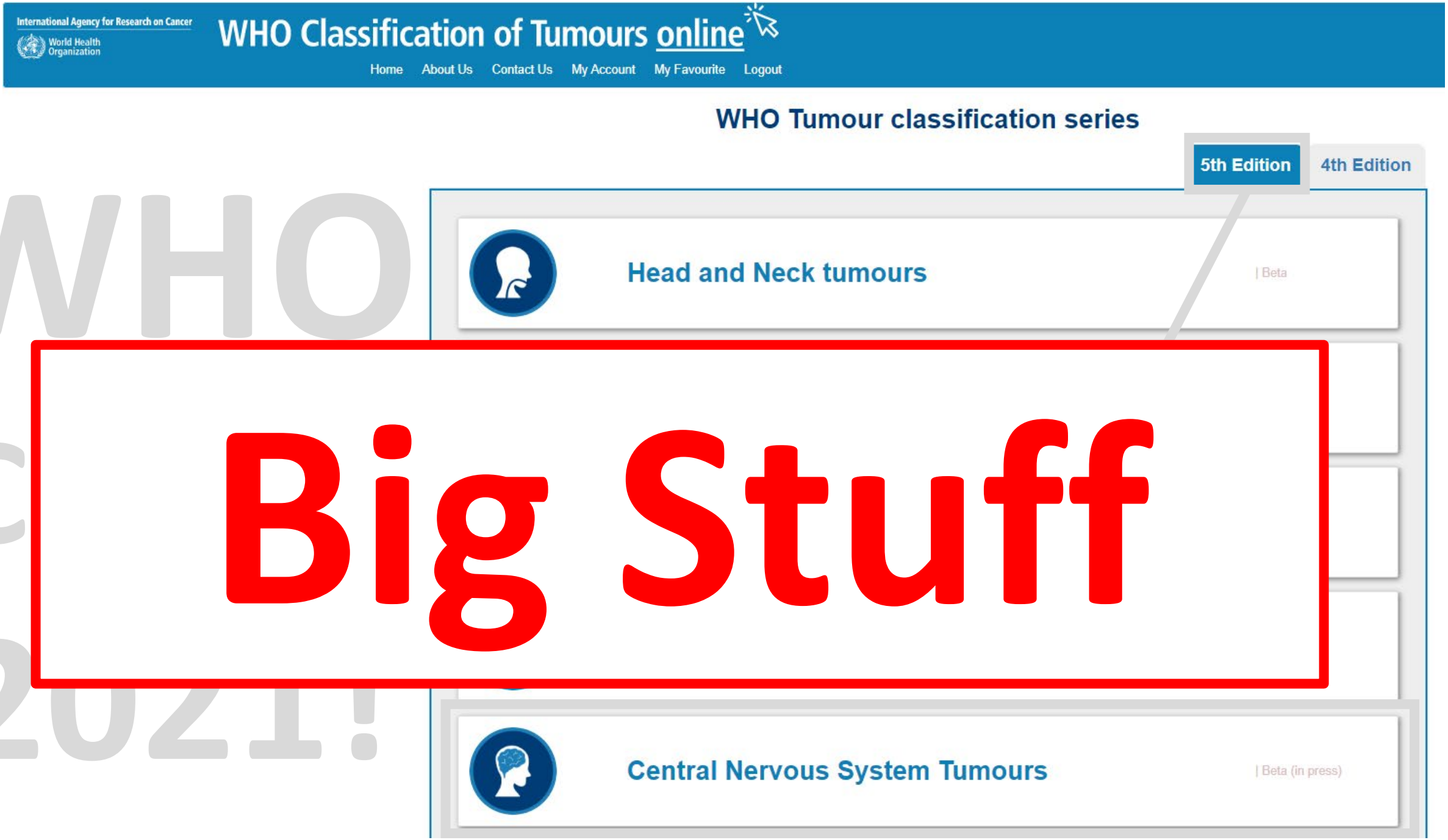
2F37.Y & XH94U0 Other specified benign neoplasm of endocrine glands & Pituitary adenoma, NOS
2F9A & XH94U0 Neoplasms of unknown behaviour of endocrine glands & Pituitary adenoma, NOS

Related terminology

Acceptable: PitNET; pituitary adenoma.

WHO CNS 5 (WHO 2021)

- **NOS Not Otherwise Specified**
- **NEC Not Elsewhere Classified**


International Agency for Research on Cancer
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| Beta
Central Nervous System Tumours
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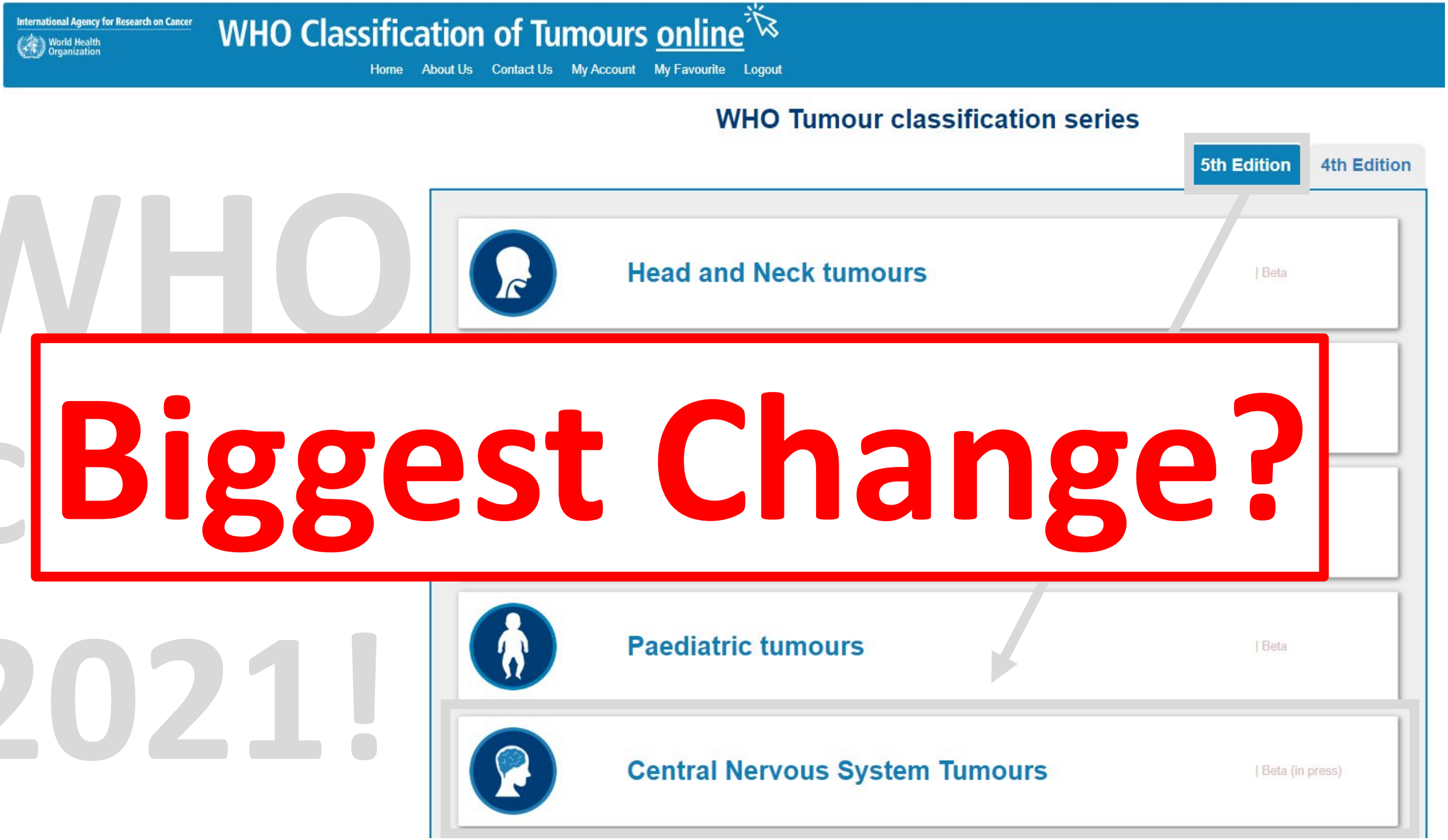
2021!
Big Stuff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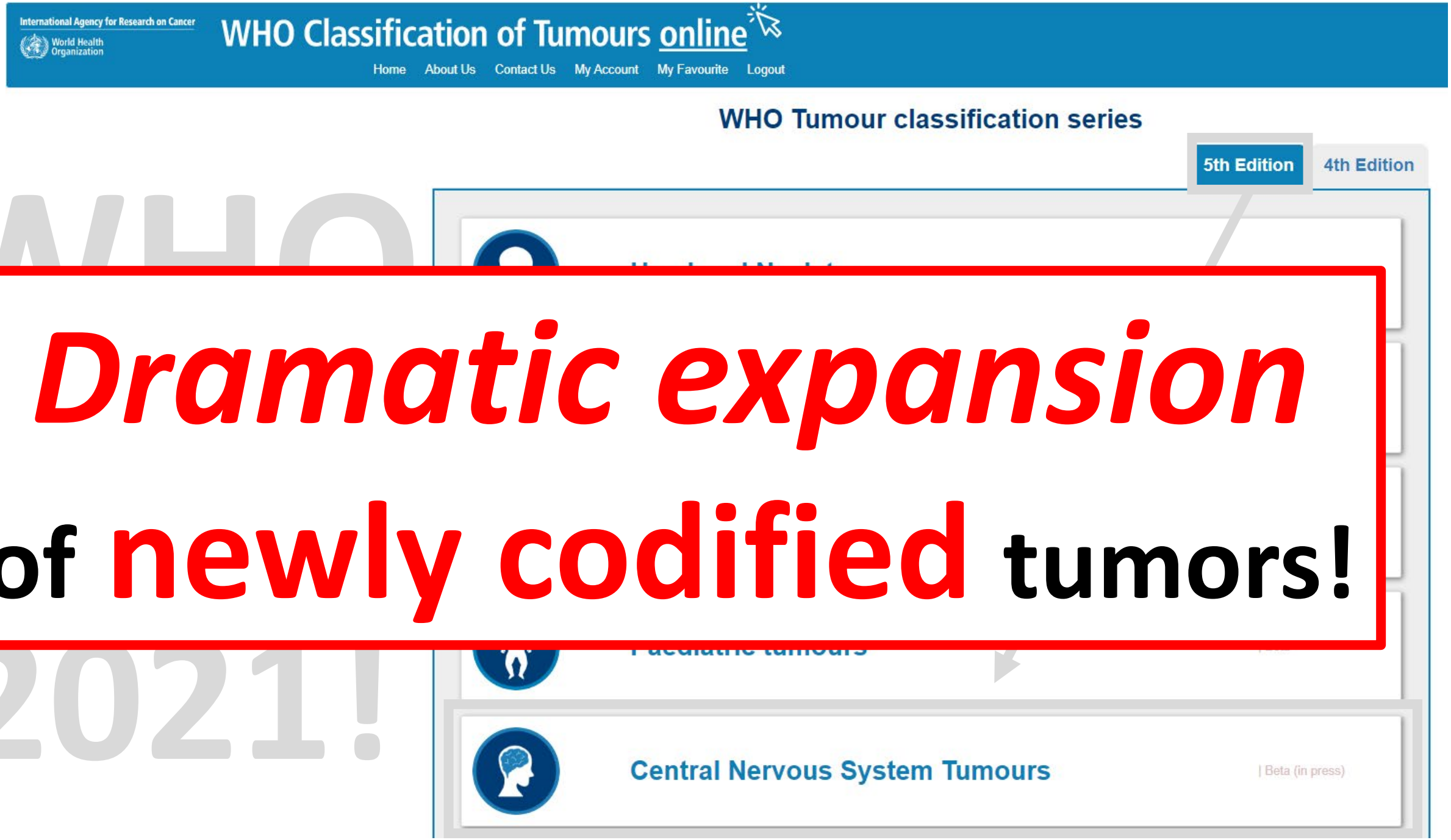
2021!
Biggest Change?



WHO 2021!

Dramatic expansion

of **newly codified** tumors!

Table 7 Newly Recognized Tumor Types in the 2021 WHO Classification of Tumors of the Central Nervous System

Newly Recognized Tumor Types
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)
Myxoid glioneuronal tumor
Multinodular and vacuolating neuronal tumor
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma, *MYCN*-amplified
Cribriform neuroepithelial tumor (provisional type)
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant
Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Pituitary blastoma

WHO 5E

22 NEW CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

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WHO 5E

12 NEW

Molecular

Signature-Defined

CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

12 NEW

Molecular Signature-Defined

CNS Tumors

Table 2 Key Diagnostic Genes, Molecules, Pathways, and/or Combinations in Major Primary CNS Tumors

Tumor Type	Genes/Molecular Profiles Characteristically Altered*
Astrocytoma, IDH-mutant	*IDH1, IDH2, ATRX, TP53, CDKN2A/B*
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1, IDH2*, 1p/19q, *TERT* promoter, *CIC, FUBP1, NOTCH1*
Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, chromosomes 7/10, *EGFR*
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	*MYB, MYBL1*
Angiocentric glioma	*MYB*
Polymorphous low-grade neuroepithelial tumor of the young	*BRAF*, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	*FGFR1, BRAF*
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53, ACVR1, PDGFRA, EGFR, EZHIP*
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53, ATRX*
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, *PDGFRA, MYCN, EGFR* (methylome)
Infant-type hemispheric glioma	NTRK family, *ALK, ROS, MET*
Pilocytic astrocytoma	*KIAA1549-BRAF, BRAF, NF1*
High-grade astrocytoma with piloid features	*BRAF, NF1, ATRX, CDKN2A/B* (methylome)
Pleomorphic xanthoastrocytoma	*BRAF, CDKN2A/B*
Subependymal giant cell astrocytoma	*TSC1, TSC2*
Chordoid glioma	*PRKCA*
Astroblastoma, *MN1*-altered	*MN1*
Ganglion cell tumors	*BRAF*
Dysembryoplastic neuroepithelial tumor	*FGFR1*
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chromosome 14, (methylome)
Papillary glioneuronal tumor	*PRKCA*
Rosette-forming glioneuronal tumor	*FGFR1, PIK3CA, NF1*
Myxoid glioneuronal tumor	*PDFGRA*
Diffuse leptomeningeal glioneuronal tumor	*KIAA1549-BRAF* fusion, 1p (methylome)
Multinodular and vacuolating neuronal tumor	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	*PTEN*
Extraventricular neurocytoma	FGFR (*FGFR1-TACC1* fusion), IDH-wildtype
Supratentorial ependymomas	*ZFTA, RELA, YAP1, MAML2*
Posterior fossa ependymomas	H3 K27me3, *EZHIP* (methylome)
Spinal ependymomas	*NF2, MYCN*
Medulloblastoma, WNT-activated	*CTNNB1, APC*
Medulloblastoma, SHH-activated	*TP53, PTCH1, SUFU, SMO, MYCN, GLI2* (methylome)
Medulloblastoma, non-WNT/non-SHH	*MYC, MYCN, PRDM6, KDM6A* (methylome)
Atypical teratoid/rhabdoid tumor	*SMARCB1, SMARCA4*
Embryonal tumor with multilayered rosettes	C19MC, *DICER1*
CNS neuroblastoma, *FOXR2*-activated	*FOXR2*
CNS tumor with *BCOR* internal tandem duplication	*BCOR*
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant	*SMARCB1*
Meningiomas	*NF2, AKT1, TRAF7, SMO, PIK3CA; KLF4, SMARCE1, BAP1* in subtypes; H3K27me3; *TERT* promoter, *CDKN2A/B* in CNS WHO grade 3
Solitary fibrous tumor	*NAB2-STAT6*
Meningeal melanocytic tumors	*NRAS* (diffuse); *GNAQ, GNA11, PLCB4, CYSLTR2* (circumscribed)
Adamantinomatous craniopharyngioma	*CTNNB1*
Papillary craniopharyngioma	*BRAF*

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43 Tumor Types

with *critical* molecular signature determinants

Neuro-Oncology 2021 PMID 34185076

WHO CNS 5 (WHO 2021)

Major Changes in the Most Common CNS Tumor Types

WHO CNS 5 (WHO 2021)

Major Changes in the Most Common CNS Tumor Types

- **Adult-type Diffuse Gliomas**
- **Pediatric-type Diffuse Gliomas**
- **Ependymomas**
- **Meningiomas**

2. Gliomas, glioneuronal tumours, and neuronal tumours

- Gliomas, glioneuronal tumours, and neuronal tumours: Introduction

Gliomas, glioneuronal tumours, and neuronal tumours

- *Adult-type diffuse gliomas*
  - Astrocytoma, IDH-mutant
  - Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  - Glioblastoma, IDH-wildtype
- *Paediatric-type diffuse low-grade gliomas*
  - Diffuse astrocytoma, MYB- or MYBL1-altered
  - Angiocentric glioma
  - Polymorphous low-grade neuroepithelial tumour of the young
  - Diffuse low-grade glioma, MAPK pathway-altered
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  - Diffuse hemispheric glioma, H3 G34-mutant
  - Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
  - Infant-type hemispheric glioma
- *Circumscribed astrocytic gliomas*
  - Pilocytic astrocytoma
  - High-grade astrocytoma with piloid features
  - Pleomorphic xanthoastrocytoma
  - Subependymal giant cell astrocytoma
  - Chordoid glioma
  - Astroblastoma, MN1-altered

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- Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma

Adult-Type Diffuse Gliomas (WHO 2000/2016)

10 entities!

Adult-Type Diffuse Gliomas (WHO 2000/2016)

10 entities!

- **Diffuse Astrocytoma, IDH-Mutant, WHO Grade II**
- **Diffuse Astrocytoma, IDH-Wildtype, WHO Grade II**
- **Anaplastic Astrocytoma, IDH-Mutant, WHO Grade III**
- **Anaplastic Astrocytoma, IDH-Wildtype, WHO Grade III**
- **Glioblastoma, IDH-Mutant, WHO Grade IV**
- **Glioblastoma, IDH-Wildtype, WHO Grade IV**
- **Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted, WHO Grade II**
- **Anaplastic Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted, WHO Grade III**
- **Oligoastrocytoma, WHO Grade II**
- **Anaplastic Oligoastrocytoma, WHO Grade III**

Adult-Type Diffuse Gliomas (WHO 2021)

Only 3 Distinct Diseases!

- **Astrocytoma, IDH-Mutant**
- **Glioblastoma, IDH-Wildtype**
- **Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted**

// Gliomas, glioneuronal tumours, and neuronal tumours

Astrocytoma, IDH-mutant

Definition

Astrocytoma, IDH-mutant, is a diffusely infiltrating *IDH1*- or *IDH2*-mutant glioma with frequent *ATRX* and/or *TP53* mutation and absence of 1p/19q codeletion (CNS WHO grade 2, 3, or 4).

ICD-O coding

9400/3 Astrocytoma, IDH-mutant, grade 2
9401/3 Astrocytoma, IDH-mutant, grade 3
9445/3 Astrocytoma, IDH-mutant, grade 4

ICD-11 coding

2A00.0Y & XH6PH6 Other specified gliomas of brain & Astrocytoma, NOS
2A00.0Y & XH2HK4 Other specified gliomas of brain & Diffuse astrocytoma, IDH-mutant

Related terminology

Not recommended: diffuse astrocytoma, IDH-mutant; anaplastic astrocytoma, IDH-mutant; glioblastoma, IDH-mutant; low-grade astrocytoma; lower-grade astrocytoma; high-grade astrocytoma; infiltrating astrocytoma; diffuse

IDH-Mutant Astrocytoma

- Astrocytoma, IDH-Mutant, CNS WHO Grade 2
- Astrocytoma, IDH-Mutant, CNS WHO Grade 3
- Astrocytoma, IDH-Mutant, CNS WHO Grade 4

IDH-Mutant Astrocytoma

Astrocytoma, IDH-Mutant, CNS WHO Grade 2

- Mitotic activity ***absent or very low***
- NO microvascular proliferation
- NO necrosis
- NO *CDKN2A/B* homozygous deletion

Astrocytoma, IDH-Mutant, CNS WHO Grade 3

- Mitotic activity ***elevated***
- NO microvascular proliferation
- NO necrosis
- NO *CDKN2A/B* homozygous deletion

Astrocytoma, IDH-Mutant, CNS WHO Grade 4

At least one of the following must be present:

- Microvascular proliferation, *or*
- Necrosis, *or*
- *CDKN2A/B* homozygous deletion

Glioblastoma, IDH-Wildtype, CNS WHO Grade 4

At least one of the following must be present:

- Microvascular proliferation, *or*
- Necrosis, *or*
- *TERT* promoter mutation, or
- *EGFR* gene amplification, or
- Combined **gain** of chr **7** with **loss** of chr **10** (**+7/–10**)

? IDH-Wildtype Astrocytoma, Grade 2, Grade 3 ?

Diffuse Astrocytoma, IDH-Wildtype, WHO Grade 2

- Mitotic activity ***absent or very low***
- **NO** microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

Anaplastic Astrocytoma, IDH-Wildtype, WHO Grade 3

- Mitotic activity ***elevated***
- **NO** microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

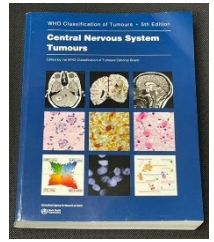
? IDH-Wildtype Astrocytoma, Grade 2, Grade 3 ?

~~**Diffuse Astrocytoma, IDH-Wildtype, WHO Grade 2**~~

- Mitotic activity ***absent or very low***
- **NO** microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

~~**Anaplastic Astrocytoma, IDH-Wildtype, WHO Grade 3**~~

- Mitotic activity ***elevated***
- **NO** microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10



Adult-type diffuse gliomas

- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas

- Diffuse astrocytoma, MYB- or MYBL1-altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumour of the young
- Diffuse low-grade glioma, MAPK pathway-altered

Paediatric-type diffuse high-grade gliomas

- Diffuse midline glioma, H3 K27-altered
- Diffuse hemispheric glioma, H3 G34-mutant
- Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma

? IDH-Wildtype Astrocytoma, Grade 2, Grade 3 ?

Diffuse Astrocytoma, IDH-Wildtype, NOS
WHO Histologic Grade 2

- Mitotic activity ***absent or very low***
- **NO** microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

Anaplastic Astrocytoma, IDH-Wildtype, NOS
WHO Histologic Grade 3

- Mitotic activity ***elevated***
- **NO** microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

Oligodendroglioma

- **Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted, CNS WHO Grade 2**

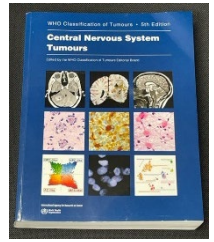
- **Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted, CNS WHO Grade 3**

Oligodendroglioma

- **Oligodendroglioma, NOS**
  CNS WHO Grade 2

- **Oligodendroglioma, NOS**
  CNS WHO Grade 3

Pediatric-Type Diffuse Gliomas



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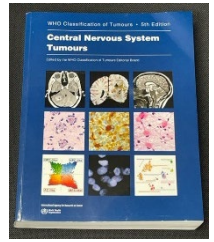

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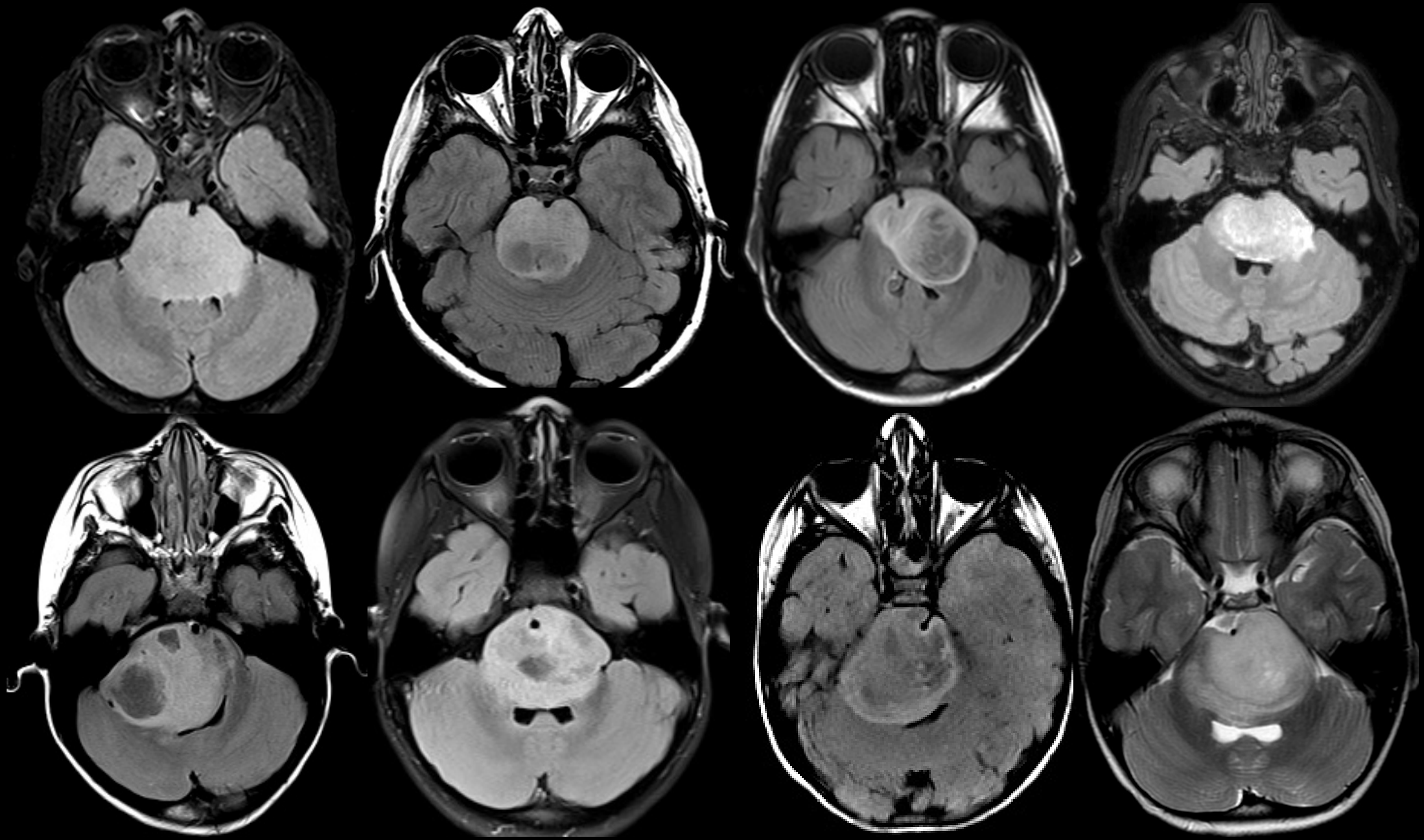
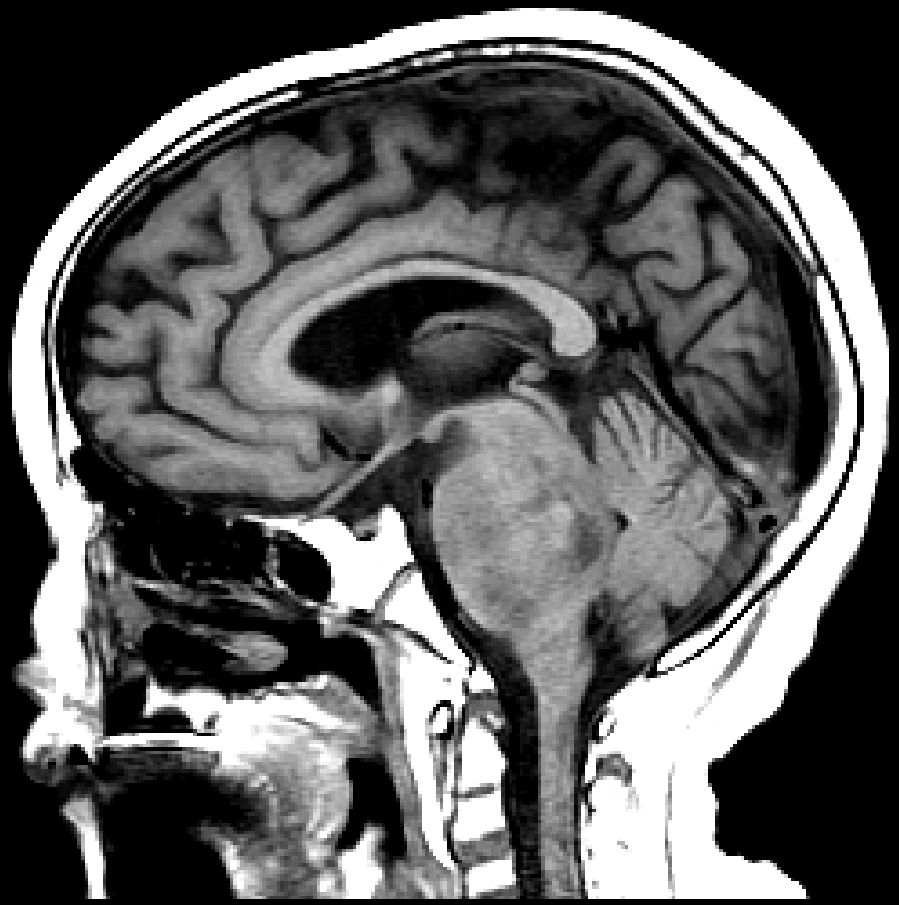
- Infant-type hemispheric glioma

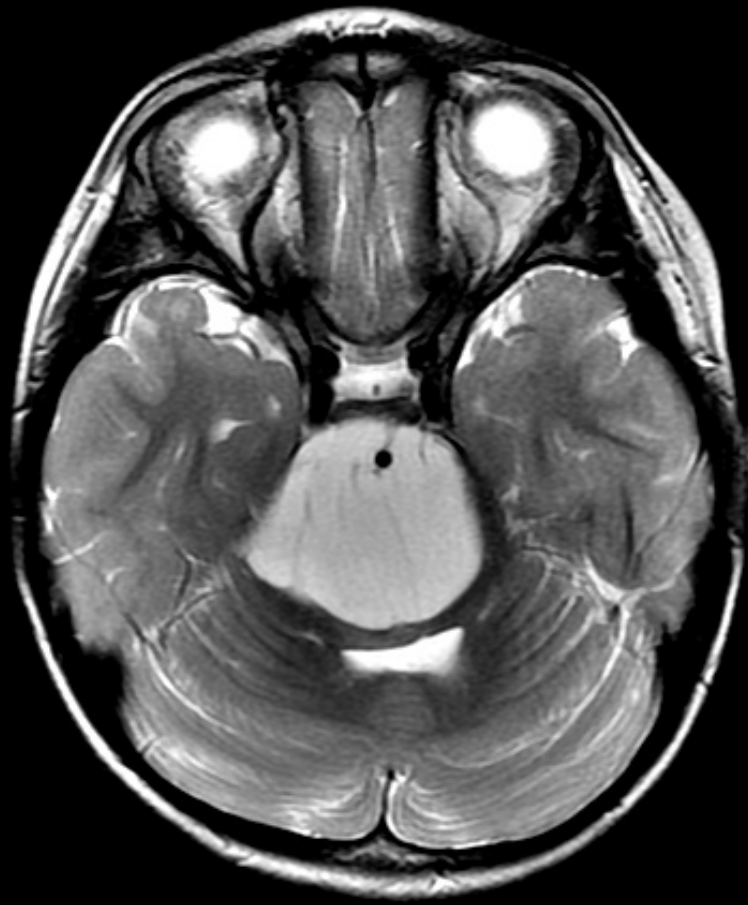
Diffuse Intrinsic Pontine Glioma (DIPG) Spectrum of Imaging Morphology (8 Patients)



Diffuse Midline Glioma, H3 K27-Altered

Classical Pontine Glioma (DIPG) 80% are H3 K27-Alt DMG

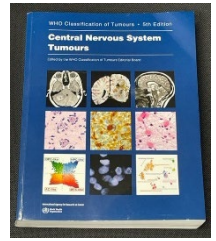




Diffuse midline glioma, H3 K27-altered

Definition

Diffuse midline glioma, H3 K27–altered, is an infiltrative midline glioma with loss of H3 p.K28me3 (K27me3) and usually either an H3 c.83A>T p.K28M (K27M) substitution in one of the histone H3 isoforms, aberrant overexpression of EZHIP, or an *EGFR* mutation (CNS WHO grade 4).



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ICD-O coding

9385/3 Diffuse midline glioma, H3 K27–altered

ICD-11 coding

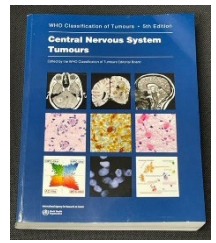
2A00.0Y & XH7692 Other specified gliomas of brain & Diffuse midline glioma, H3 K27M–mutant

Related terminology

Acceptable: diffuse intrinsic pontine glioma.

Subtype(s)

Diffuse midline glioma, H3.3 K27–mutant; diffuse midline glioma, H3.1 or H3.2 K27–mutant; diffuse midline glioma, H3-wildtype with EZHIP overexpression; diffuse midline glioma, *EGFR*-mutant



Pediatric Diffuse Gliomas

Histone H3 Mutation

- **H3 K27-Altered** in the **MIDLINE**

  Diffuse Midline Glioma, H3 K27-Altered

- **H3 G34-Mutant** in the **Cerebral Hemisphere**

  Diffuse Hemispheric Glioma, G34-Mutant

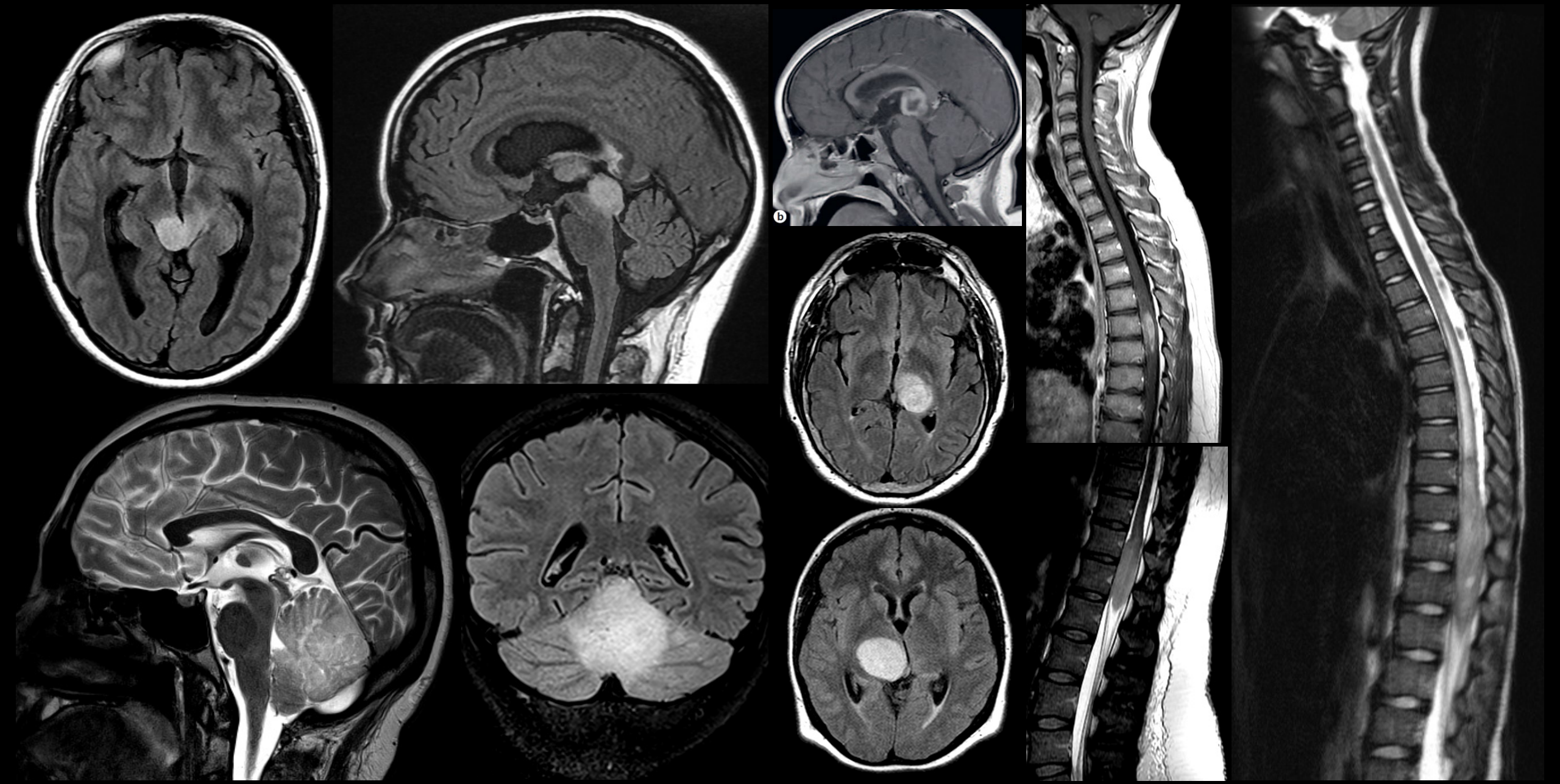
Histone H3 Mutation Nomenclature

Histone H3 nomenclature can be based on either on the amino acid numbering of the mature processed protein (K27 / G34) or on the DNA codon numbering (K28 / G35)

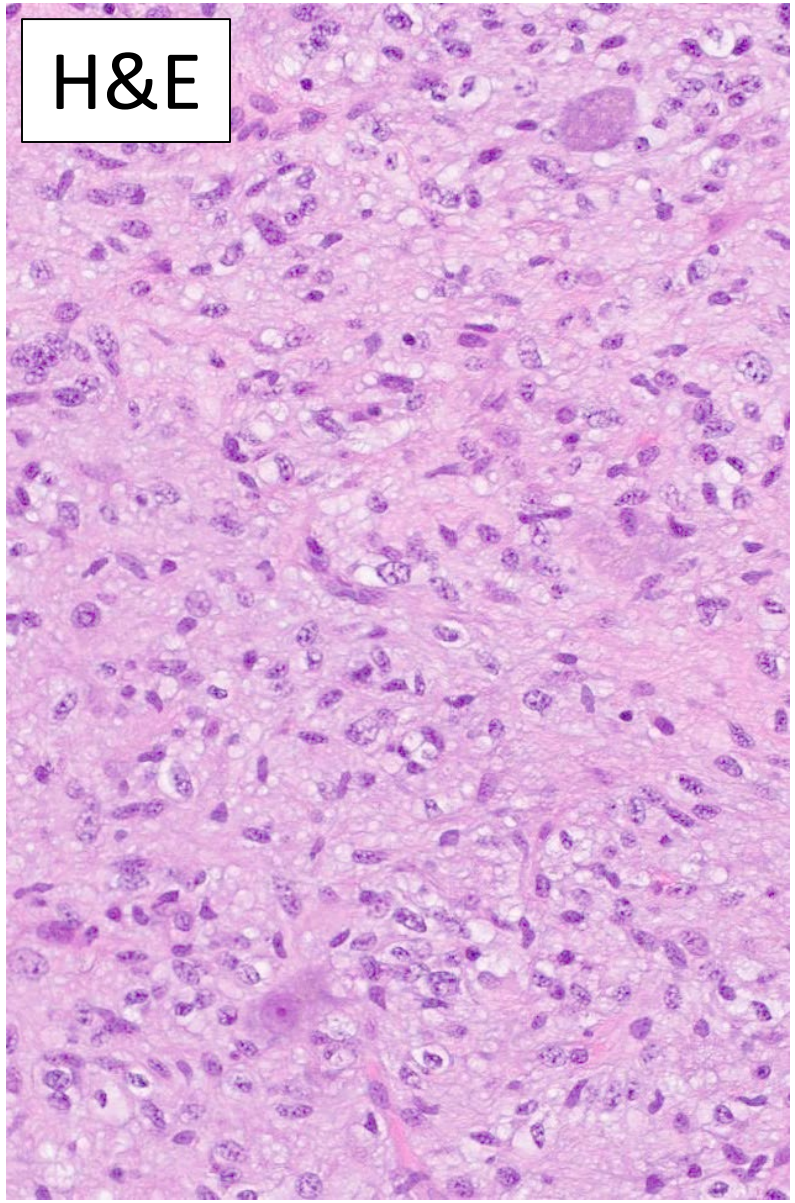
- **H3 K27 and H3 G34 are entrenched in the neuro-oncologic literature**
- **H3 K28 and H3 G35 are favored by most (if not all) Next Generation Sequencing (NGS) reference laboratories**
- **In this context, H3 K27 = H3 K28, and H3 G34 = H3 G35**

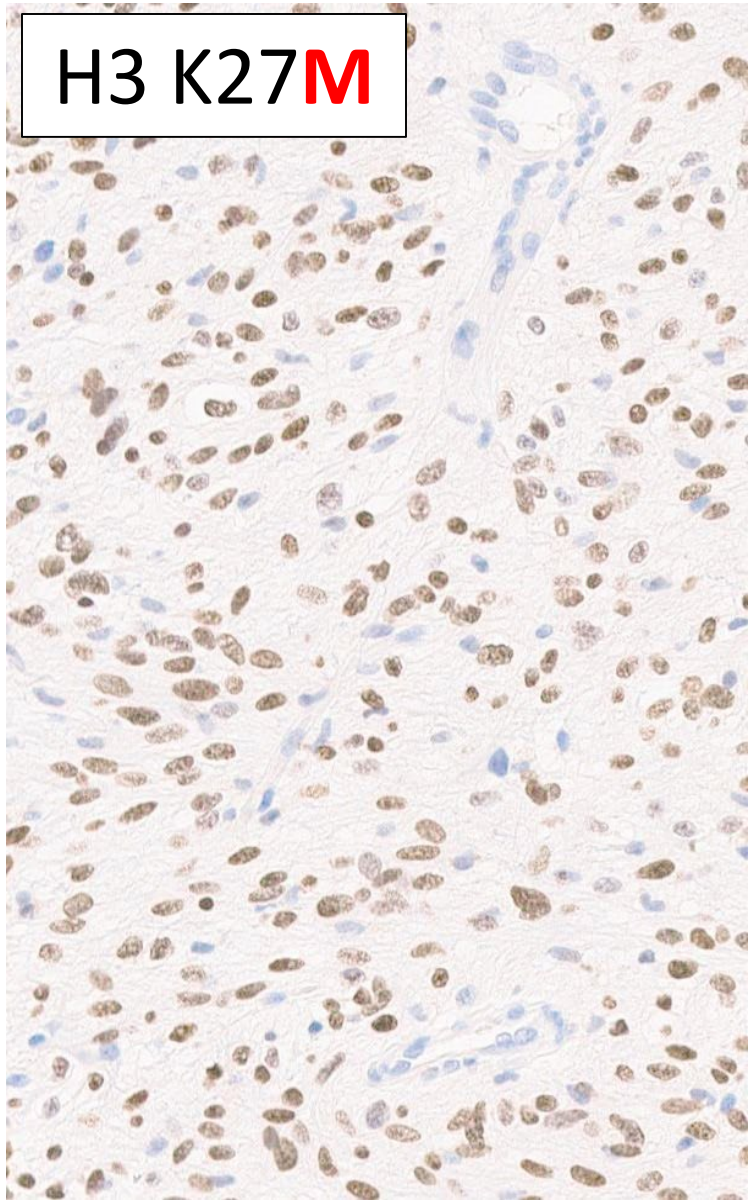
DMG, H3 K27-Altered

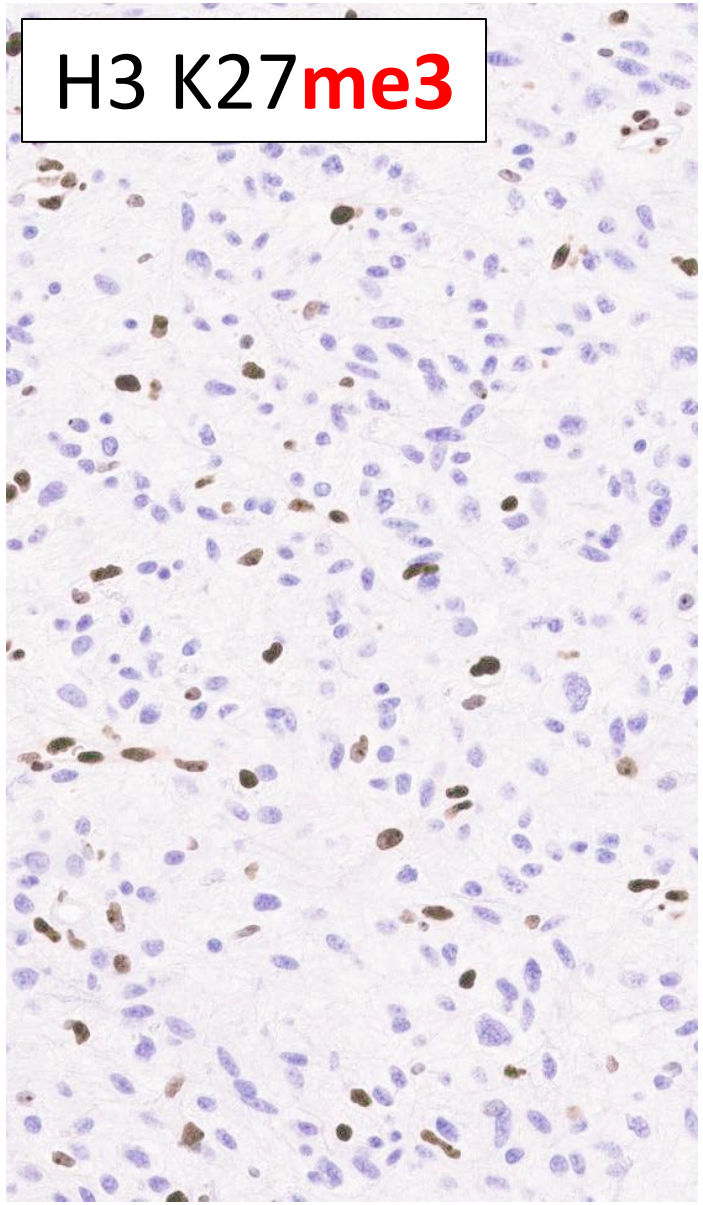
Spectrum of Anatomic Locations



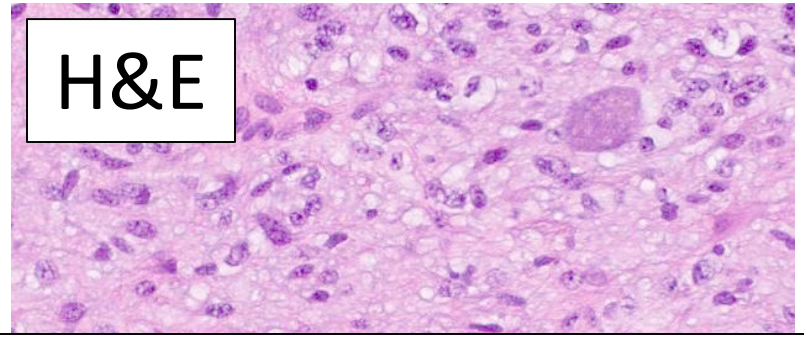
DMG, H3 K27-Altered HISTOLOGY

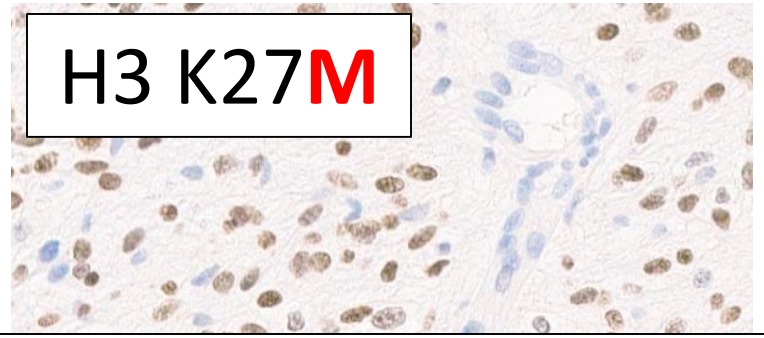


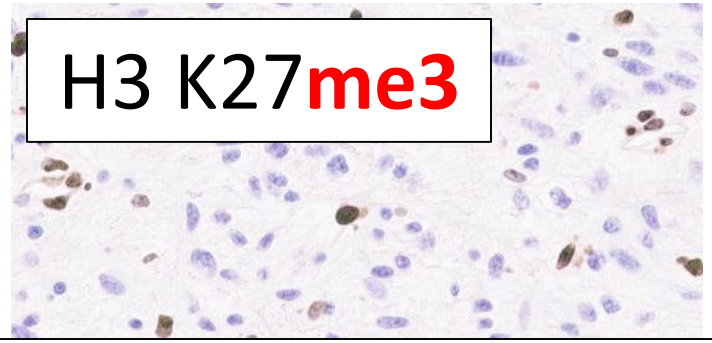




DMG, H3 K27-Altered HISTOLOGY

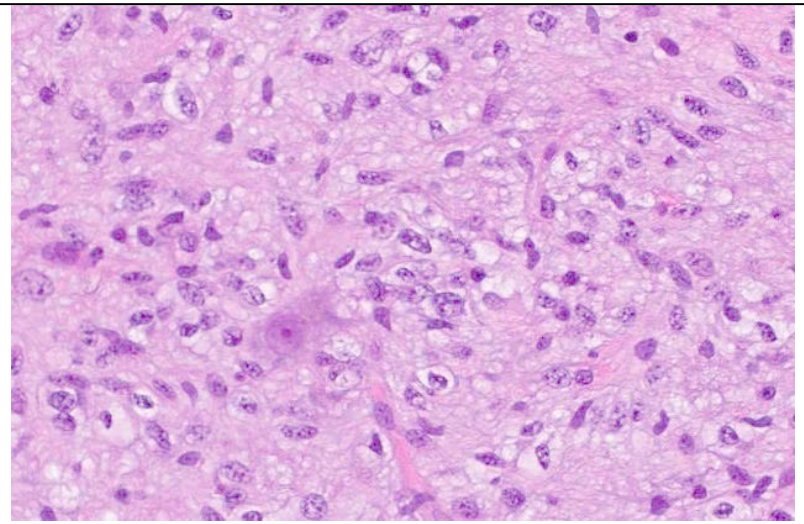


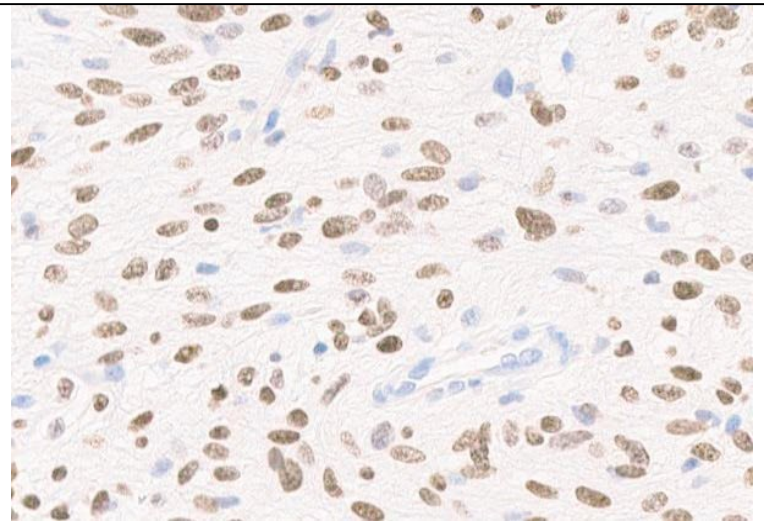


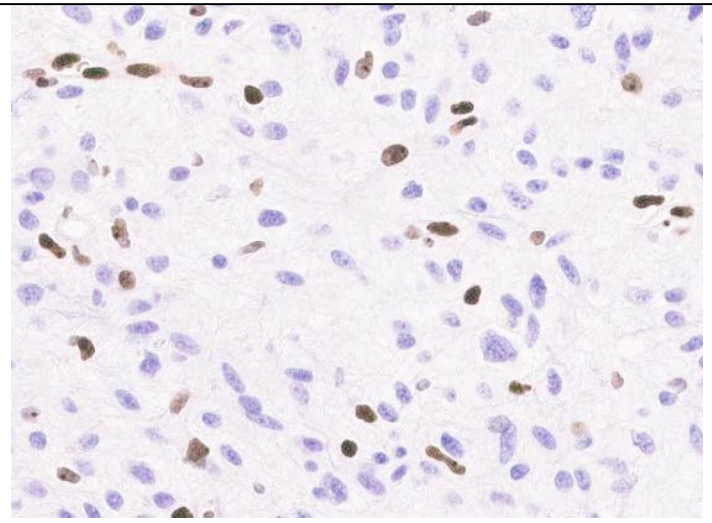


Diffuse Midline Glioma, H3 K27-Altered

CNS WHO Grade 4







Ependymoma Classification

- **Supratentorial** Ependymoma
- **Posterior Fossa** Ependymoma
- **Spinal Cord** Ependymoma

Ependymoma Classification

Supratentorial Ependymoma

- *RELA* Fusion-Positive (poor prognosis)
- *YAP1* Fusion-Positive
- NOS / NEC

Ependymoma Classification

Supratentorial Ependymoma

- ~~*RELA*~~ Fusion-Positive (poor prognosis)
- *YAP1* Fusion-Positive
- NOS / NEC

Ependymoma Classification

Supratentorial Ependymoma

- *C11orf95* Fusion-Positive (poor prognosis)
- *YAP1* Fusion-Positive
- NOS / NEC

Ependymoma Classification

Supratentorial Ependymoma

- ~~*C11orf95*~~ Fusion-Positive (poor prognosis)
- *YAP1* Fusion-Positive
- NOS / NEC

Ependymoma Classification

Supratentorial Ependymoma

- ***ZFTA*** Fusion-Positive (poor prognosis)
- *YAP1* Fusion-Positive
- NOS / NEC

Ependymoma Classification

Posterior Fossa Ependymoma

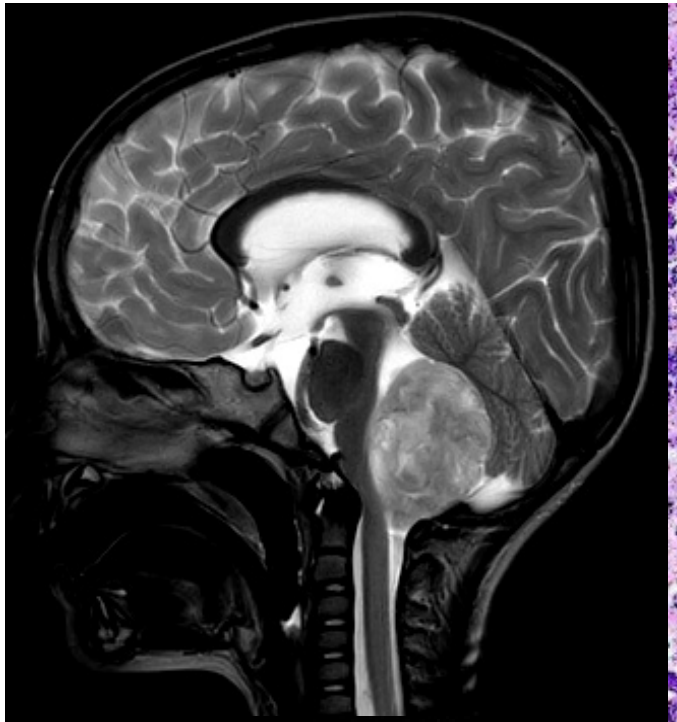
- Pediatric-Type (PFA) (poor prognosis)
- Adult-Type (PFB)
- NOS / NEC

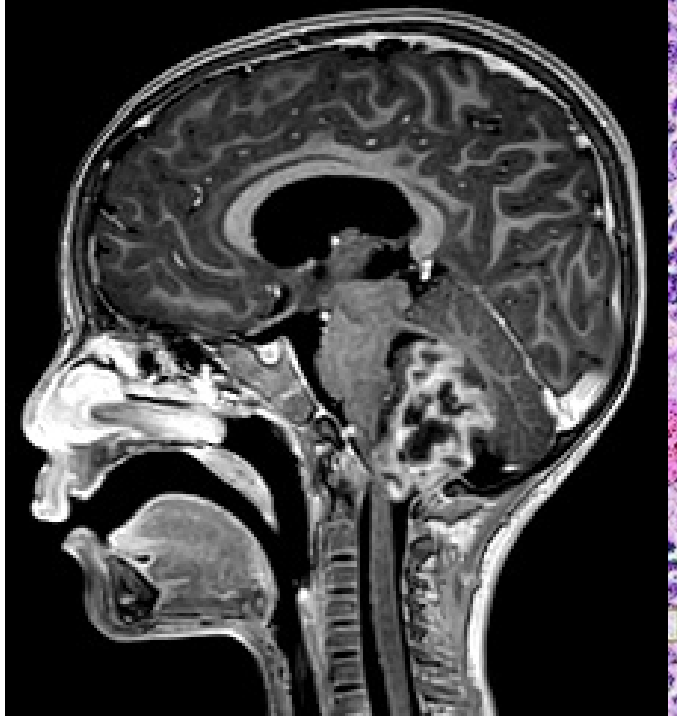
Ependymoma Classification

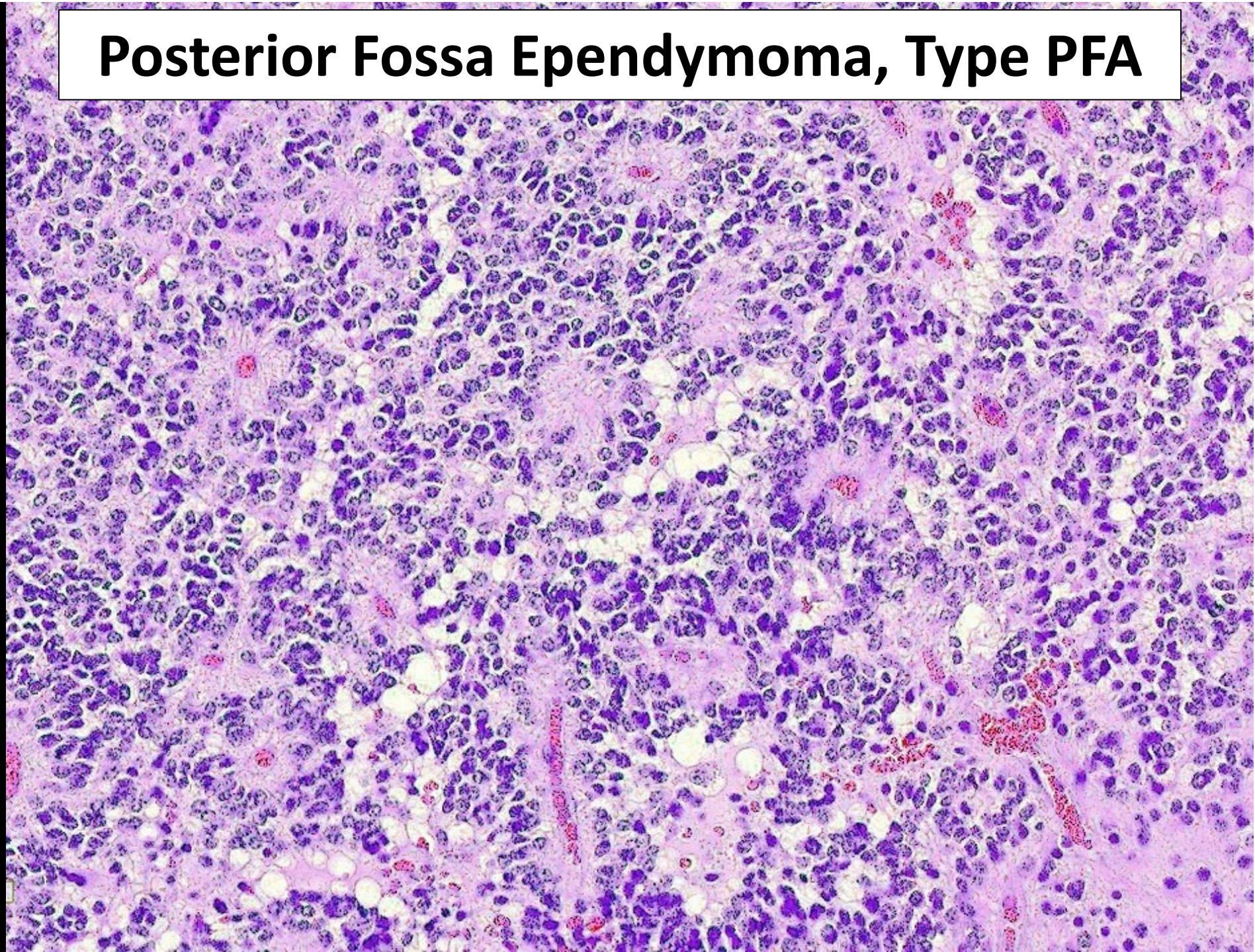
Spinal Ependymoma

- *MYCN*-Amplified
- NOS / NEC

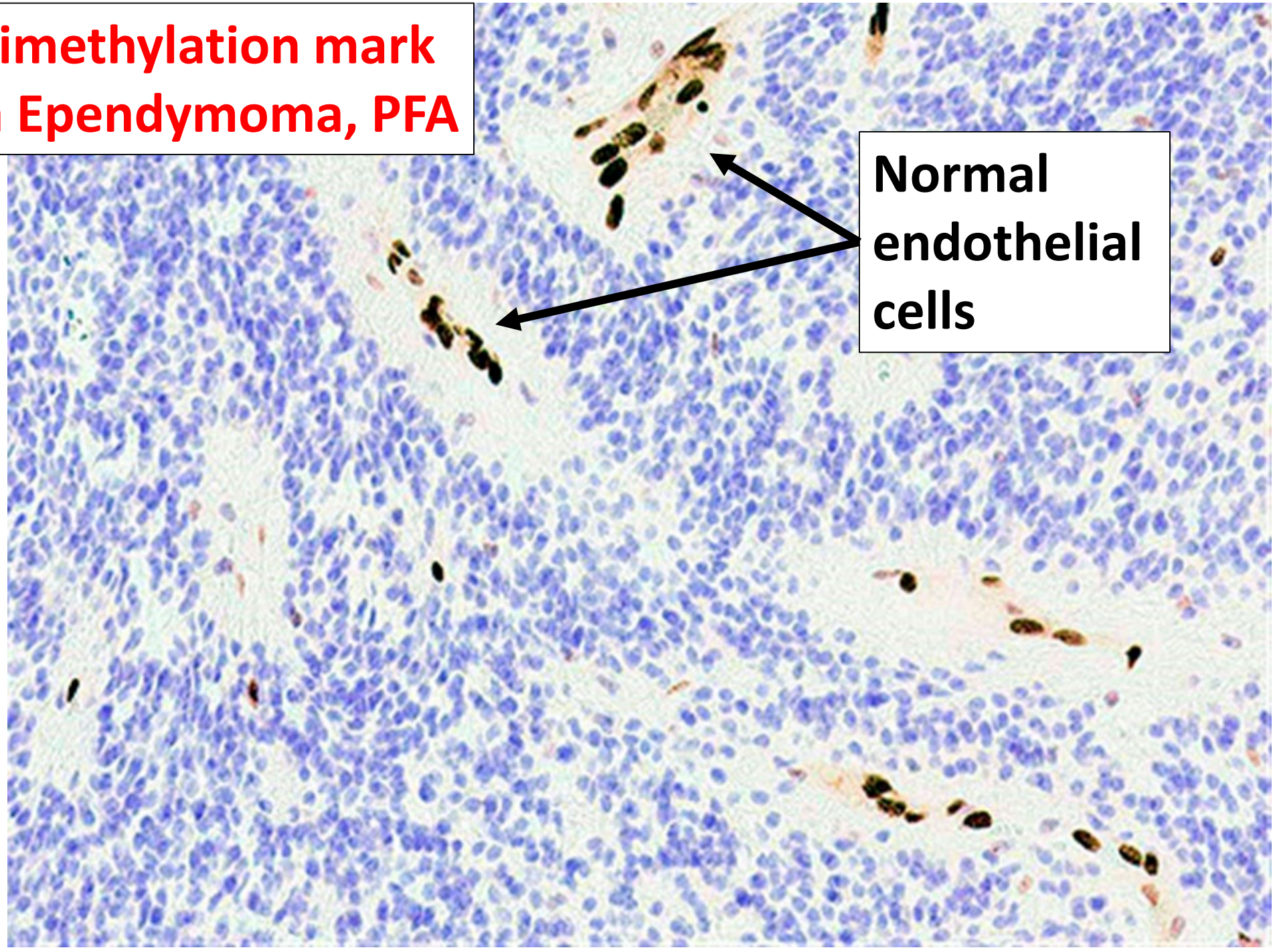
Posterior Fossa Ependymoma, Type PFA







LOSS of H3 K27 trimethylation mark in Posterior Fossa Ependymoma, PFA



Meningiomas

Meningioma

Definition

Meningiomas comprise a family of neoplasms that are most likely derived from the meningothelial cells of the arachnoid mater (CNS WHO grade 1, 2, or 3).

ICD-O coding

9530/0 Meningioma

ICD-11 coding

2A01.0Z Meningiomas, unspecified

Related terminology

None

Subtype(s)

See #19607Box 7.01 .

Localization

However, some genetic changes (e.g. *TERT* promoter mutation or homozygous *CDKN2A* and/or *CDKN2B* deletion) are evidence for diagnosing CNS WHO grade 3 meningioma

However, some genetic changes (e.g. *TERT* promoter mutation or homozygous *CDKN2A* and/or *CDKN2B* deletion) are evidence for diagnosing CNS WHO grade 3 meningioma (see below), so consideration should be given to *TERT*, *CDKN2A*, and *CDKN2B* analysis in clinically aggressive atypical meningiomas or those with borderline CNS WHO grade 2/3 features.

Anaplastic (malignant) meningioma

Anaplastic (malignant) meningioma is a high-grade meningioma with overtly malignant cytomorphology (anaplasia) that can (1) resemble carcinoma, high-grade sarcoma, or melanoma; (2) display markedly elevated mitotic activity;

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Anaplastic (malignant) meningioma is a high-grade meningioma with overtly malignant cytomorphology (anaplasia) that can (1) resemble carcinoma, high-grade sarcoma, or melanoma; (2) display markedly elevated mitotic activity; (3) harbour a *TERT* promoter mutation; and/or (4) have a homozygous *CDKN2A* and/or *CDKN2B* deletion.

Anaplastic (malignant) meningioma

(3) harbour a *TERT* promoter mutation; and/or (4) have a homozygous *CDKN2A* and/or *CDKN2B*

2022 Update

One Caveat!

ADULT Diffuse Astrocytic Disease – WHO 2021

Glioblastoma, IDH-Wildtype, CNS WHO Grade 4

At least one of the following must be present:

- Microvascular proliferation, *or*
- Necrosis, *or*
- *TERT* promoter mutation, or
- *EGFR* gene amplification, or
- Combined **gain** of chr **7** with **loss** of chr **10** (**+7/–10**)

Isolated *TERT* promoter mutation

as the *sole molecular criterion* for upgrading

Histologic Grade 2 IDH-WT Diffuse Astrocytoma to

GLIOBLASTOMA, IDH-WT, CNS WHO GRADE 4

PMID 33173941

Neuro-Oncology

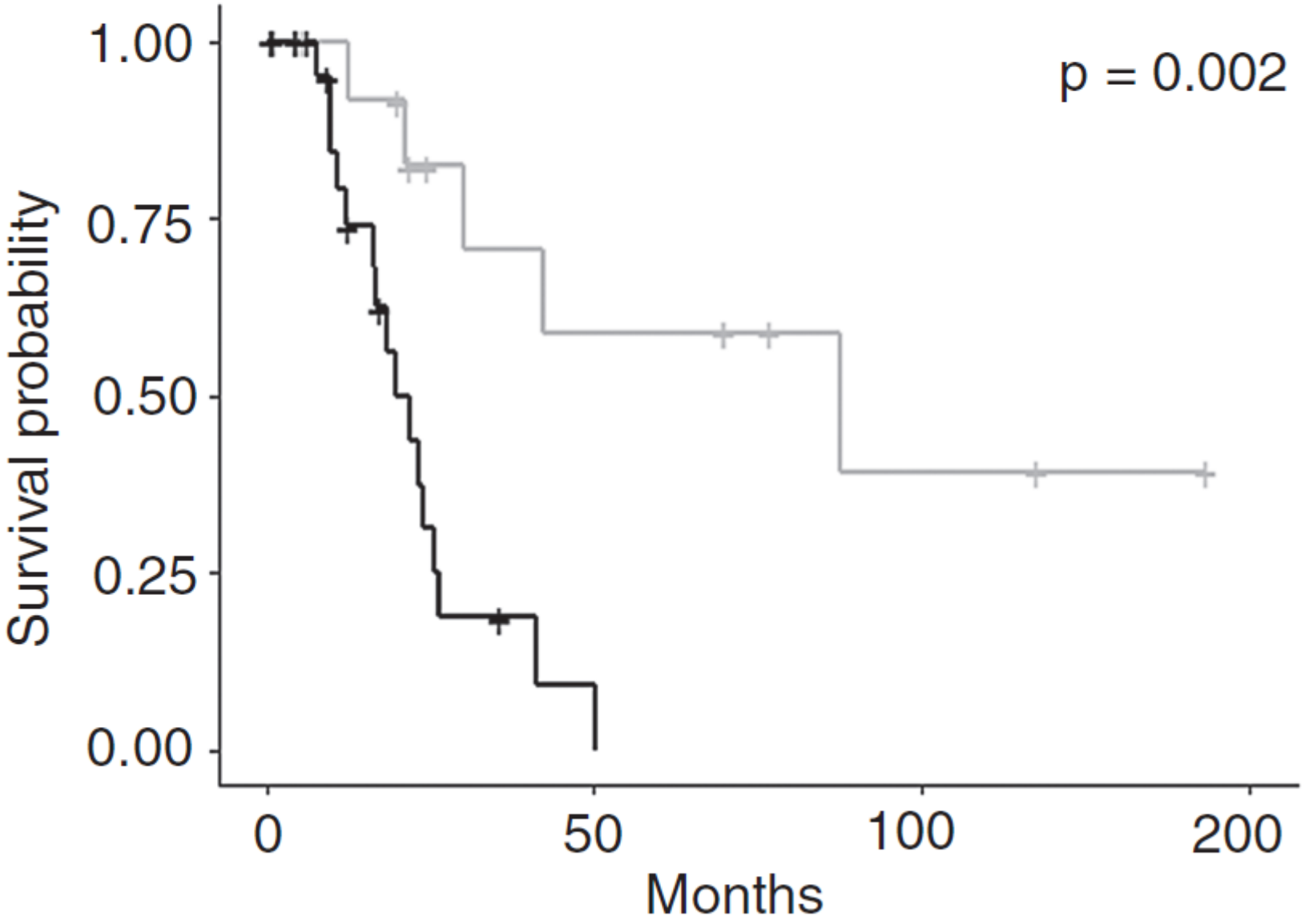
23(6), 955–966, 2021 | doi:10.1093/neuonc/noaa258 | Advance Access date 11 November 2020

IDH-wildtype lower-grade diffuse gliomas: the importance of histological grade and molecular assessment for prognostic stratification

Giulia Berzero, Anna Luisa Di Stefano, Susanna Ronchi, Franck Bielle, Chiara Villa, Erell Guillerm, Laurent Capelle, Bertrand Mathon, Alice Laurenge, Marine Giry, Yohann Schmitt, Yannick Marie, Ahmed Idbaih, Khe Hoang-Xuan, Jean-Yves Delattre, Karima Mokhtari, and Marc Sanson

E

Isolated *TERT* promoter mutations:
I*DH*wt grade II vs. grade III



PMID 33173941

PMID 33173941

Key Points

1. *IDH*-wildtype diffuse grade II gliomas should be distinguished from grade III because of a lower burden of genetic alterations (including *EGFR* amplifications, whole chromosome 7 gain/whole chromosome 10 loss, *TERT* promoter mutations, *TP53* mutations, deletions of cyclin-dependent kinase inhibitor 2A, and chromosome 9p loss) and a much better outcome.
2. With a median overall survival of 88 months, *IDH*-wildtype grade II gliomas with isolated *TERT* promoter mutations should not be assimilated to molecular glioblastomas.

PMID 33173941

Importance of the Study

The cIMPACT-NOW update 3 has recently established that *IDH*wt histological grade II and III diffuse gliomas with *EGFR* amplifications, and/or combined whole chromosome 7 gain and whole chromosome 10 loss, and/or *TERT* promoter mutations should be considered as bona fide glioblastomas. Our data suggest that, while true for histological grade III gliomas, these considerations do not fit a subset of grade II gliomas, and namely those with isolated *TERT* promoter mutations (median overall survival: 88 mo). These findings highlight the importance of histological grade, in parallel to molecular profile, for the prognostic stratification of *IDH*wt lower-grade gliomas and suggest that *IDH*wt gliomas with grade II histology (<2 mitosis per 10 high power fields) and isolated *TERT* promoter mutations should not be assimilated to molecular glioblastomas.

Neuro-Oncology

PMID 33660766

23(6), 865–866, 2021 | doi:10.1093/neuonc/noab052 | Advance Access date 28 February 2021

TERT promoter mutation: is it enough to call a WHO grade II astrocytoma IDH wild-type glioblastoma?

Caterina Giannini and Felice Giangaspero

PMID 33660766

While it may be too late for the results of this paper to be incorporated in the upcoming 2021 WHO classification for CNS Tumor, clinicians and pathologists should be aware of its conclusions. Histological grade is still useful for prognostic stratification of *IDH*-wt gliomas and *pTERTmut* in isolation in strictly defined grade II astrocytoma does not appear to be sufficient to assume that the tumor will behave as glioblastoma, wild-type (WHO CNS grade 4) as proposed in cIMPACT-NOW update 6.[4]

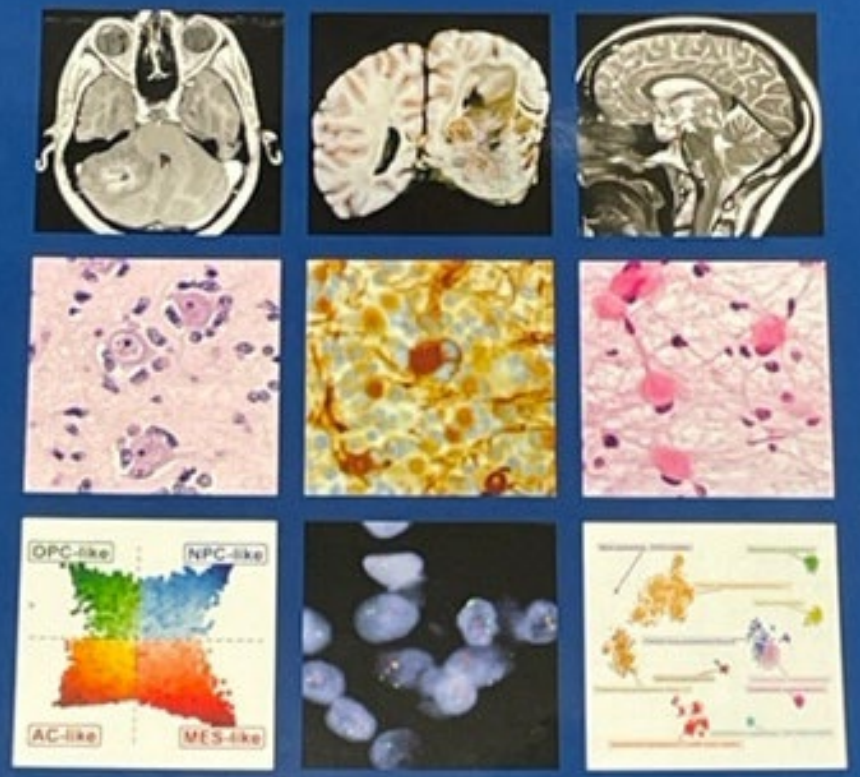
A *Brief History* of the World Health Organization Classification of Tumours of the Central Nervous System

WHO CNS “Blue Books”

WHO Classification of Tumours • 5th Edition

Central Nervous System Tumours

Edited by the WHO Classification of Tumours Editorial Board



International Agency for Research on Cancer

World Health Organization

WHO Classification of Tumours • 5th Edition

Central Nervous System Tumours

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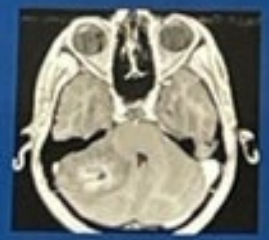
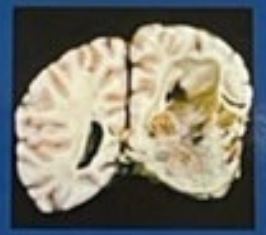
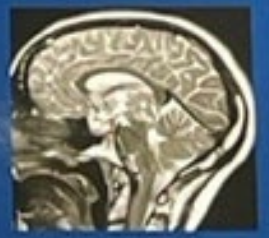
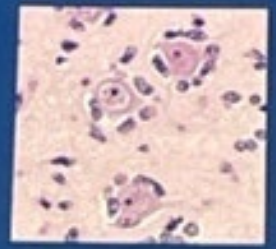
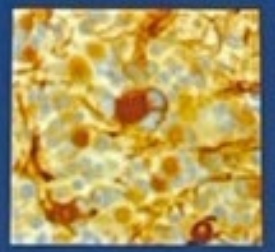
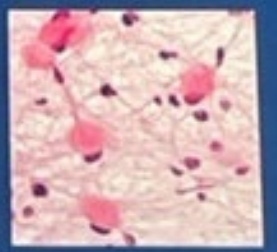
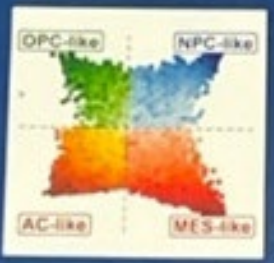


International Agency for Research on Cancer

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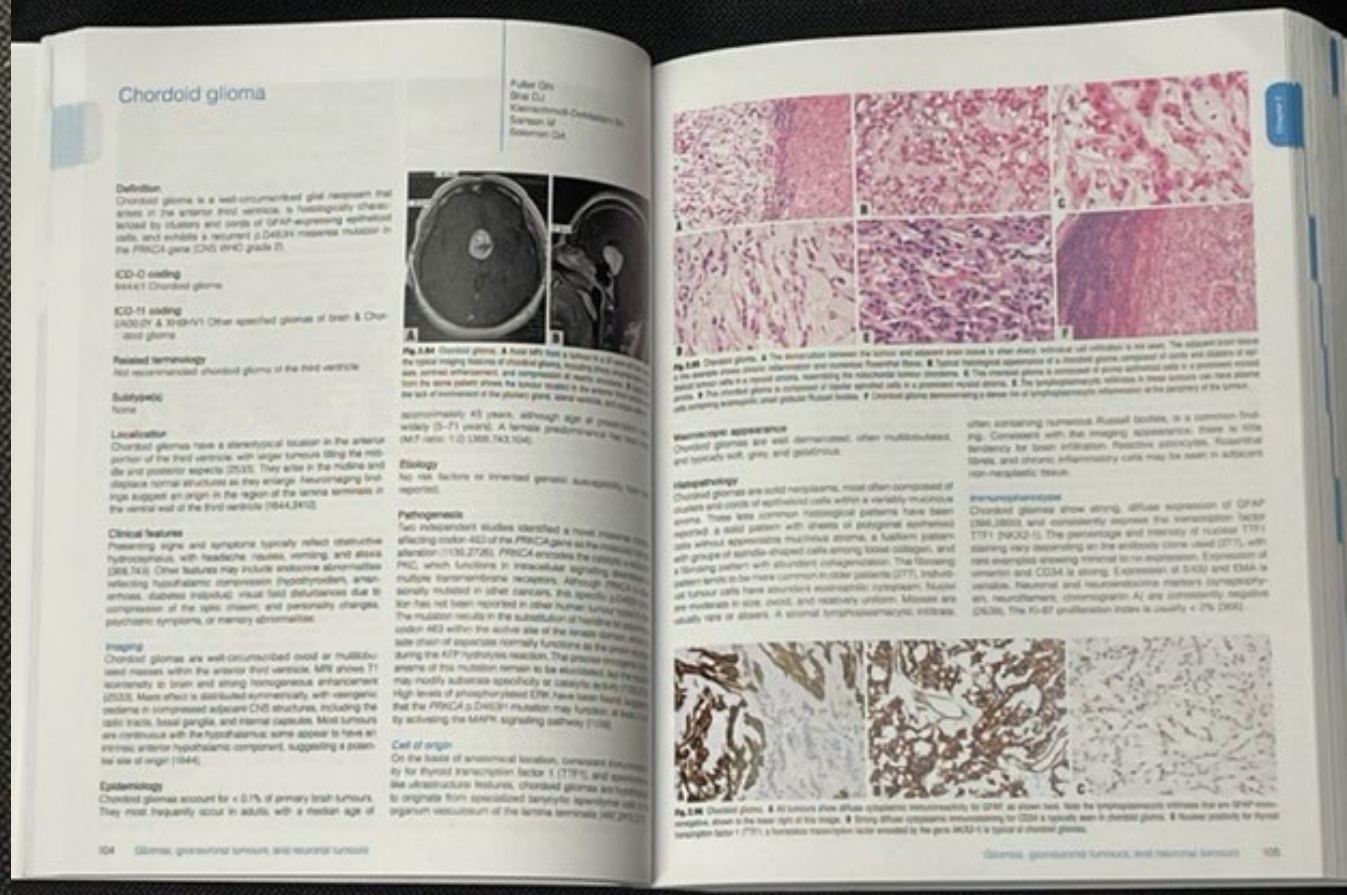

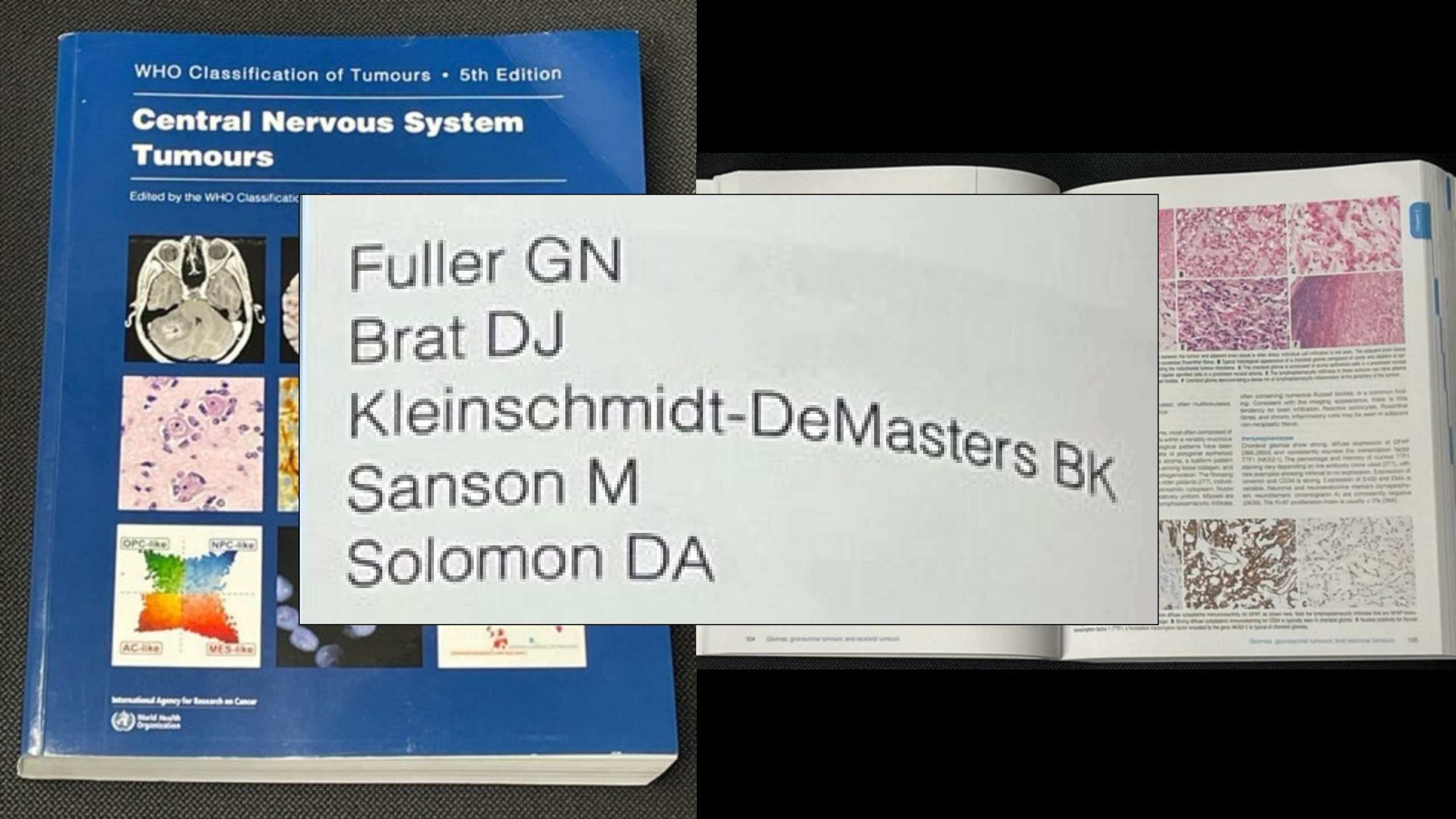
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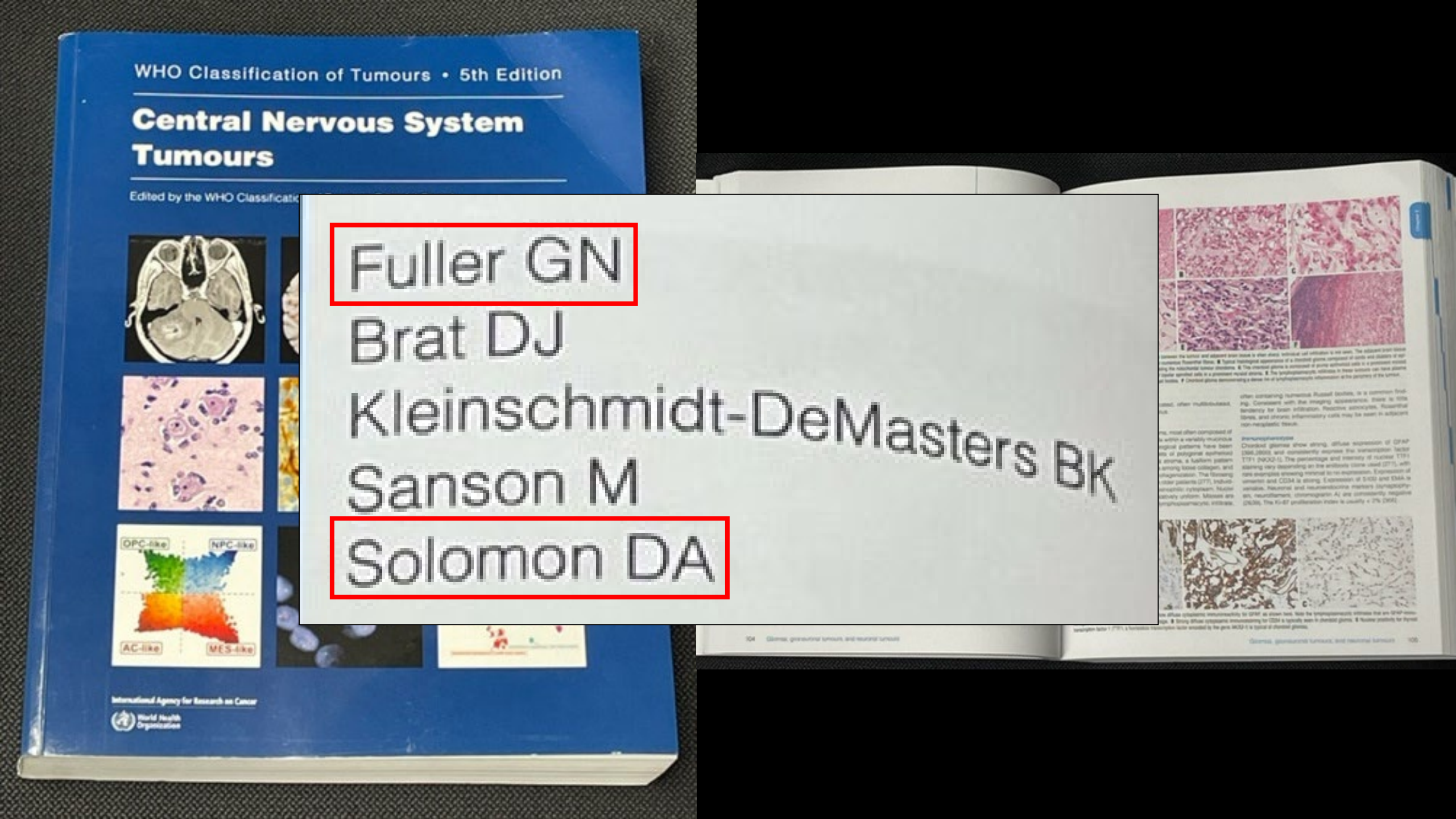
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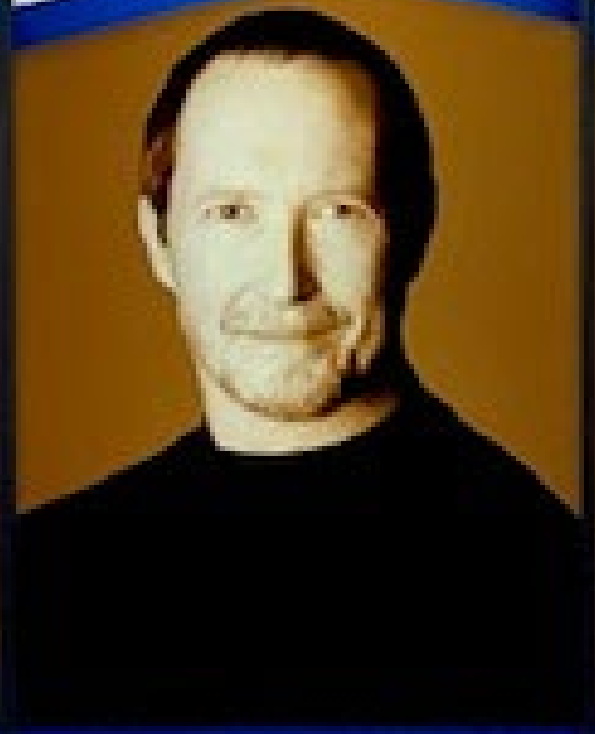

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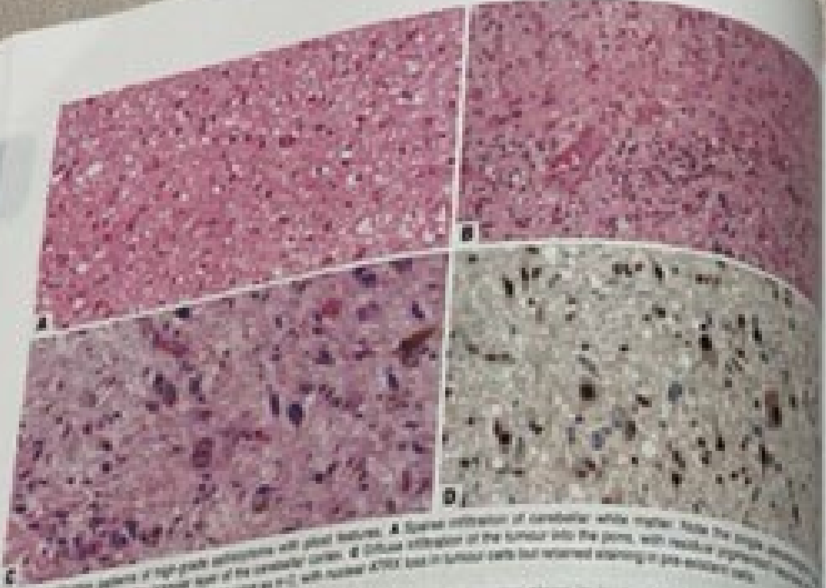


Fig. 2.78 Infiltration patterns of high-grade astrocytoma with piloid features. A Sparse infiltration of cerebellar white matter. Note the [illegible] B Infiltration of the tumour into the granular layer of the cerebellar cortex. C Diffuse infiltration of the tumour into the pons, with residual [illegible] D ATRX immunohistochemistry of the same case as in C, with nuclear ATRX loss in tumour cells but retained staining in pre-existent cells.

histologically defined cerebellar glioblastomas molecularly represented HGAP [2644].

Cytology

Not clinically relevant

Diagnostic molecular pathology

Currently, DNA methylation profiling is the only method for definitively establishing a diagnosis of HGAP [2643]. The molecular class is included in widely used [illegible] based classifiers [460]. A combination of [illegible] genetic markers may be suggestive of the [illegible] not clearly distinguish these tumours from other [illegible] as pleomorphic xanthoastrocytoma or [illegible]

A variety of MAPK pathway gene alterations [illegible] reported [1040,2643], the most frequent being [illegible] KIAA1549::BRAF fusions, and FGFR1 mutations [illegible] one tumour, an NF1 alteration was combined [illegible]

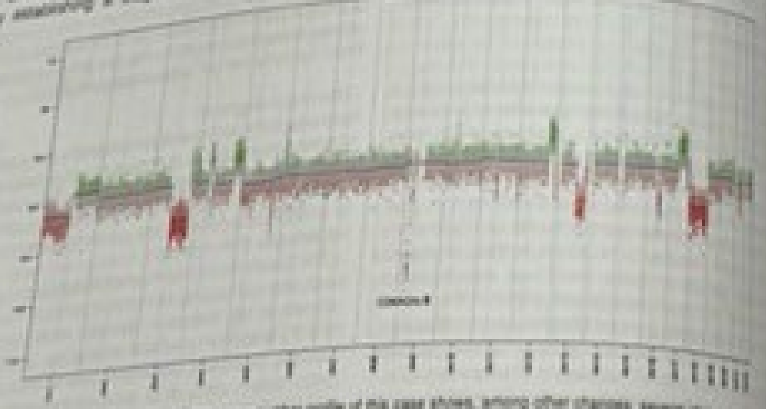


Fig. 2.79 High-grade astrocytoma with piloid features. The DNA copy-number profile of this case shows, among other changes, several chromosomal [illegible] rarely occur in the tumour type: homozygous deletion of CDKN2A and/or CDKN2B (observed in close to 80%), partial gain of 12q and 17q (each in ~[illegible]

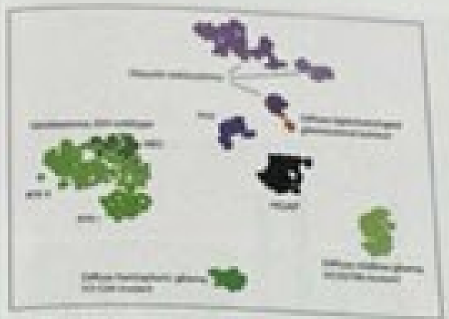


Fig. 2.80 High-grade astrocytoma with piloid features (HGAP) is defined by a specific DNA methylation profile. t-distributed stochastic neighbour embedding (t-SNE) of DNA methylation data of HGAP and several relevant differential diagnoses. HGAP forms a distinct molecular group. Data combined from [460] and [2643]. MES, mesenchymal; PXA, pleomorphic xanthoastrocytoma; RTK, receptor tyrosine kinase.

Table 2.04 Frequency of MAPK alterations detected to date in high-grade astrocytoma with piloid features

Type of MAPK alteration	Frequency
NF1 mutation[a]	18%
NF1 heterozygous deletion[a]	12%
KIAA1549::BRAF fusion	20%
BRAF p.V600E mutation	1%
FGFR1 p.K656E/N or p.N546D/K mutation	11%
FGFR1::TACC1 fusion	2%
NTRK2 mutation	3%

[a]Those cases had both an NF1 mutation and an NF1 heterozygous deletion.
Data from Reinhardt et al. [2643].

mutation, but MAPK pathway gene mutations otherwise occur in a mutually exclusive fashion [2643]. The rate of occurrence of BRAF p.V600E is notably low, and the overall frequencies of reported MAPK pathway gene alterations are remarkably different from those of pleomorphic xanthoastrocytoma and pilocytic astrocytoma.

In one study of 74 cases, homozygous deletion (or, very rarely, mutation) of CDKN2A and/or CDKN2B occurred in about 80% of tumours [2643]. Alternatively, CDK4 amplifications were observed in some cases [2643]. ATRX mutations and/or loss of ATRX expression was observed in 33 (45%) of cases. In rare instances without ATRX alteration, TERT promoter mutations were detected (2 [3%] of 74, both p.C228T mutations) [2643]. In 2 (3%) of the 74 tumours, H3 p.K28M (K27M) mutations were identified, but the definitive classification of these tumours has yet to be established [2643].

Box 2.13 Diagnostic criteria for high-grade astrocytoma with piloid features

Essential:
An astrocytic glioma
AND
A DNA methylation profile of high-grade astrocytoma with piloid features
Desirable:
MAPK pathway gene alteration
Homozygous deletion or mutation of CDKN2A and/or CDKN2B, or amplification of CDK4
Mutation of ATRX or loss of nuclear ATRX expression
Anaplastic histological features

Essential and desirable diagnostic criteria

See Box 2.13.

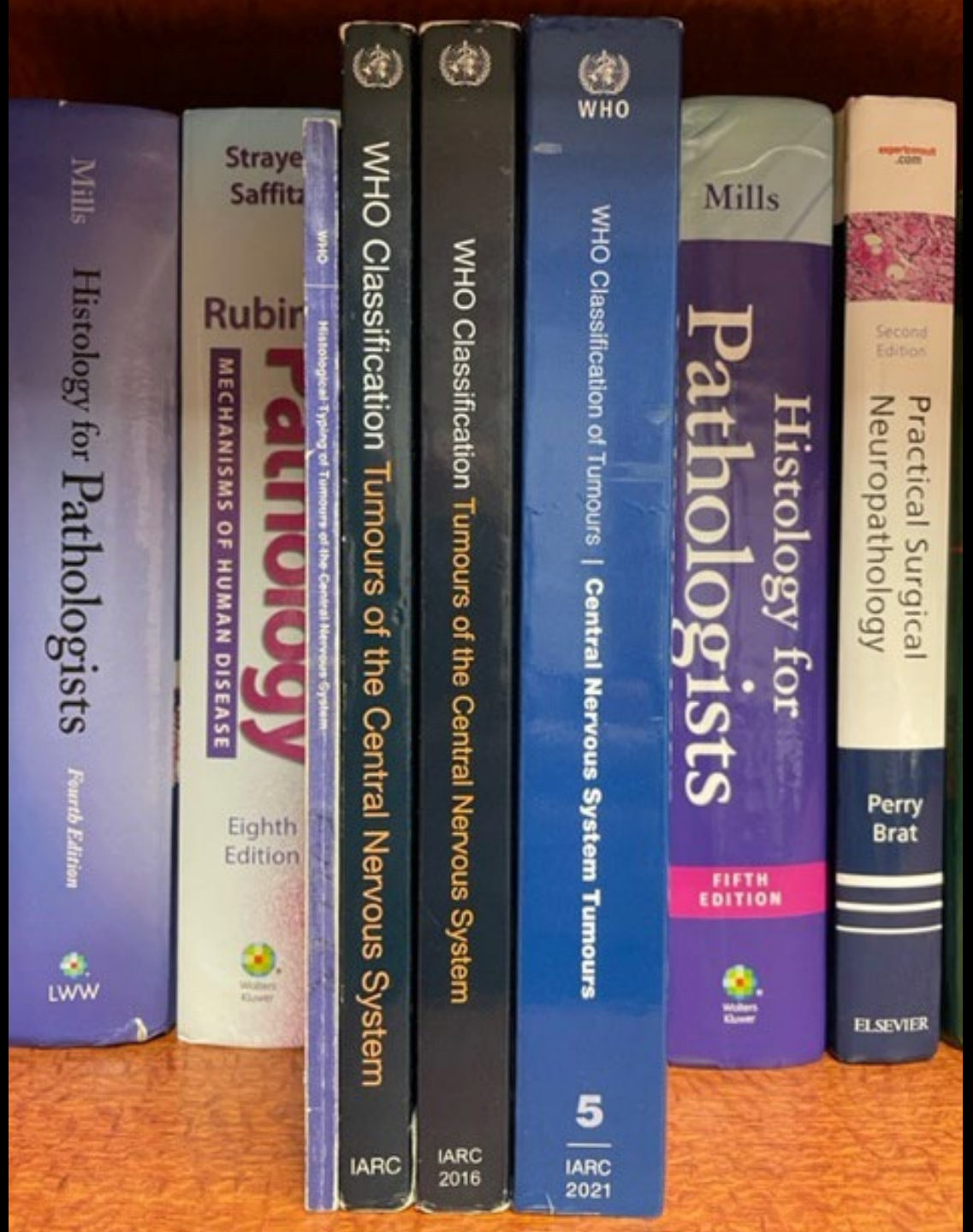
Staging

Not established

Prognosis and prediction

Prognostic data on patients diagnosed with HGAP are, to date, only available from a single retrospective study [2643]. In this study, the 5-year overall survival rate of patients diagnosed with HGAP was approximately 50%. Overall survival was shorter than that of patients with conventional pilocytic astrocytoma (CNS WHO grade 1) and IDH-mutant astrocytoma (CNS WHO grade 3), longer than that of patients with IDH-wildtype glioblastoma, and approximately comparable to that of patients with IDH-mutant astrocytoma (CNS WHO grade 4) [2643]. Associations of prognosis and histological features were not identified, and fatal outcomes were also seen in patients whose tumours lacked necrosis (8 of 28 patients died within 2 years of diagnosis) or lacked mitoses (3 of 10 patients died within 2 years). A methylated MGMT promoter was reported in 46% of HGAPs, without a statistical association with patient outcome; however, information on treatment of the patients by alkylating agent chemotherapy was not available [2643]. More data are required for assignment of a definitive CNS WHO grade, but current data suggest a clinical behaviour roughly corresponding to CNS WHO grade 3.

WHO CNS “Blue Books”



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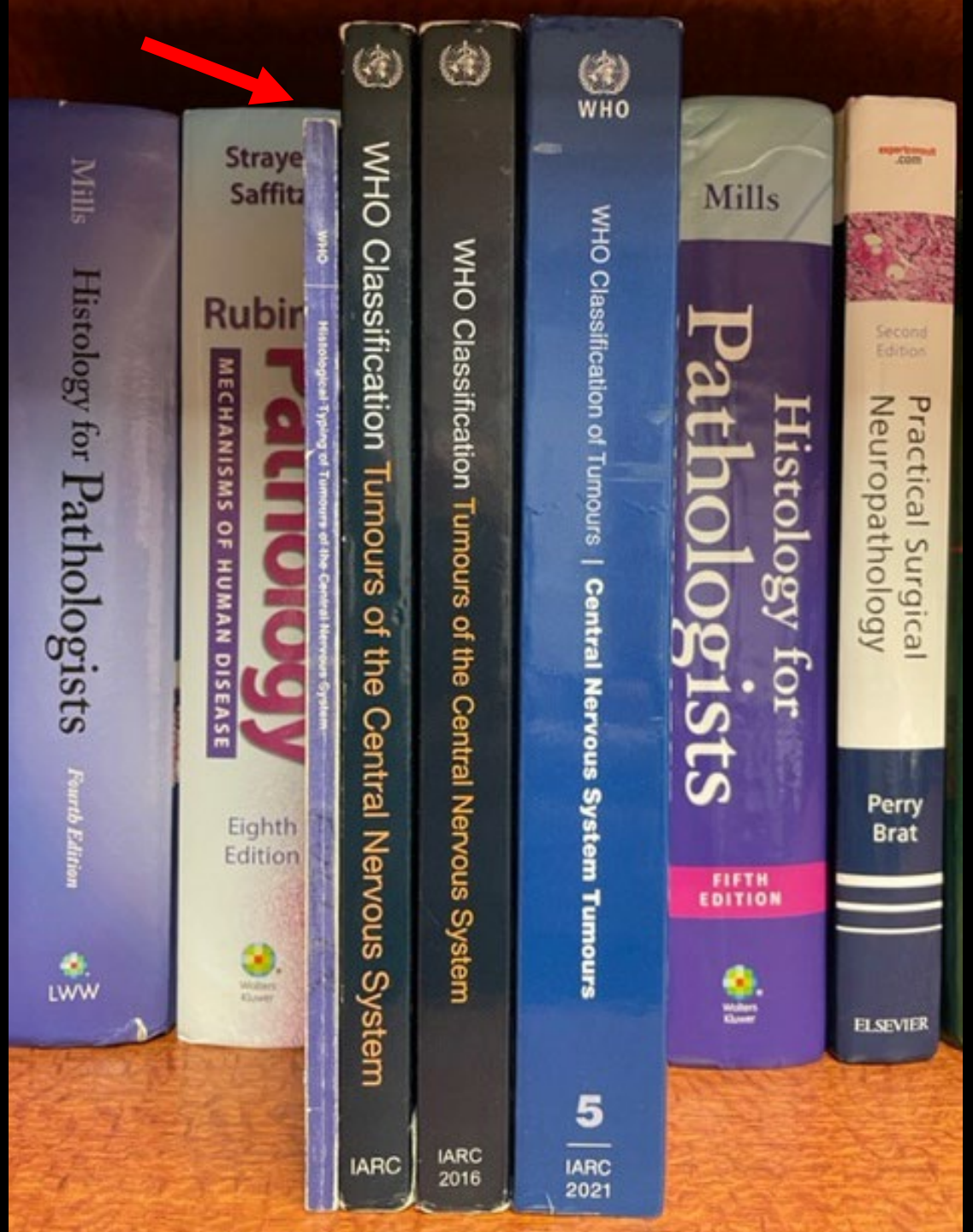


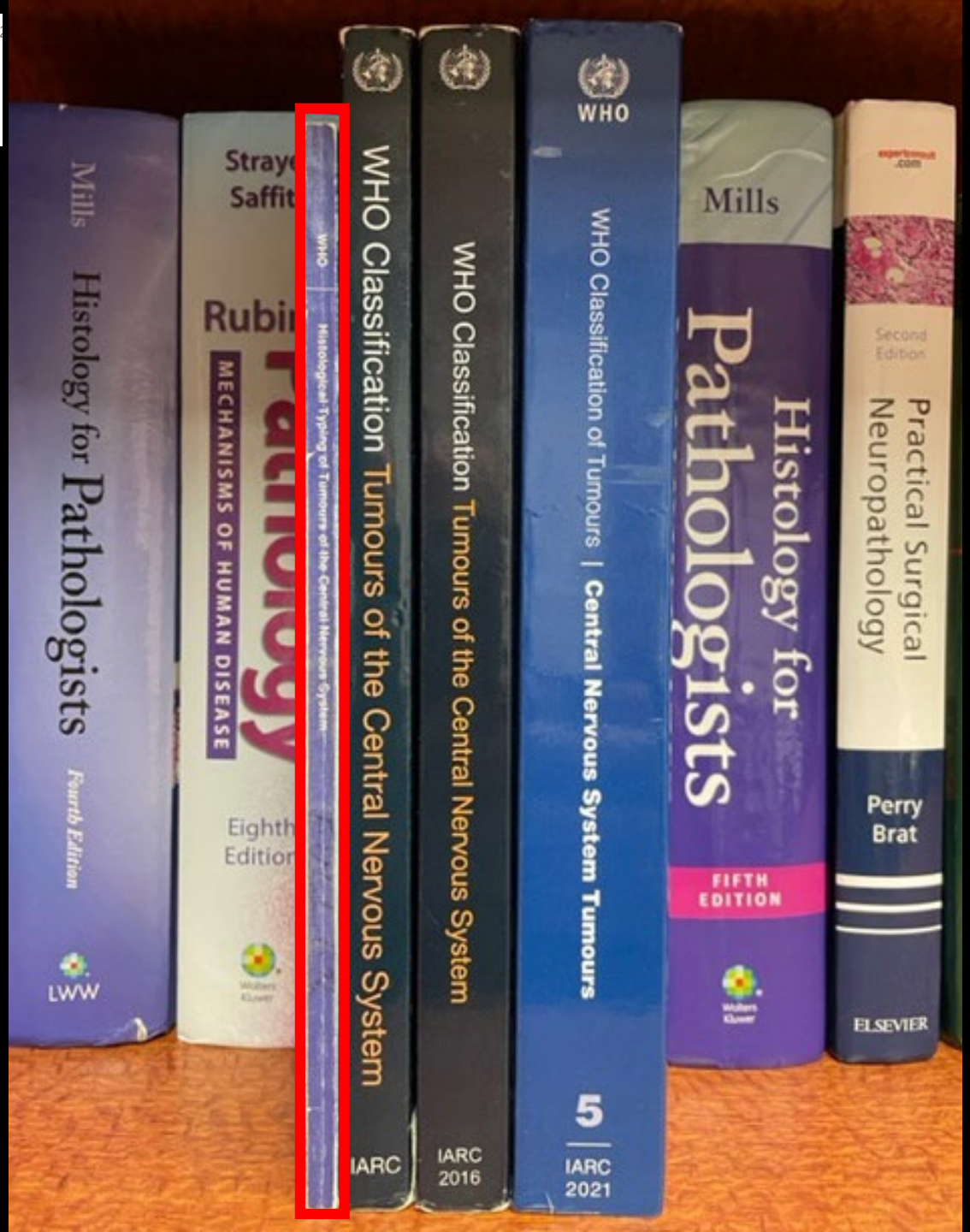
Review > Brain Pathol. 1993 Jul;3(3):255-68. doi: 10.1111/j.1750-3639.1993.tb0075

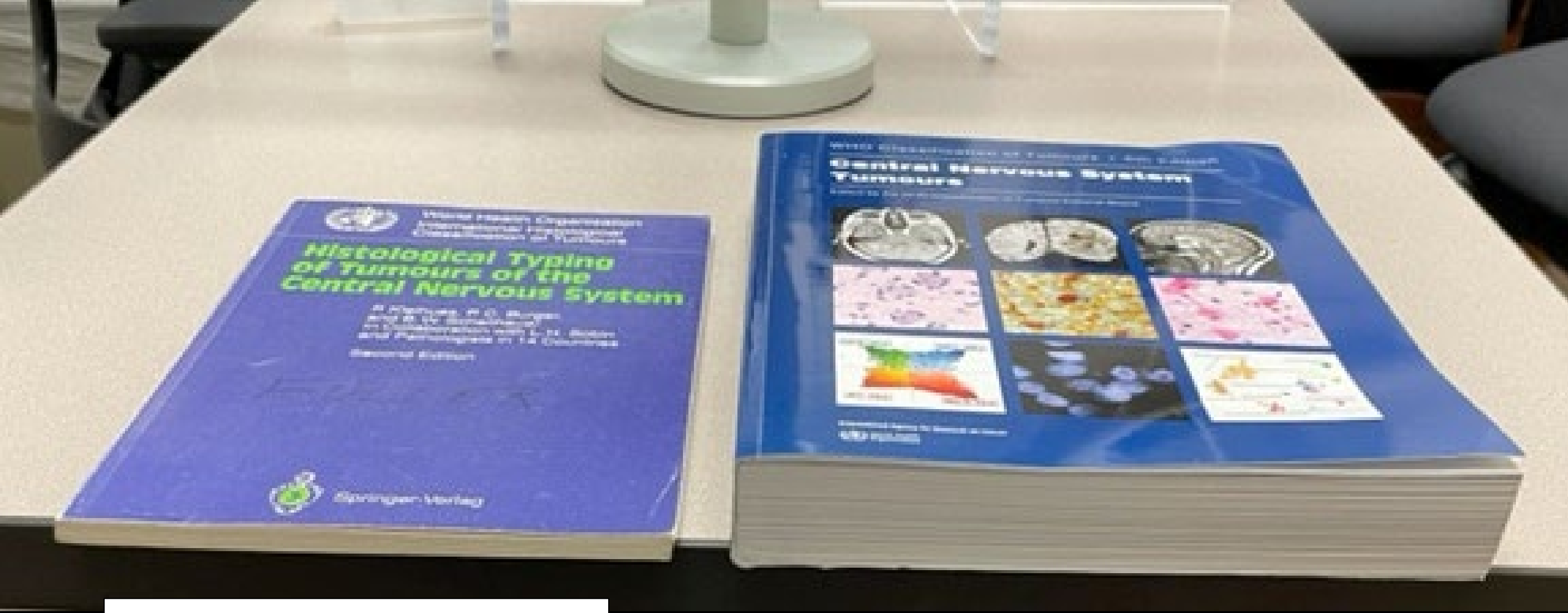
The new WHO classification of brain tumours

P Kleihues [1], P C Burger, B W Scheithauer

"WHO II" 1993

Kleihues, Burger, Scheithauer

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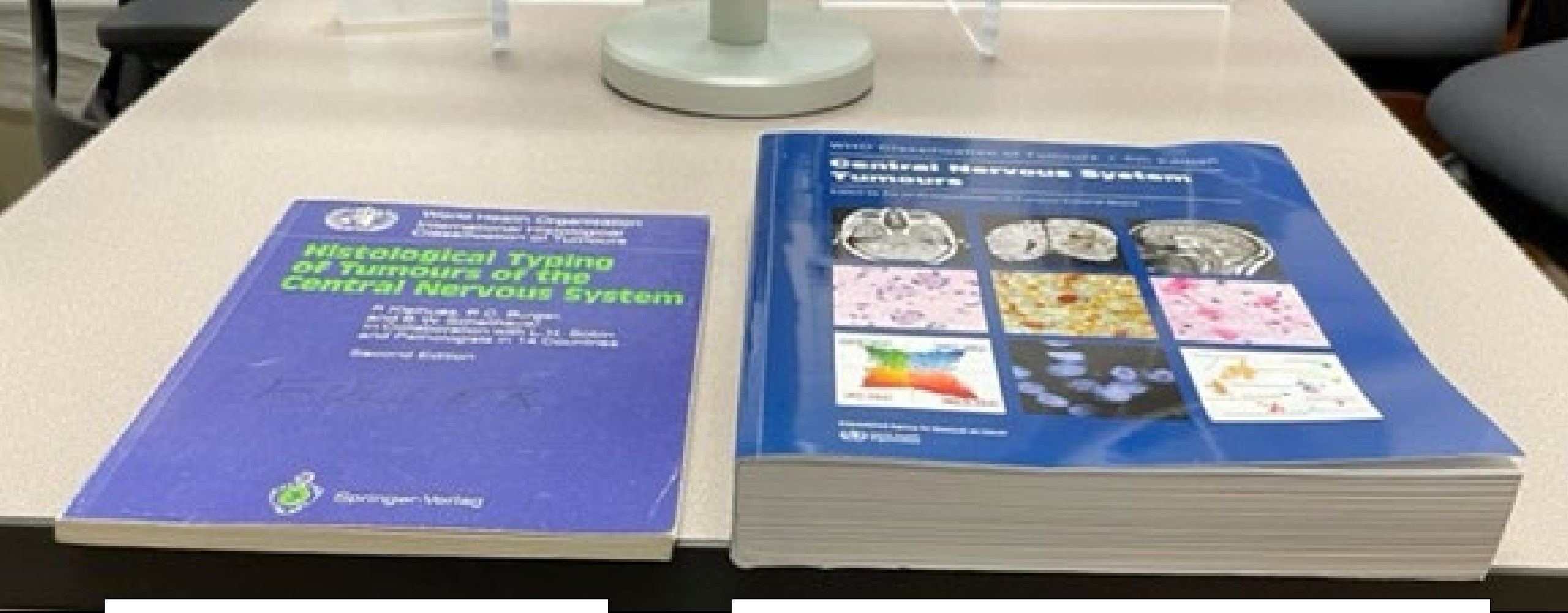

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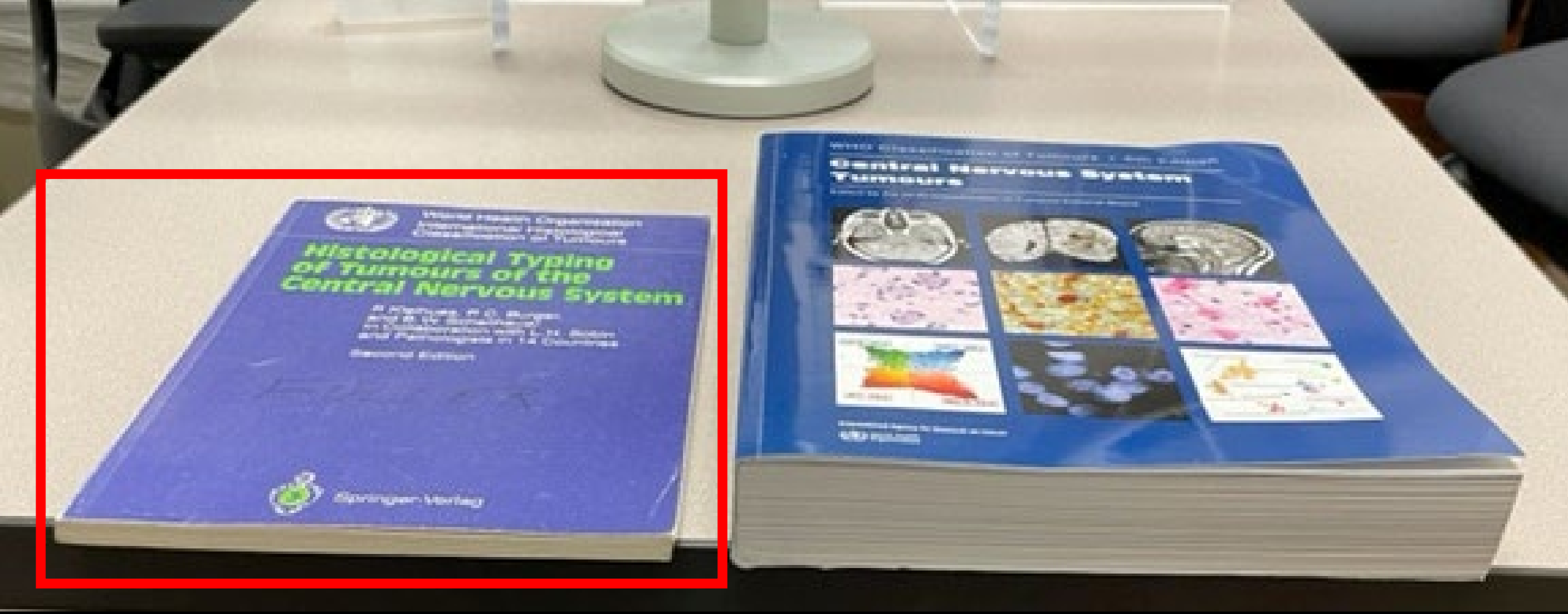
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Biological behaviour: Glioblastomas correspond histologically to Grade IV.

1.1.3.1 Giant Cell Glioblastoma (Fig. 10)

A glioblastoma with a marked predominance of bizarre, multinucleated giant cells and, on occasion, an abundant stromal reticulin network. GFAP expression may be highly variable. Giant cell glioblastomas tend to be macroscopically well-circumscribed.

1.1.3.2 Gliosarcoma (Figs. 11, 12)

A glioblastoma admixed with a sarcomatous component. The latter is presumed to originate from malignant transformation of the hyperplastic vascular elements typically observed in glioblastomas. The sarcomatous tissue often resembles fibrosarcoma, but pleomorphism can be considerable. The sarcoma may predominate in some cases. Reticulin stains and immunoreactivity for GFAP or S-100 protein readily distinguish the components.

1.1.4 Pilocytic Astrocytoma (Figs. 13–16)

A circumscribed astrocytoma composed, at least in part, of bipolar, fusiform or 'piloid' cells with dense fibrillation. Tumour cells tend to form compact parallel bundles. Particularly common is a biphasic pattern in which pilocytic areas are intimately associated with a loosely structured microcystic component consisting of protoplasmic, poorly fibrillated neoplastic astrocytes.

Hyperchromatic, bizarre nuclei may be present and are not, in the absence of significant mitotic activity, associated with a poor prognosis. GFAP expression is always demonstrable, although to a varying degree. The microcysts apparently coalesce to larger cysts which may, when situated in the posterior fossa, displace the vermis or large parts of the cerebellar hemisphere. The stroma consists of irregularly disposed blood vessels which may be hyalinized. Glomeruloid capillary or even endothelial proliferation is not uncommon, both within the tumour and in the wall of cysts, but does not signify malignancy. Elongated eosinophilic, club-shaped structures (Rosenthal fibres) and eosinophilic intracytoplasmic protein droplets ("granular bodies") are histopathological hallmarks of this neoplasm. Calcification may also be seen but is usually inconspicuous. Local invasion of the subarachnoid space is frequent and may be accompanied by a desmoplastic leptomeningeal reaction, but does not indicate malignancy.

In contrast to the above mentioned diffuse astrocytic tumours, the pilocytic astrocytoma is more circumscribed, expands into the surrounding brain only slowly, and very rarely shows a tendency for progression to anaplasia. This tumour occurs mainly in children, with a peak incidence around the age 10 years, and in young adults. Pilocytic astrocytomas are typically located in midline structures, e.g. optic nerve (optic nerve glioma), third ventricle, thalamus, median temporal lobe, brain stem and in the cerebellum ("cystic and solid cerebellar astrocytoma"). The cerebral hemispheres are affected less frequently.

Biological behaviour: This slowly growing tumour corresponds histologically to Grade I. Malignant transformation occurs very rarely, in which case the tumour is categorized as an anaplastic (pilocytic) astrocytoma (Grade III).

1.1.5 Pleomorphic Xanthoastrocytoma (Figs. 17–19)

An astrocytoma with a mixture of pleomorphic tumour cells, ranging from ordinary fibrillary astrocytes to giant, multinucleated forms. The latter typically contain lipid vacuoles; thus they are xanthomatous, but express GFAP.

The superficial, in particular the leptomeningeal, portions of these tumours, exhibit a dense intercellular reticulin network due to the presence of pericellular basement membranes. Mitoses are rare and necrosis as well as vascular proliferation are absent. This rare variant of astrocytoma often occurs in children or young adults and affects the cerebral hemispheres, particularly the temporal lobe. It is typically superficial in location, shows an intimate relation to the meninges and may be associated with an underlying cyst.

Biological behaviour: Despite its pleomorphic appearance, this neoplasm is usually rather well-demarcated. A generally favourable prognosis justifies its inclusion in Grade II gliomas. A minority of pleomorphic xanthoastrocytomas do, however, progress to anaplastic astrocytoma (Grade III) or glioblastoma (Grade IV).

1.1.6 Subependymal Giant Cell Astrocytoma (Tuberous Sclerosis) (Figs. 20, 21)

A circumscribed, usually calcified intraventricular tumour arising from the walls of the lateral ventricles. It is composed mainly of large plump cells resembling astrocytes.

Biological behaviour: Glioblastomas correspond histologically to Grade IV.

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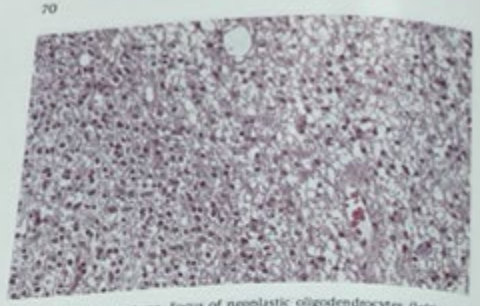

Fig.35. *Oligo-astrocytoma.* Focus of neoplastic oligodendrocytes (left) next to a less cellular area with astrocytic differentiation

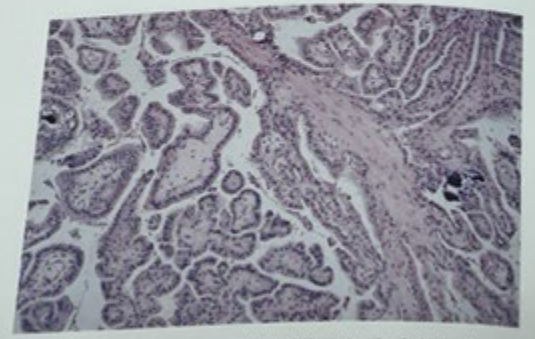

Fig.36. *Choroid plexus papilloma.* Highly differentiated cuboidal cells cover papillary connective tissue cores. Occasional calcifications are typical

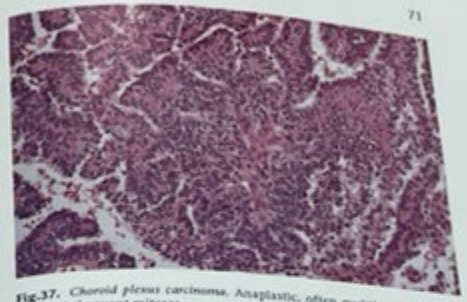

Fig.37. *Choroid plexus carcinoma.* Anaplastic, often multilayered tumour cells with frequent mitoses

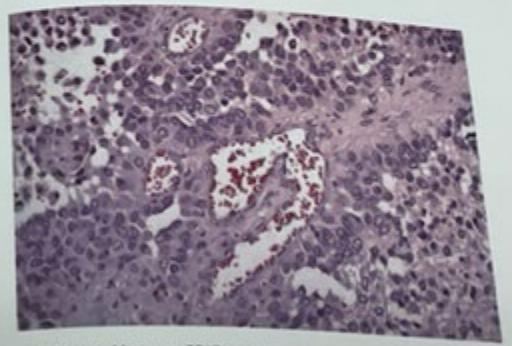

Fig.38. *Astroblastoma.* GFAP expressing neoplastic astrocytes with broad processes radiating towards central blood vessels

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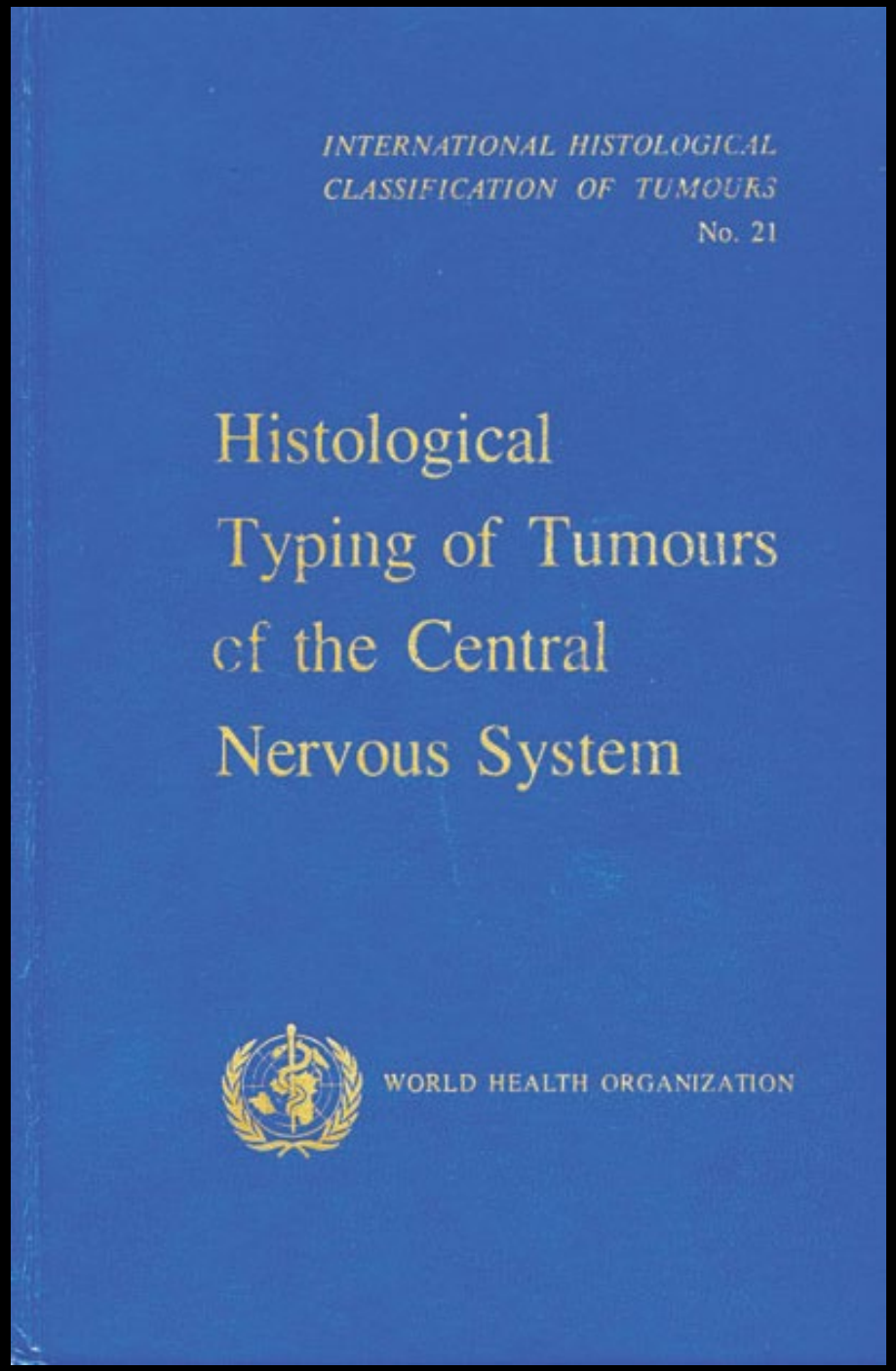

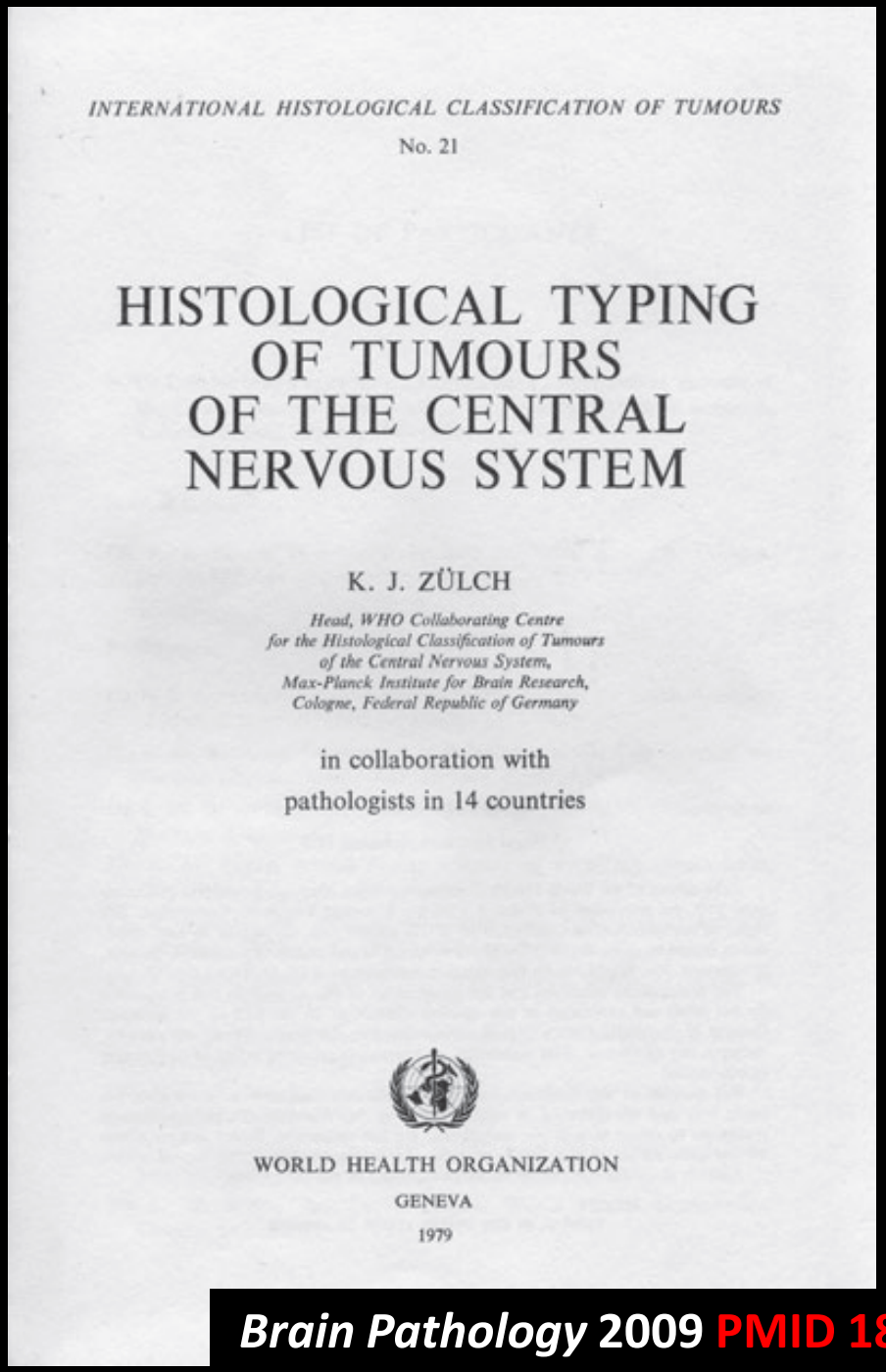

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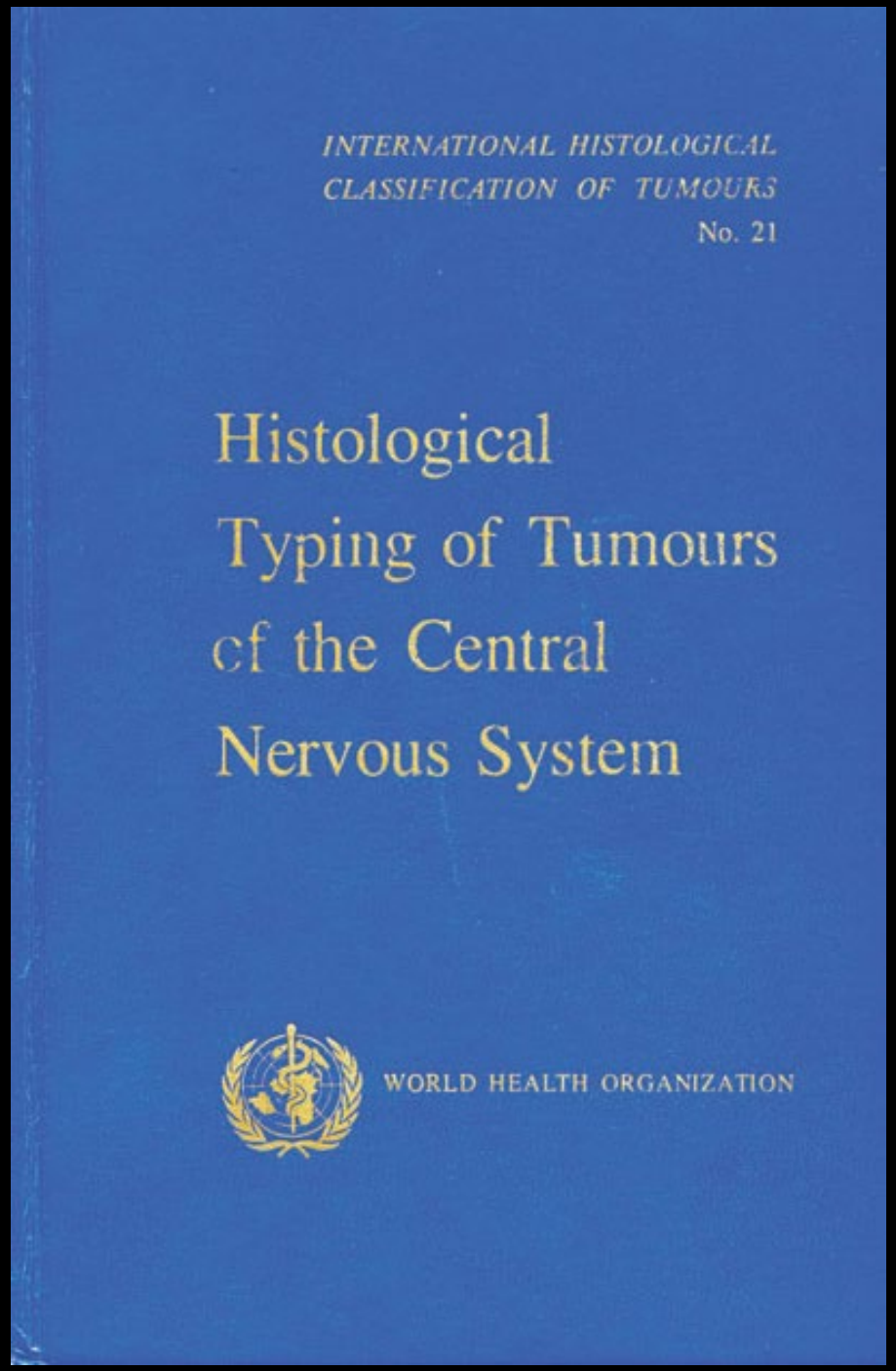

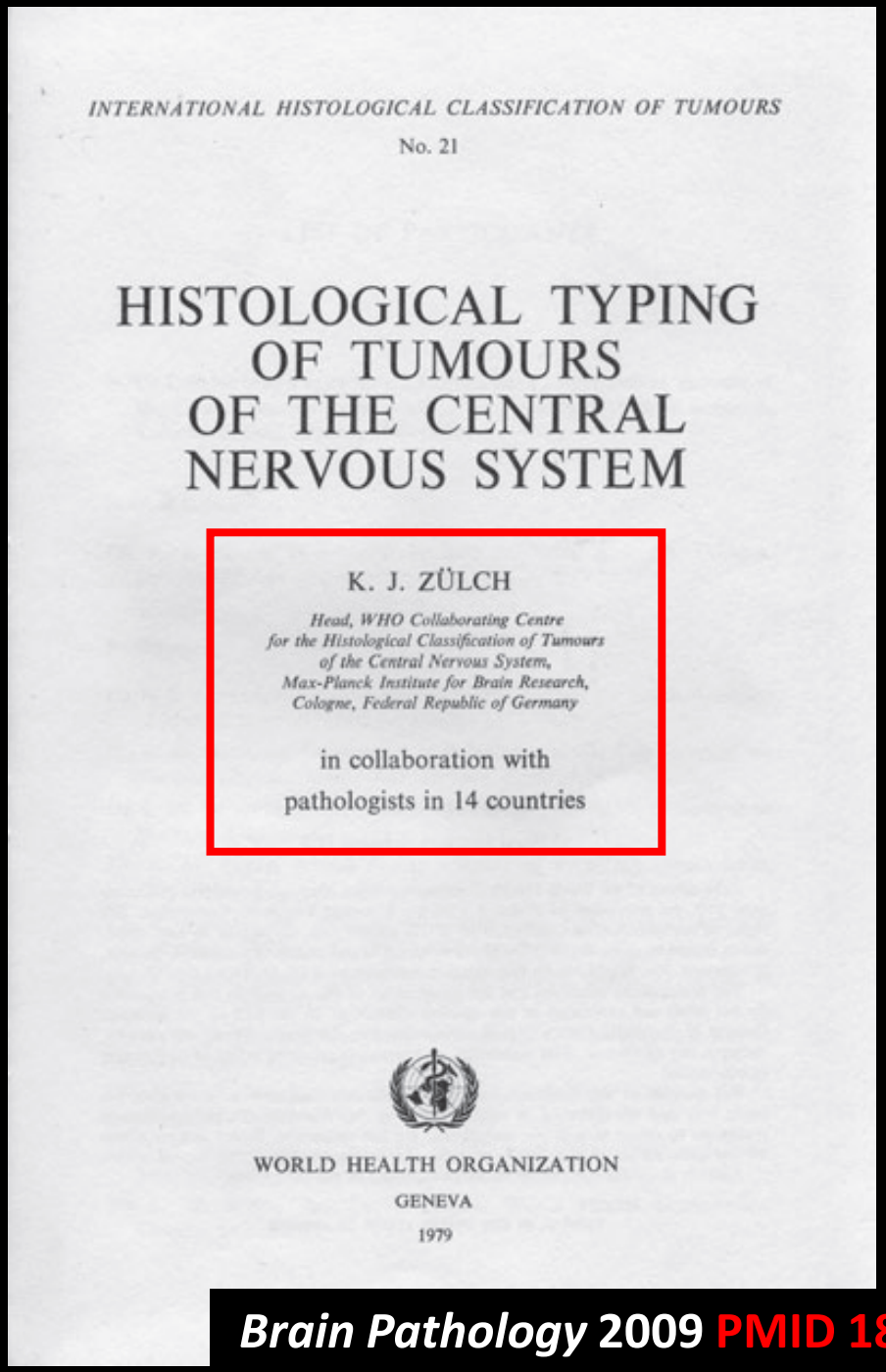

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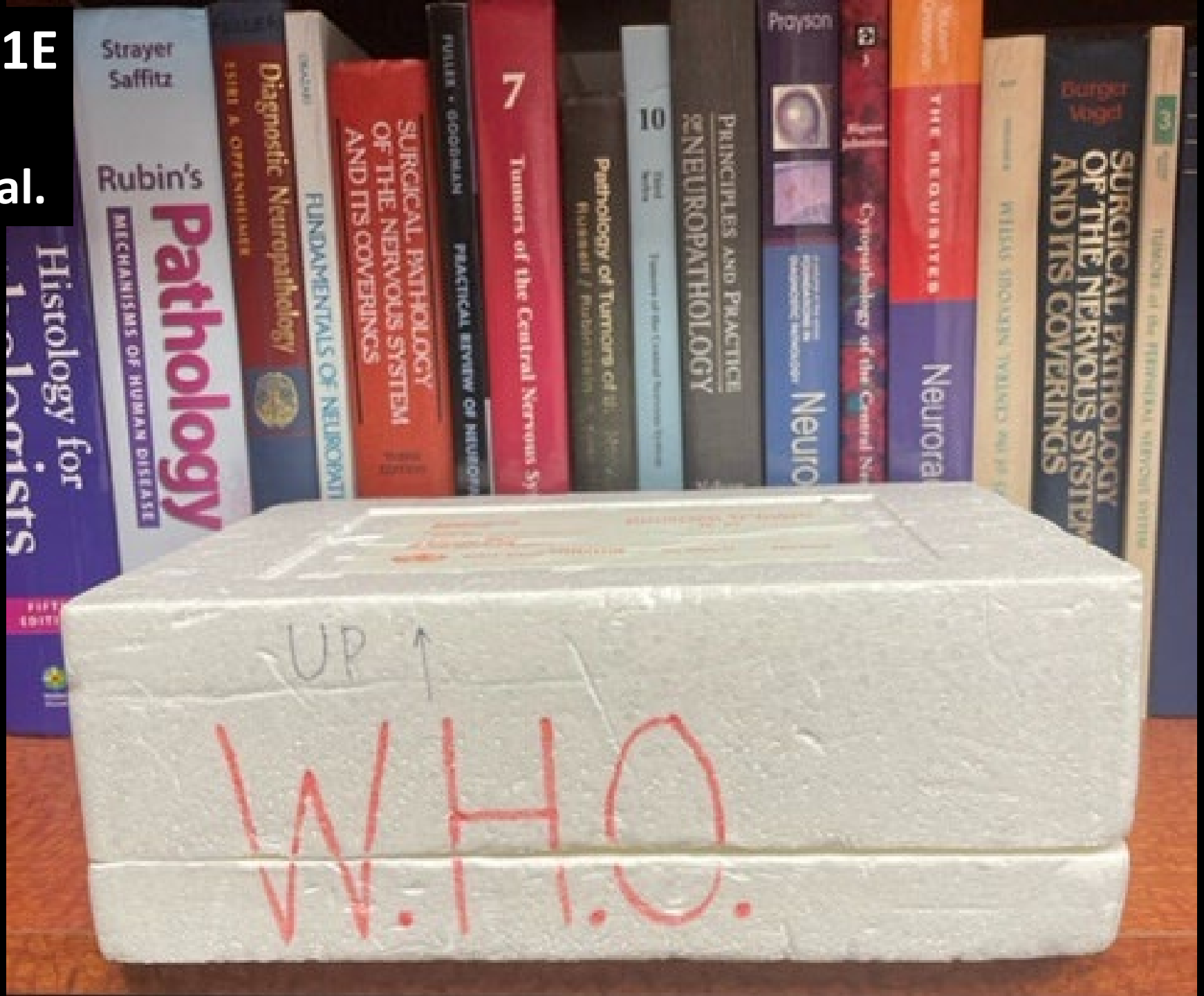

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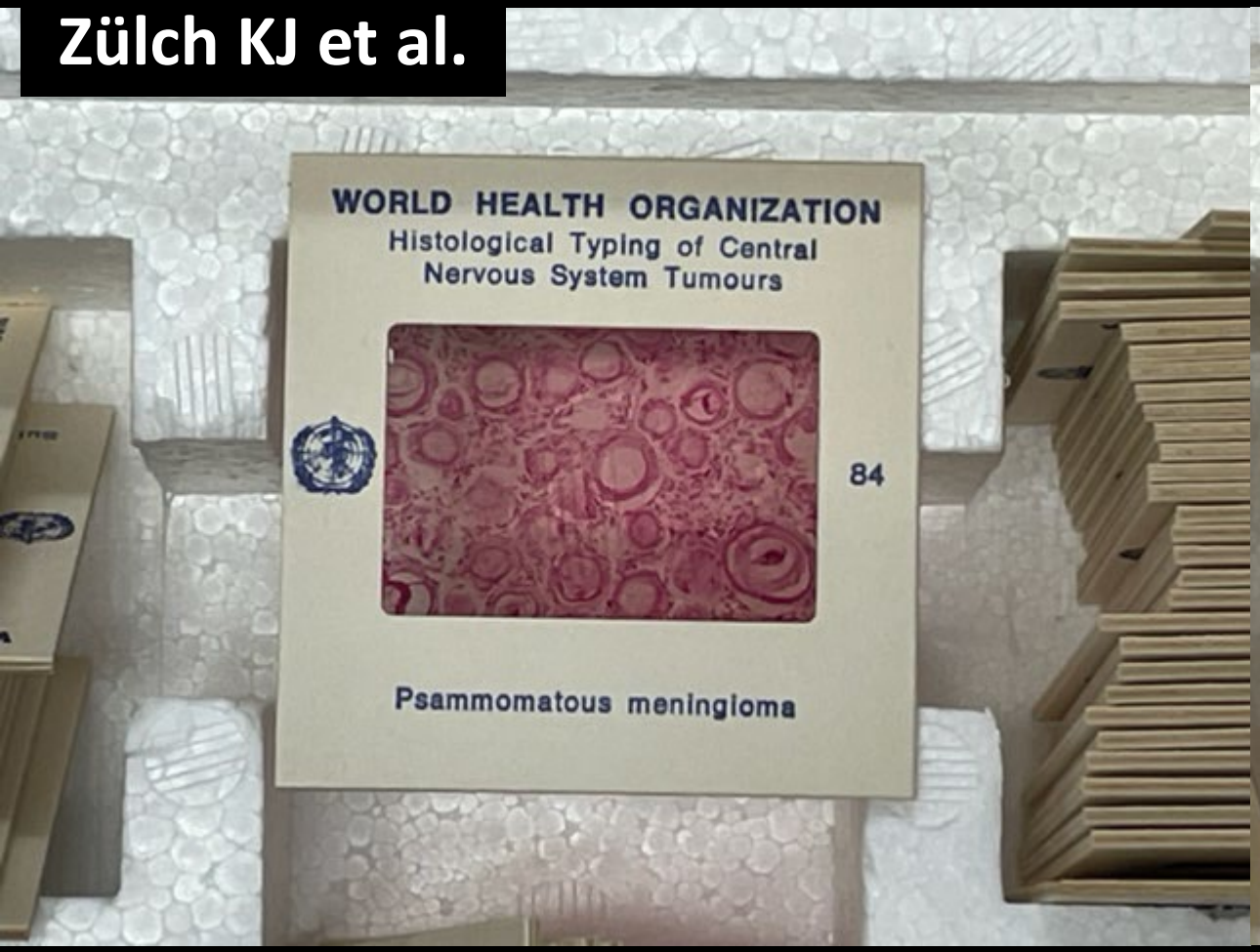

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CNS 5E

2021

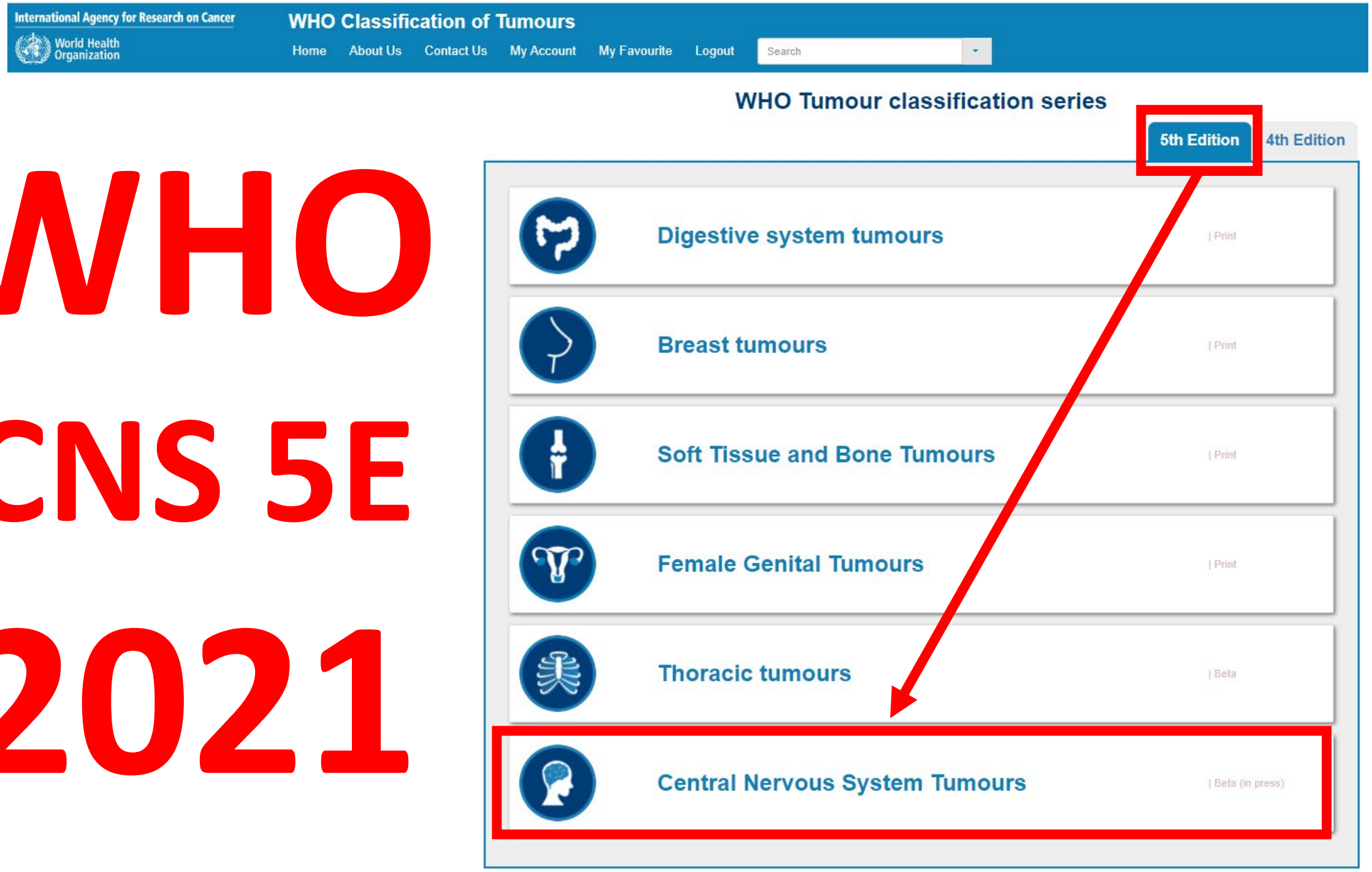

Table 7 Newly Recognized Tumor Types in the 2021 WHO Classification of Tumors of the Central Nervous System

Newly Recognized Tumor Types
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)
Myxoid glioneuronal tumor
Multinodular and vacuolating neuronal tumor
Supratentorial ependymoma, *YAP1* fusion-positive
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma, *MYCN*-amplified
Cribriform neuroepithelial tumor (provisional type)
CNS neuroblastoma, *FOXR2*-activated
CNS tumor with *BCOR* internal tandem duplication
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant
Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1*-mutant
Pituitary blastoma

WHO 5E

22 NEW CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

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Pituitary blastoma

WHO 5E

12 NEW

Molecular

Signature-Defined

CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

Table 2 Key Diagnostic Genes, Molecules, Pathways, and/or Combinations in Major Primary CNS Tumors

Tumor Type	Genes/Molecular Profiles Characteristically Altered*
Astrocytoma, IDH-mutant	*IDH1, IDH2, ATRX, TP53, CDKN2A/B*
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1, IDH2*, 1p/19q, *TERT* promoter, *CIC, FUBP1, NOTCH1*
Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, chromosomes 7/10, *EGFR*
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	*MYB, MYBL1*
Angiocentric glioma	*MYB*
Polymorphous low-grade neuroepithelial tumor of the young	*BRAF*, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	*FGFR1, BRAF*
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53, ACVR1, PDGFRA, EGFR, EZHIP*
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53, ATRX*
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, *PDGFRA, MYCN, EGFR* (methylome)
Infant-type hemispheric glioma	NTRK family, *ALK, ROS, MET*
Pilocytic astrocytoma	*KIAA1549-BRAF, BRAF, NF1*
High-grade astrocytoma with piloid features	*BRAF, NF1, ATRX, CDKN2A/B* (methylome)
Pleomorphic xanthoastrocytoma	*BRAF, CDKN2A/B*
Subependymal giant cell astrocytoma	*TSC1, TSC2*
Chordoid glioma	*PRKCA*
Astroblastoma, *MN1*-altered	*MN1*
Ganglion cell tumors	*BRAF*
Dysembryoplastic neuroepithelial tumor	*FGFR1*
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chromosome 14, (methylome)
Papillary glioneuronal tumor	*PRKCA*
Rosette-forming glioneuronal tumor	*FGFR1, PIK3CA, NF1*
Myxoid glioneuronal tumor	*PDFGRA*
Diffuse leptomeningeal glioneuronal tumor	*KIAA1549-BRAF* fusion, 1p (methylome)
Multinodular and vacuolating neuronal tumor	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	*PTEN*
Extraventricular neurocytoma	FGFR (*FGFR1-TACC1* fusion), IDH-wildtype
Supratentorial ependymomas	*ZFTA, RELA, YAP1, MAML2*
Posterior fossa ependymomas	H3 K27me3, *EZHIP* (methylome)
Spinal ependymomas	*NF2, MYCN*
Medulloblastoma, WNT-activated	*CTNNB1, APC*
Medulloblastoma, SHH-activated	*TP53, PTCH1, SUFU, SMO, MYCN, GLI2* (methylome)
Medulloblastoma, non-WNT/non-SHH	*MYC, MYCN, PRDM6, KDM6A* (methylome)
Atypical teratoid/rhabdoid tumor	*SMARCB1, SMARCA4*
Embryonal tumor with multilayered rosettes	C19MC, *DICER1*
CNS neuroblastoma, *FOXR2*-activated	*FOXR2*
CNS tumor with *BCOR* internal tandem duplication	*BCOR*
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant	*SMARCB1*
Meningiomas	*NF2, AKT1, TRAF7, SMO, PIK3CA; KLF4, SMARCE1, BAP1* in subtypes; H3K27me3; *TERT* promoter, *CDKN2A/B* in CNS WHO grade 3
Solitary fibrous tumor	*NAB2-STAT6*
Meningeal melanocytic tumors	*NRAS* (diffuse); *GNAQ, GNA11, PLCB4, CYSLTR2* (circumscribed)
Adamantinomatous craniopharyngioma	*CTNNB1*
Papillary craniopharyngioma	*BRAF*

WHO 5E

43 Tumor Types

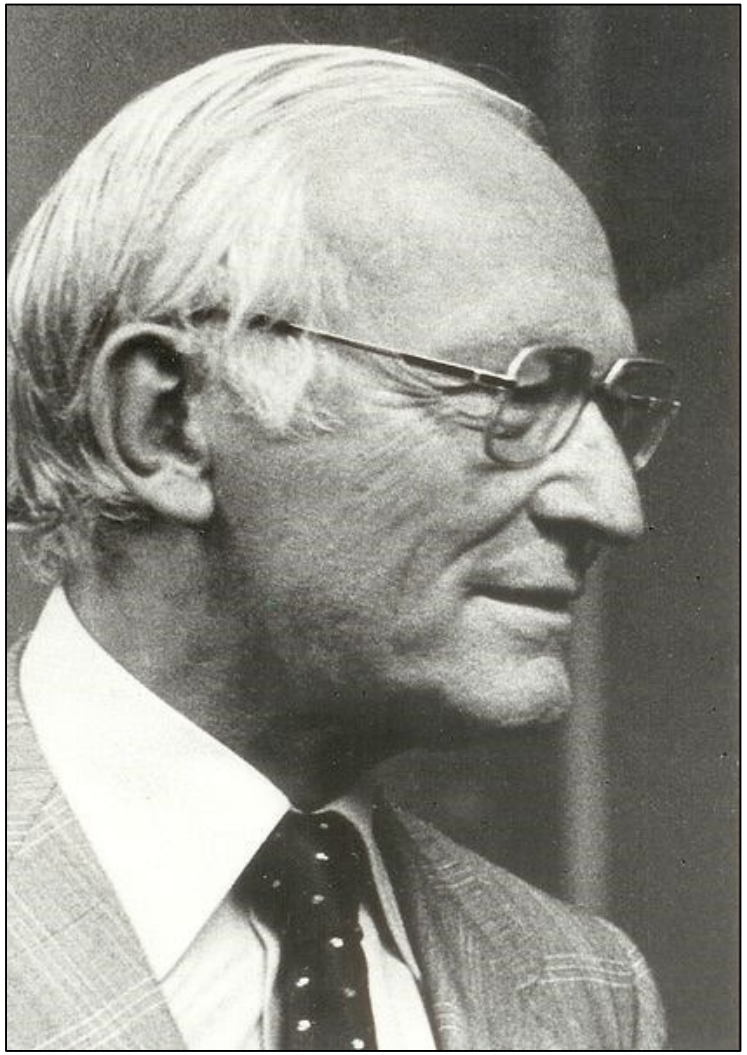
with *critical* molecular signature determinants

Neuro-Oncology 2021 PMID 34185076


THE
INTIMIDATING
CLASSIFICATION
IS BACK BABY!

History of WHO Classification of CNS Tumors

- **1979** **1st Edition. Zulch KJ, et al. Histological Typing of Tumours of the Central Nervous System. World Health Organization, Geneva.**



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- **2000** 3rd Edition. Kleihues, Cavenee. Classification of Tumours: Pathology and Genetics of Tumours of the Nervous System. IARC Press, Lyon. (First volume of the 3rd Edition of the WHO Series)

- **2007** 4th Edition. Louis, Ohgaki, Wiestler, Cavenee. WHO Classification of Tumours of the Central Nervous System. (First volume of the 4TH Edition of the WHO Series)

- **2016** Revised 4th Edition. Louis, Ohgaki, Wiestler, Cavenee, Ellison, Figarella-Branger, Perry, Reifenberger, von Deimling. WHO Classification of Tumours of the Central Nervous System.

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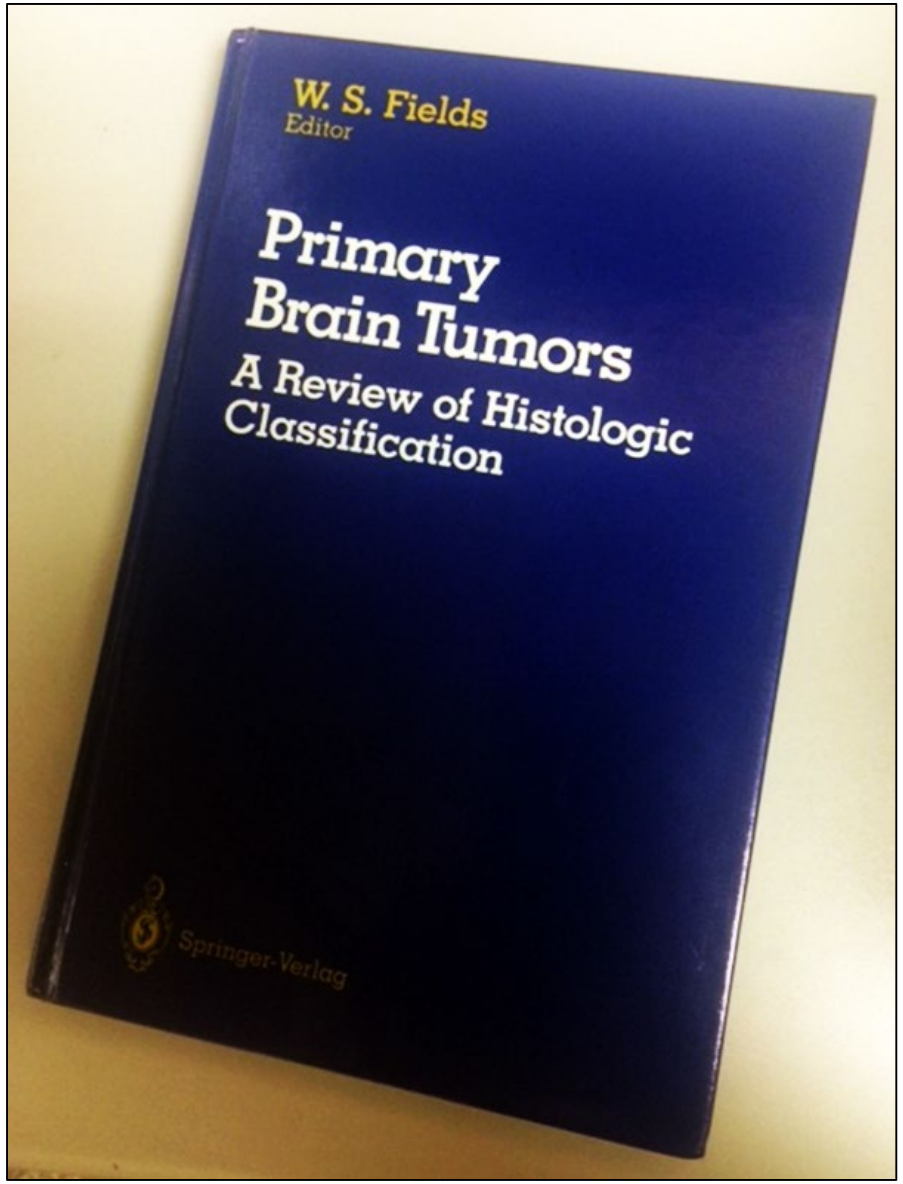
- 2016 Revised 4th Edition

History of WHO Classification of CNS Tumors



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History of WHO Classification of CNS Tumors

Planning Colloquia and Consensus Conferences

- 1988
- 1990
- 2006
- 2014
- 2015

Review > Brain Pathol. 1993

"WHO II"

PMID 8293185

The new WHO classification of brain tumours

P Kleihues [1], P C Burger, B W Scheithauer

The New WHO Classification of Brain Tumours

PMID 8293185

Paul Kleihues [1], Peter C. Burger [2] and Bernd W. Scheithauer [3]

[1] Institute of Neuropathology, Department of Pathology, University Hospital, CH-8091 Zurich, Switzerland
[2] Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD 21287, U.S.A.
[3] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, U.S.A.

The new edition of the World Health Organization (WHO) book on 'Histological Typing of Tumours of the Central Nervous System' reflects the progress in brain tumour classification which has been achieved since publication of the first edition in 1979. Several new tumour entities have been added, including the pleomorphic xanthoastrocytoma, central neurocytoma, the infantile desmoplastic astrocytoma / ganglioglioma, and the dysembryoplastic neuro-

(CNS) neoplasms and, particularly, their histogenesis. Considering that immunohistochemistry was not yet available, the task was enormous. However, the result of the collaborative effort was quite successful as the "Blue Book" rapidly gained popularity world-

Preparation of the second edition, just published, was initiated during a consensus meeting held in Houston, Texas, in 1988 (2).

still has the same scope, i.e., to propose a uniform nomenclature for CNS neoplasms that can be used internationally and which serves as a reliable guideline in day-to-day surgical pathology and as a unifying basis for the evaluation of brain tumour therapy trials. In this article, the major alterations and amendments are briefly reviewed, some with comments on the opinions expressed by participants of the WHO working group.

Astrocytic Tumours and Glioma Progression

The working group unanimously proposed that a

History of WHO Classification of CNS Tumors
Planning Colloquia and Consensus Conferences

- **1988 Houston M D ANDERSON Cancer Center**
- 1990 Geneva
- 2006 Heidelberg
- 2014 Haarlem
- 2015 Heidelberg

History of WHO Classification of CNS Tumors

1988 Planning Colloquia and Consensus Conference

- Dawna **Armstrong**
- Robin **Barnard**
- Laurence **Becker**
- Darell **Bigner**
- Jean-Marie **Brucher**
- Janet **Bruner**
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- Catherine **Daumas-Duport**
- Richard **Davis**
- Kenneth **Earle**
- William **Fields**
- Floyd **Gilles**
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- Kurt **Jellinger**
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- Joel **Kirkpatrick**
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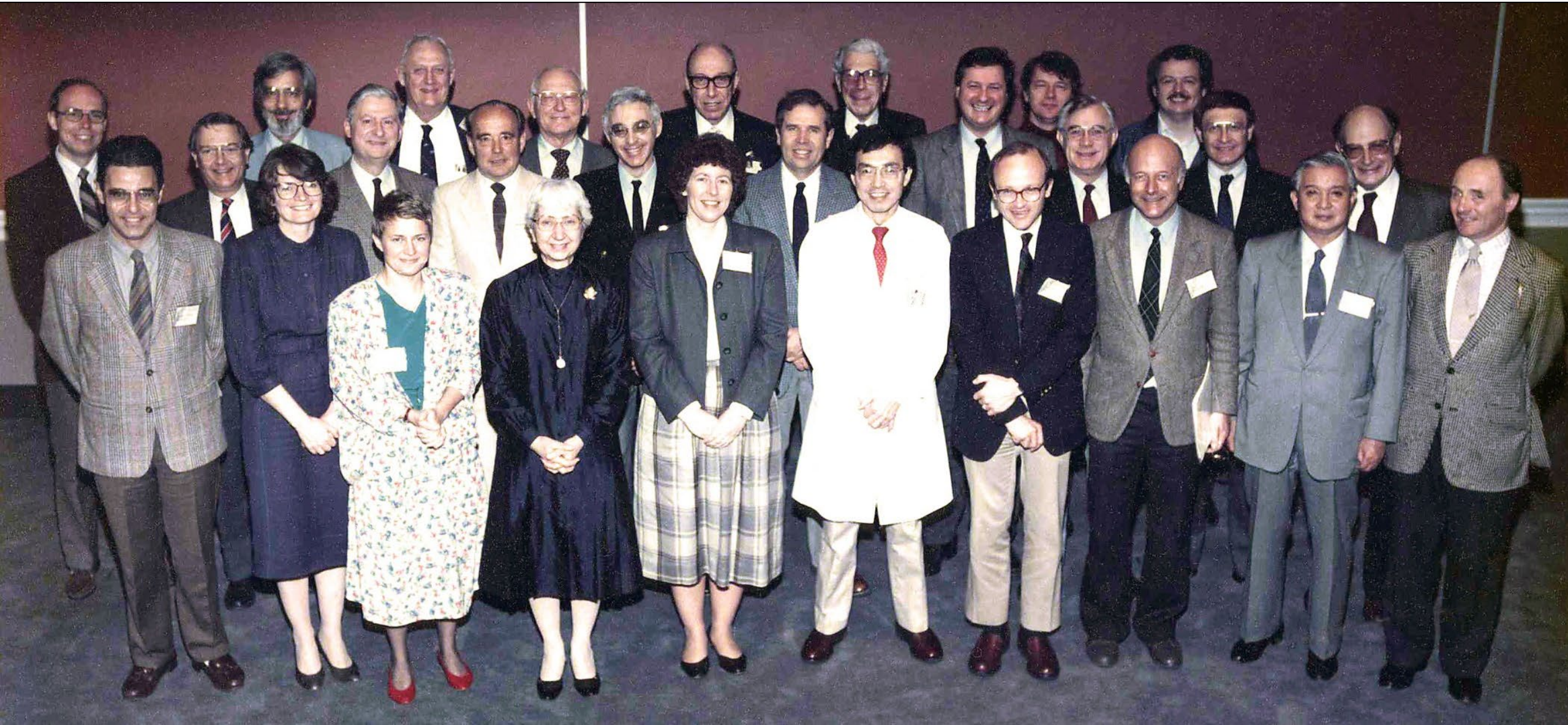
History of WHO Classification of CNS Tumors 1988 Planning Conference

Houston M D Anderson Cancer Center



History of WHO Classification of CNS Tumors

Planning Colloquia and Consensus Conferences

1988 Houston M D ANDERSON

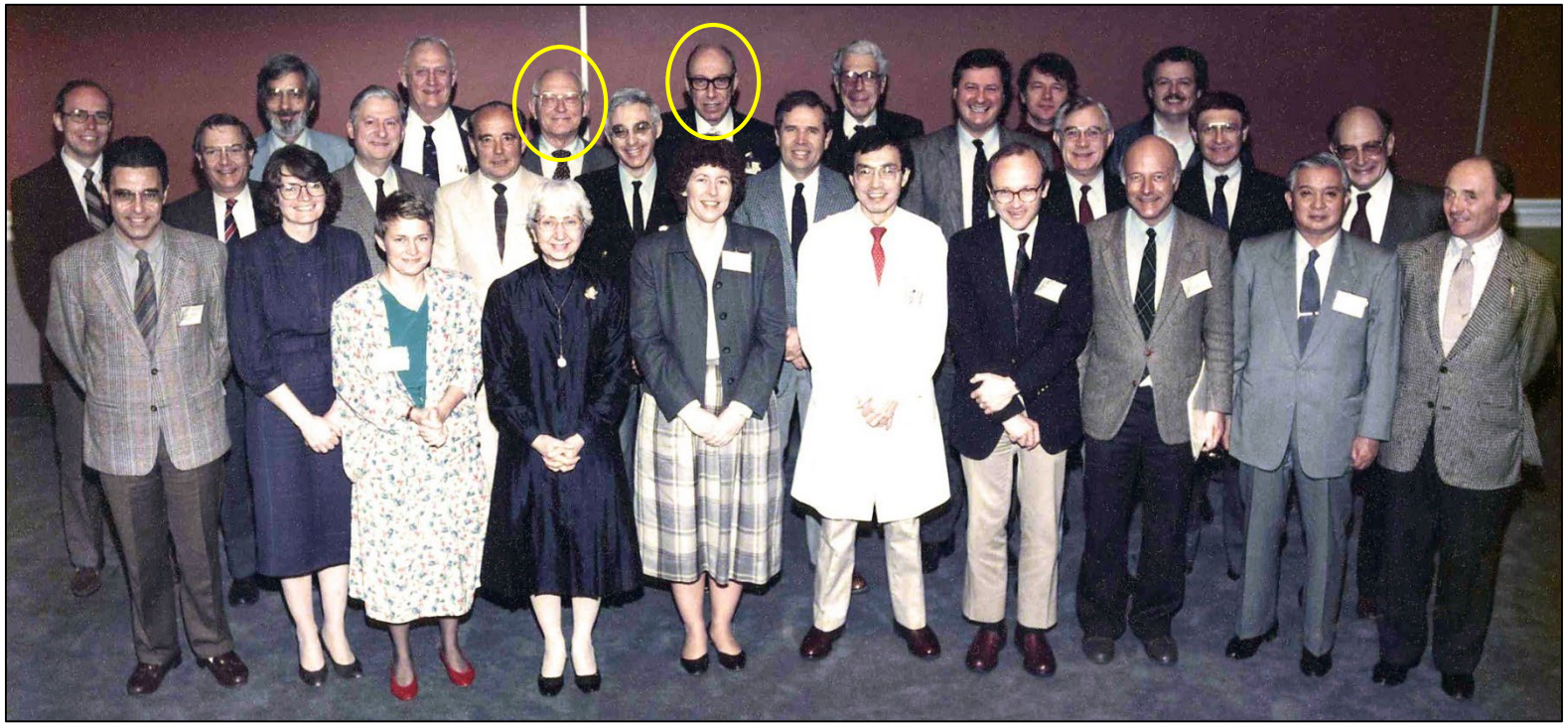
Why Houston?

History of WHO Classification of CNS Tumors

Planning Colloquia and Consensus Conferences

1988 Houston M D ANDERSON

- **W. S. Fields**



History of WHO Classification of CNS Tumors

Planning Colloquia and Consensus Conferences

1988 Houston M D ANDERSON

- W. S. Fields
- “The Zulch-Texas Connection”

What is the Connection between Klaus Zulch and Texas?

What is the Connection between Klaus Zulch and Texas?

North Zulch, Texas

Where and *What* is North Zulch, Texas?

North Zulch Texas

North Zulch, Texas

From Wikipedia, the free encyclopedia

Coordinates: 30°55'04"N 96°06'30"W

North Zulch is an unincorporated community in Madison County, Texas, United States at the intersection of U.S. Highway 190 and State Highway 21 and is six miles from the Navasota River and thirteen miles west of Madisonville in west central Madison County.

Education [edit]

The North Zulch Independent School District has served the community for over 100 years and is home to the North Zulch High School Bulldogs. The 2A school is rich in tradition and history.

External links [edit]

- North Zulch, Texas (and Zulch, Texas) from the Handbook of Texas Online
- U.S. Geological Survey Geographic Names Information System: North Zulch, Texas

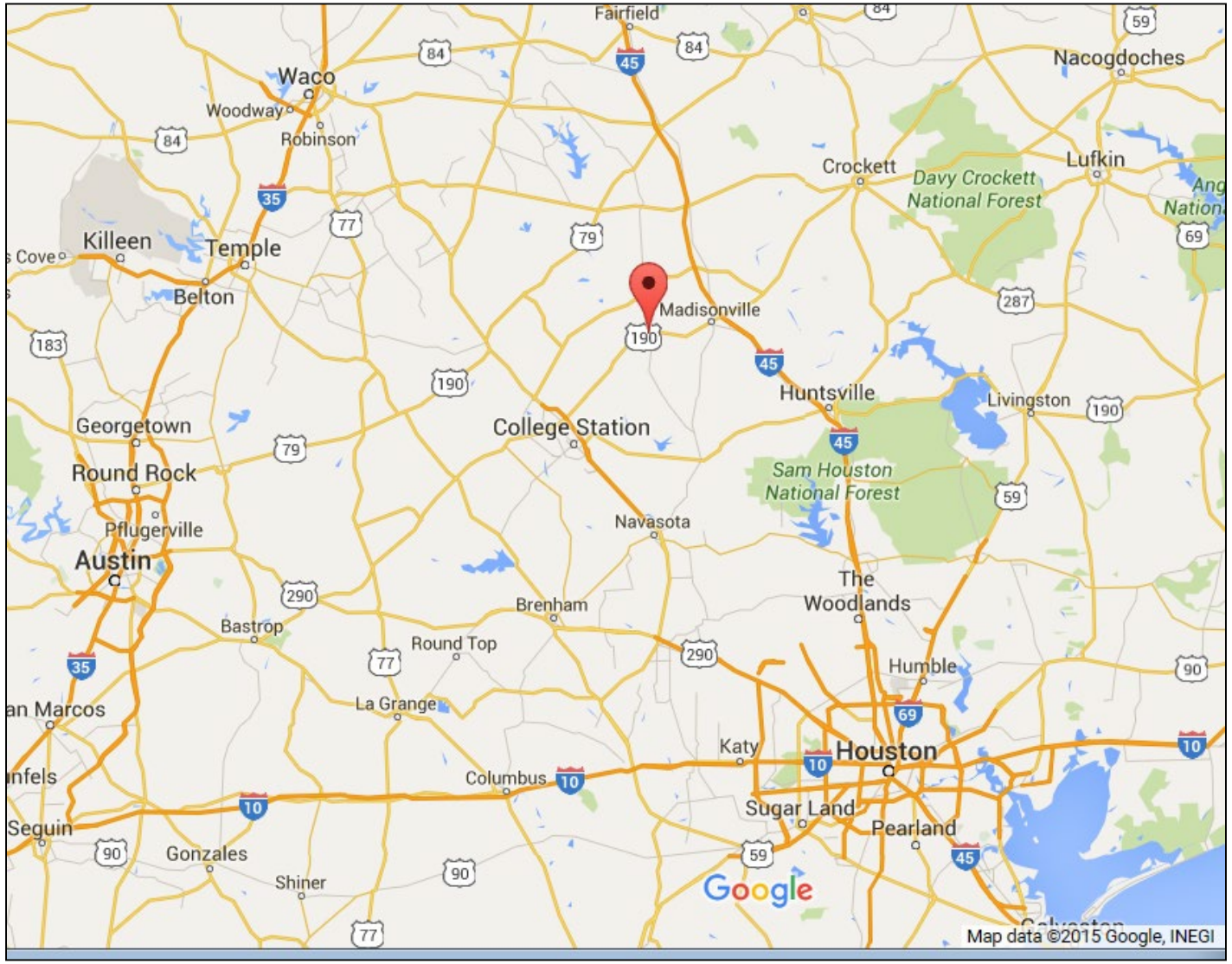
North Zulch, Texas

Unincorporated community

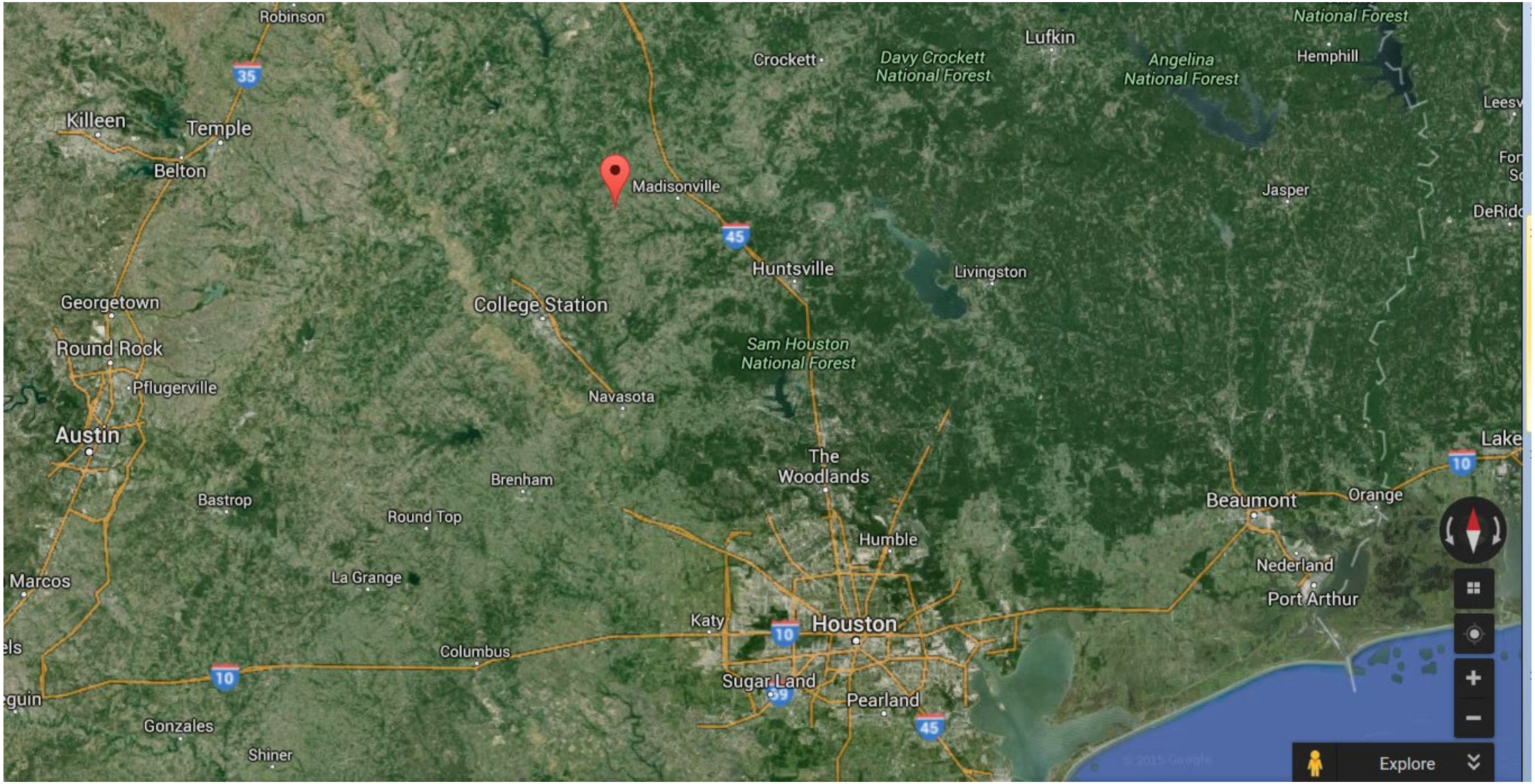
Old Coca Cola Sign at North Zulch Grocery

Country	United States
State	Texas
County	Madison
Elevation	318 ft (97 m)
Population Estimated	
• **Total**	100
Time zone	Central (CST) (UTC-6)
• **Summer (DST)**	CDT (UTC-5)
Area code(s)	936

North Zulch Texas



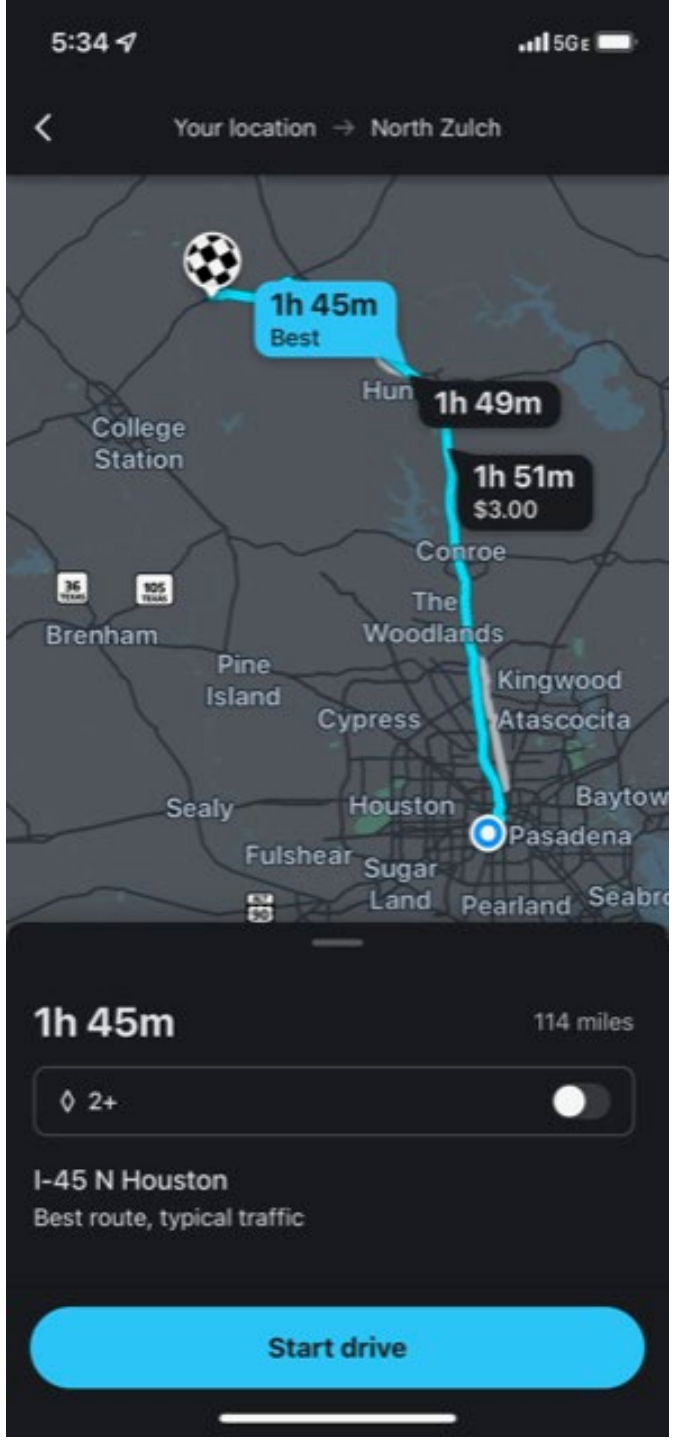
North Zulch Texas



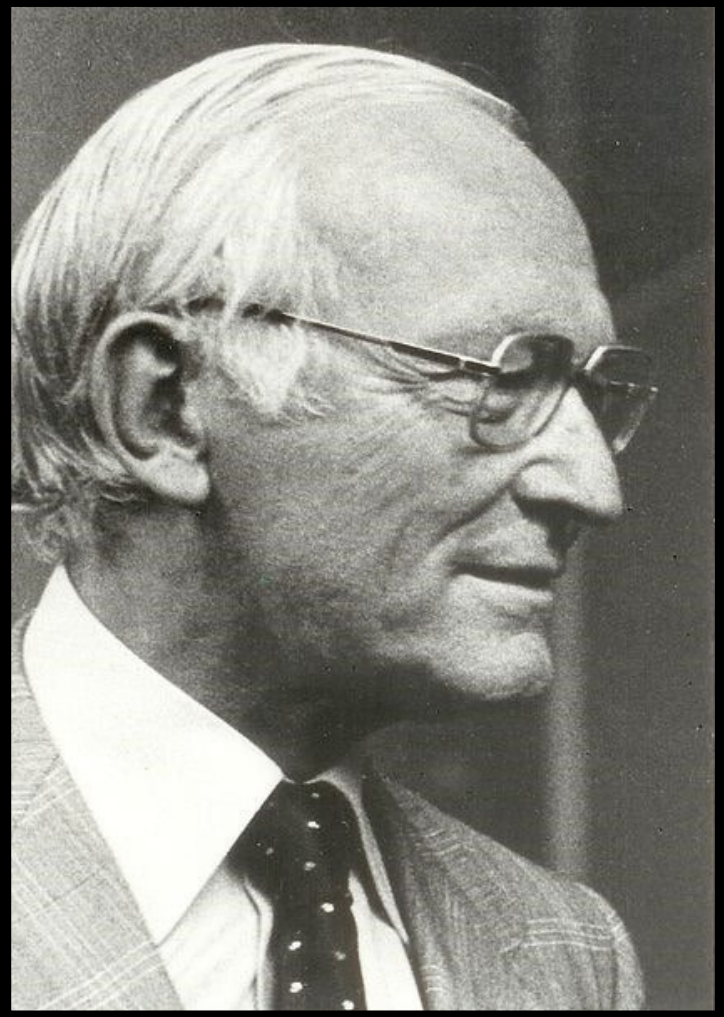
Google Earth

How far is North Zulch, Texas from my office at MDACC?

TMC to North Zulch Texas



What is the Connection between Klaus Zulch and North Zulch TX?



The Zulch-Texas Connection

Julius Zulch

The Zulch-Texas Connection

Julius Zulch

Klaus Zulch's Grandfather's Brother

The Zulch-Texas Connection: Julius Zulch

- **1850 Julius Zulch, Brother of Klaus Zulch's Grandfather immigrated to Texas, arriving in the United States by ship in**

The Zulch-Texas Connection: Julius Zulch

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The Zulch-Texas Connection: Julius Zulch

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The Zulch-Texas Connection: Julius Zulch

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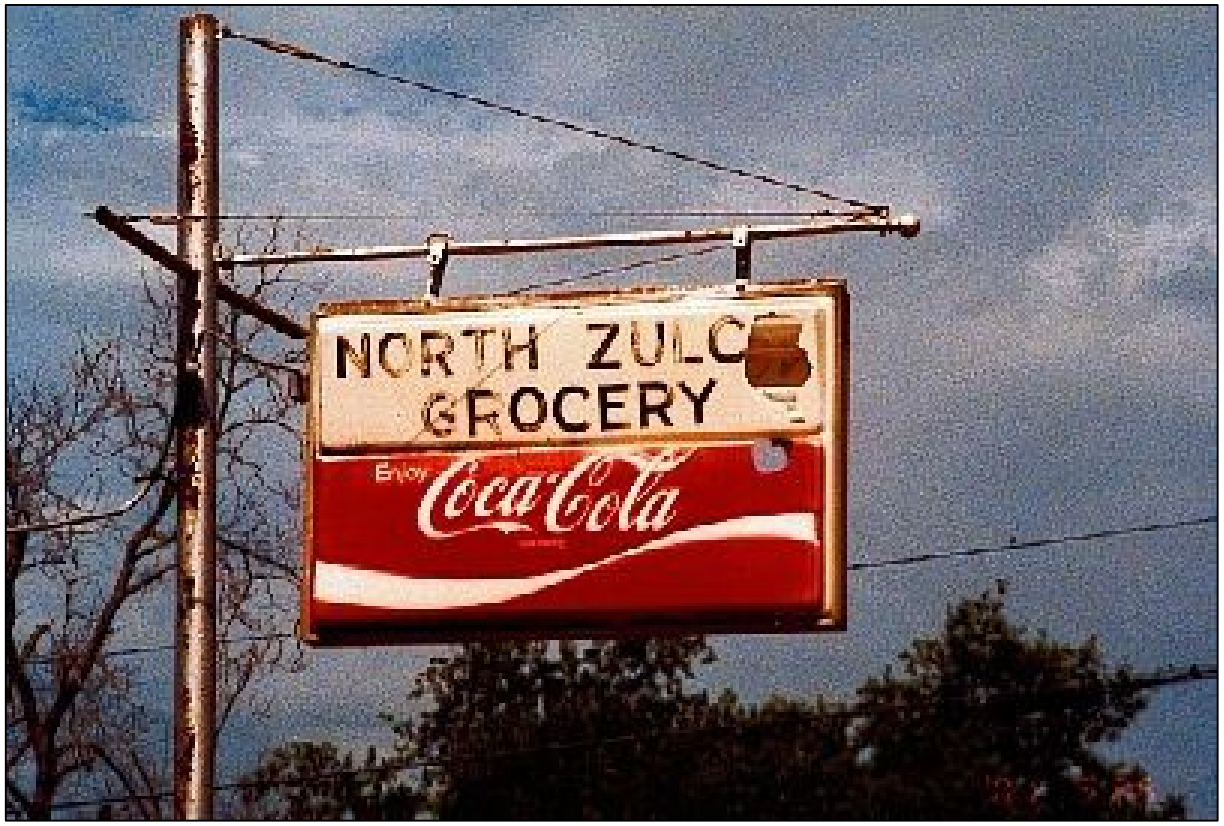
- **1907** The Trinity and Brazos Railway built a spur adjacent to the HTC spur
- **The Zulch population began migrating north to be closer to the railway – and thus North Zulch was established! Zulch proper slowly shrank away…**

The WHO-Zulch-Texas Connection

Julius Zulch and his legacy, North Zulch



Bulldogs
NORTH ZULCH
INDEPENDENT SCHOOL DISTRICT

This was a **Brief History**

of the

WHO CNS Classification

according to **Fuller…**

But there is a **Better History**

of the

WHO CNS Classification

Scheithauer

HISTORICAL PERSPECTIVE

Development of the WHO Classification of Tumors of the Central Nervous System: A Historical Perspective

Bernd W. Scheithauer, MD

Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, Mi.

***Brain Pathology* 2009**

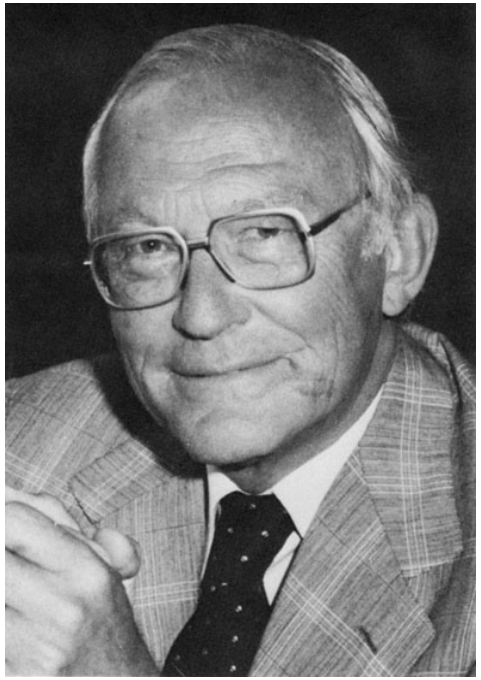
PMID **18771526**

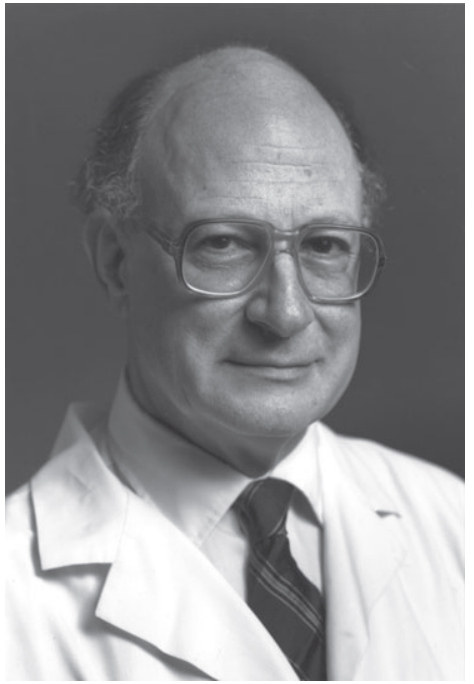
Keywords
brain tumors, classification, historical development, World Health Organization.

Corresponding author:
Bernd W. Scheithauer, MD, Mayo Clinic, Department of Laboratory Medicine and Pathology, 200 First Street, SW, Rochester, MN 55905 (E-mail: *scheithauer.bernd@mayo.edu*)

Abstract

The classification of brain tumors has undergone numerous changes over the past half century. The World Health Organization has played a key role in the effort. Four versions of its *Classification of Tumours of the Central Nervous System* have been published. The present work chronicles their progress, placing emphasis on the historical context of the earliest effort.





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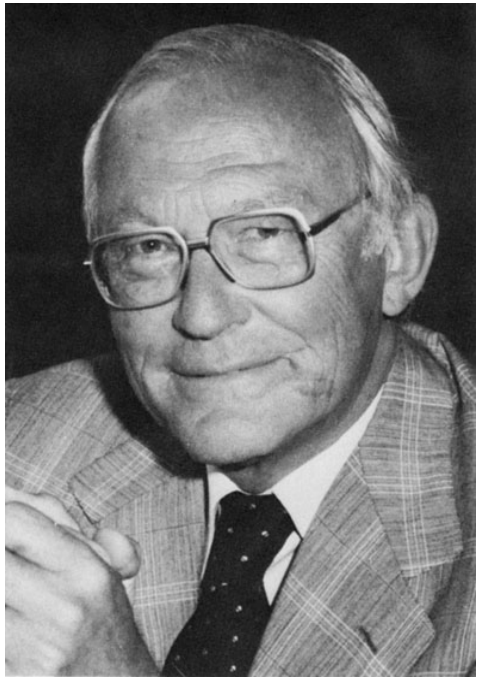
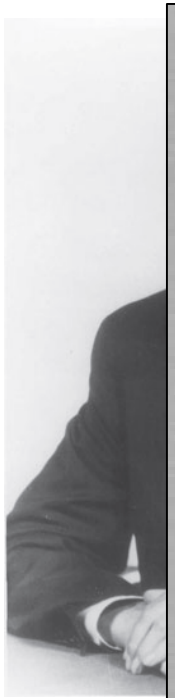
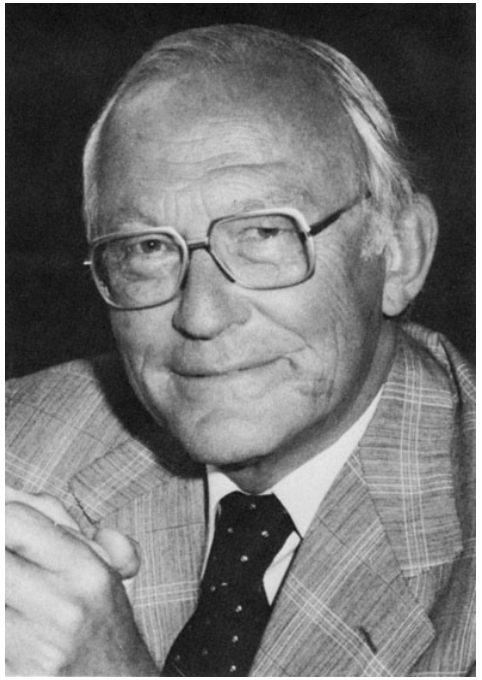



From: Wikipedia



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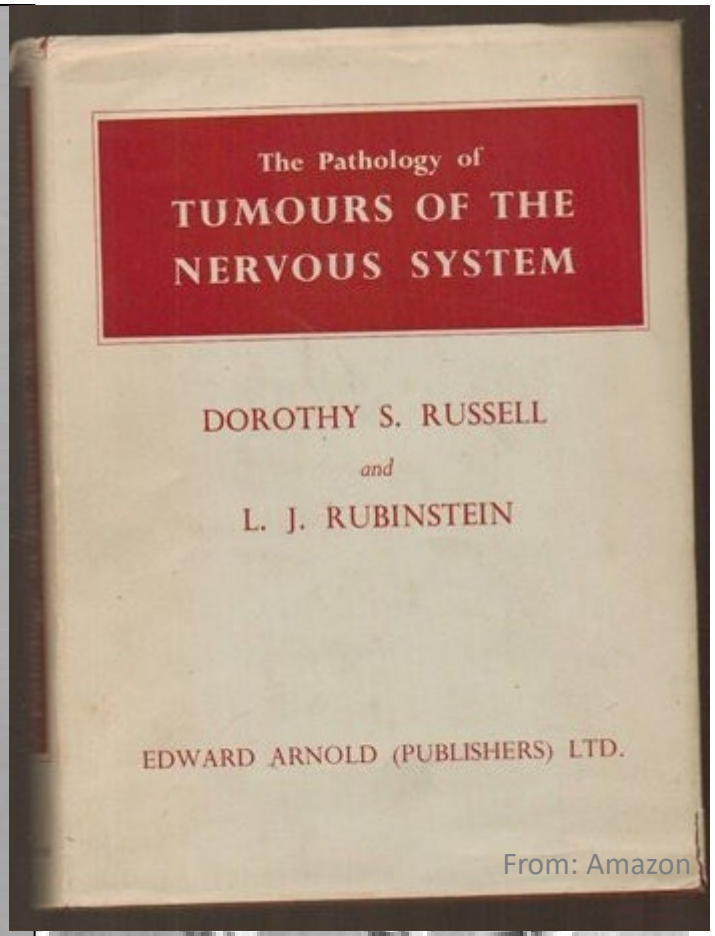

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From: Wikipedia