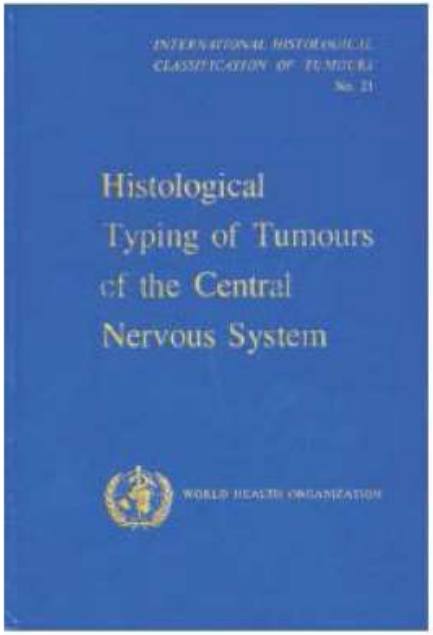
Epidemiologi, etiologi og patologi av primære CNS tumores

Pitt Niehusmann, 31. januar, Gardermoen

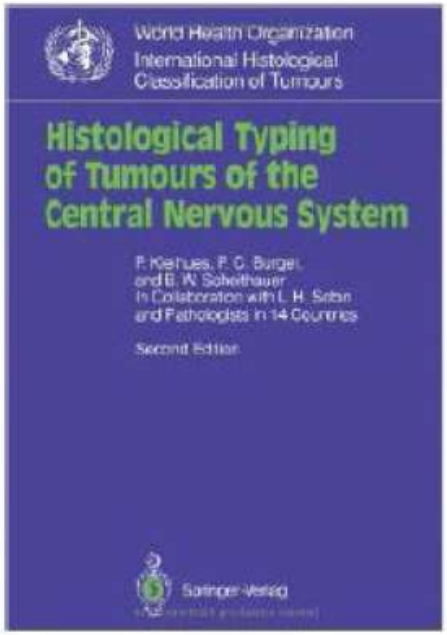
UiO : Universitetet i Oslo

Oslo University Hospital

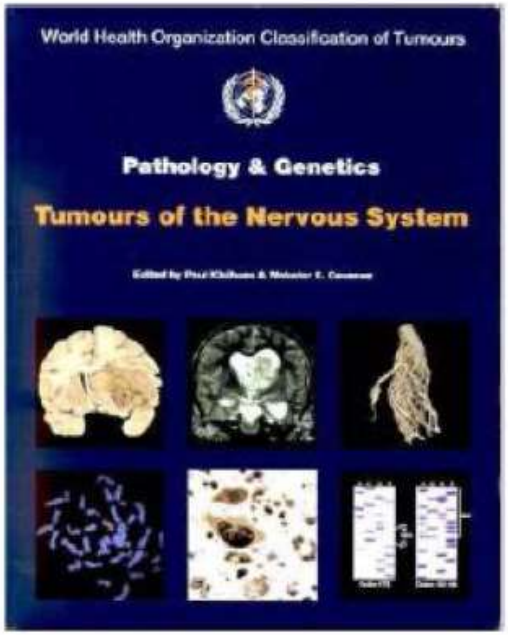
WHO Classification of CNS Tumors



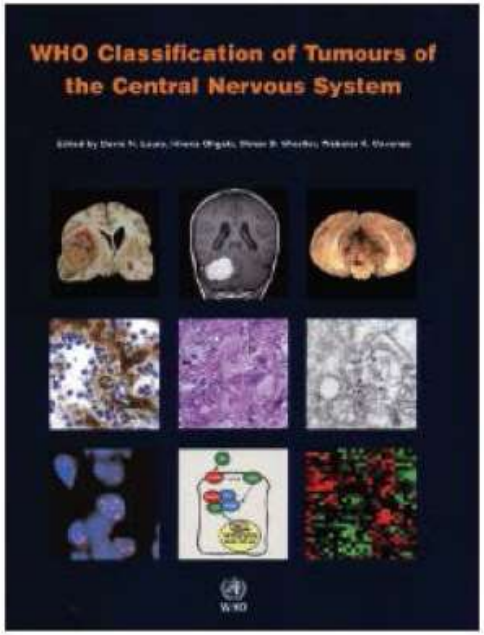
1st edition
1979



2nd edition
1993

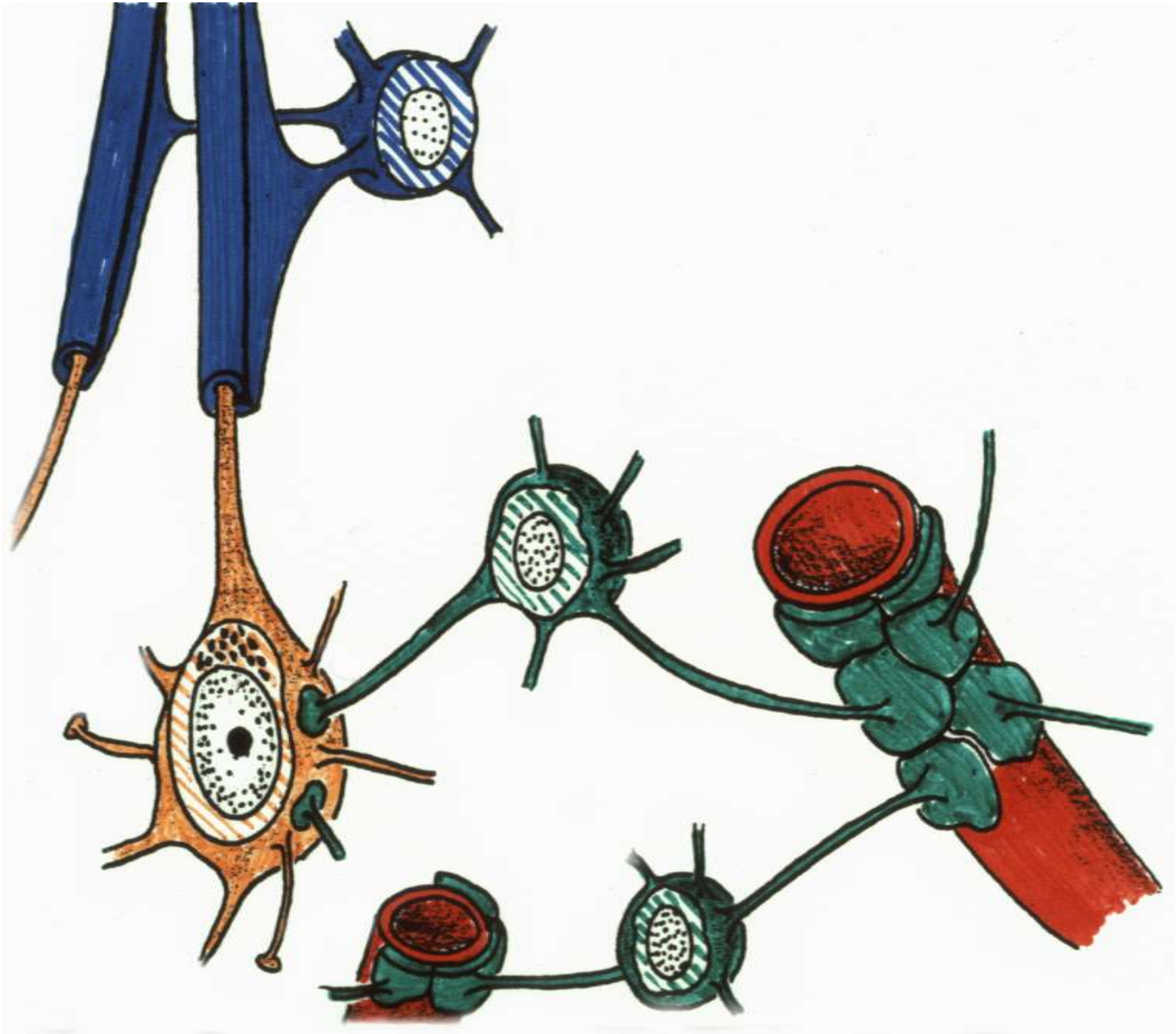


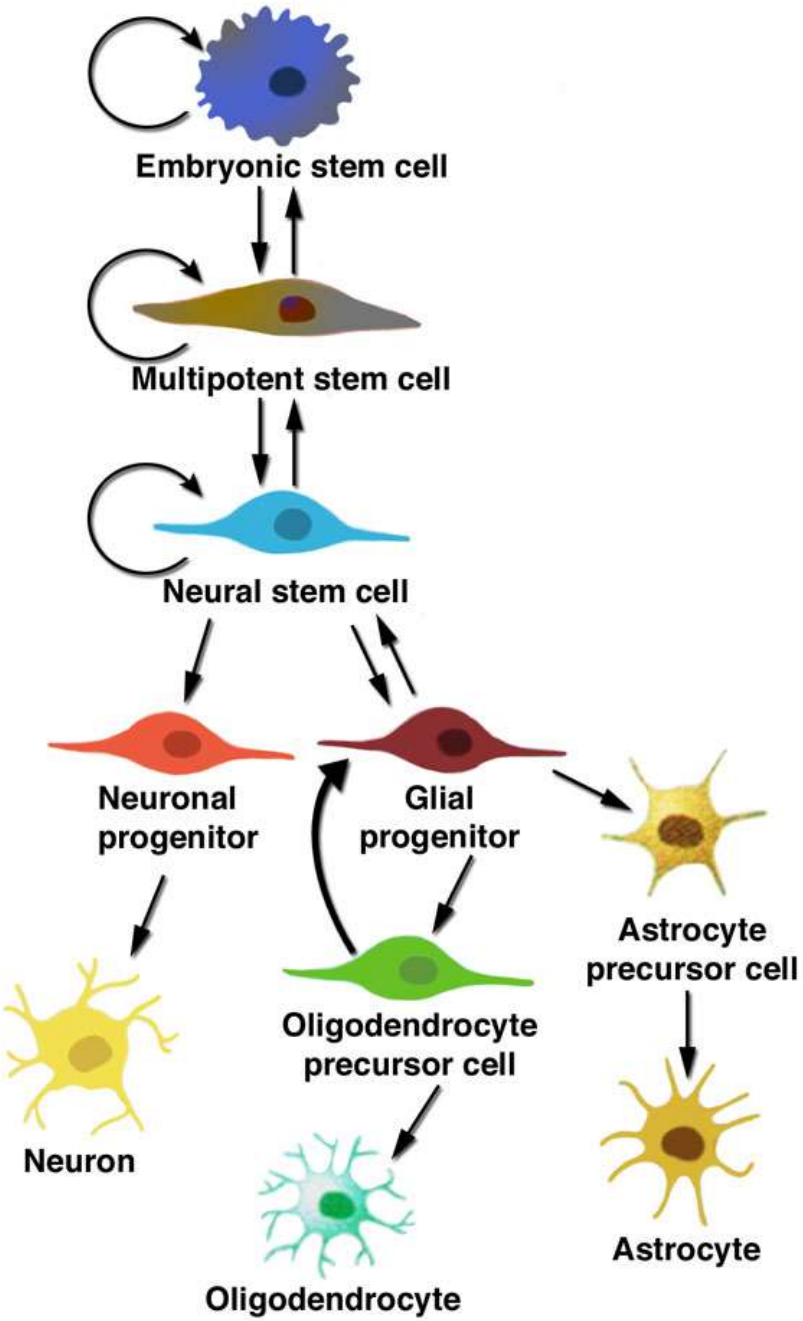
3rd edition
2000



4th edition
2007

- Dominated by a morphologic approach
  - Histological classification on the basis of similarity with putative cells of origin (normal brain cells)



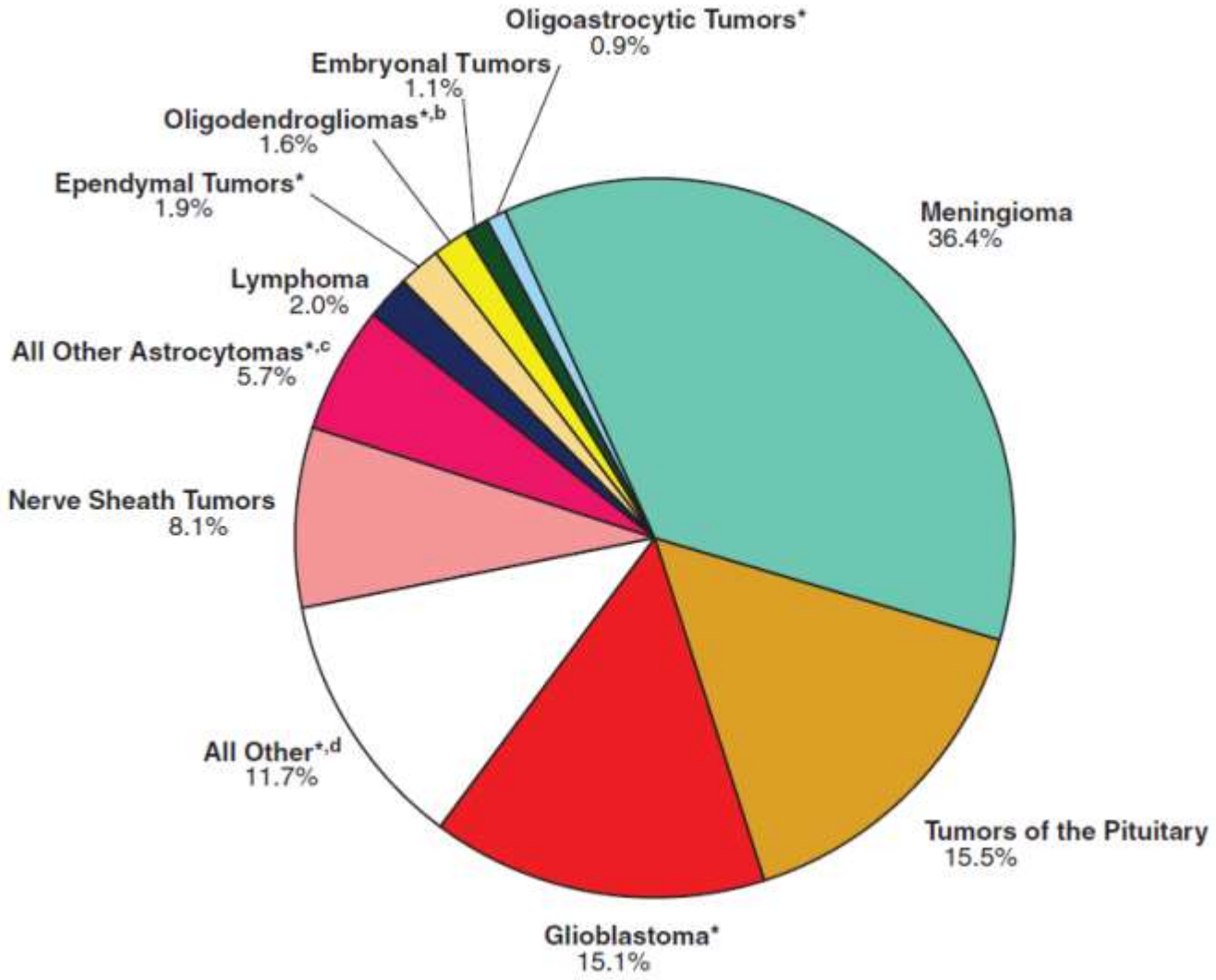

Embryonic stem cell
Multipotent stem cell
Neural stem cell
Neuronal progenitor
Glial progenitor
Astrocyte precursor cell
Neuron
Oligodendrocyte precursor cell
Astrocyte
Oligodendrocyte

Biological Grading of Brain Tumors

- Cellularity
- Cellular and nuclear polymorphism
- Mitotic and proliferative activity
- Vascular proliferates
- Tumor necroses

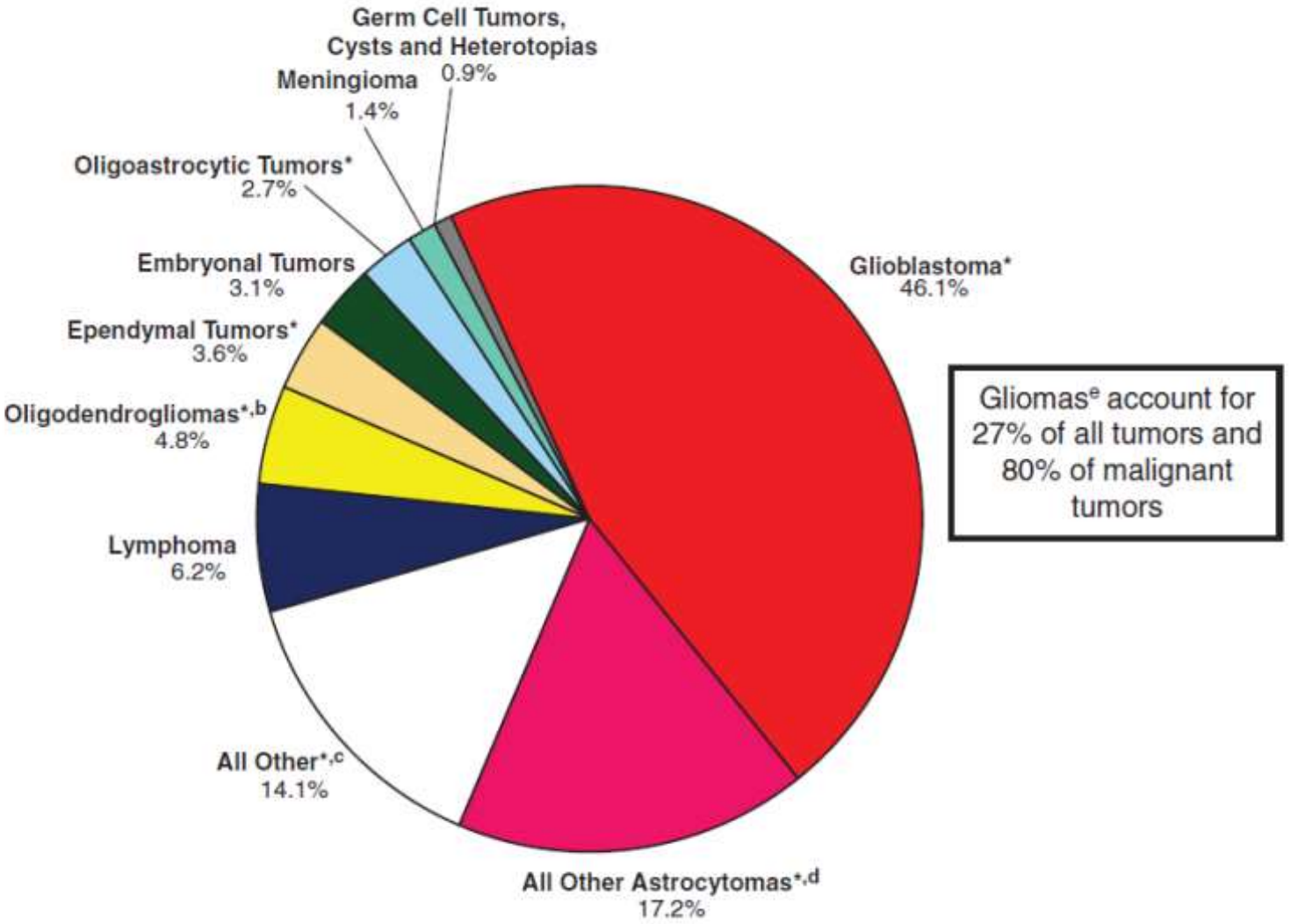
• Benign Tumor	WHO Grade I
• Signs of Atypia	WHO Grade II
• Signs of Anaplasia	WHO Grade III
• Highly malignant Tumor	WHO Grade IV

Distribution of Primary Brain and CNS Tumors



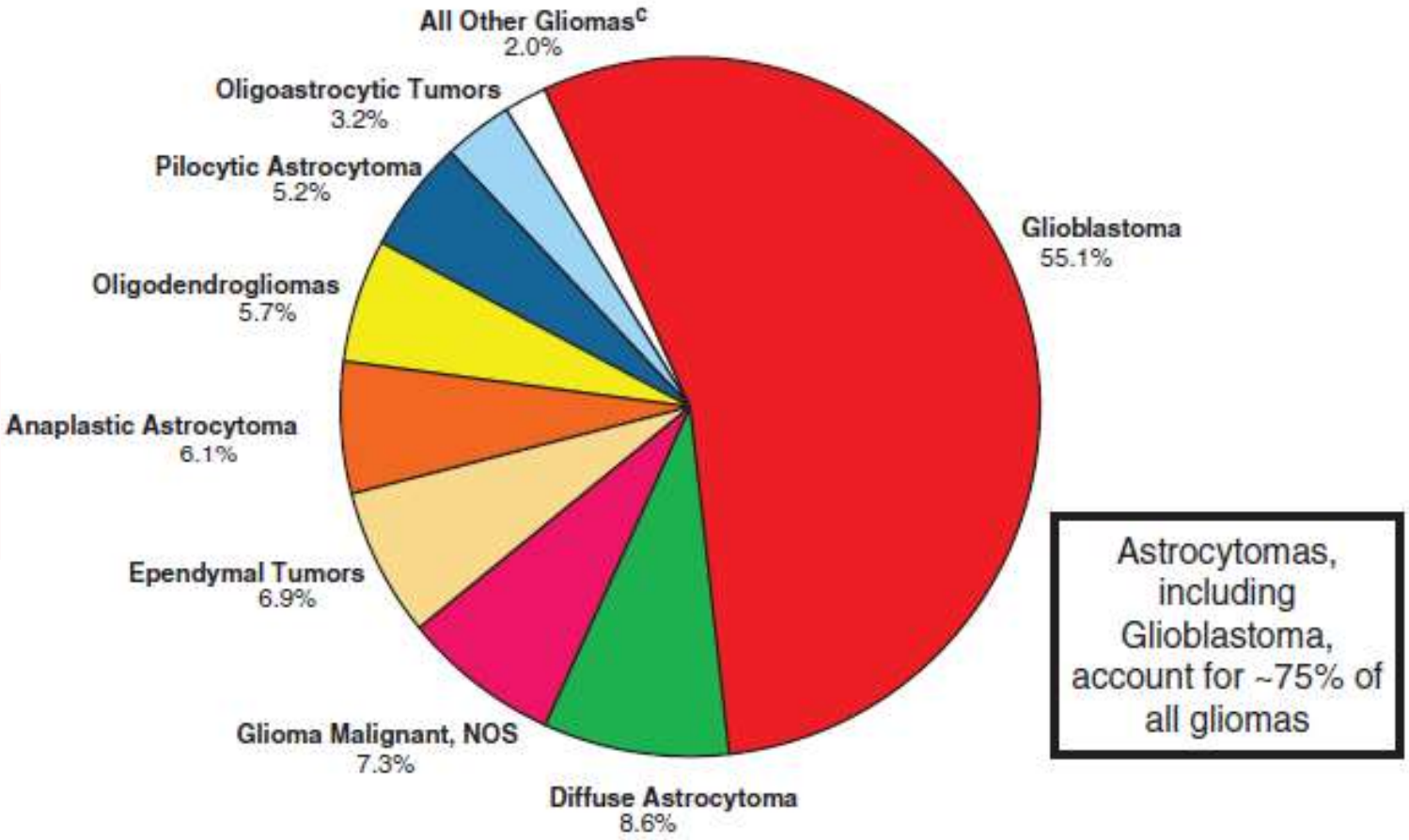
Quinn T. Ostrom et al. Neuro Oncol 2015;17:iv1-iv62
CBTRUS Histology Groupings and Histology (N = 356,858), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

Distribution of Malignant Primary Brain / CNS Tumors



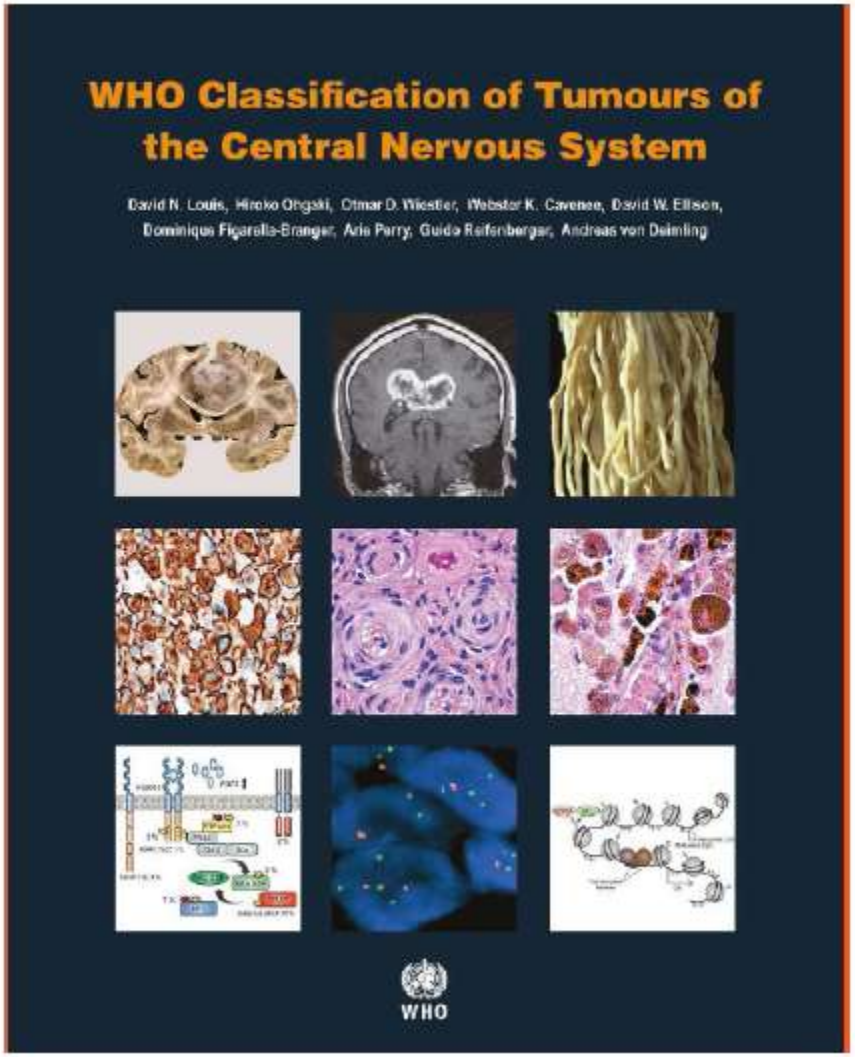
Quinn T. Ostrom et al. Neuro Oncol 2015;17:iv1-iv62
CBTRUS Histology Groupings and Histology (N = 117,023), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

Distribution of Primary Brain and CNS Gliomas



Quinn T. Ostrom et al. Neuro Oncol 2015;17:iv1-iv62
(N = 97,910), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

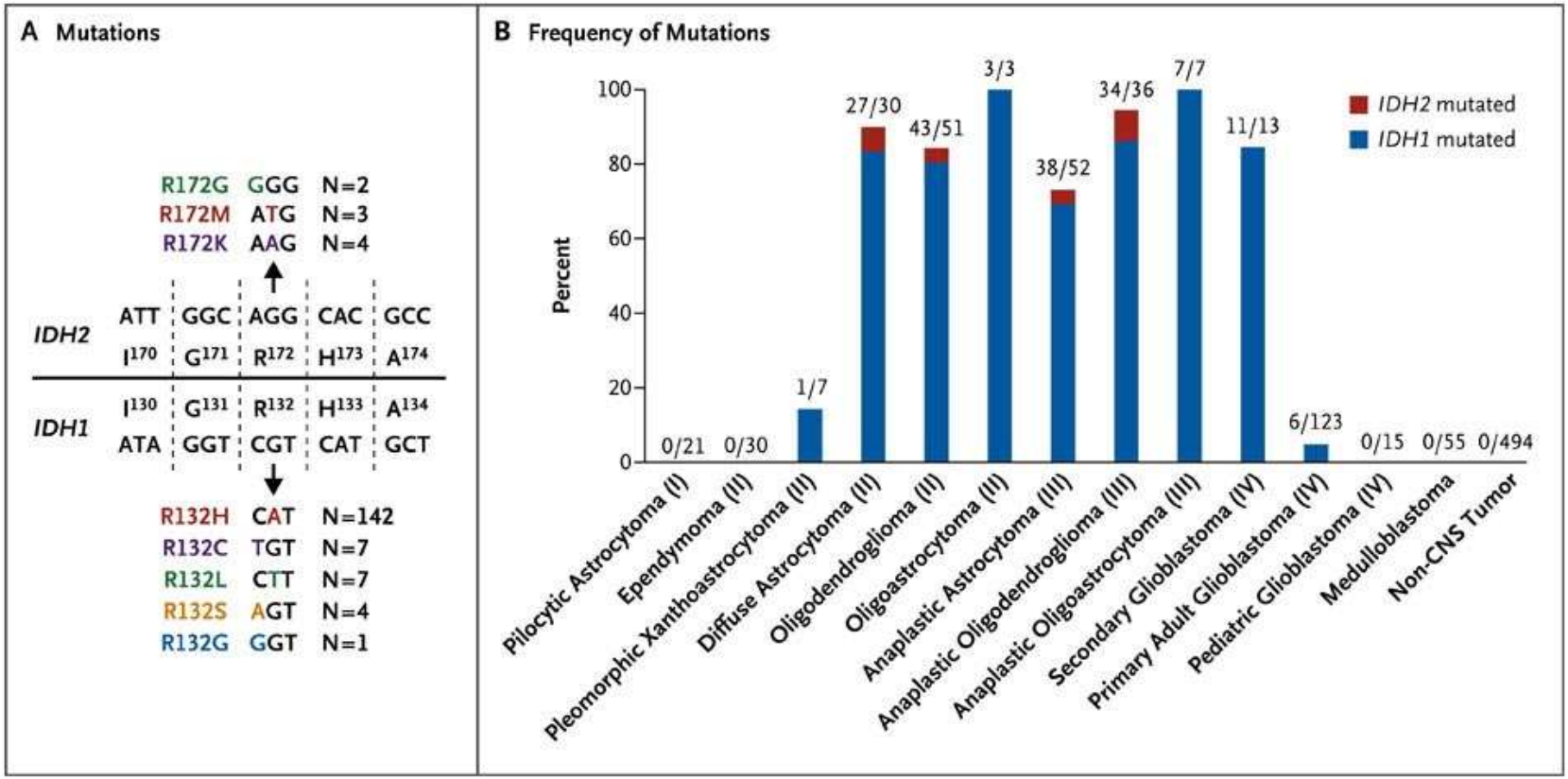
WHO Classification of CNS Tumors



Revised 4th edition, 2016

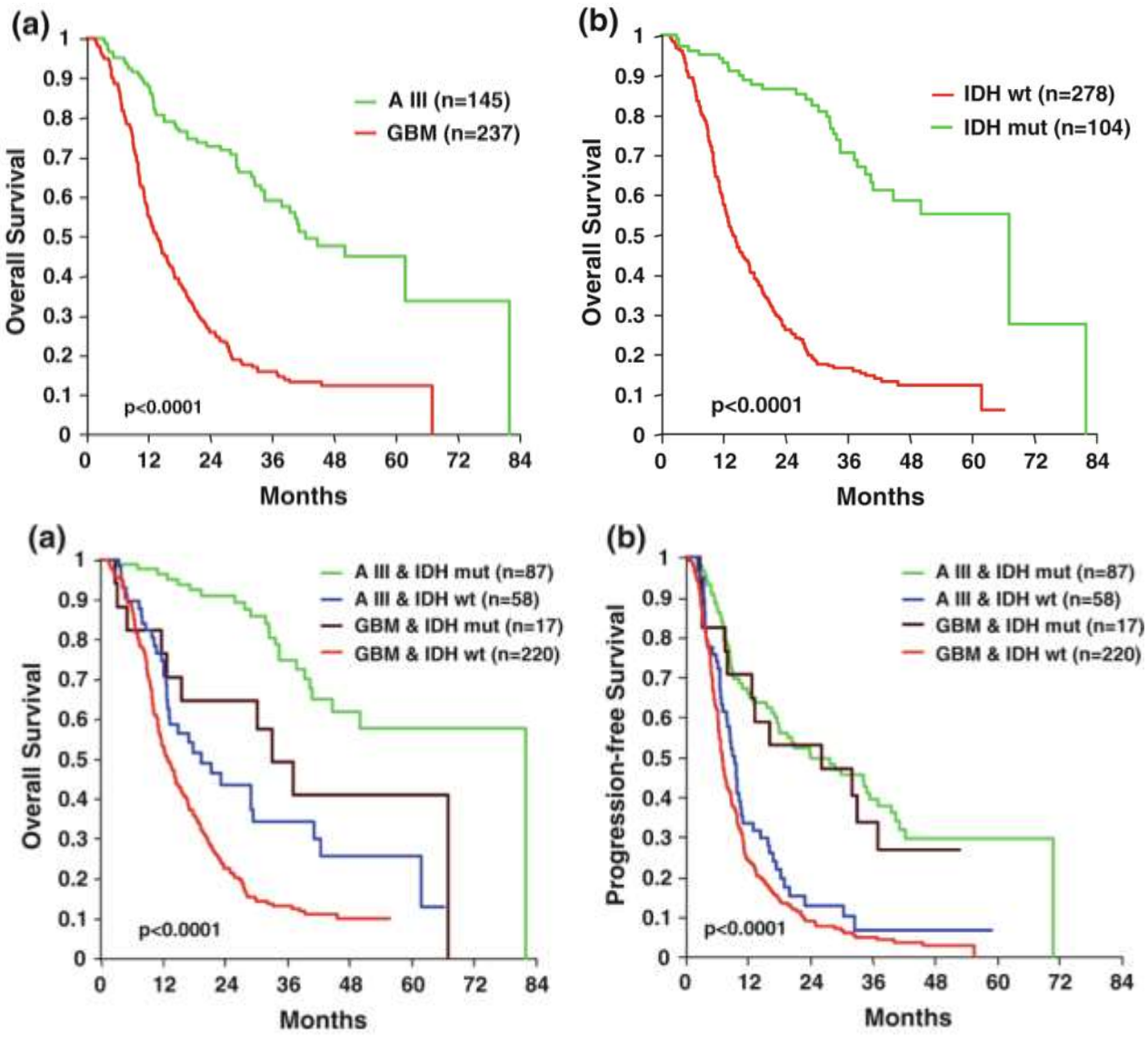
- Combined histological-molecular classification
  - Incorporation of well-etablished molecular parameters
  - Layered approach with histopathological diagnosis, WHO grade and molecular profile as integrated diagnosis

IDH1 and *IDH2* Mutations in Human Gliomas



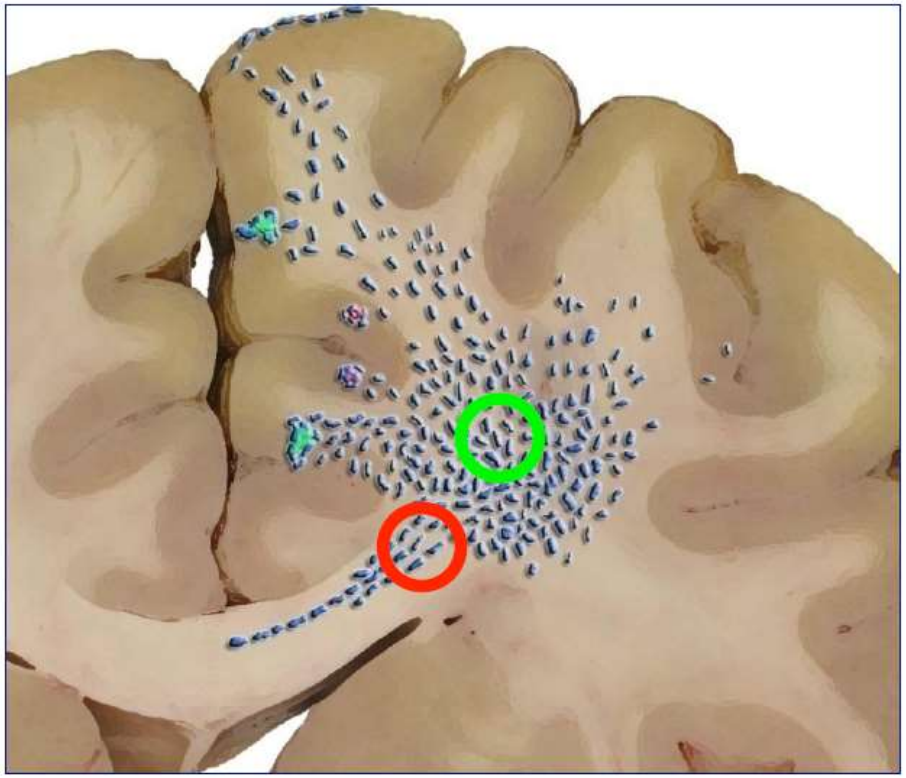
Yan et al., N Engl J Med (2009) 360:765-773

Isocytrate-Dehydrogenase (IDH)



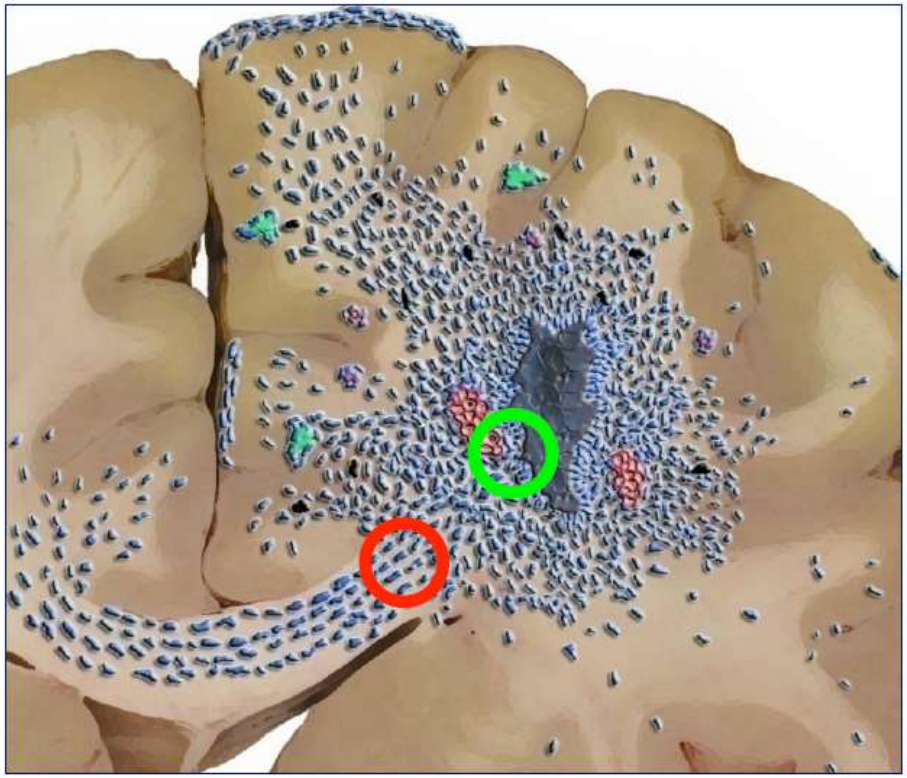
Hartmann et al., Acta Neuropathol (2010)120:707-718

Cave-sampling error!



low grade diffuse glioma

- low grade diffuse astrocytoma (= true)
- low grade diffuse astrocytoma (= true)

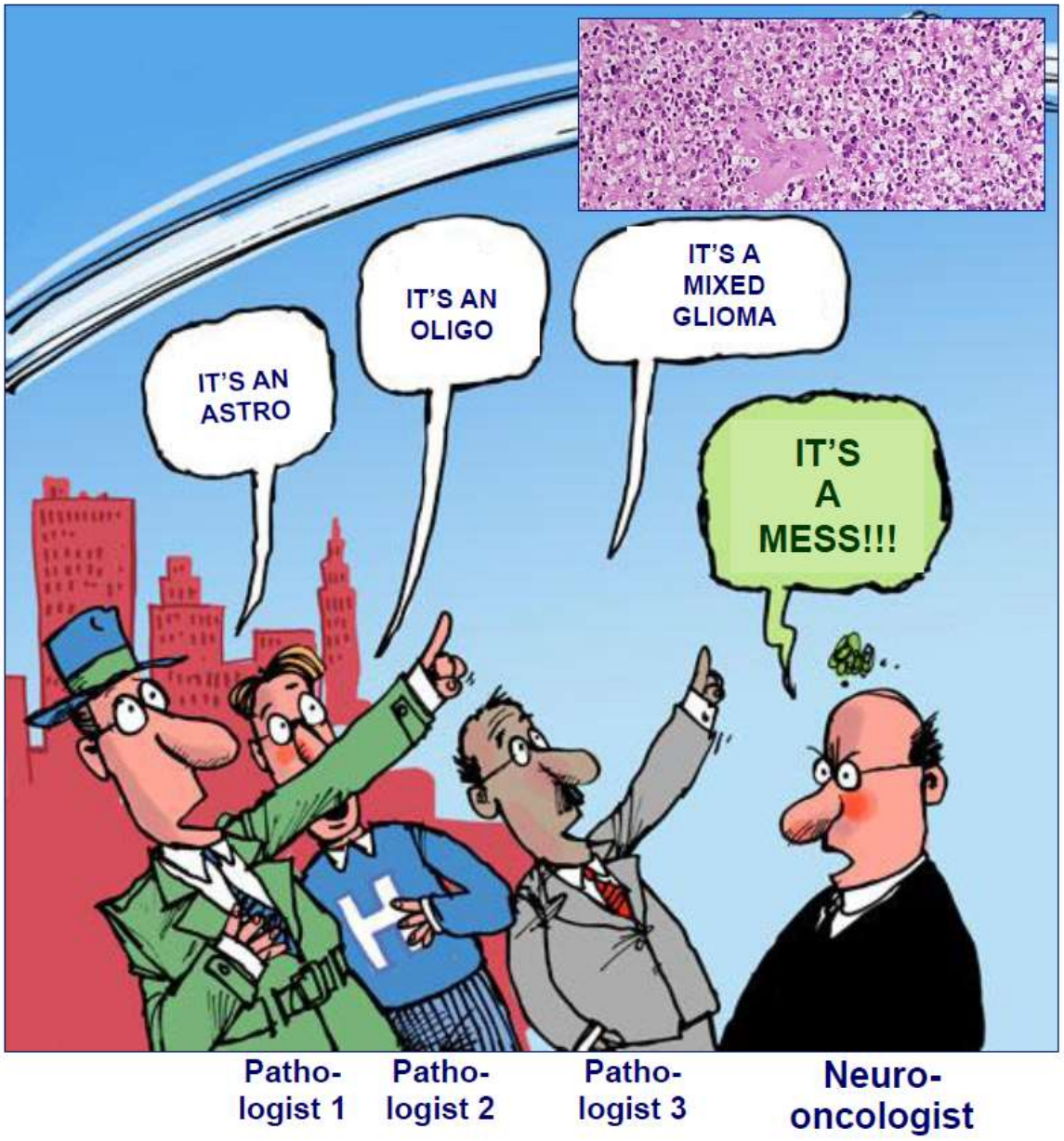


high grade diffuse glioma

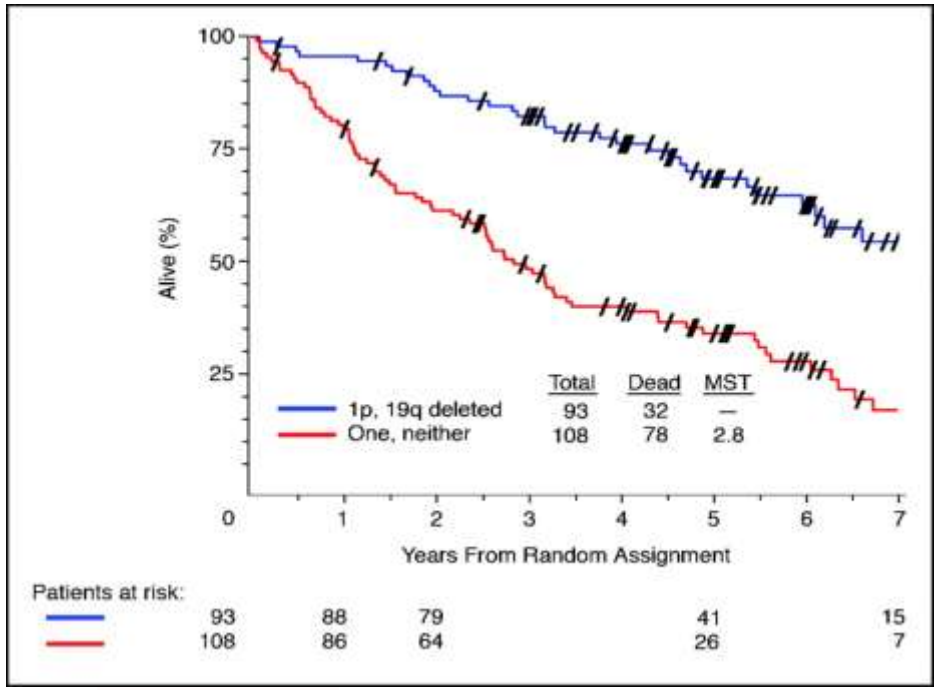
- glioblastoma (= true)
- low grade diffuse astrocytoma (= false!)

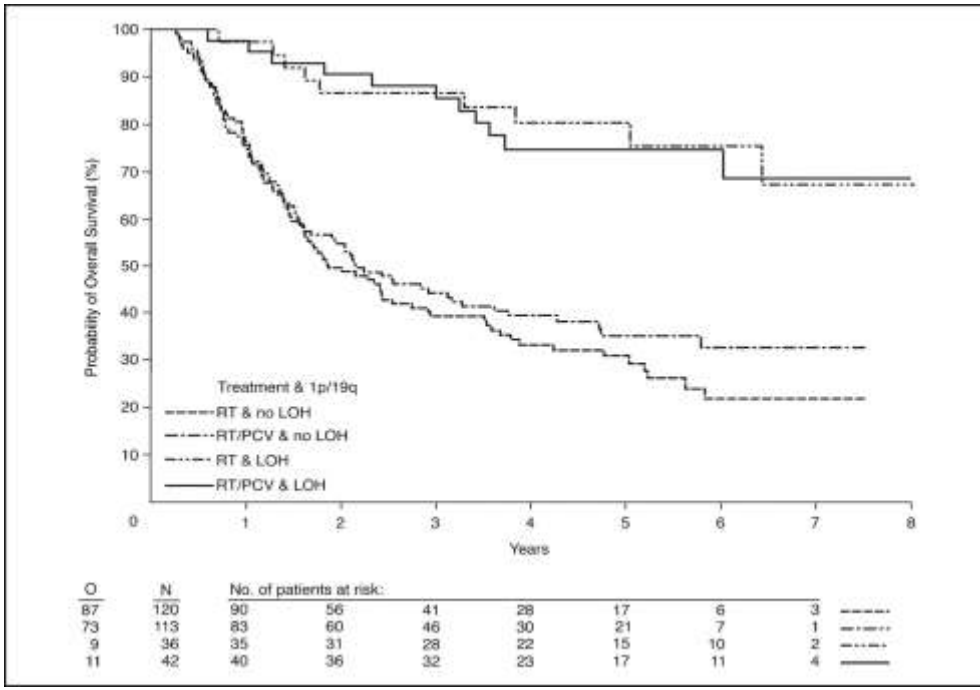
Claes et al., Acta Neuropathol (2007)114:443-458

Inter-observer variation in glioma diagnosis



Prognostic value of 1p/19q loss





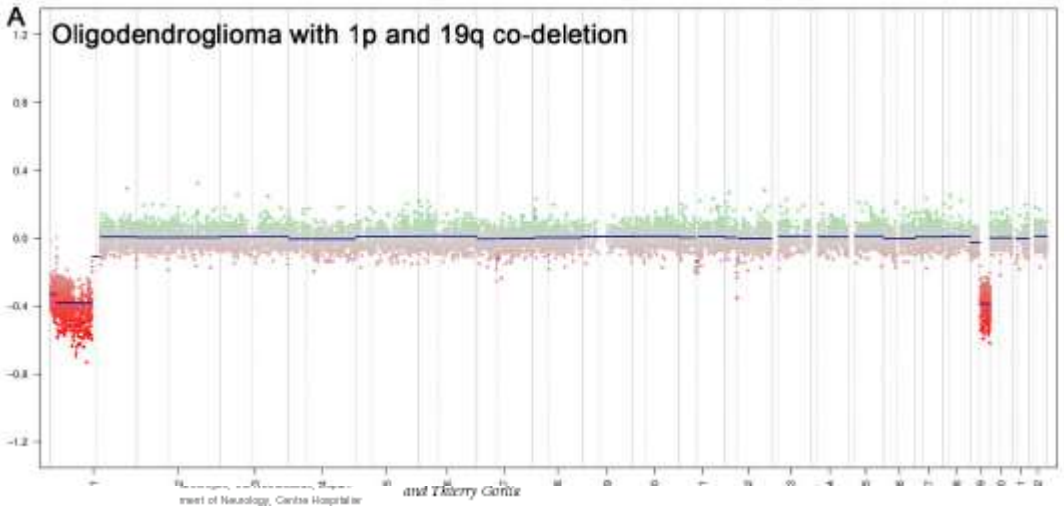
Cairncross et al., RTOG

VOLUME 24 · NUMBER 18 · JUNE 20 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REP

Phase III Trial of Chemotherapy Plus Radiother
Compared With Radiotherapy Alone for Pure a
Anaplastic Oligodendroglioma: Intergroup Radi
Therapy Oncology Group Trial 9402

Gregory Cairncross, Brian Berkey, Edward Shaw, Robert Jenkins, Bernd Scheithauer, Dan
Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, and Walt



Gliomas 2007 versus 2016

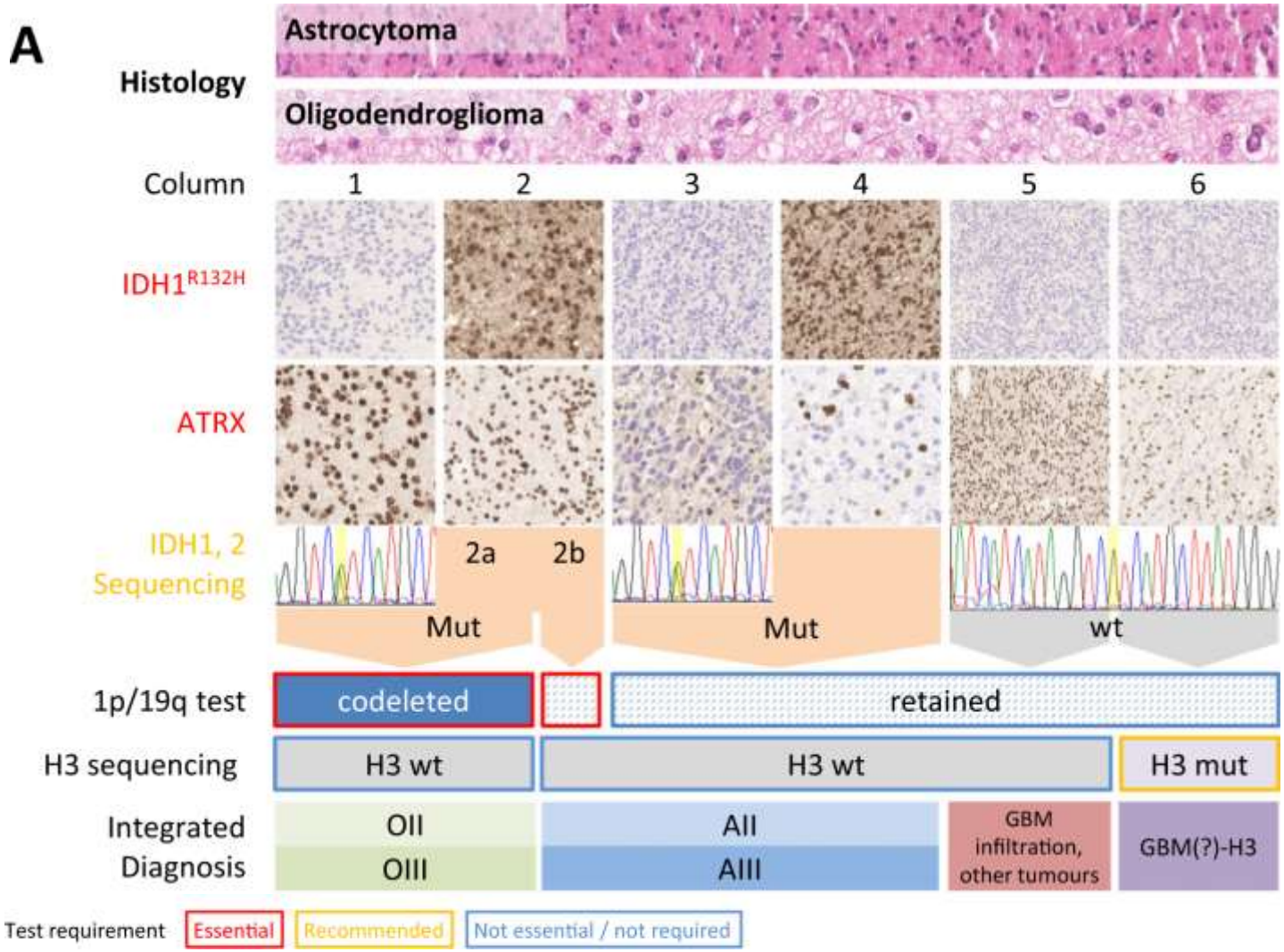
2007 WHO classification

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3

2016 WHO classification

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*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
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*

IDH1 and ATRX IHC for Glioma Classification



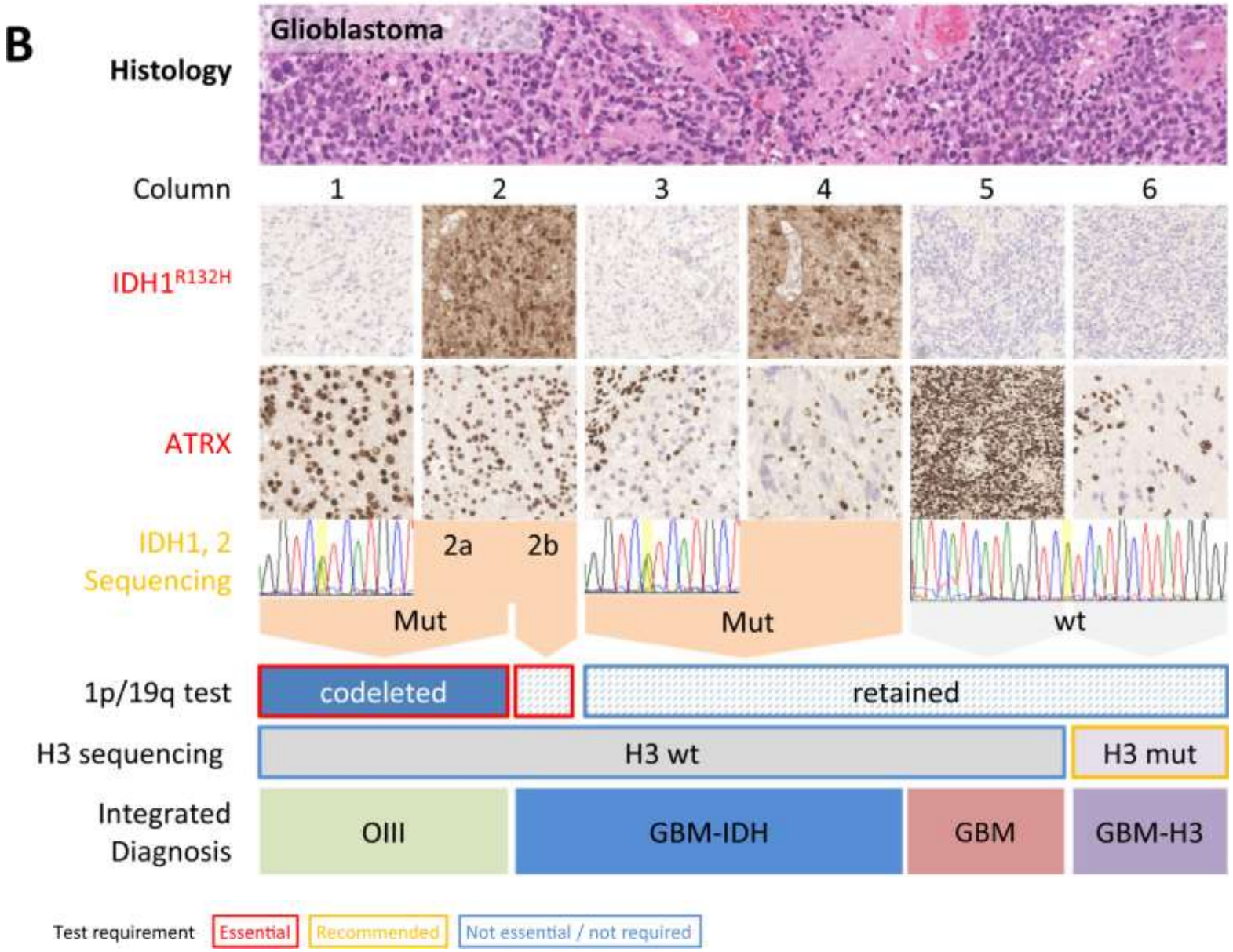
Neuropathology and Applied Neurobiology (2015), **41**, 694–720 doi: 10.1111/nan.12246

ATRX = Alpha Thalassemia/Mental Retardation Syndrome X-Linked

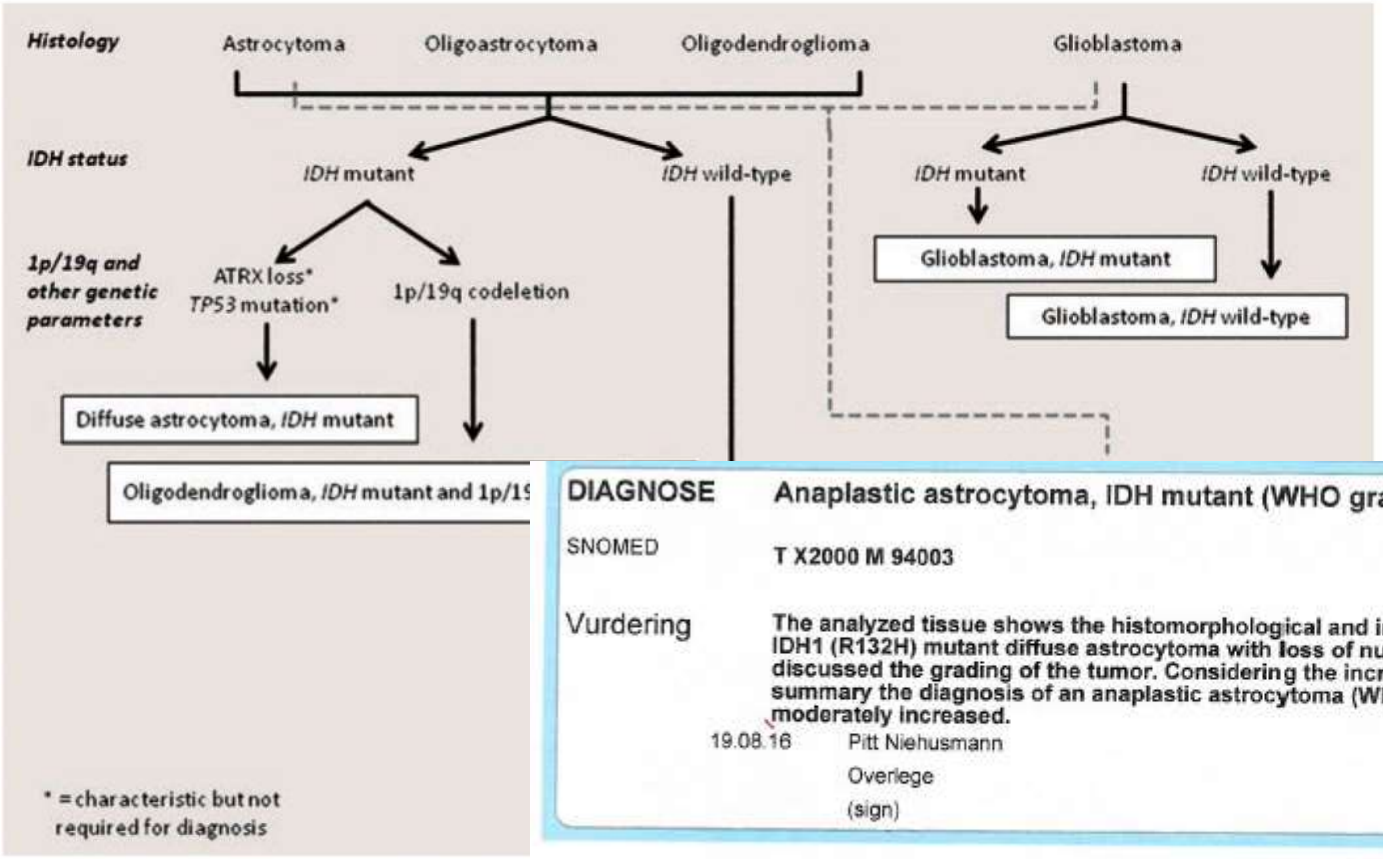
Invited review: Diagnostic, prognostic and predictive relevance of molecular markers in gliomas

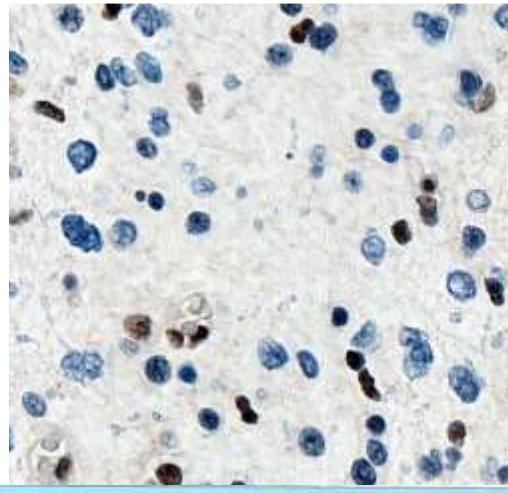
S. Brandner*† and A. von Deimling‡§

IDH1 and ATRX IHC for Glioma Classification



Diffuse glioma – integrated diagnosis





DIAGNOSE Anaplastic astrocytoma, IDH mutant (WHO grade III).

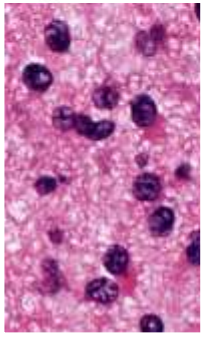
SNOMED T X2000 M 94003

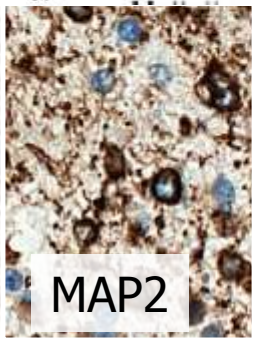
Vurdering The analyzed tissue shows the histomorphological and immunohistochemical characteristics of an IDH1 (R132H) mutant diffuse astrocytoma with loss of nuclear ATRX expression. We intensely discussed the grading of the tumor. Considering the increased pleomorphy and cellularity favor we in summary the diagnosis of an anaplastic astrocytoma (WHO grad III), even if the mitotic activity is only moderately increased.

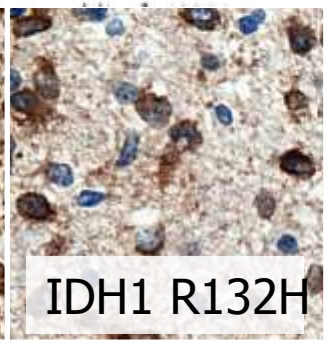
19.08.16 Pitt Niehusmann
Overlege
(sign)
sekr.

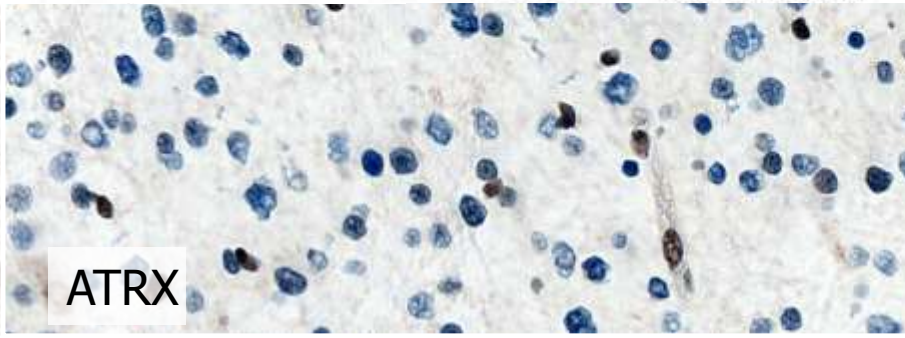
Fig. 1.01 Diffuse gliomas: from histology, IDH

Makroskopisk undersøkelse Dato: 16.08.16 Init.: thmber/thmb

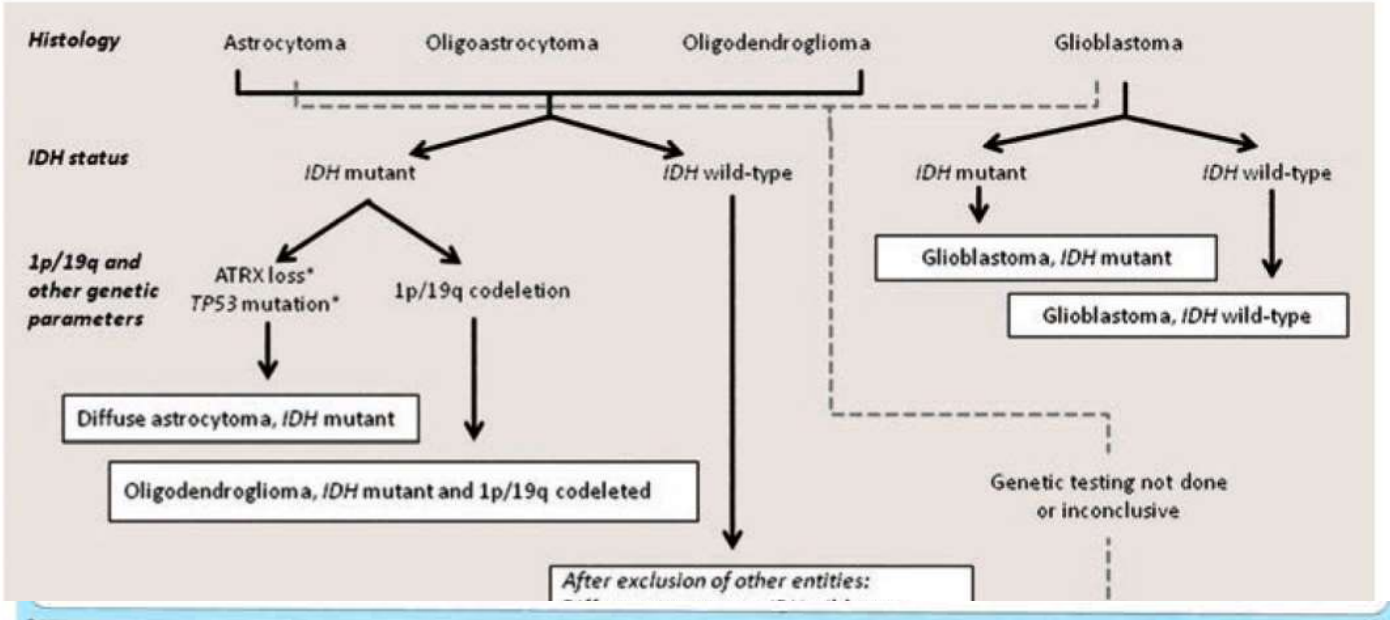








Diffuse glioma – integrated diagnosis



FORELØPIG DIAGNOSE Diffuse glioma, IDH mutant.

ENDELIG SVAR

In the meantime we received the results from the molecular pathological MLPA-analysis, which showed evidence for a combined loss of 1p/19q (see our MP16 6022). The tumor fulfils therefore the criteria for the diagnosis of an oligodendroglioma, IDH mutant and 1p/19q-codeleted (WHO grade II).

ENDELIG DIAGNOSE **Oligodendroglioma, IDH mutant and 1p/19q-codeleted (WHO grade II).**

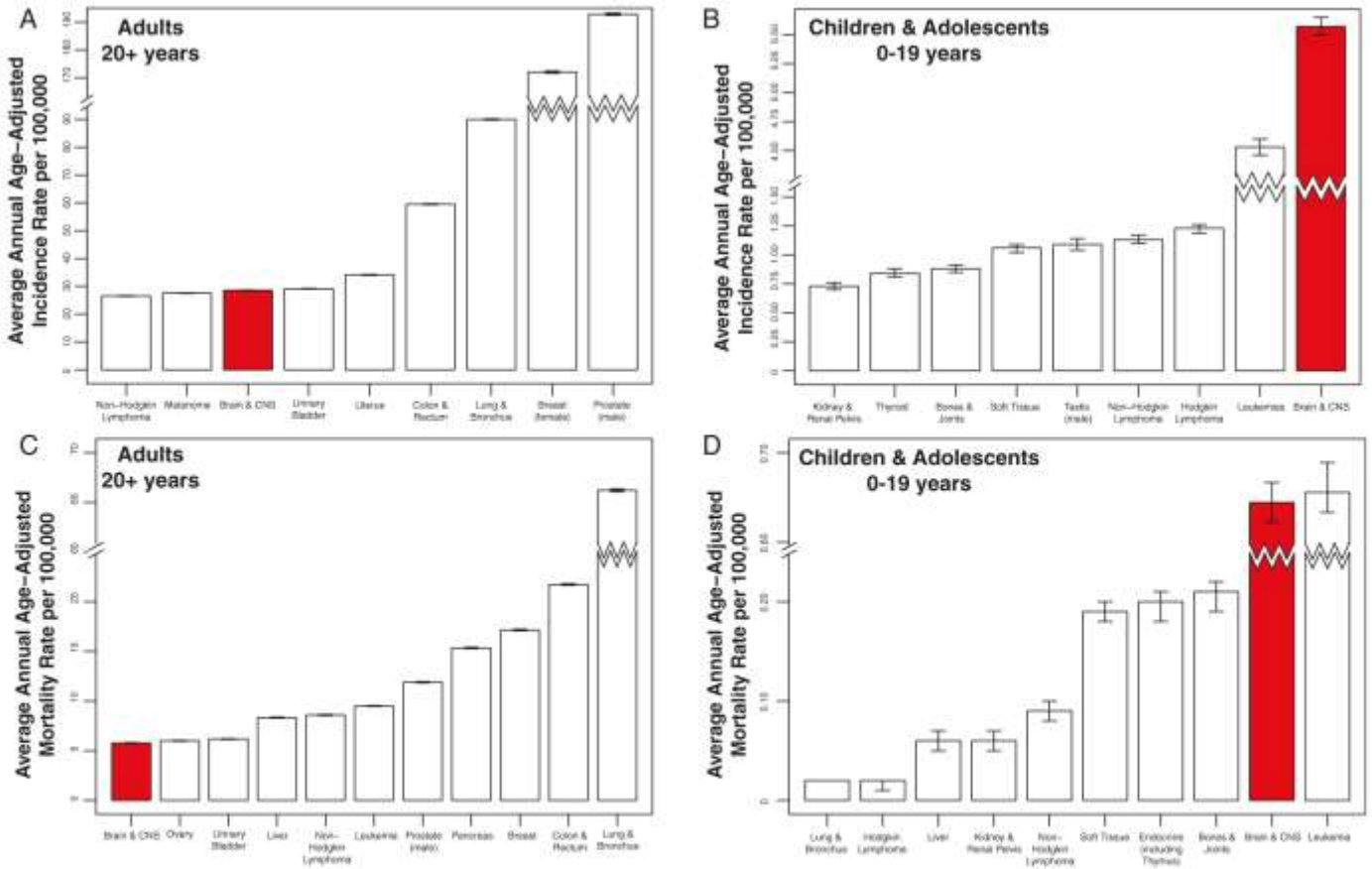
SNOMED T X2000 M 94503

31.08.16 Pitt Niehusmann
Overlege
(sign)
sekr.

Rekvirent

Makroskopisk undersøkelse Dato: 11.08.16 Init.: abustetu/ab

Incidence and mortality of CNS tumors (USA 2008-2012)



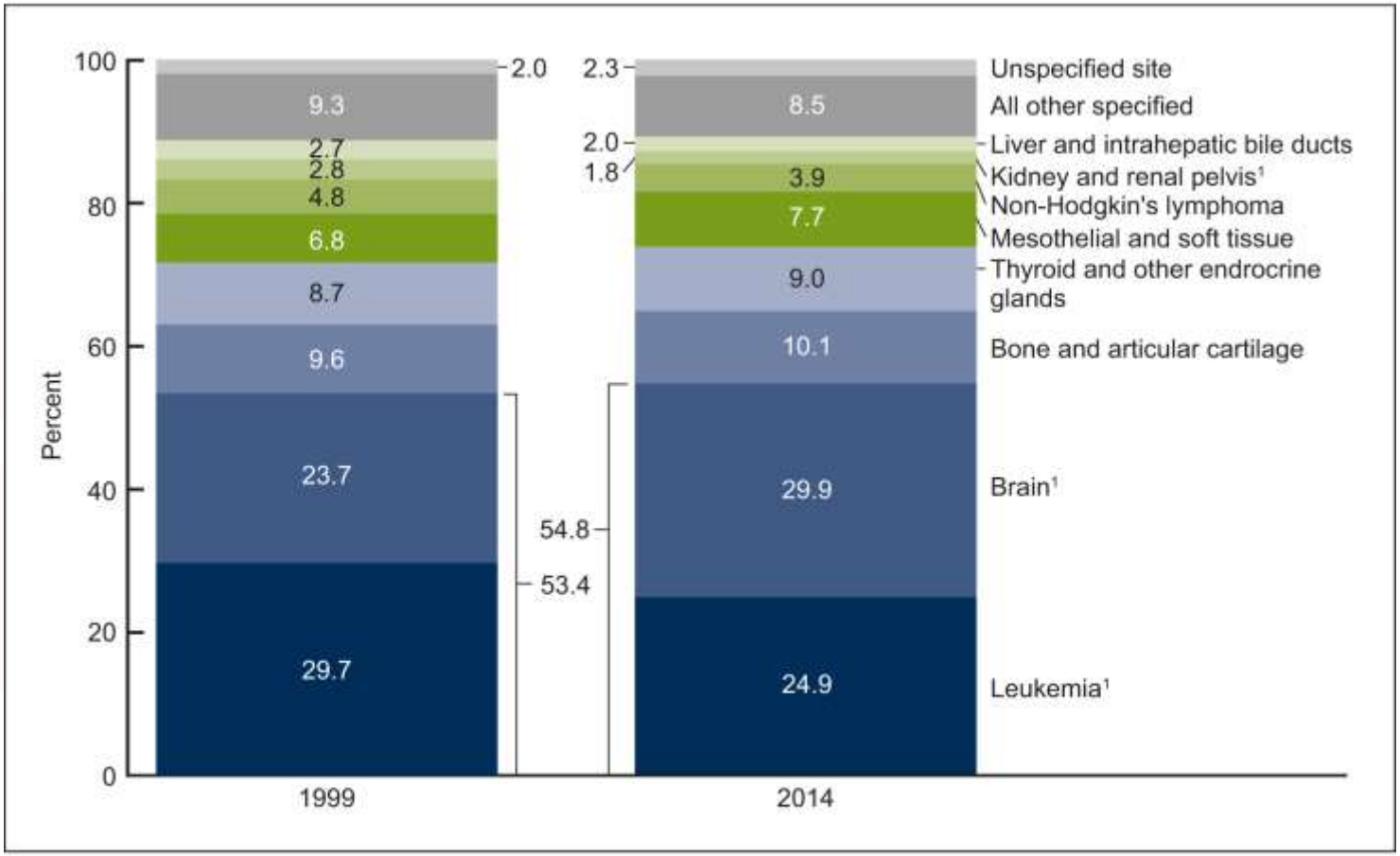
a. All incidence rates other than Brain & CNS Tumors were estimated using United States Cancer Statistics (USCS). USCS data from 2012 were not available at time of publication.

Fig. 2. Average Annual Age-Adjusted Incidence Rates[a] of All Primary Brain and CNS Tumors in Comparison to Other Common Cancers for A) Adults (Age 20+ years) and B) Children and Adolescents (Age 0-19 years) and Mortality Rates of All Primary Brain and CNS Tumors in Comparison to Other Common Cancers in C) Adults (Age 20+ years) and D) Children and Adolescents (Age 0-19 years), CBTRUS Statistical Report: NPCR and SEER 2008-2012, USCS 2008-2011[b], NCVS 2008-2012.

Quinn T. Ostrom et al. Neuro Oncol 2015;17:iv1-iv62
CBTRUS Histology Groupings and Histology (N = 356,858), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

Pediatric cancer death rates (USA) II

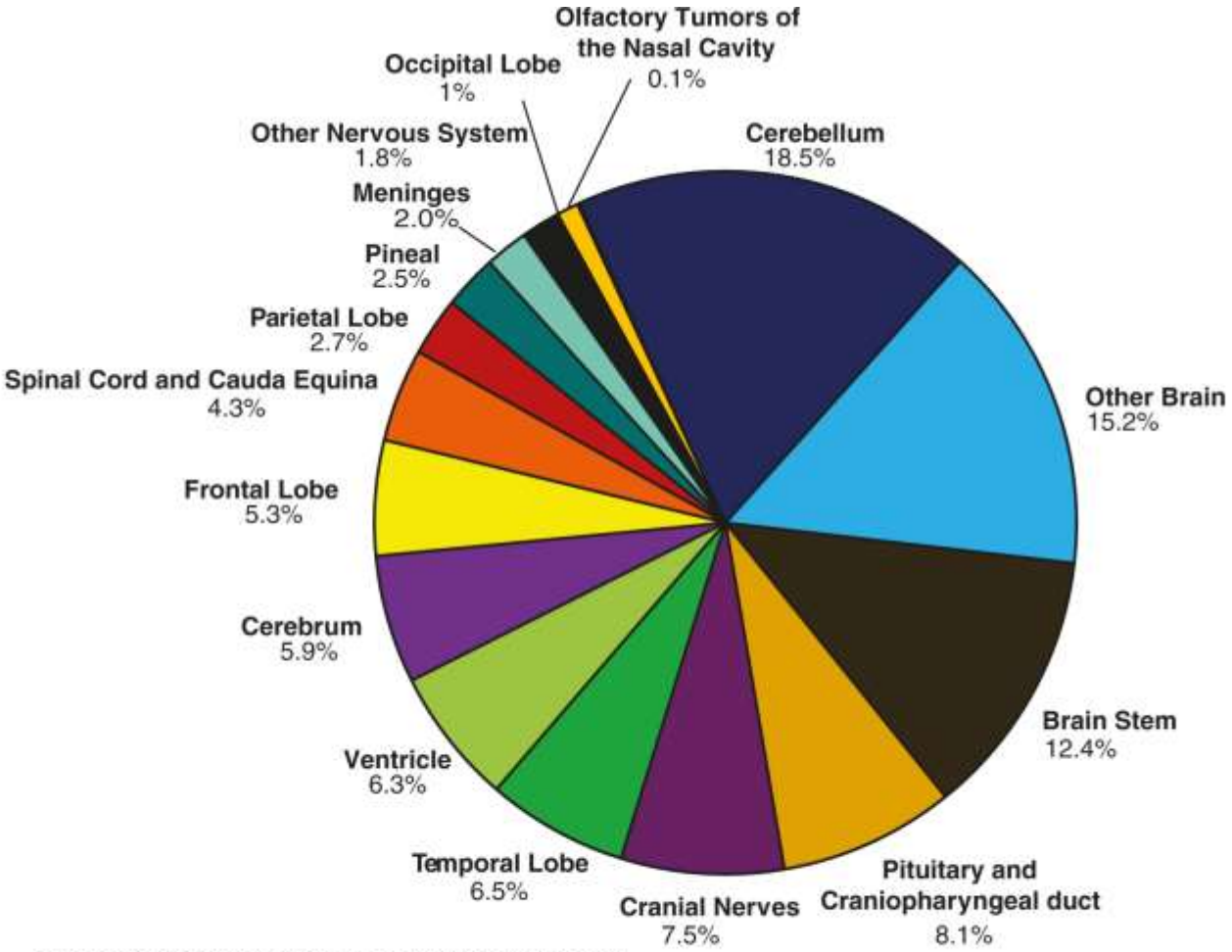
Figure 4. Percent distribution of cancer deaths for children and adolescents aged 1–19 years, by anatomical site: United States, 1999 and 2014



[1]Difference in percentages for 1999 and 2014 was statistically significant ($p < 0.05$).
NOTE: Access data table for Figure 4 at: http://www.cdc.gov/nchs/data/databriefs/db257_table.pdf#4.
SOURCE: NCHS, National Vital Statistics System, ICD–10 underlying cause-of-death codes: Leukemia (C91–C95), brain cancer (C71), bone and articular cartilage (C40–C41), thyroid and other endocrine glands (C73–C75), mesothelial and soft tissue (C45–C49), non-Hodgkin's lymphoma (C82–C85), kidney and renal pelvis (C64–C65), liver and intrahepatic bile ducts (C22), all other specified sites not shown separately (C00–C97), and unspecified site (C80).

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

Regional distribution of CNS-tumors in patients < 20 years



a. Percentages may not add up to 100% due to rounding.

Fig. 17a. Distribution[a] in Children and Adolescents (Age 0-19 years) of Primary Brain and CNS Tumors by Site (N = 23,113), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

Quinn T. Ostrom et al. Neuro Oncol 2015;17:iv1-iv62
CBTRUS Histology Groupings and Histology (N = 356,858), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

Histological distribution of CNS-tumors in patients < 20 years

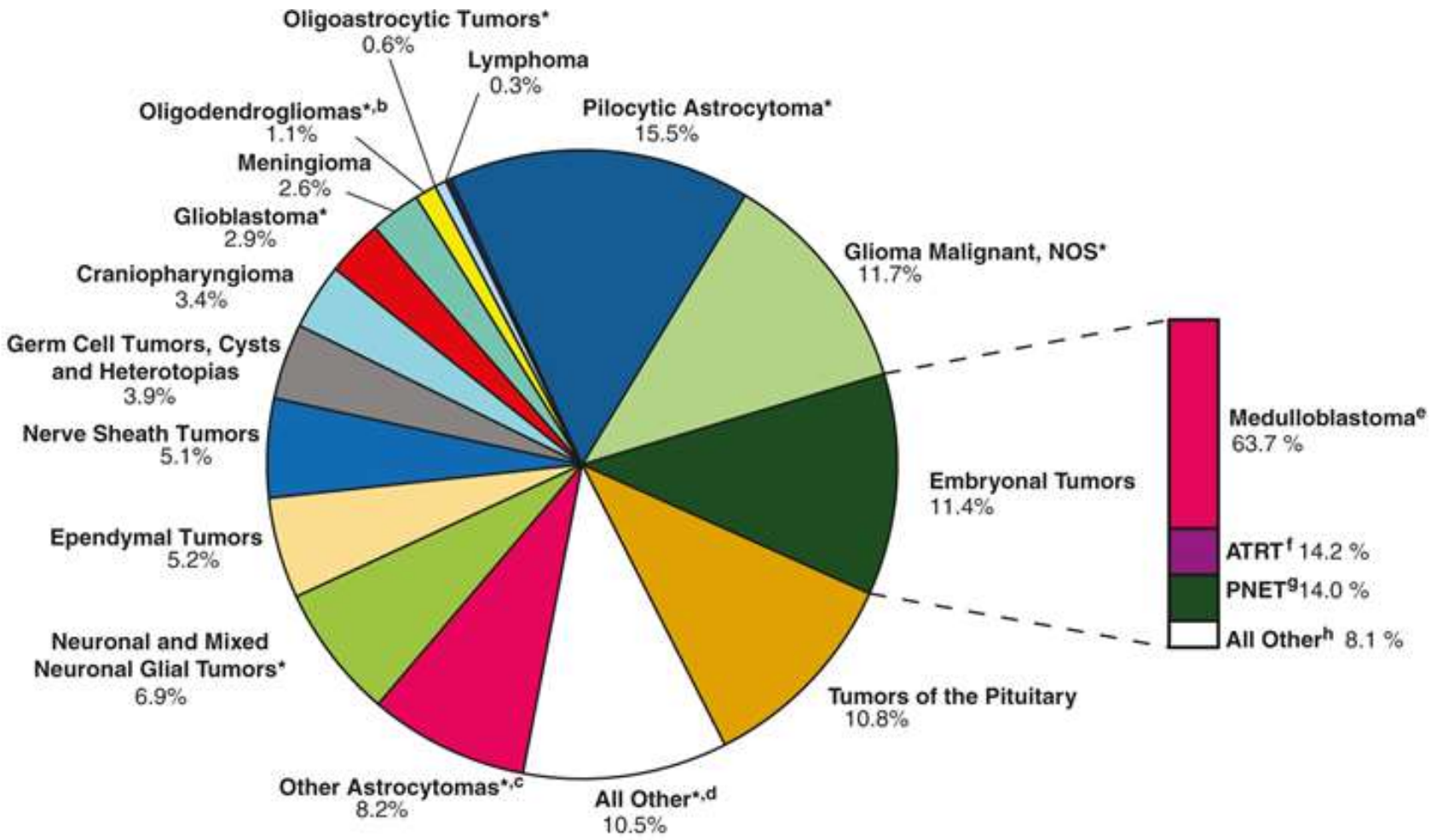
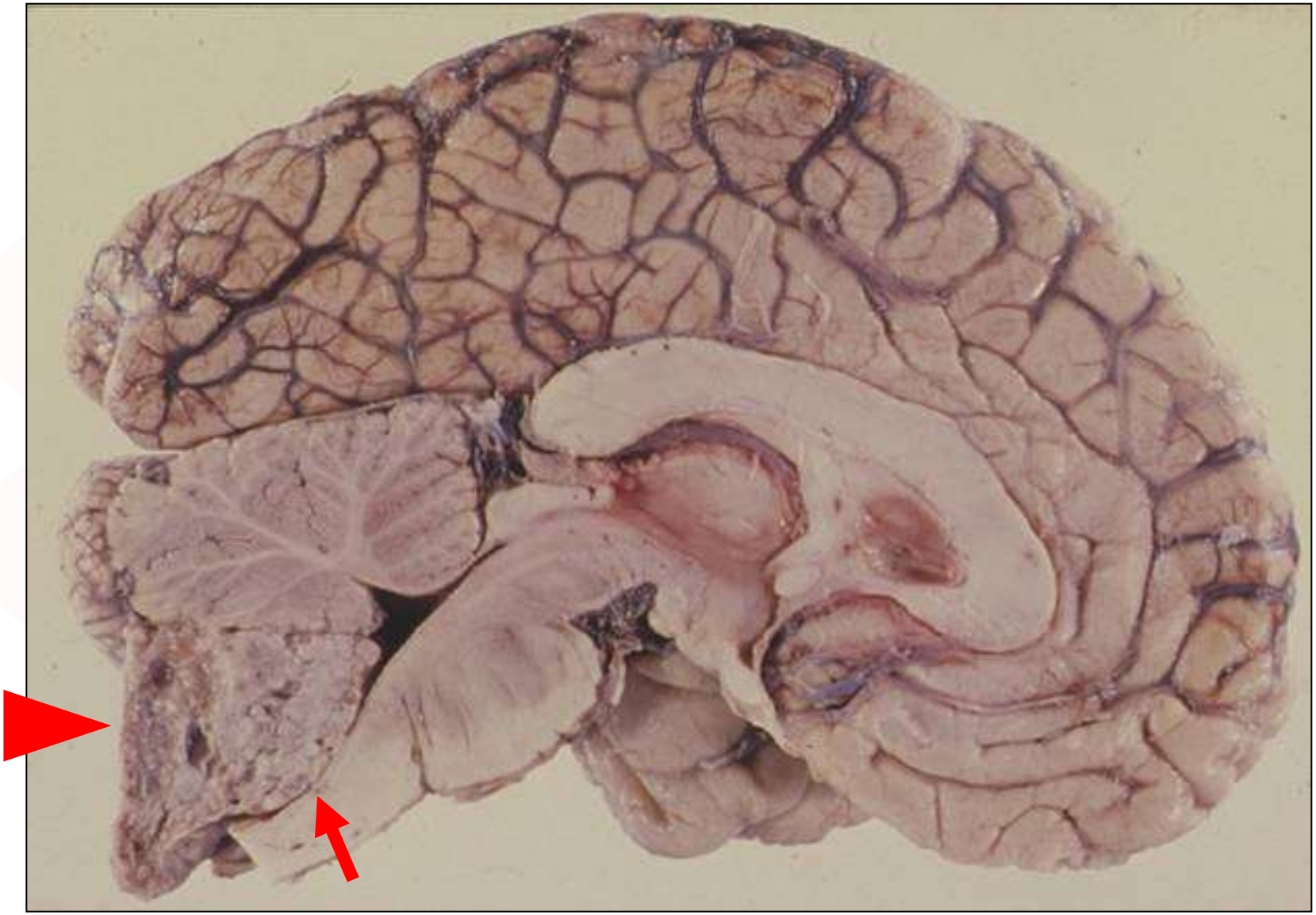


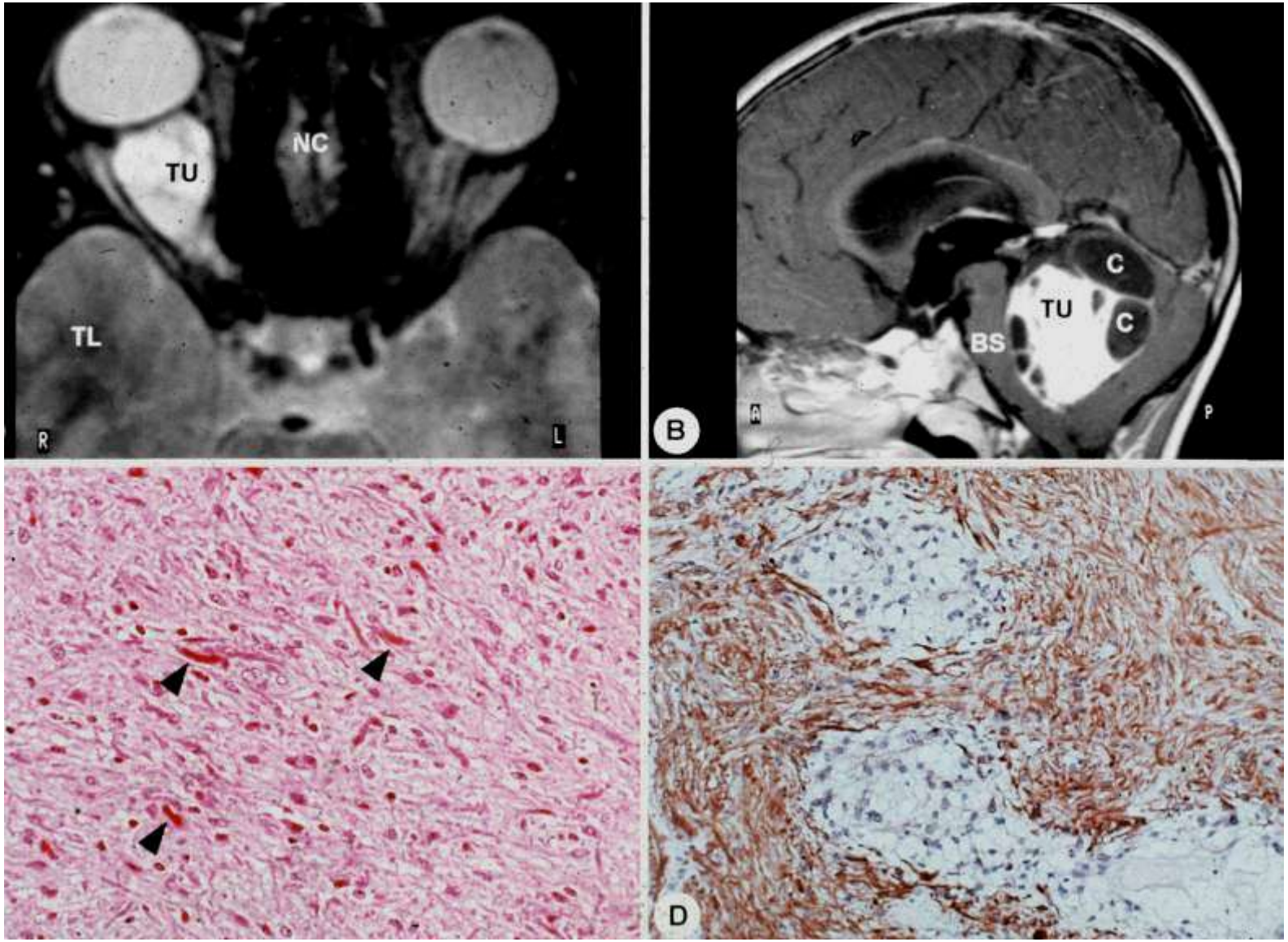
Fig. 17b. Distribution[a] in Children and Adolescents (Age 0-19 years) of Primary Brain and CNS Tumors by CBTRUS Histology Groupings and Histology (N = 23,113), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

Quinn T. Ostrom et al. Neuro Oncol 2015;17:iv1-iv62
CBTRUS Histology Groupings and Histology (N = 356,858), CBTRUS Statistical Report: NPCR and SEER, 2008-2012.

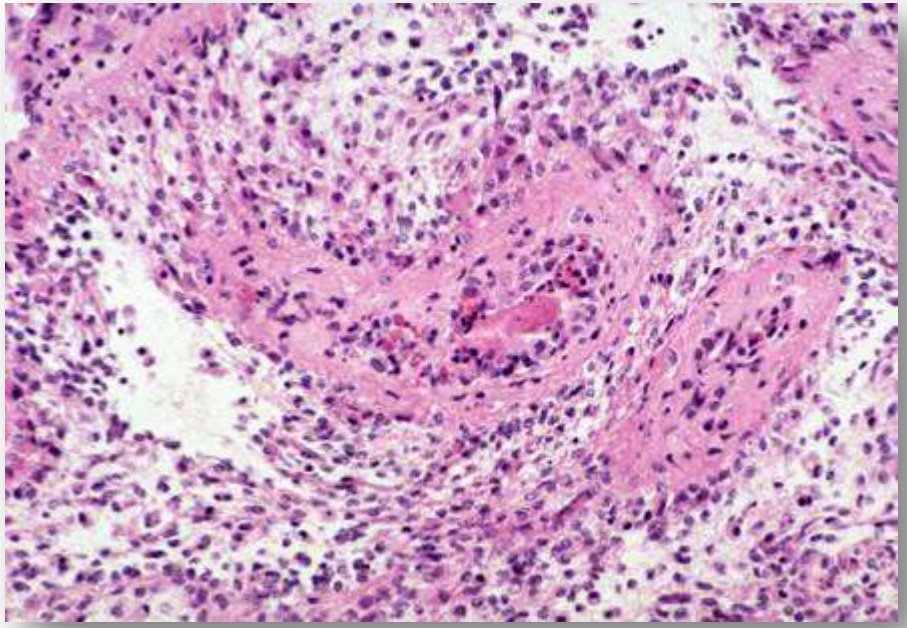
Pilocytic Astrocytoma



Pilocytic Astrocytoma WHO Grade I

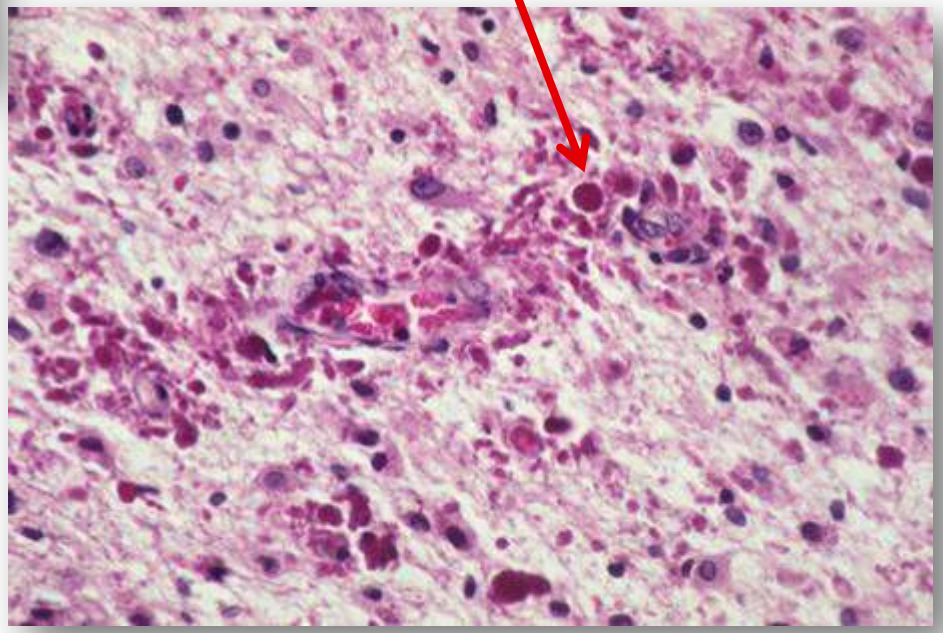


Pilocytic astrocytoma

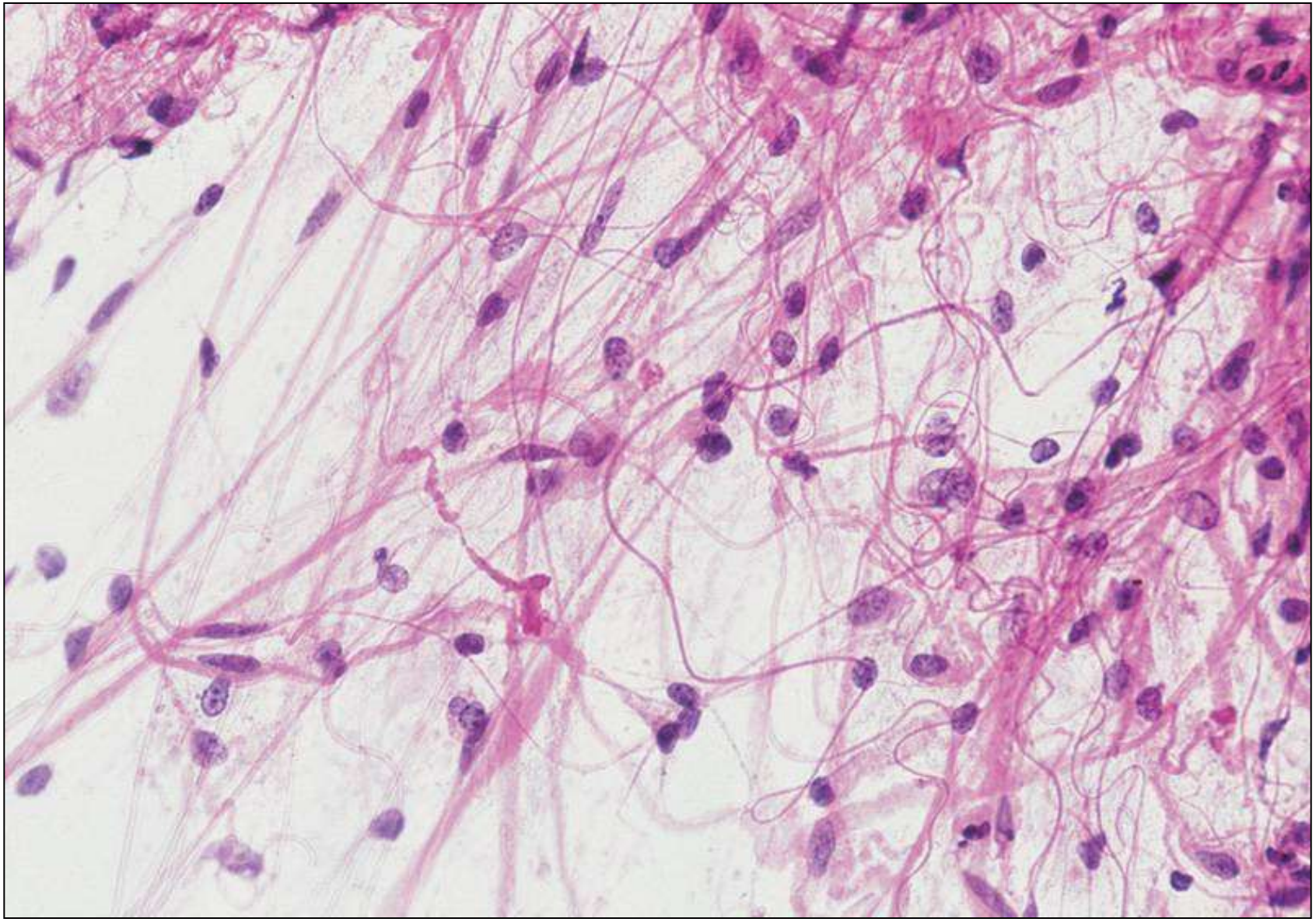


Rosenthal fibers, eosinophilic granular bodies, and microcysts are often present; necrosis and mitoses are rare.

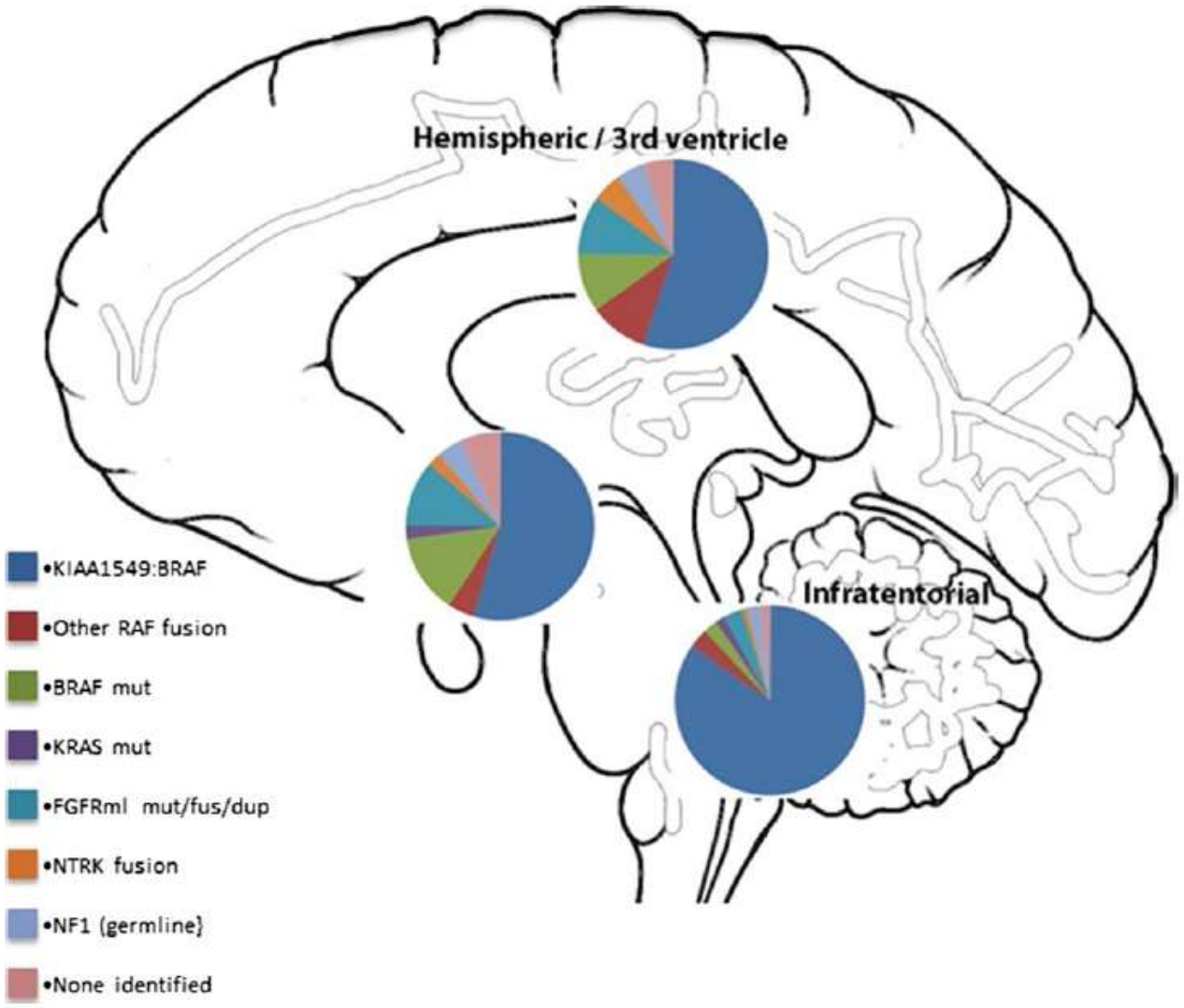
bipolar cells with long, thin "hairlike" processes that are GFAP-positive



Smear preparation – bipolar tumour cells



Pilocytic astrocytoma – genetical alterations



Collins et al., Acta Neuropathol (2015) 129:775–788

2007

CHAPTER 8

Embryonal Tumours

Medulloblastoma (WHO grade IV)
A malignant, invasive embryonal tumour of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation, and an inherent tendency to metastasize via CSF pathways.

Central nervous system primitive neuroectodermal tumours (WHO grade IV)
A heterogeneous group of tumours occurring predominantly in children and adolescents. They may arise in the cerebral hemispheres, brain stem or spinal cord, and are composed of undifferentiated or poorly differentiated neuroepithelial cells which may display divergent differentiation along neuronal, astrocytic, and ependymal lines. CNS/supratentorial PNET is an embryonal tumour composed of undifferentiated or poorly differentiated neuroepithelial cells. Tumours with only neuronal differentiation are termed cerebral neuroblastomas or, if ganglion cells are also present, cerebral ganglioneuroblastomas. Tumours that recreate features of neural tube formation are termed medulloepitheliomas. Tumours with ependymoblastic rosettes are termed ependymoblastomas. Features common to all CNS PNET variants include early onset and aggressive clinical behaviour.

Atypical teratoid/rhabdoid tumour (WHO grade IV)
A highly malignant CNS tumour predominantly manifesting in young children, typically containing rhabdoid cells, often with primitive neuroectodermal cells and with divergent differentiation along epithelial, mesenchymal, neuronal or glial lines; associated with inactivation of the *INI1/hSNF5* gene in virtually all cases.

2016

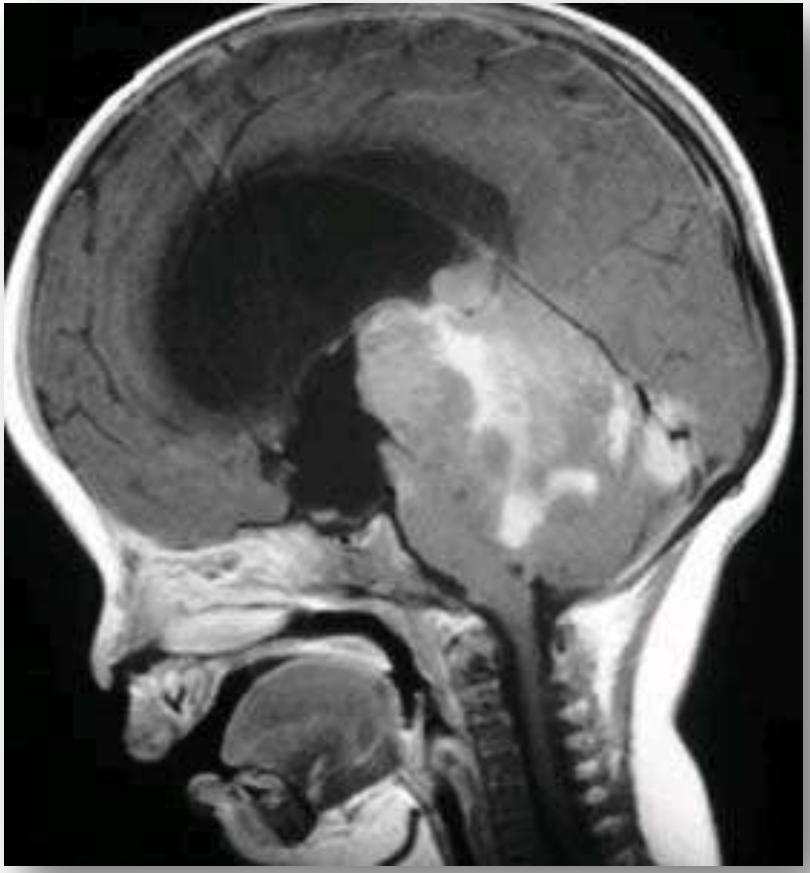
CHAPTER 8

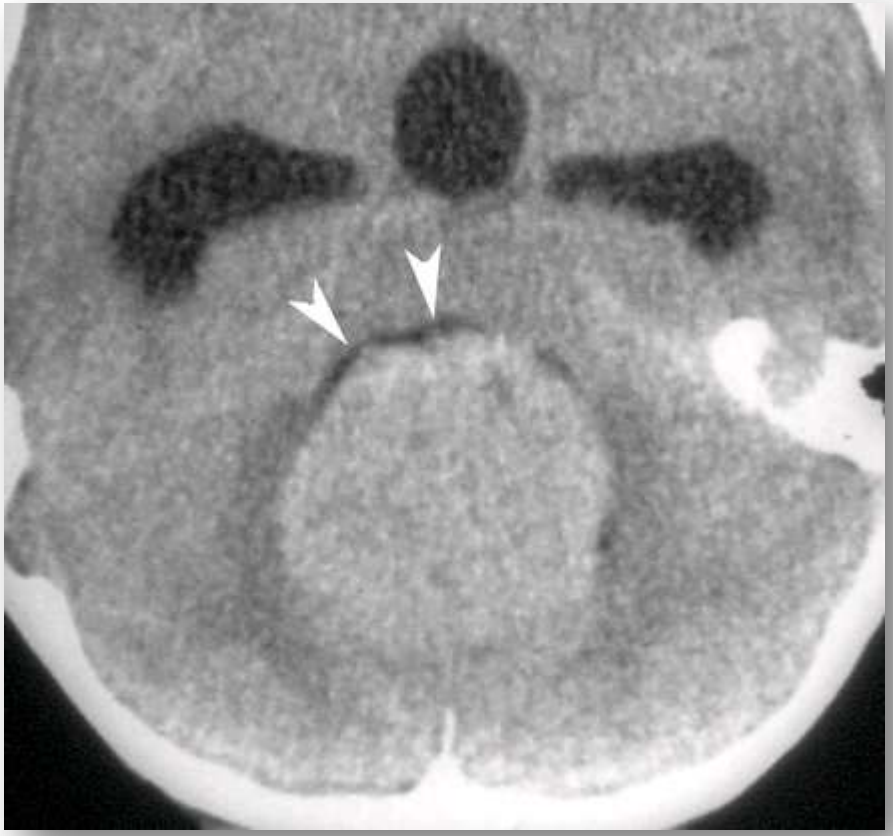
Embryonal tumours

Medulloblastomas, genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined
Medulloblastoma, classic
Desmoplastic/nodular medulloblastoma
Medulloblastoma with extensive nodularity
Large cell / anaplastic medulloblastoma

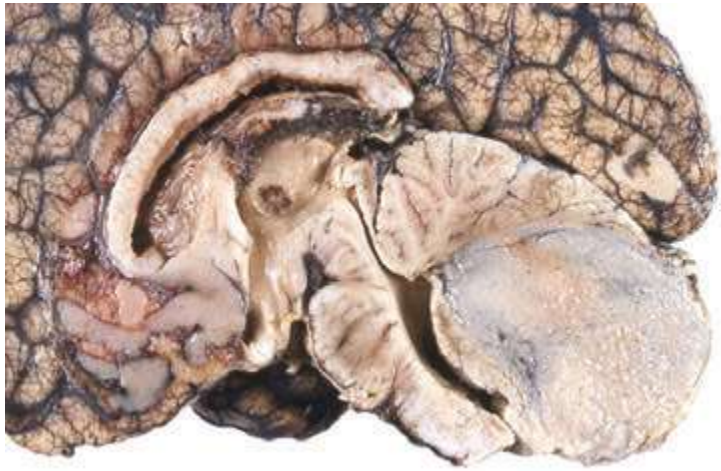
Embryonal tumour with multilayered rosettes, C19MC-altered
Medulloepithelioma
CNS neuroblastoma
CNS ganglioneuroblastoma
CNS embryonal tumour, NOS
Atypical teratoid/rhabdoid tumour

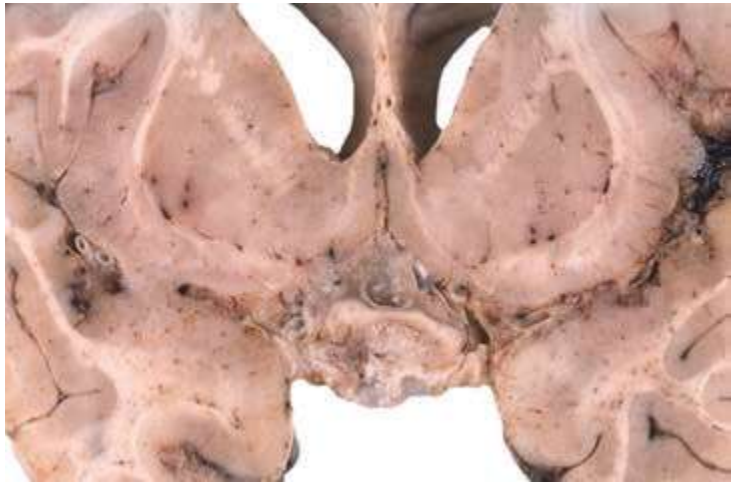
MRI / CT





Medulloblastoma





seeding

Louis et al., 2016. WHO classification of tumours of the central nervous system

Medulloblastoma

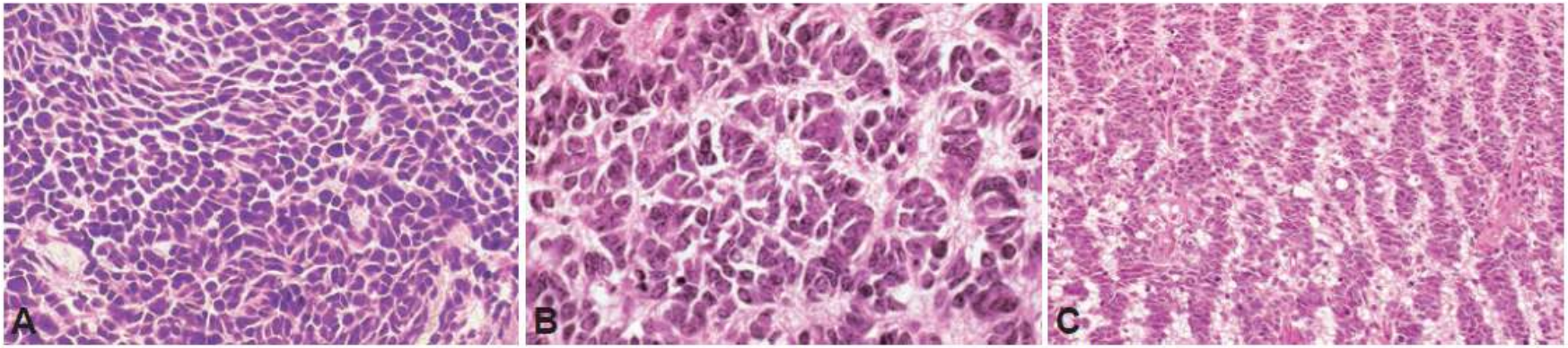
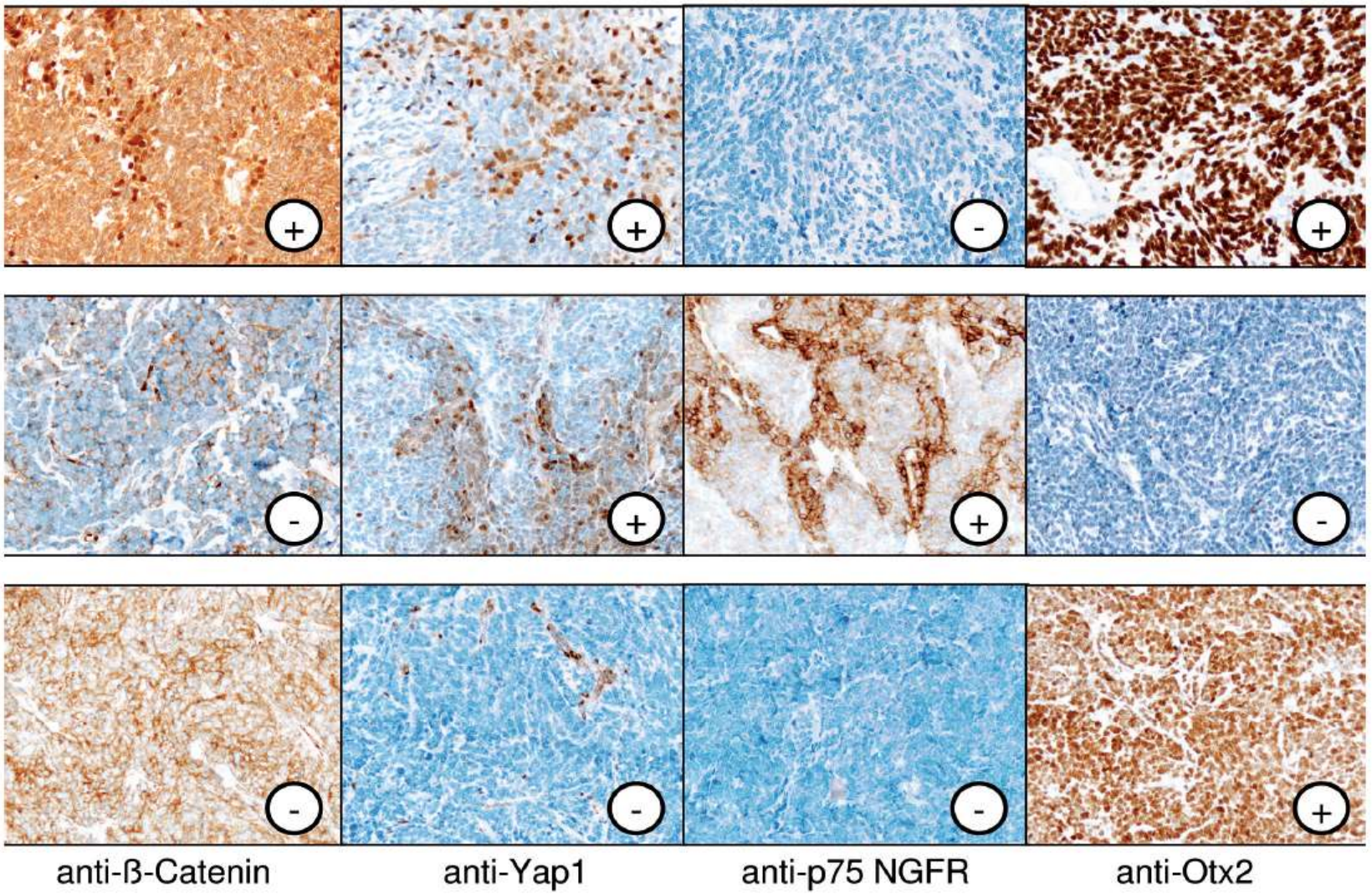


Fig. 8.11 Histopathological features of the classic medulloblastoma. **A** Typical syncytial arrangement of undifferentiated tumour cells. **B** Area with Homer Wright (neuroblastic) rosettes. **C** Arrangement of tumour cells in parallel rows (spongioblastic pattern).

2016 WHO classification of medulloblastomas
Medulloblastomas, genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and *TP53*-mutant
Medulloblastoma, SHH-activated and *TP53*-wildtype
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, group 3
Medulloblastoma, group 4
Medulloblastomas, histologically defined
Medulloblastoma, classic
Desmoplastic/nodular medulloblastoma
Medulloblastoma with extensive nodularity
Large cell / anaplastic medulloblastoma
Medulloblastoma, NOS

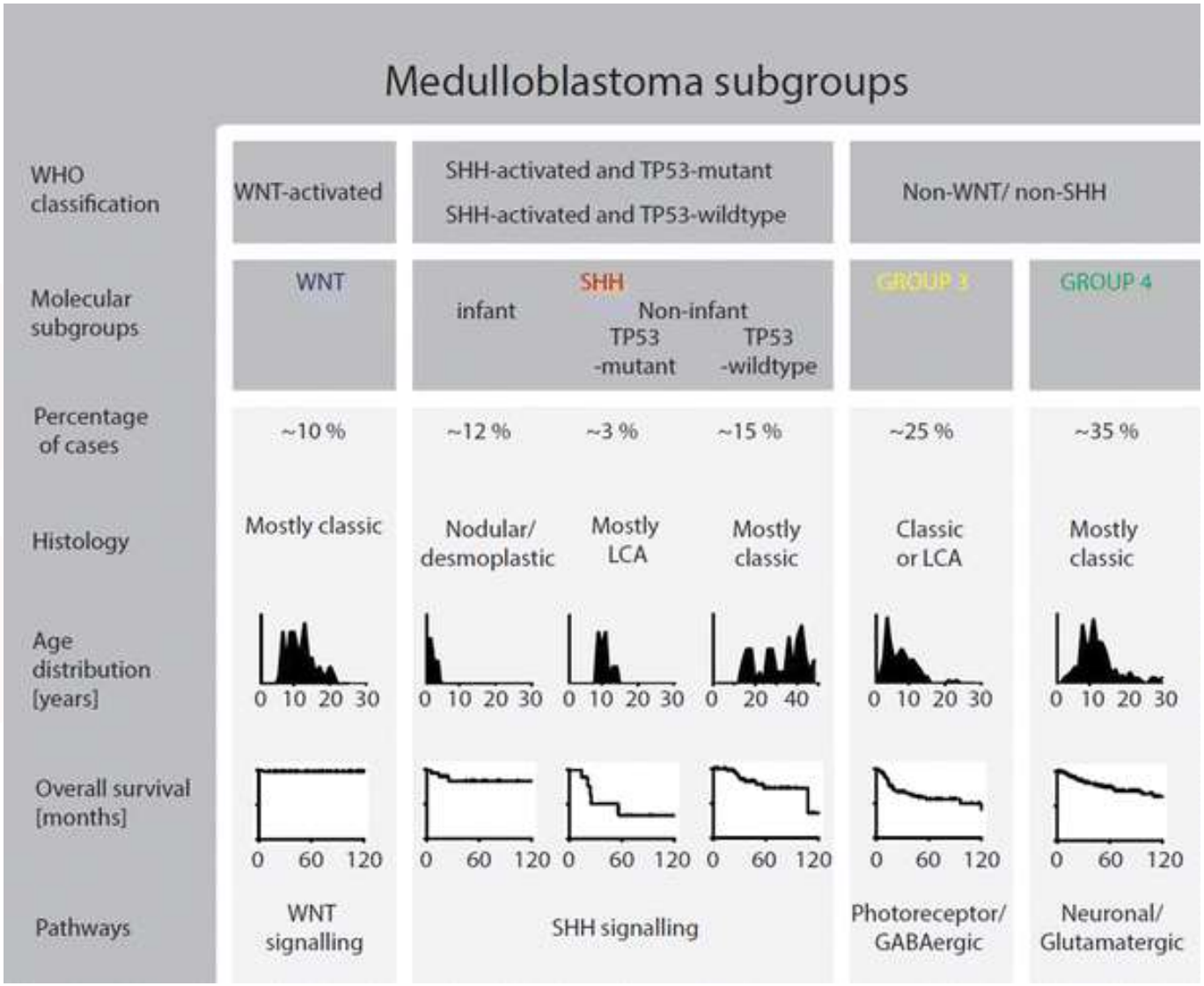
Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic/nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic/nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

Classification of genetically defined MB using IHC



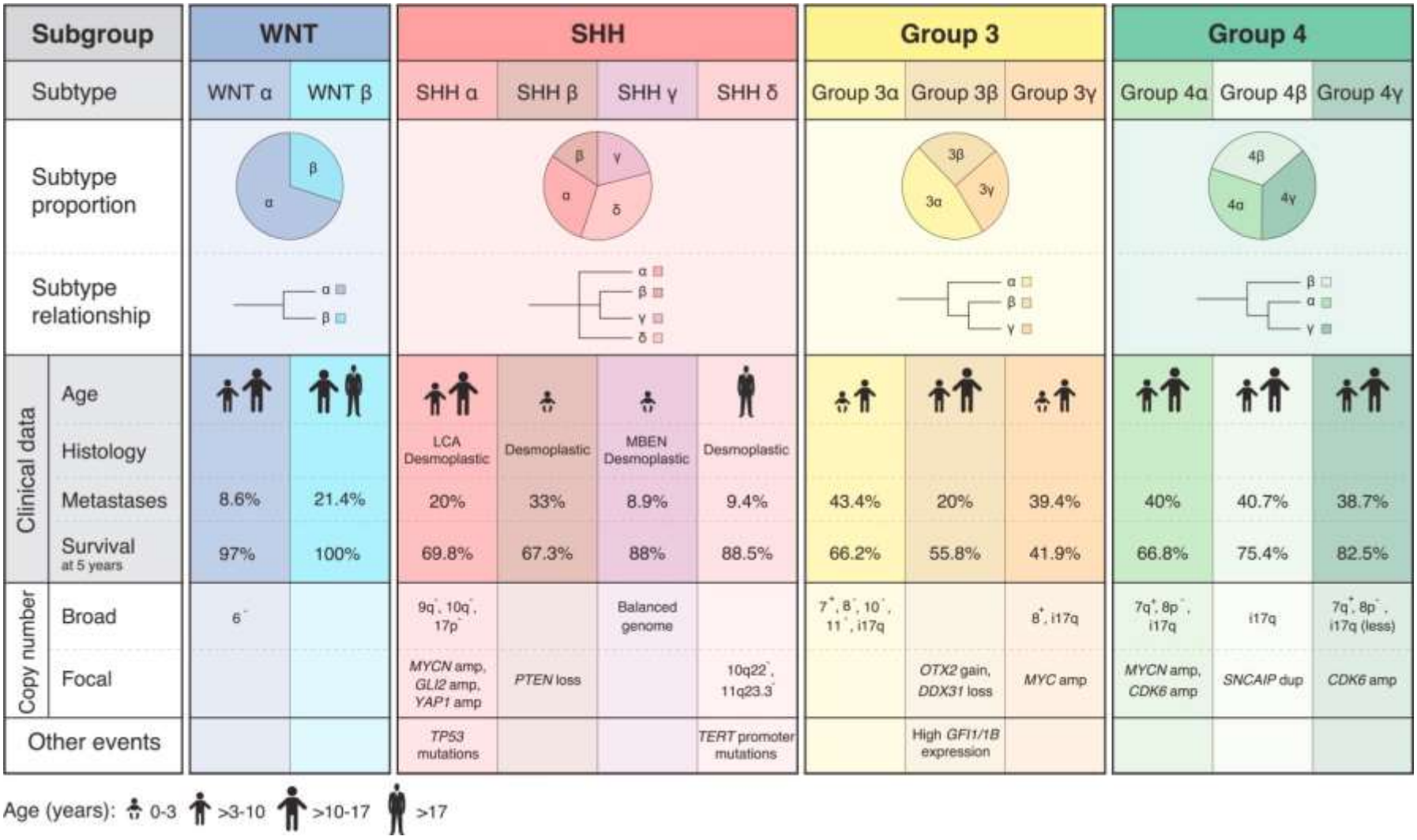
Pietsch & Haberle, Clinical Neuropathology (2016) 35:344-352.

Molecular subgroups of medulloblastomas



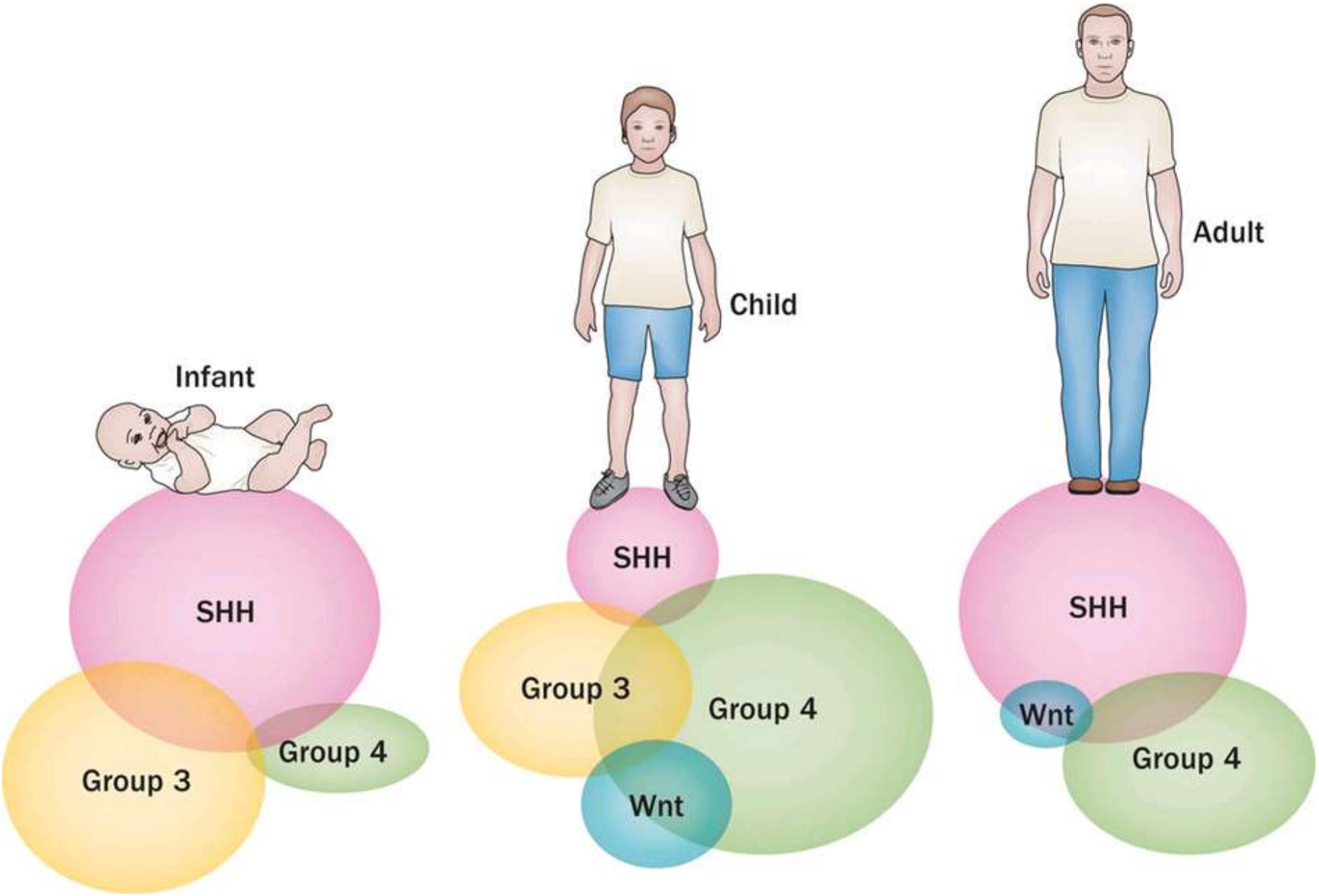
Neumann et al., Medulloblastoma: experimental models and reality. Acta Neuropathol. 2017

Molecular subgroups of medulloblastomas and outcome

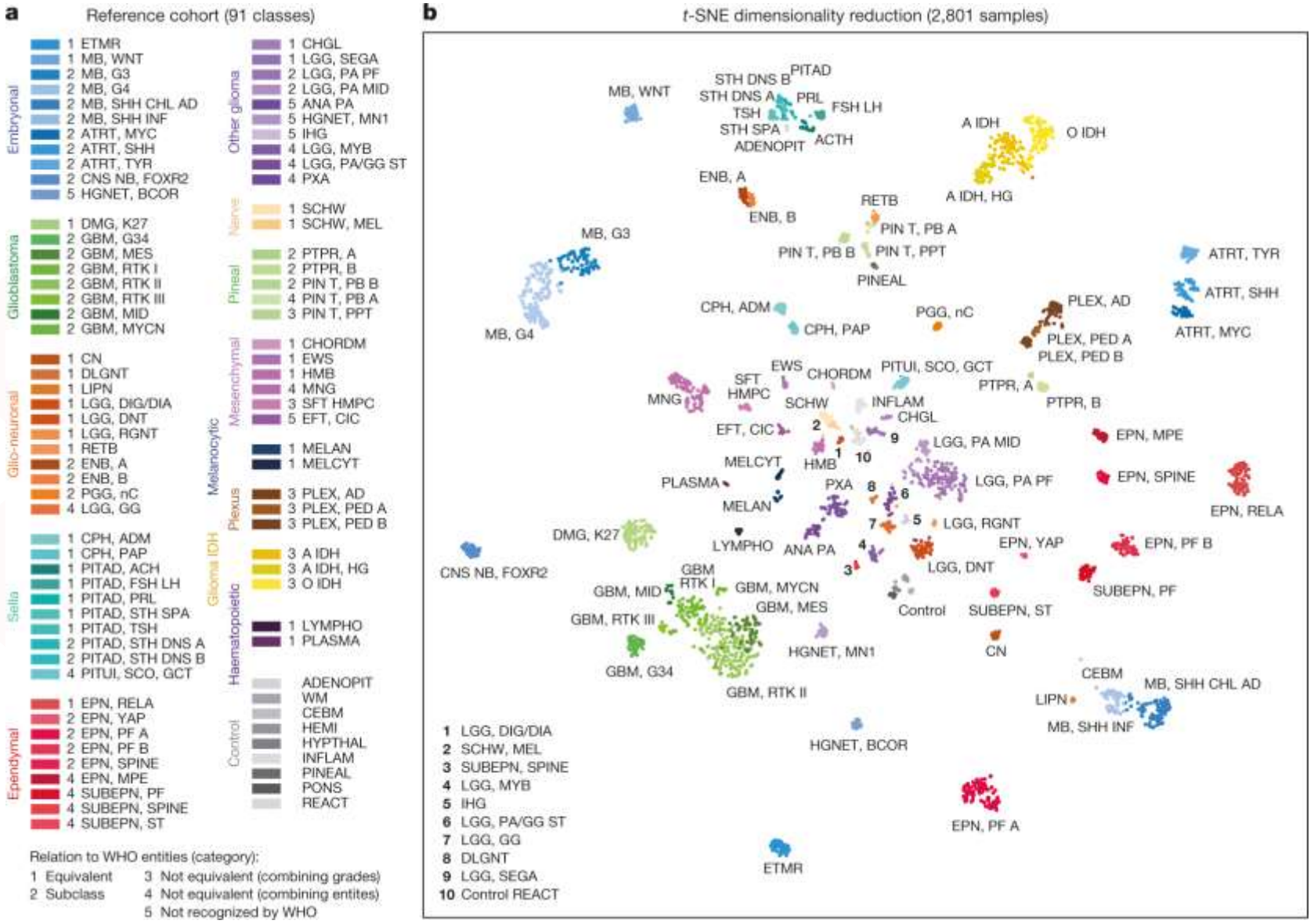


Cavalli et al., Cancer Cell 2017 31, 737-754

Medulloblastomas



DNA-methylation based classification of CNS-tumors



Capper et al, Nature 555:469–474 (22. March 2018)

Methylation profiling report

GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Heidelberg University Hospital

MolecularNeuropathology.org

Supplier information

Sample identifier:	**Sample 1**
Sentrix ID:	**3999078080_R05C02**
Material type:	**FFPE DNA**
Gender:	**male**
Supplier diagnosis:	**Glioblastoma (WHO grade IV)**

Automatic prediction		
Array type:	**450k**	
Material type:	**FFPE DNA**	✔
Gender:	**male**	✔

Legend: ✔ OK ! Supplier information or prediction not available ✘ Warning, missmatch of prediction and supplier information

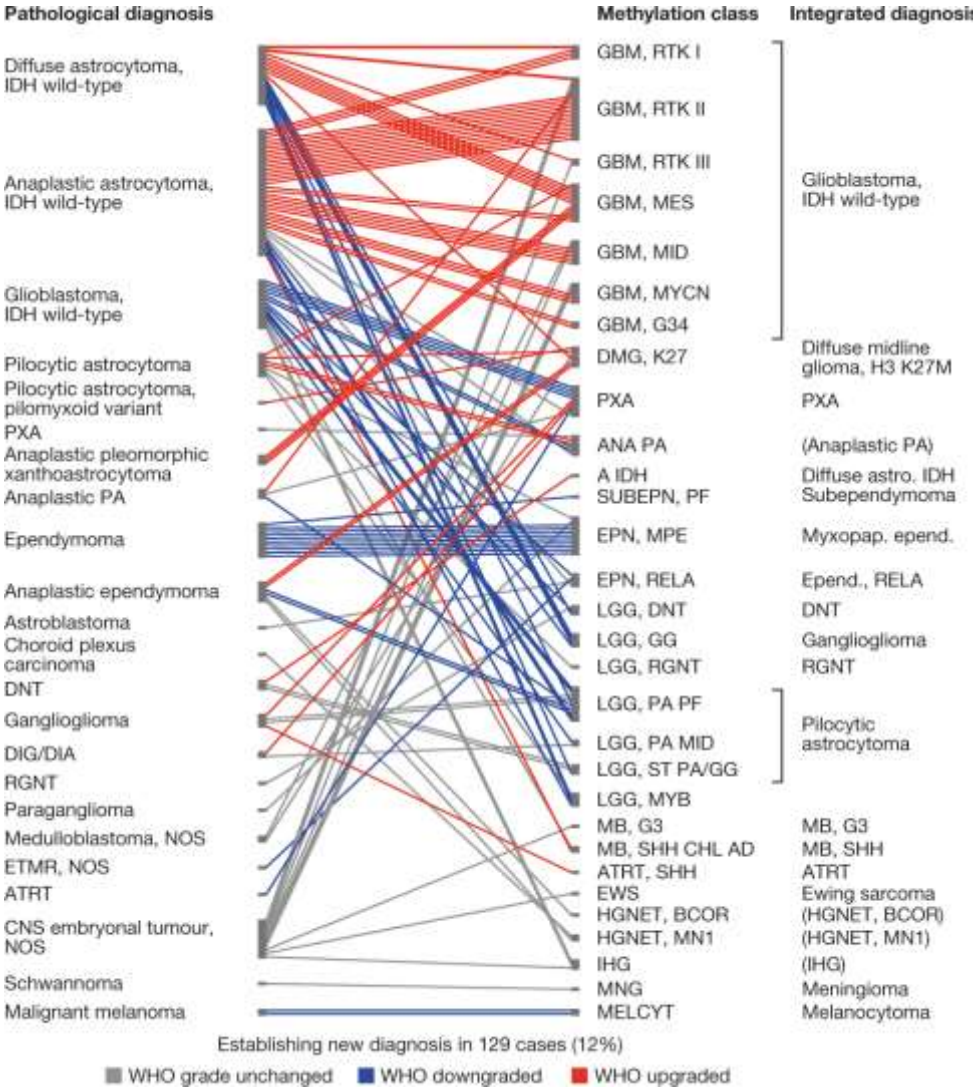
Brain tumor methylation classifier results (v11b2)

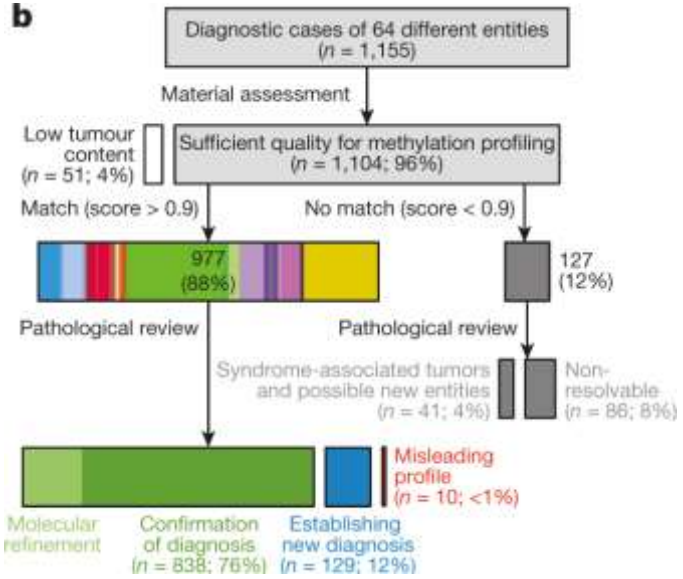
Methylation classes (MCs with score >= 0.3)	**Calibrated score**	**Interpretation**	
methylation class family Glioblastoma, IDH wildtype	0.99	match	✔
MC family members with score >= 0.1			
methylation class glioblastoma, IDH wildtype, subtype RTK II	0.78	match	●
methylation class glioblastoma, IDH wildtype, subtype RTK I	0.18		

Legend: ✔ Match (score >= 0.9) ✘ No match (score < 0.9): possibly still relevant for low tumor content and low DNA quality cases. ● Match to MC family member (score >= 0.5)

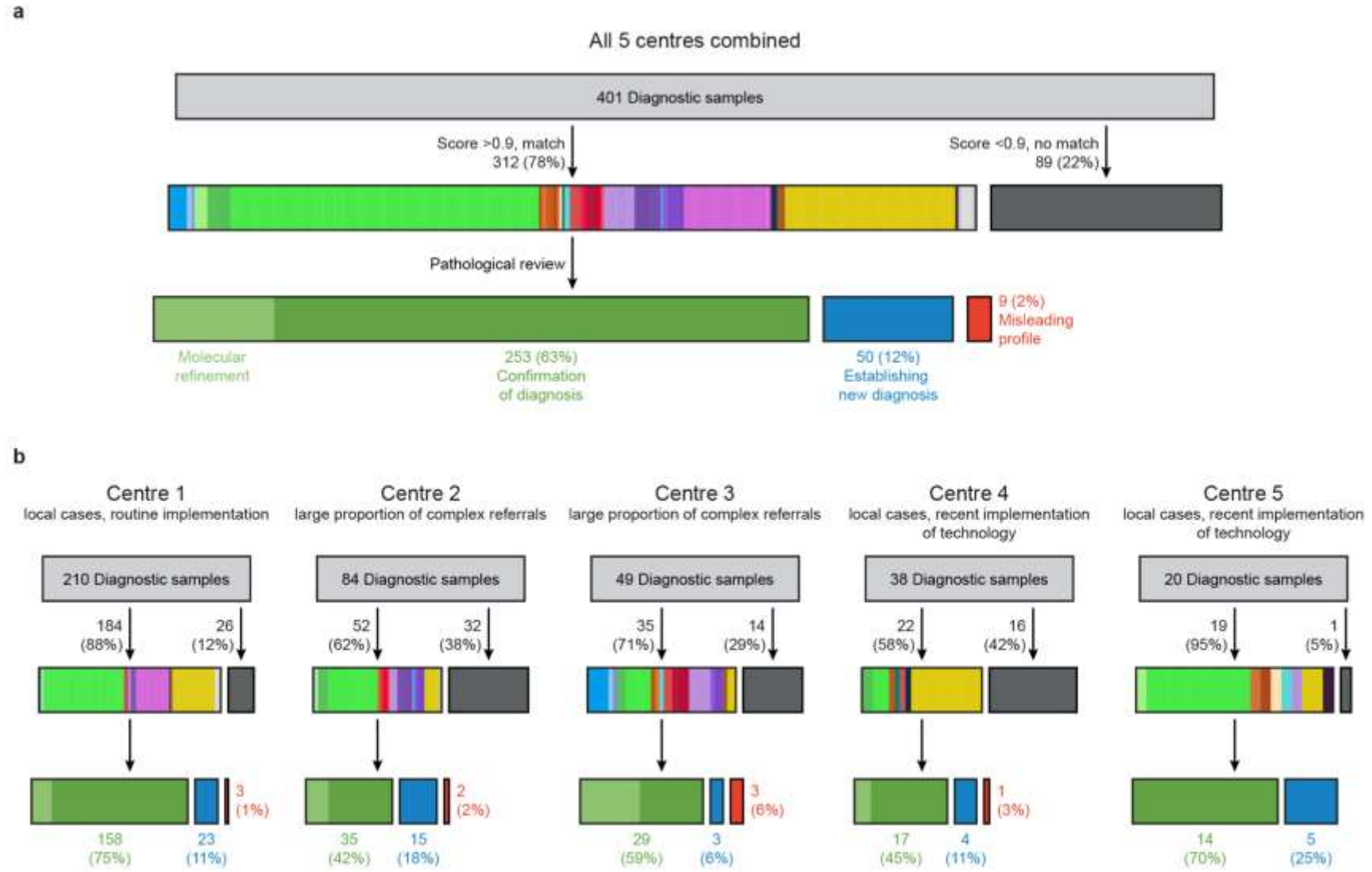
ARTICLE
doi:10.1038/nature26000

DNA methylation–based classification of central nervous system tumours



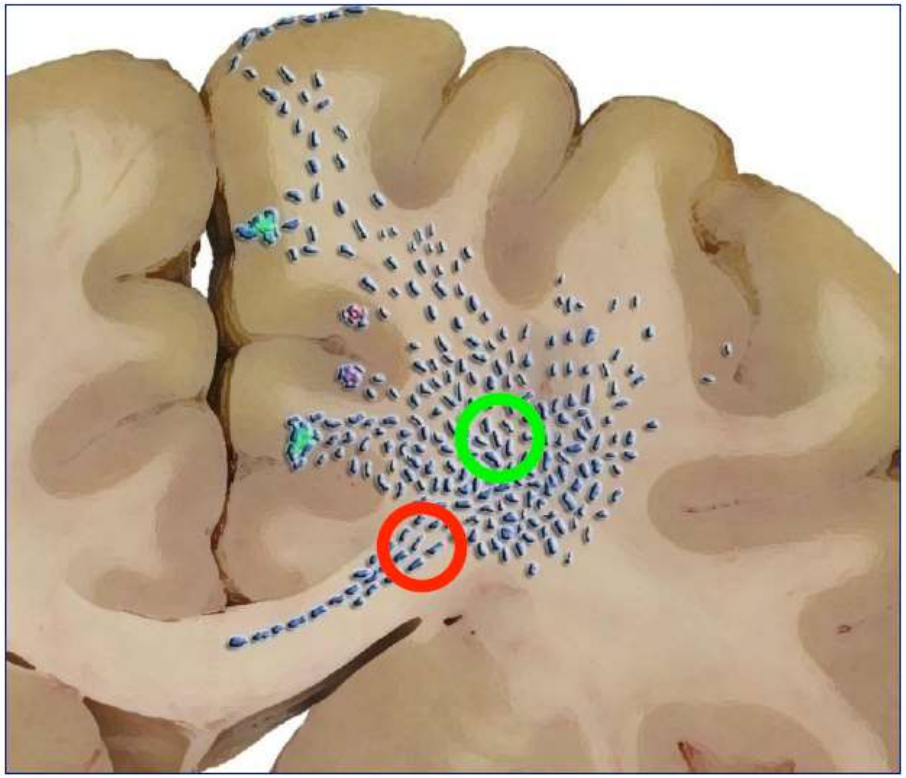


Capper et al, Nature 2018



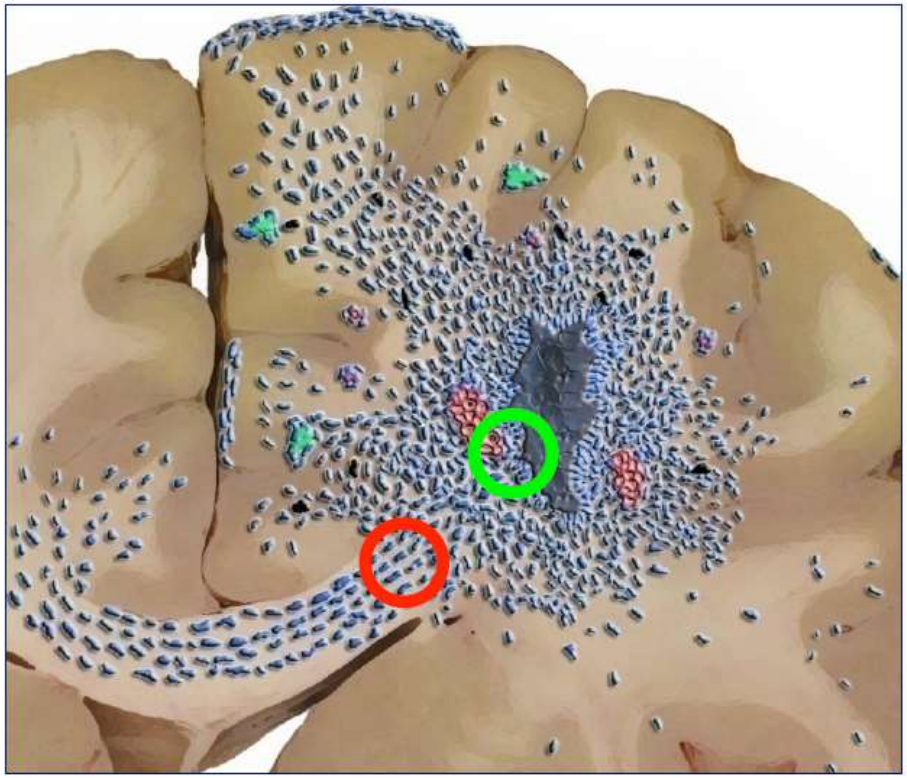
Extended Data Figure 6 | Diagnostic utility of the DNA methylation-based classifier, assessed at different centres. a, Implementation of the DNA methylation classifier by five external centres. In total, 401 independent biological samples were analysed. 78% matched to an established class with a cut-off score of ≥0.9 (class colours as in Fig. 1a). A new diagnosis was established in 12% of cases. **b**, Depiction of individual centre results, illustrating the different composition of samples included in the analysis, variation in the rate of non-matching cases, and of cases for which a new diagnosis was established. Case-by-case details are provided in Supplementary Table 6.

Cave-sampling error!



low grade diffuse glioma

- low grade diffuse astrocytoma (= true)
- low grade diffuse astrocytoma (= true)



high grade diffuse glioma

- glioblastoma (= true)
- low grade diffuse astrocytoma (= false!)

Claes et al., Acta Neuropathol (2007)114:443-458

Acta Neuropathologica (2018) 136:805–810
https://doi.org/10.1007/s00401-018-1913-0

CORRESPONDENCE

cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Guido Reifenberger[6] · Brent A. Orr[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Michael Weller[14]

Received: 1 August 2018 / Revised: 19 September 2018 / Accepted: 19 September 2018

We reached consensus that the following were the minimal molecular criteria for identifying an IDH-wildtype diffuse astrocytic glioma that, despite appearing histologically as a WHO grade II or III neoplasm, would follow an aggressive clinical course more closely resembling that of an IDH-wildtype glioblastoma:

1. *EGFR* amplification

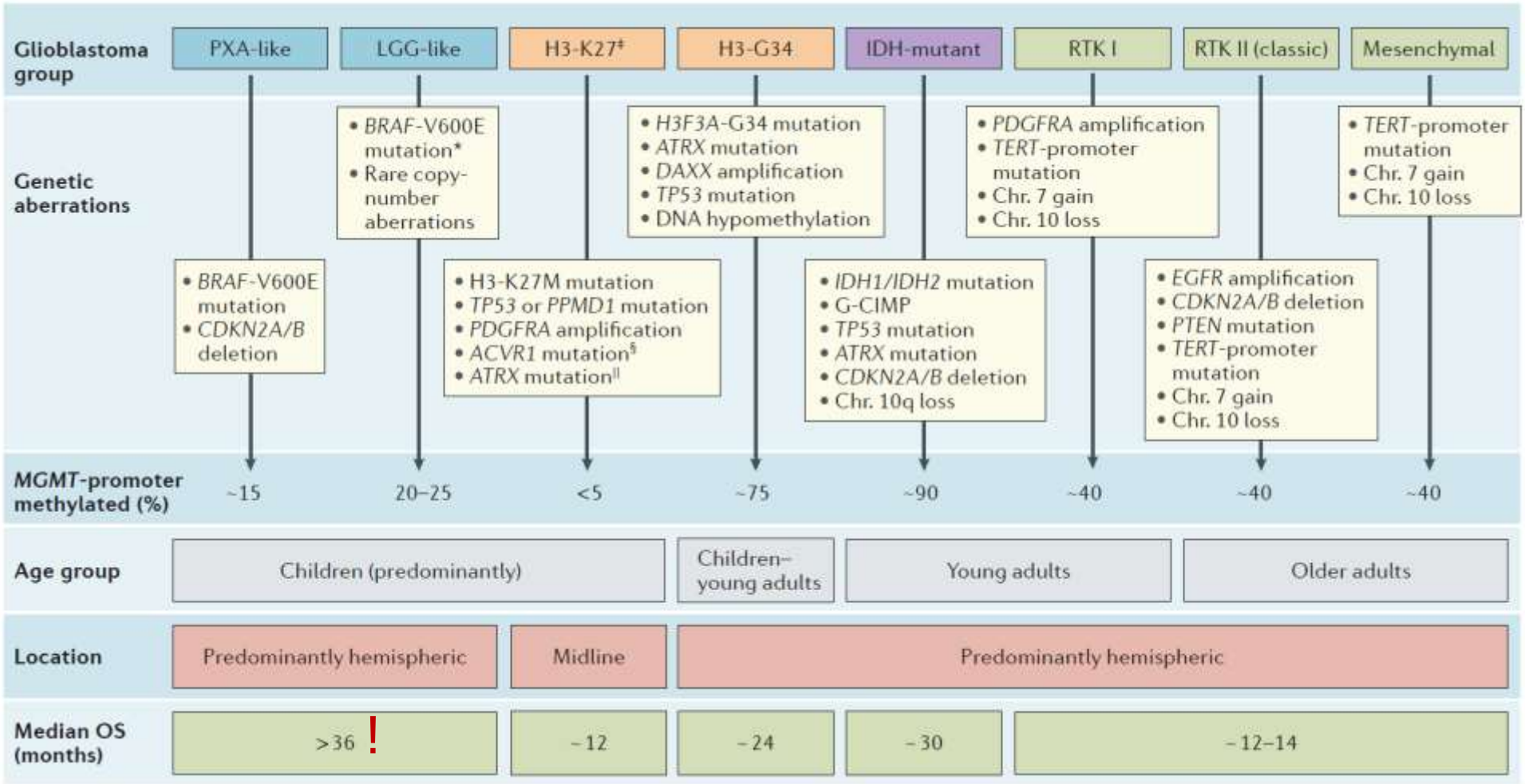
   OR

2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+ 7/− 10)

   OR

3. *TERT* promoter mutation

Molecular subgroups of glioblastomas and outcome



Reifenberger et al., Advances in the molecular genetics of gliomas - implications for classification and therapy. Nat Rev Clin Oncol. 2017 Jul;14(7):434-452.

FINISHED.