Molecular diagnostics in CNS Tumours

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Objectives

- To describe the current landscape of molecular diagnosis in brain tumours, focussing on:
  - Tests that are currently available
  - Tests that alter clinical management or prognosis
  - The incorporation of the tests in to more traditional pathology


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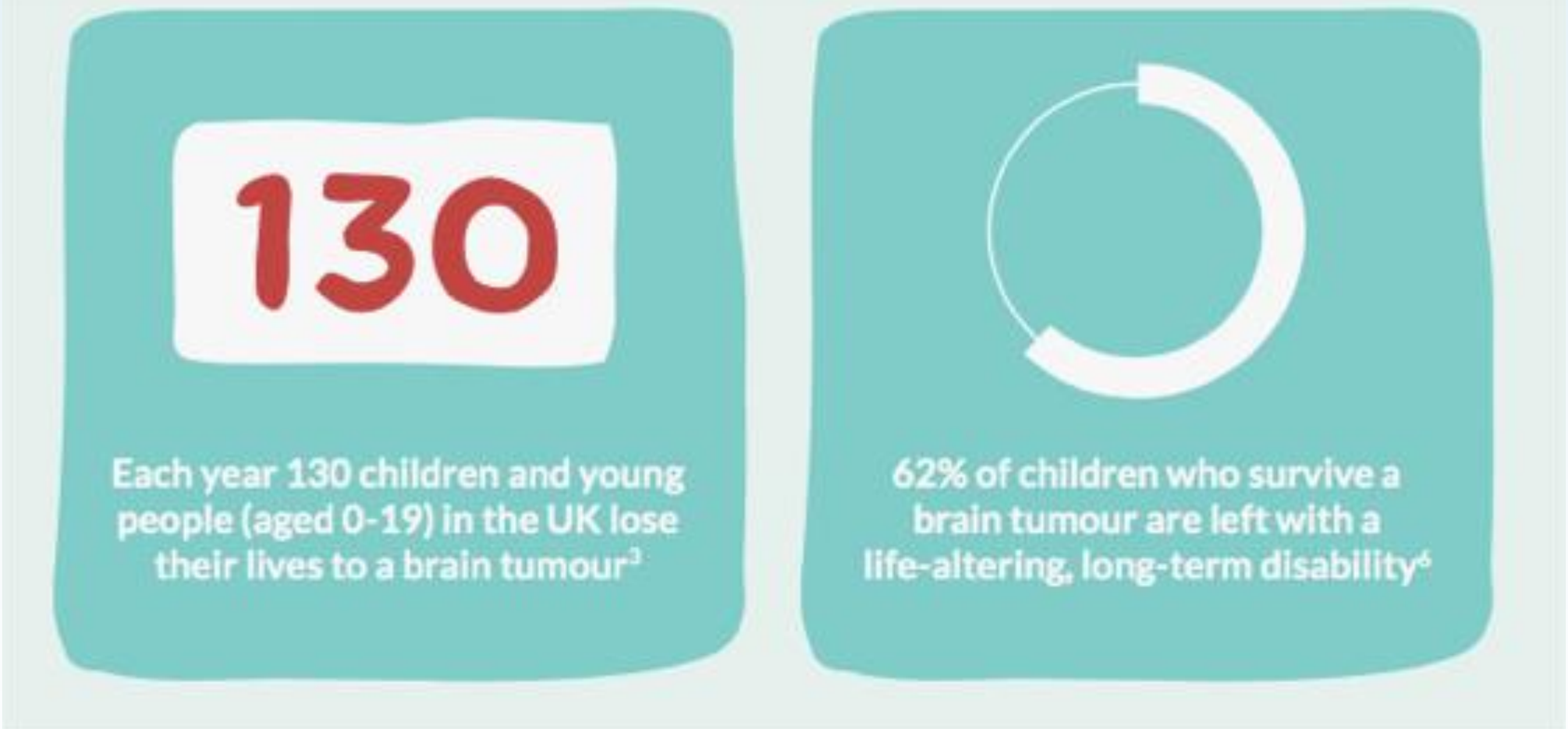
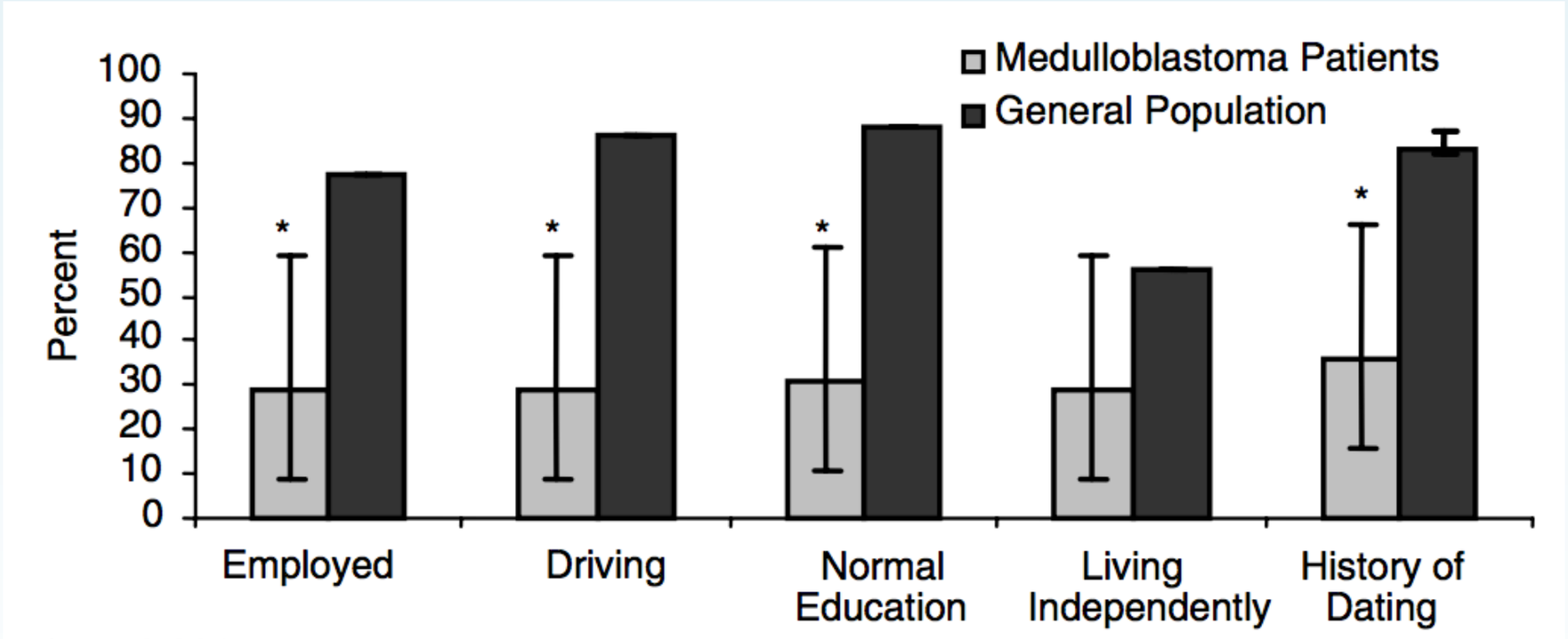
HOSPITAL FOR CHILDREN

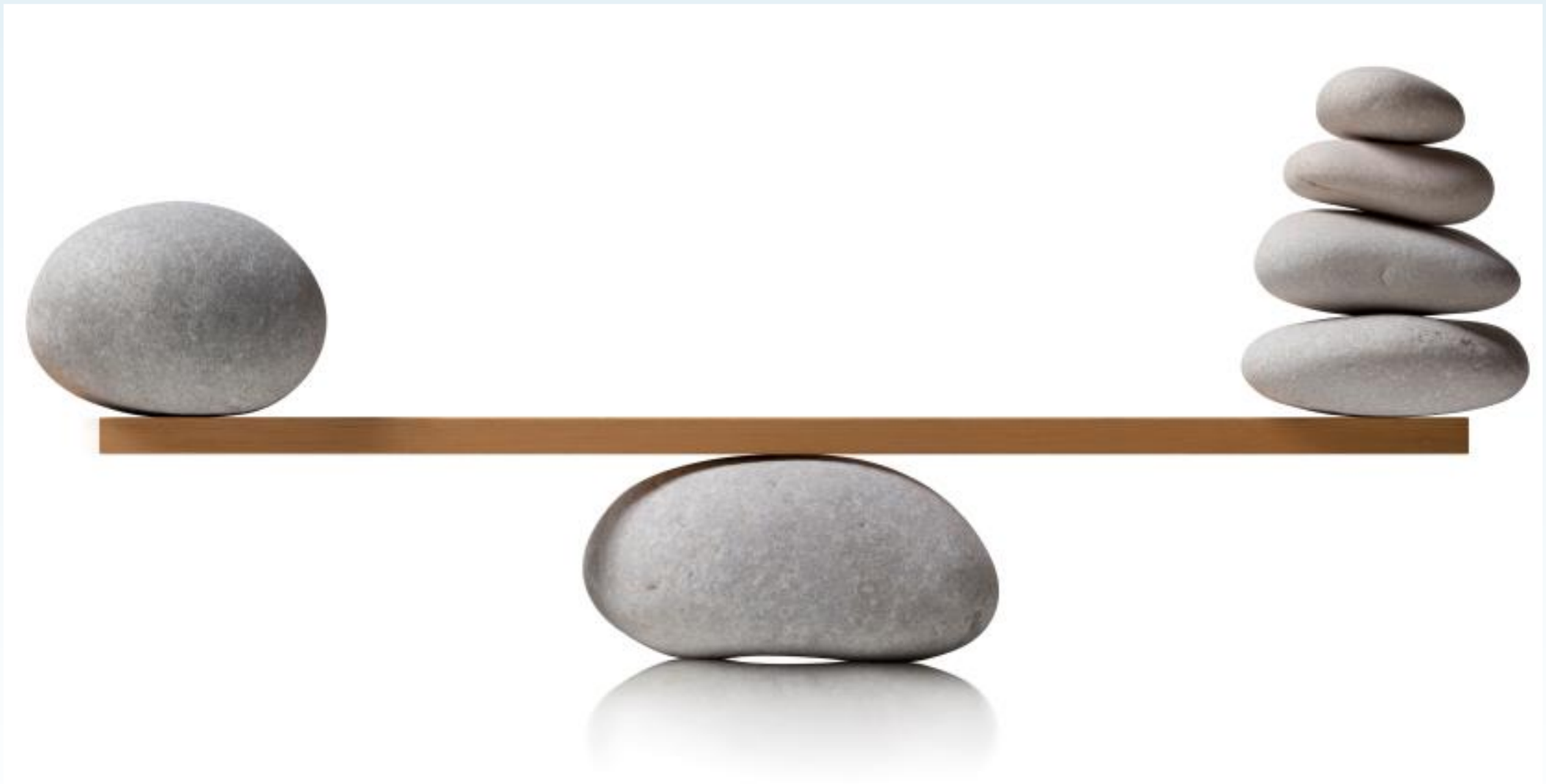
What distinguishes neuropathology for children?


130
Each year 130 children and young people (aged 0-19) in the UK lose their lives to a brain tumour[3]
62% of children who survive a brain tumour are left with a life-altering, long-term disability[6]

Survival is at the cost of long-term disability



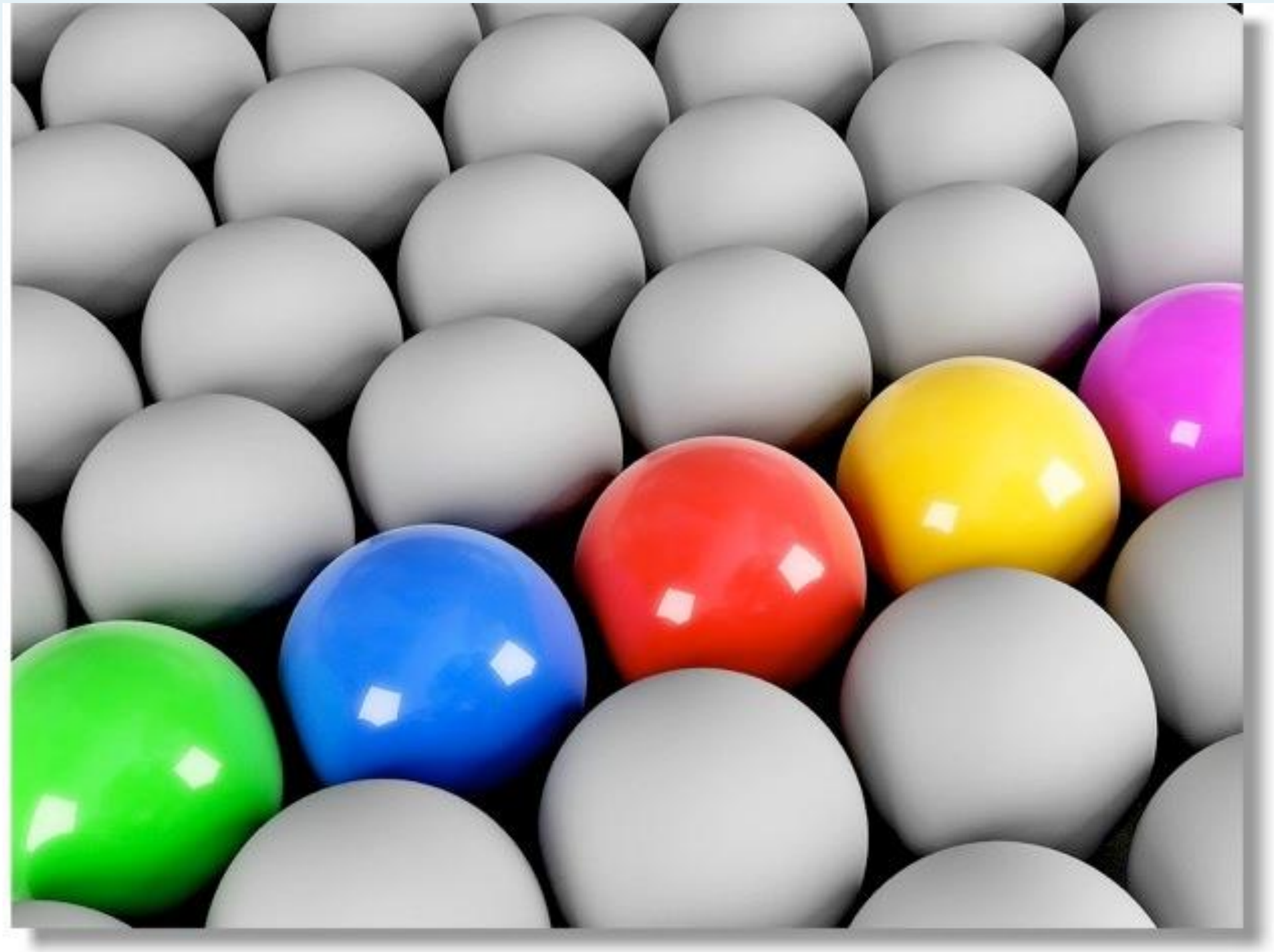
* p = 0.001



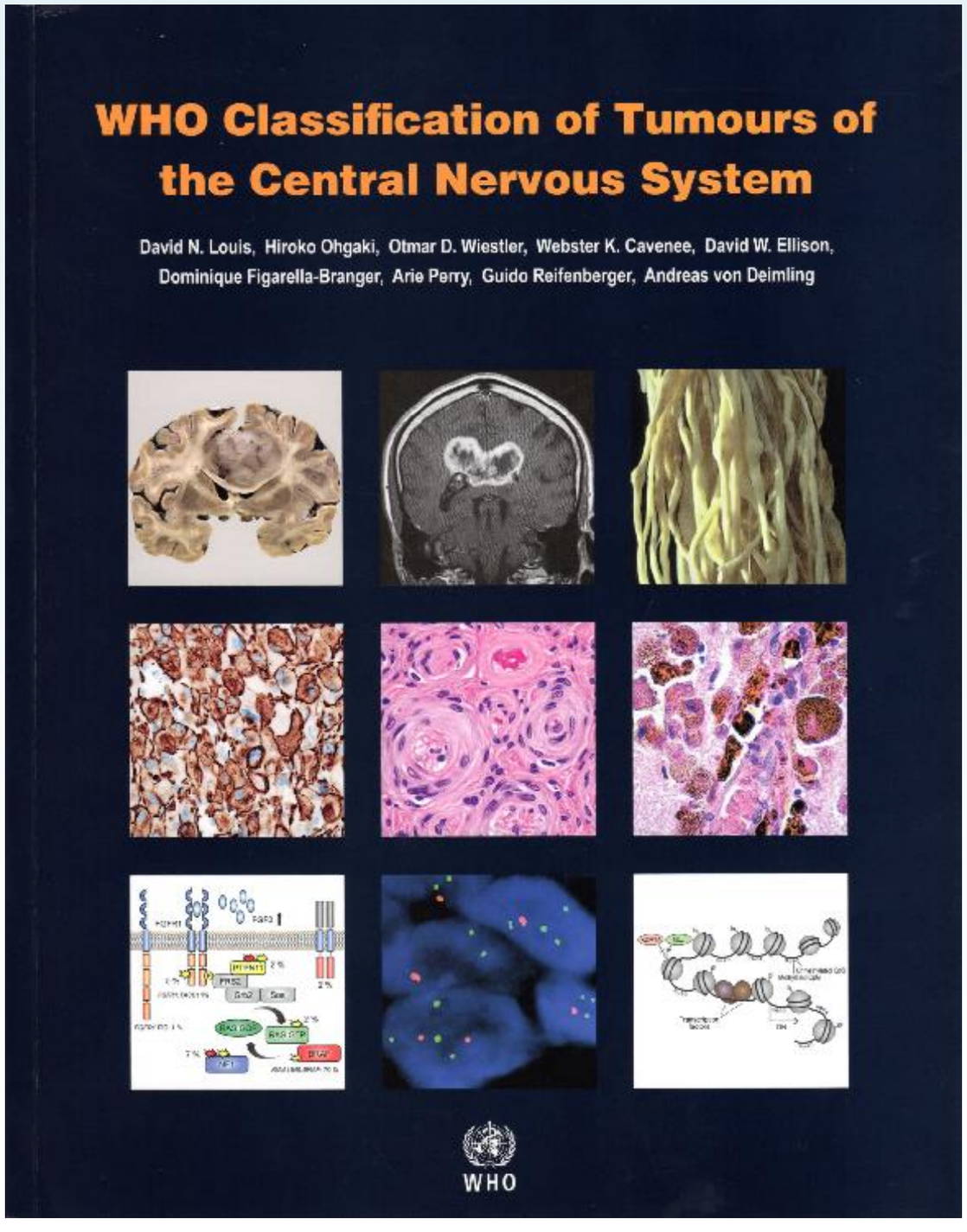
Late effects

Long term cure

The challenges of the numbers



The WHO classification



Molecularly defined tumours

Medulloblastoma, SHH-activated and *TP53*-mutant

Eberhart C.G.
Giangaspero F.
Ellison D.W.
Haapasalo H.
Pietsch T.
Wiestler O.D.
Pfister S.

Definition

A poorly differentiated embryonal tumour of the cerebellum with evidence of SHH pathway activation and either germline or somatic TP53 *mutation*

In large series of tumours, SHH-activated medulloblastomas tend to have similar transcriptome, methylome, and microRNA profiles. SHH pathway activation in *TP53*-mutant tumours is associated with amplification of *GLI2*, *MYCN*, or *SHH*. Mutations in *PTCH1*, *SUFU*, and *SMO* are generally absent. Large cell / anaplastic morphology and chromosome 17p loss are also common in SHH-activated and *TP53*-mutant tumours. Patterns of chromosome shattering known as chromothripsis are often present.

SHH-activated tumours account for approximately 30% of all medulloblastomas and originate from rhombic lip–derived cerebellar granule neuron precursors, the proliferation of which is dependent on SHH signalling activity. SHH-activated and *TP53*-mutant medulloblastomas are rare and generally found in children aged 4–17 years. Clinical outcomes in patients with SHH-activated and *TP53*-mutant tumours are very poor.

ICD-O code 9476/3

Grading

Like all medulloblastomas, SHH-activated and *TP53*-mutant medulloblastoma corresponds histologically to WHO grade IV.

Epidemiology

SEER data from 1973–2007 suggest medulloblastoma incidence rates of 6.0 cases per 1 million children aged 1–9 years and 0.6 cases per 1 million adults aged > 19 years {2382}. SHH-activated medulloblastomas in general show a bimodal age distribution, being most common in infants and young adults, with a male-to-female ratio of approximately 1.5:1 {1804}. In contrast, SHH-activated and *TP53*-mutant tumours in particular are generally found in children aged 4–17 years {1333}. In one study that included 133 SHH-activated medulloblastomas, 28 patients (21%) had a *TP53* mutation, and the median age of these patients was approximately 15 years {2870}.

Localization

SHH-activated medulloblastomas were proposed in one study report to predominantly involve the lateral cerebellum, due to their origin from granule neuron precursors {831}. A subsequent study that included 17 SHH-activated medulloblastomas found that although 9 of those tumours were hemispheric, the other 8 were centred in, or significantly involved, the midline vermis {2534}. The localization of SHH-activated tumours may be age-dependent. A third study found that in older children and young adults, SHH-activated medulloblastomas grow predominantly in the rostral cerebellar hemispheres, whereas in infants they more frequently involve the vermis {2716}. Specific data on the localization of SHH-activated and *TP53*-mutant medulloblastoma are not available.

Imaging

On CT and MRI, medulloblastomas present as solid, intensely contrast-enhancing masses. SHH-activated medulloblastomas are most often identified in the lateral hemispheres, but can also involve midline structures {831,2534}. Oedema was relatively common in one imaging series that included 12 desmoplastic/nodular medulloblastomas and 9 medulloblastomas with extensive nodularity {743}. A nodular, so-called grape-like pattern on MRI often characterizes medulloblastoma with extensive nodularity because of the tumour's distinctive and diffuse nodular architecture {820,1744}. Medulloblastomas involving the peripheral cerebellar hemispheres in adults occasionally present as extra-axial lesions

Medulloblastoma, SHH-activated and *TP53*-mutant

Definition

A poorly differentiated embryonal tumour of the cerebellum with evidence of SHH pathway activation and either germline or somatic TP53 *mutation*

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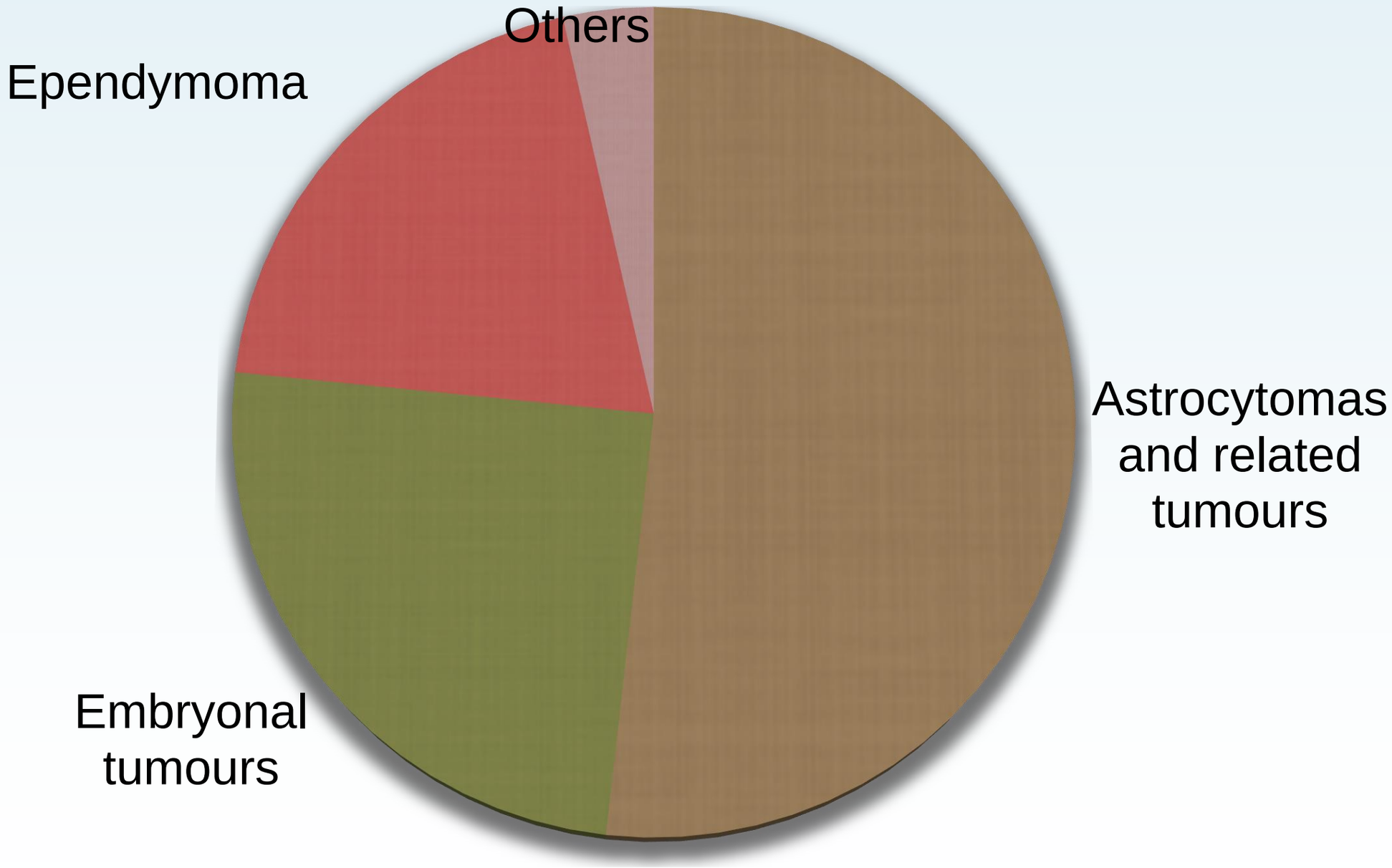
Integrated Diagnosis

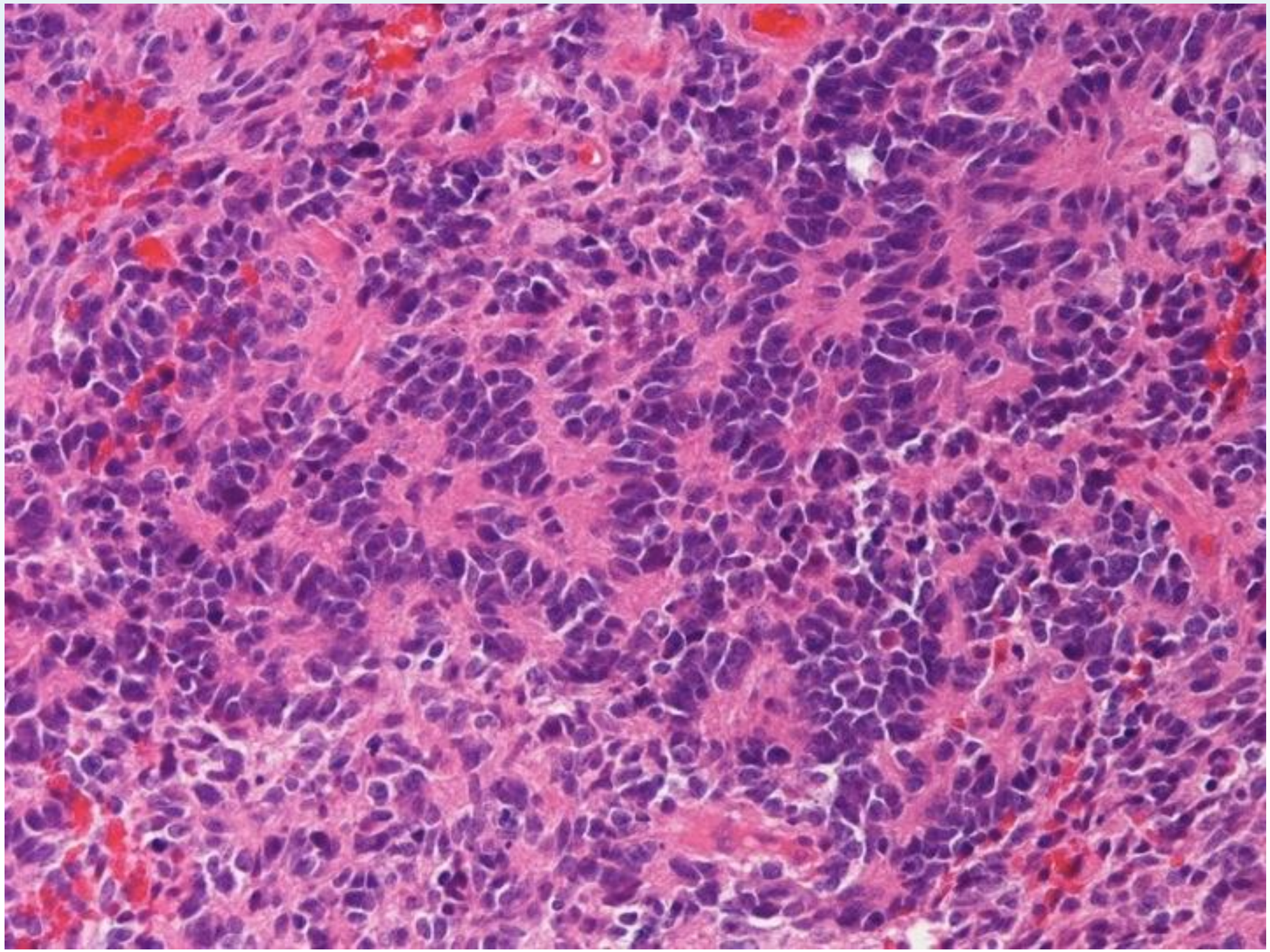
INTEGRATED DIAGNOSIS: Medulloblastoma, SHH-activated, *TP53*-mutant

- Histological Diagnosis: Medulloblastoma
- Histological Grade: IV
- Molecular Data: SHH activated, *TP53* mutated

There are 3 common brain tumour groups in children



CNS Embryonal Tumours



Classification of CNS Embryonal Tumours

Medulloblastoma

Non-Medulloblastoma

CHAPTER 8

Embryonal tumours

Medulloblastoma, genetically defined

Medulloblastoma, WNT-activated

Medulloblastoma, SHH-activated and TP53-mutant

Medulloblastoma, SHH-activated and TP53-wildtype

Medulloblastoma, non-WNT/non-SHH

Medulloblastoma, histologically defined

Medulloblastoma, classic

Desmoplastic/nodular medulloblastoma

Medulloblastoma with extensive nodularity

Large cell / anaplastic medulloblastoma

Embryonal tumour with multilayered rosettes, C19MC-altered

Embryonal tumour with multilayered rosettes, NOS

Medulloepithelioma

CNS neuroblastoma

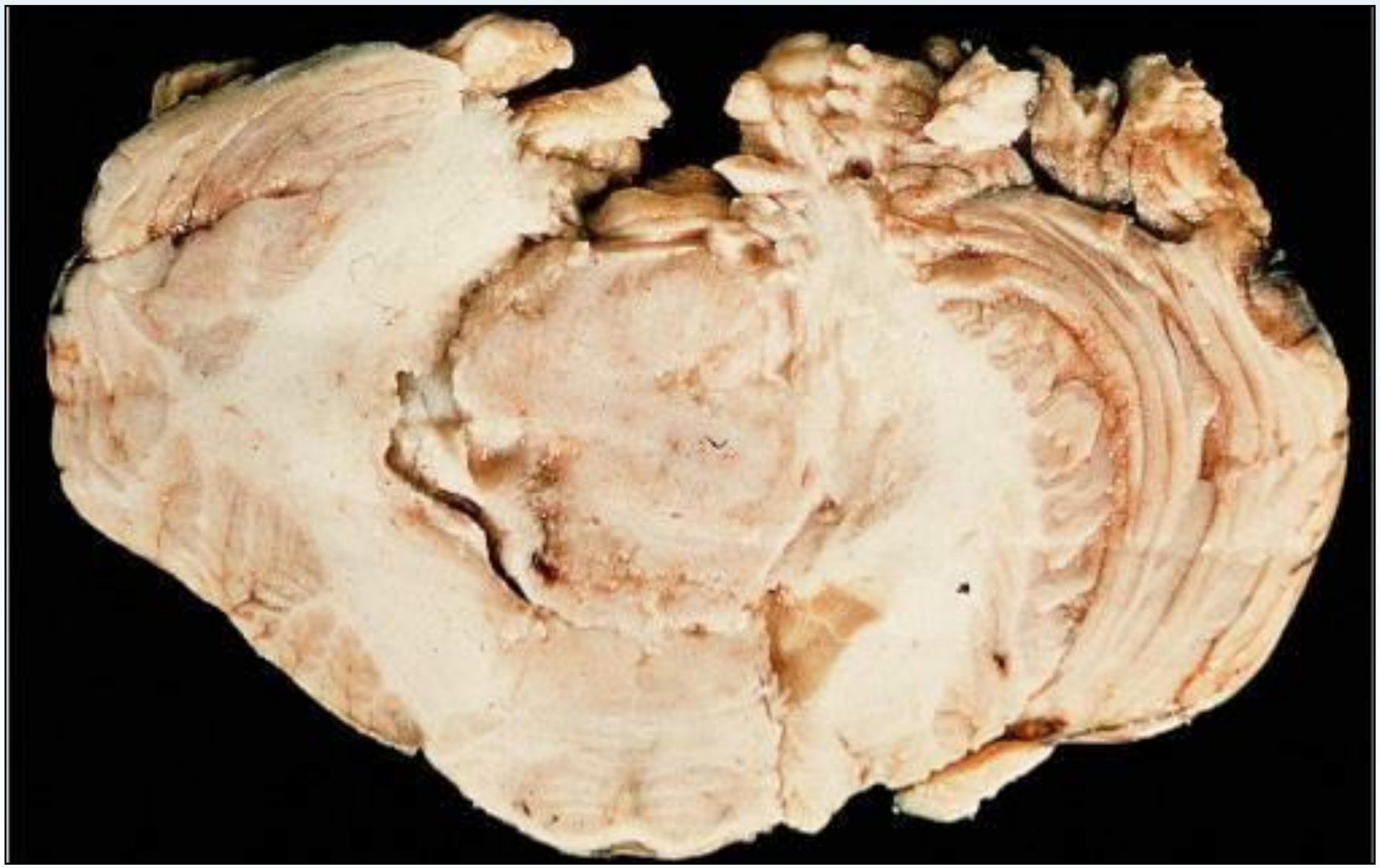
CNS ganglioneuroblastoma

CNS embryonal tumour, NOS

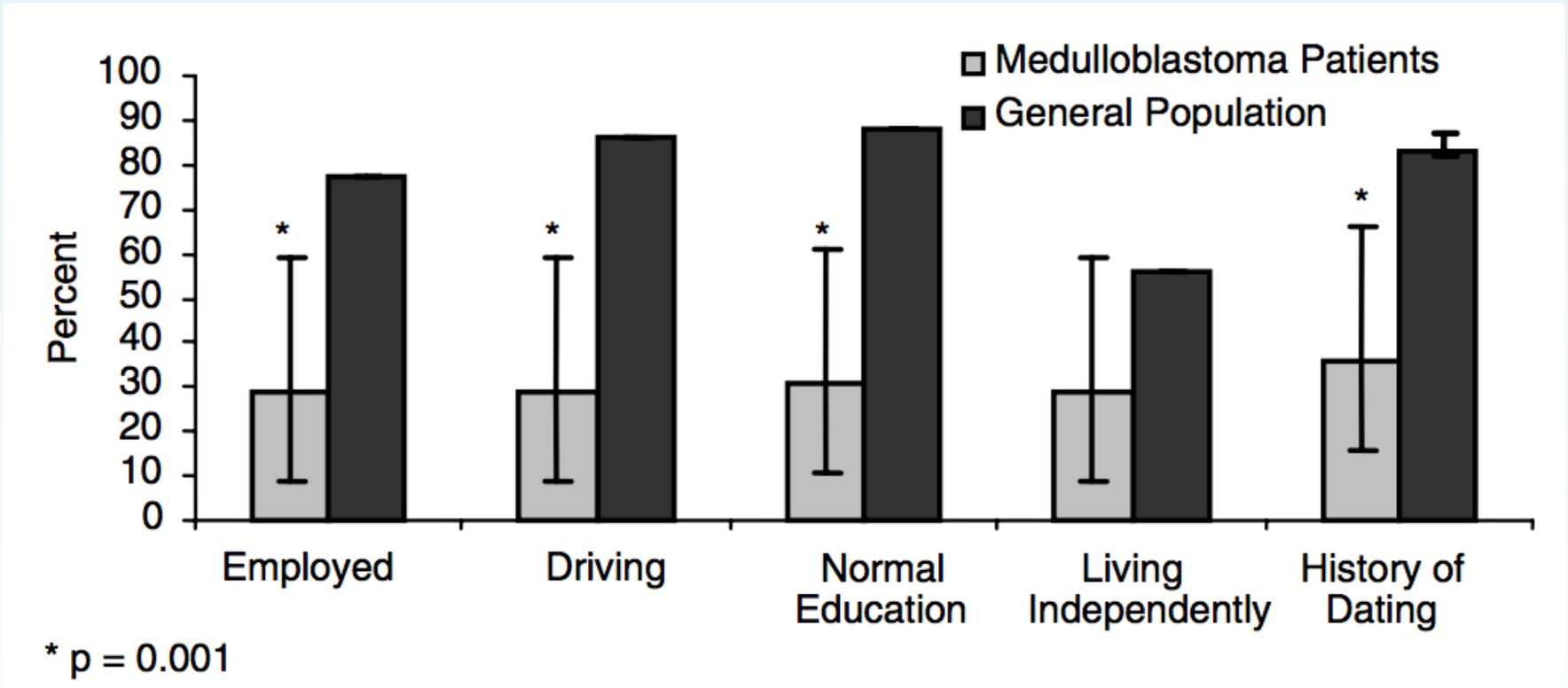
Atypical teratoid/rhabdoid tumour

CNS embryonal tumour with rhabdoid features

Medulloblastoma



Survival is at the cost of long-term complications



Maddgrey et al. 2005

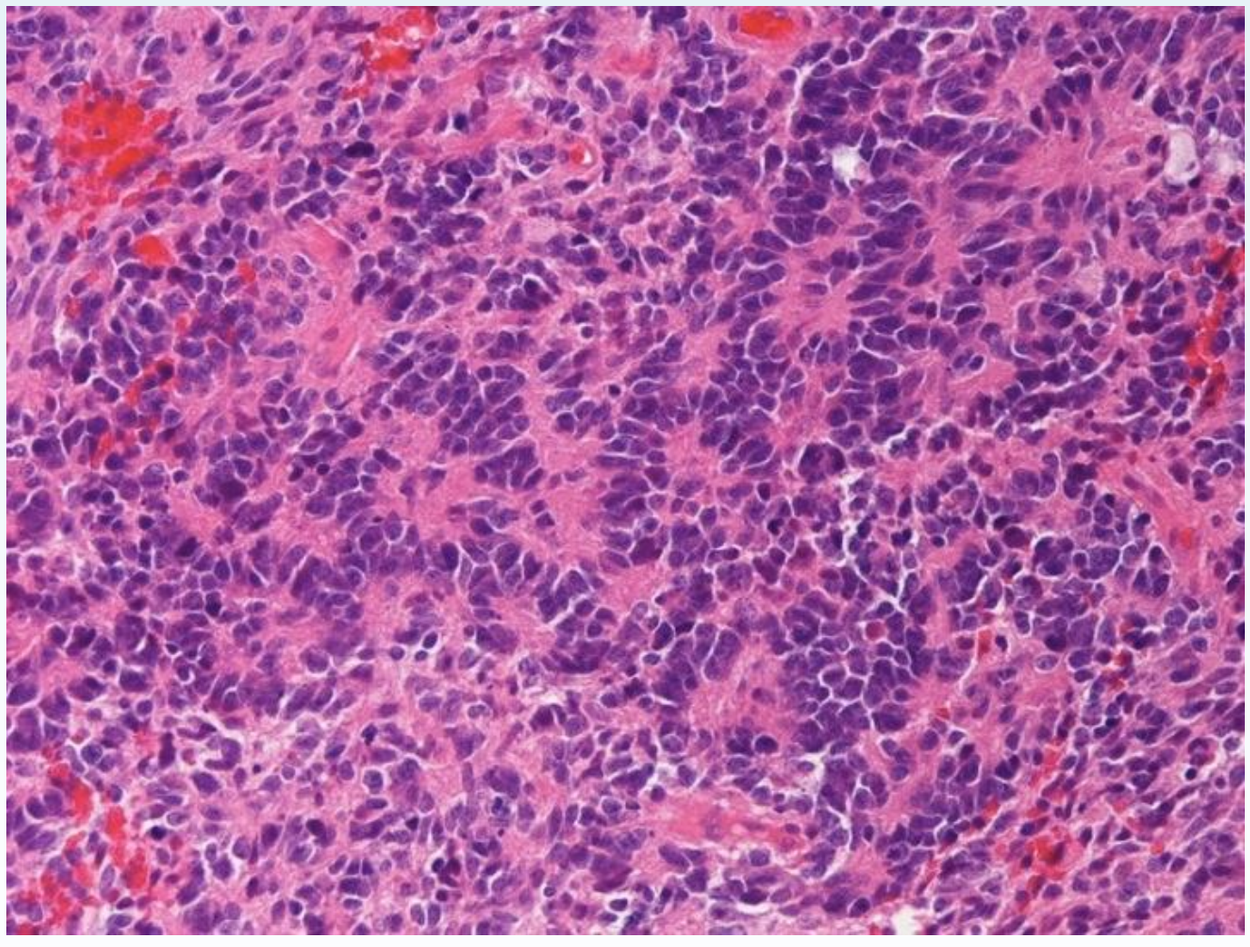
Classification-genetics and histology

Medulloblastoma, genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, SHH-activated and TP53-wildtype
Medulloblastoma, non-WNT/non-SHH

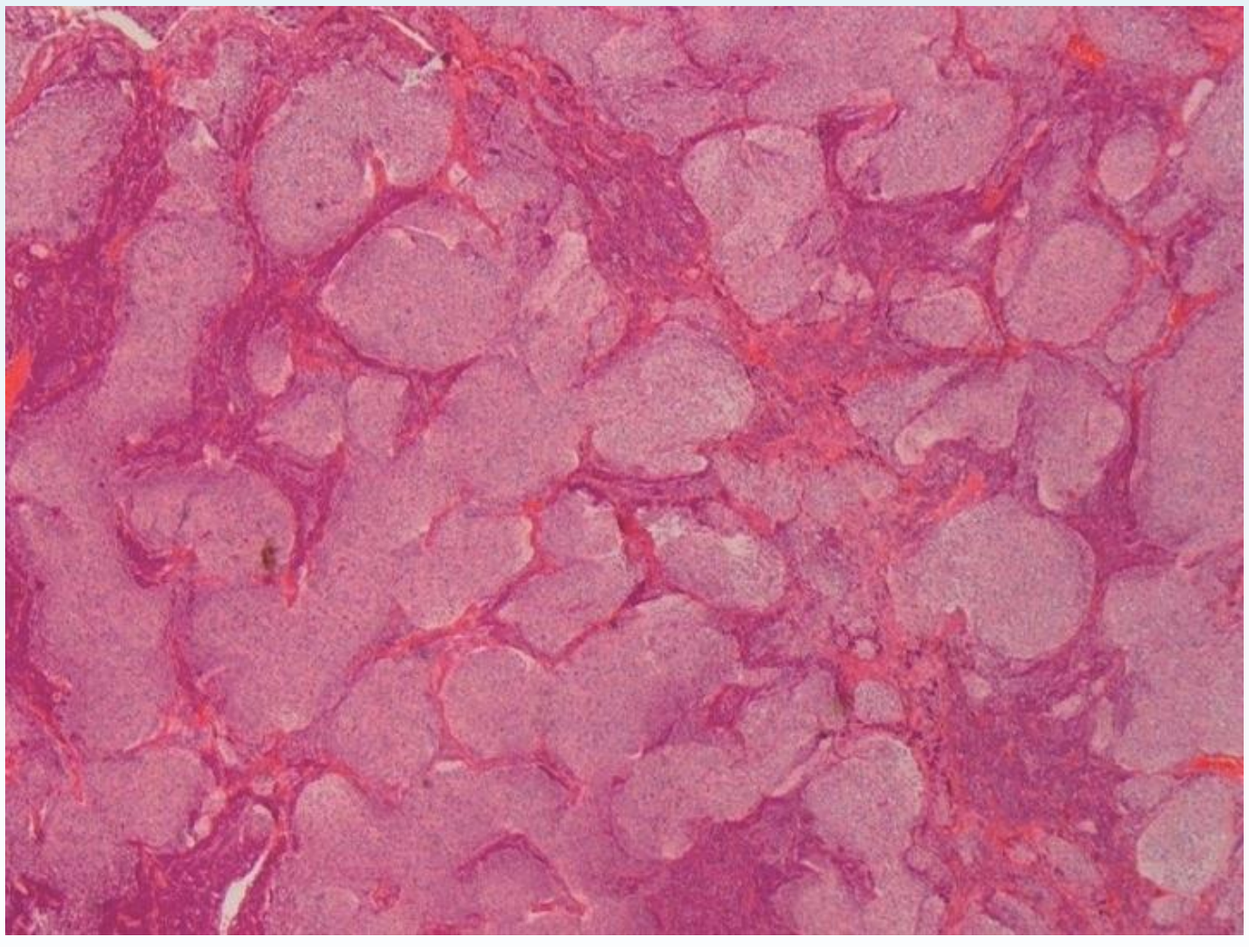
Medulloblastoma, histologically defined
Medulloblastoma, classic
Desmoplastic/nodular medulloblastoma
Medulloblastoma with extensive nodularity
Large cell / anaplastic medulloblastoma

Risk stratification-conventional histology

Medulloblastoma-Architecture

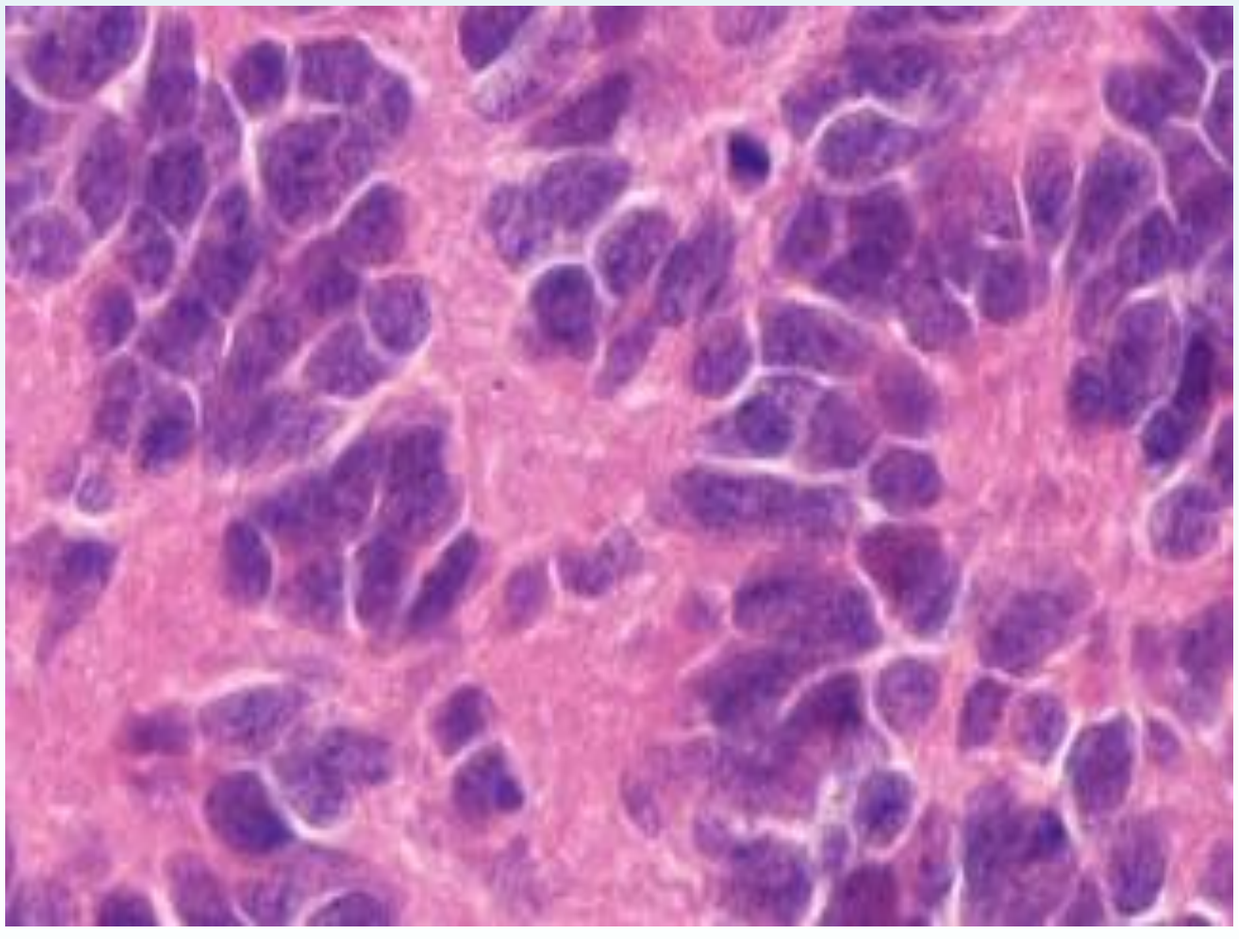


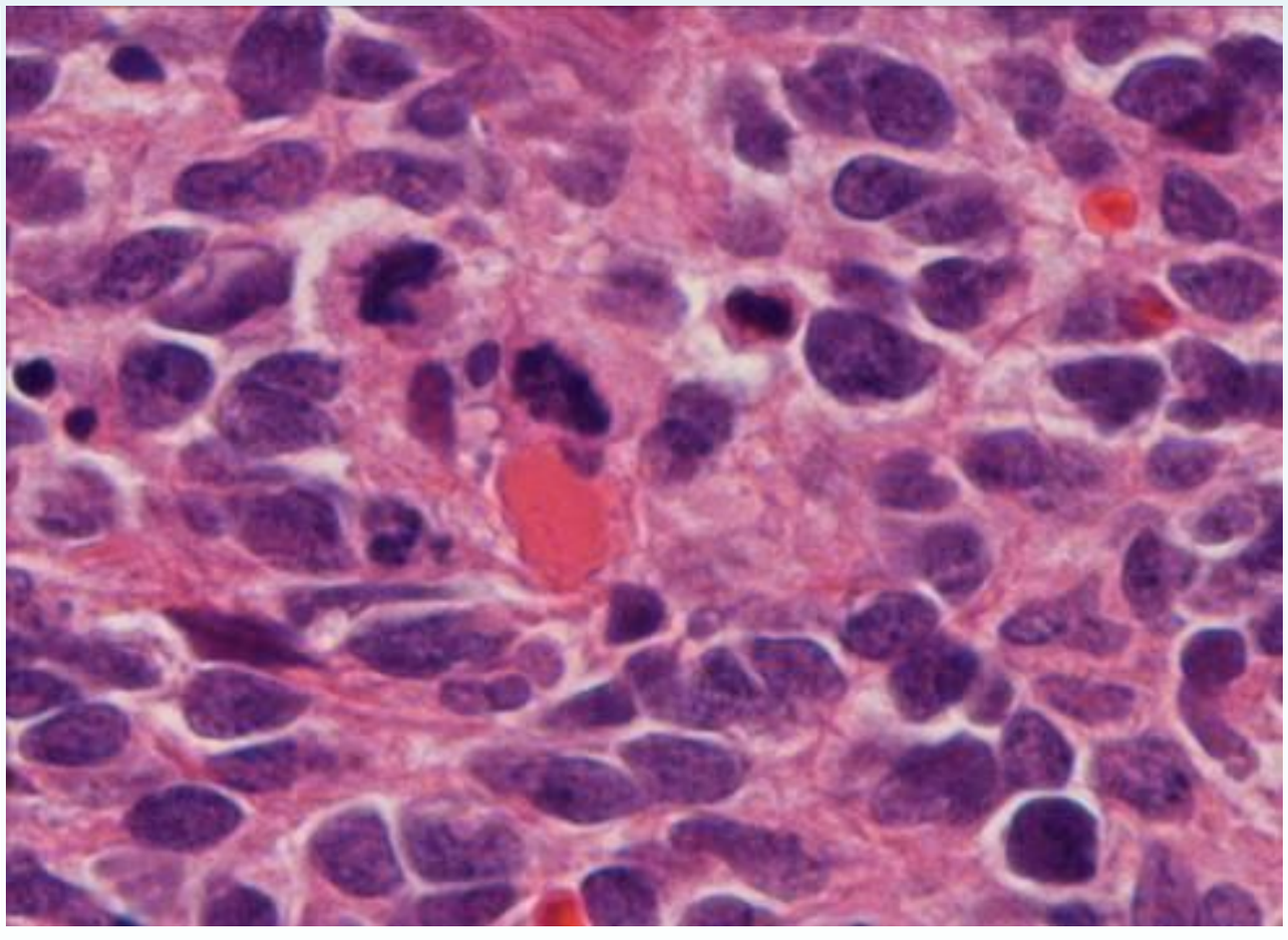
Diffuse



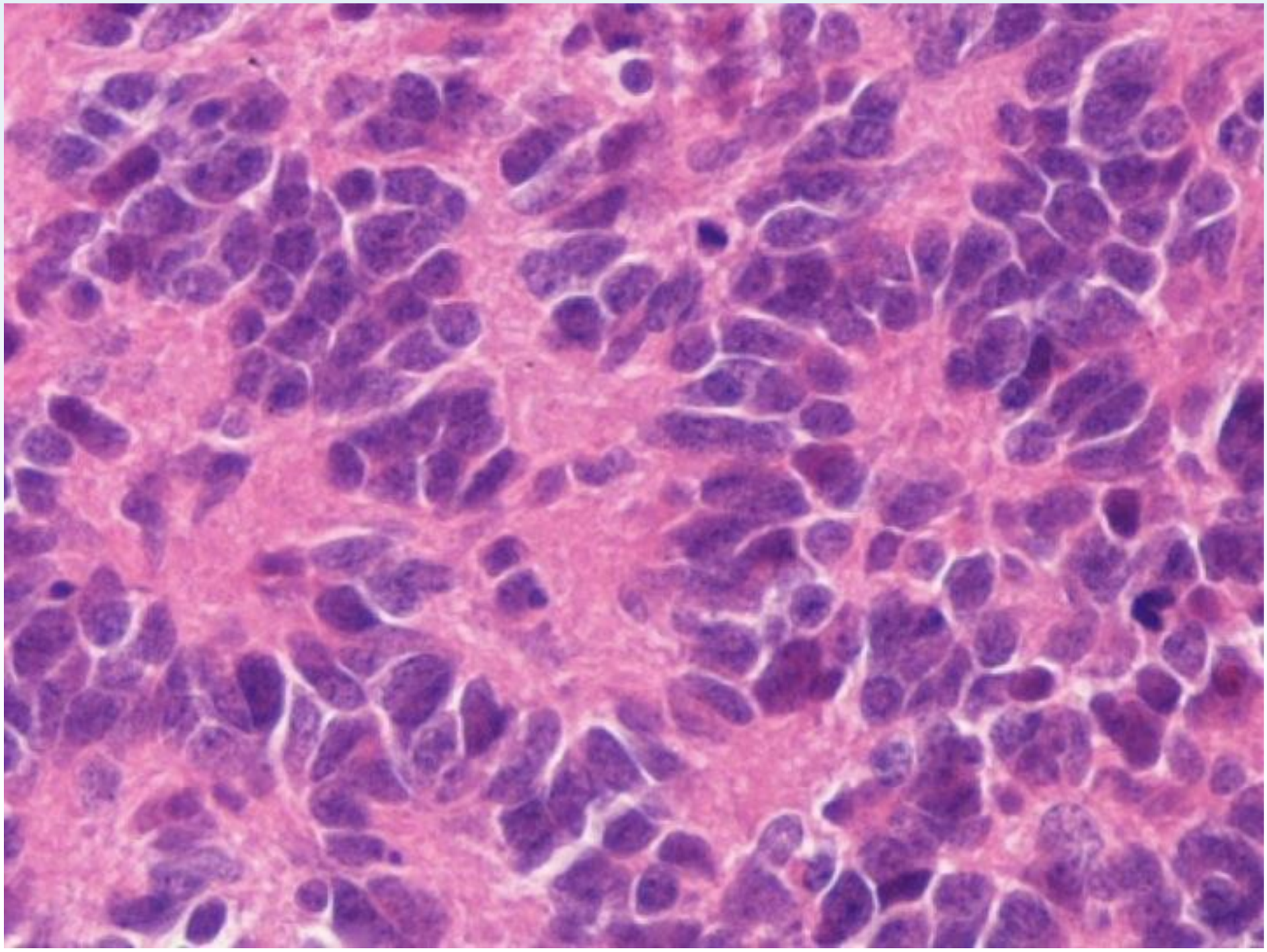
Nodular

Medulloblastoma-Cytology

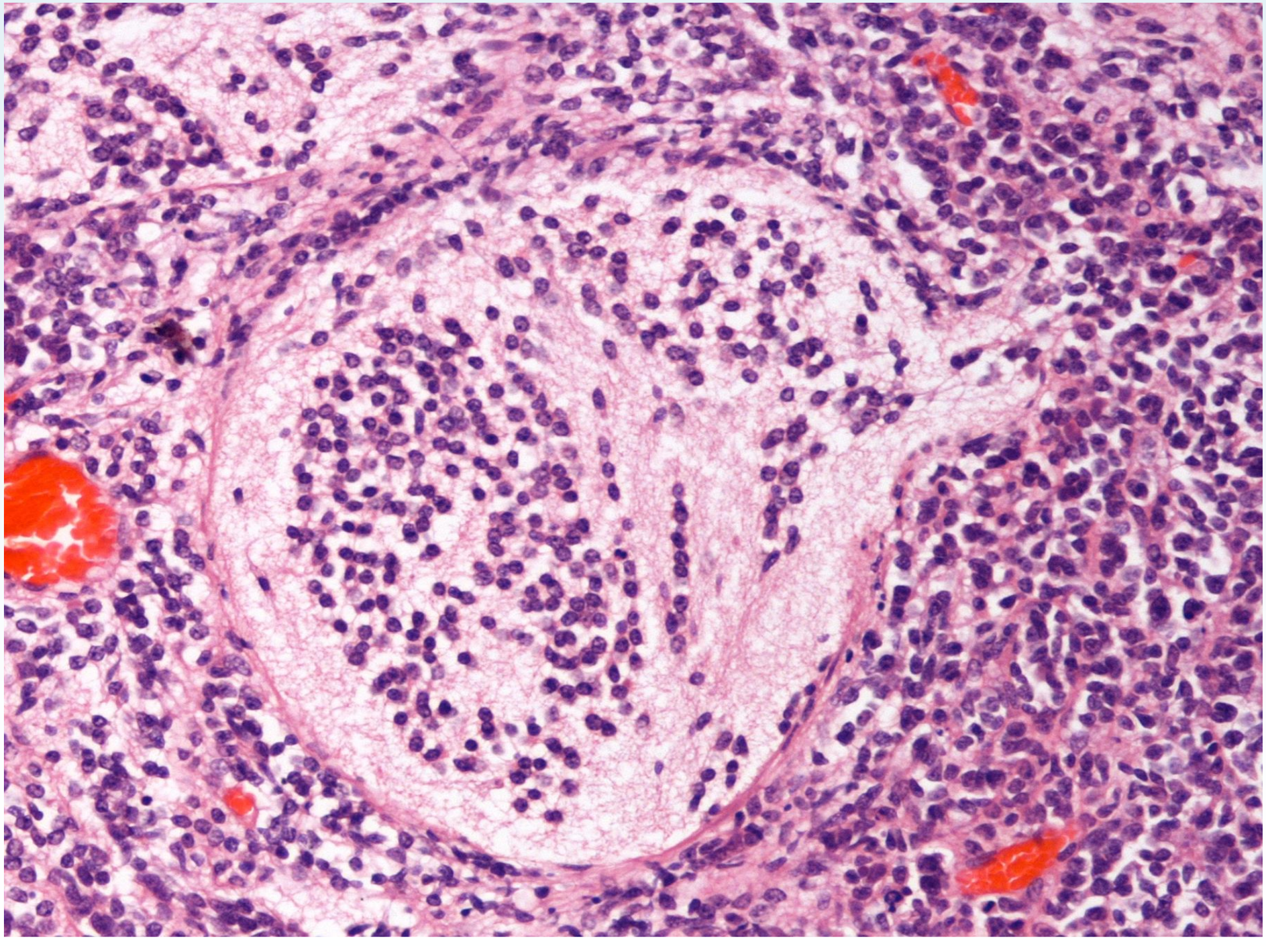




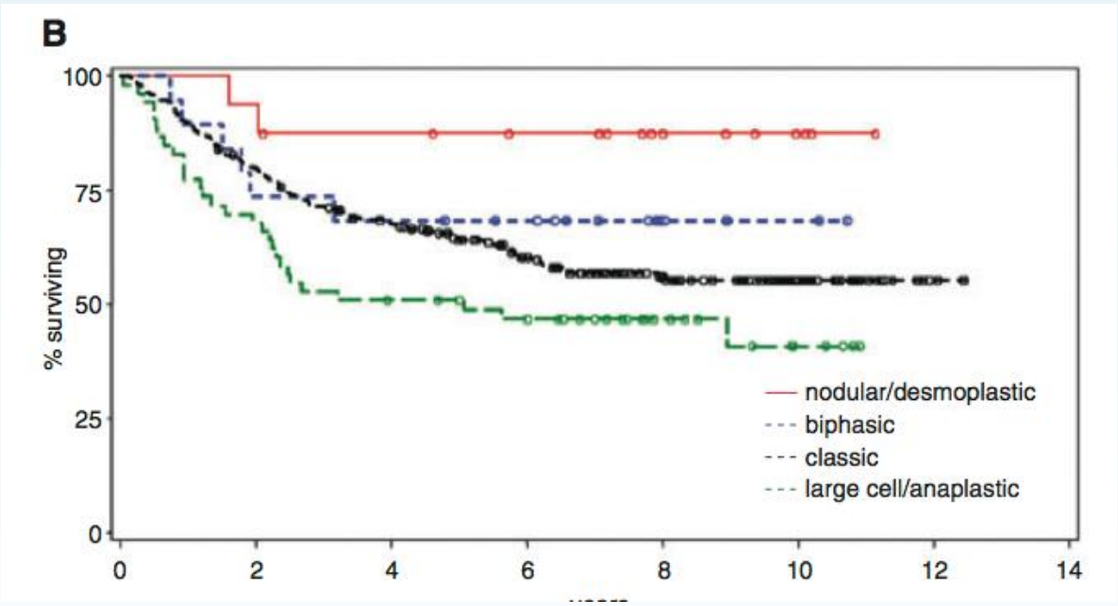
Homer Wright rosettes



Variants-Nodular Medulloblastoma



Nodularity is associated with a better prognosis



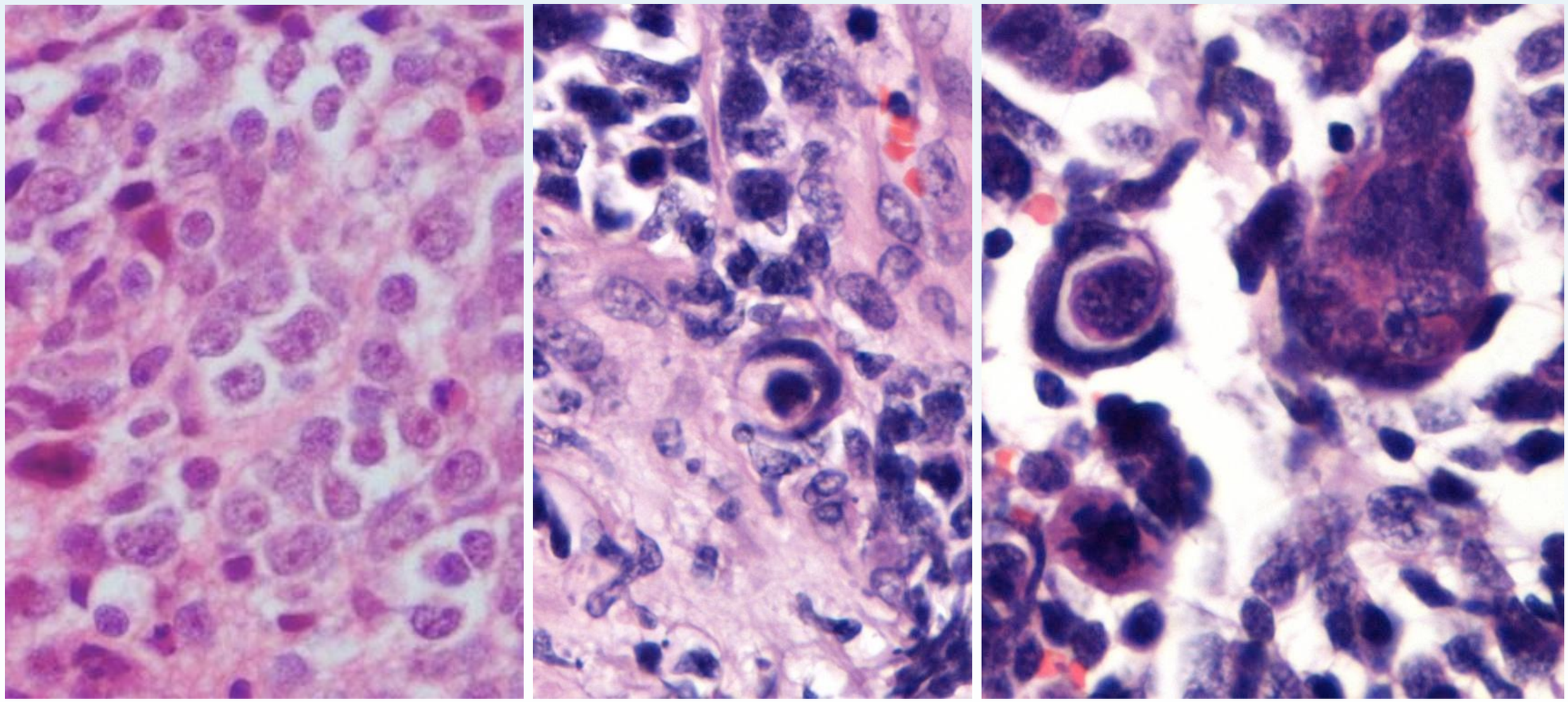
RESEARCH ARTICLE

DOI 10.1111/j.1750-3639.2007.00058.x

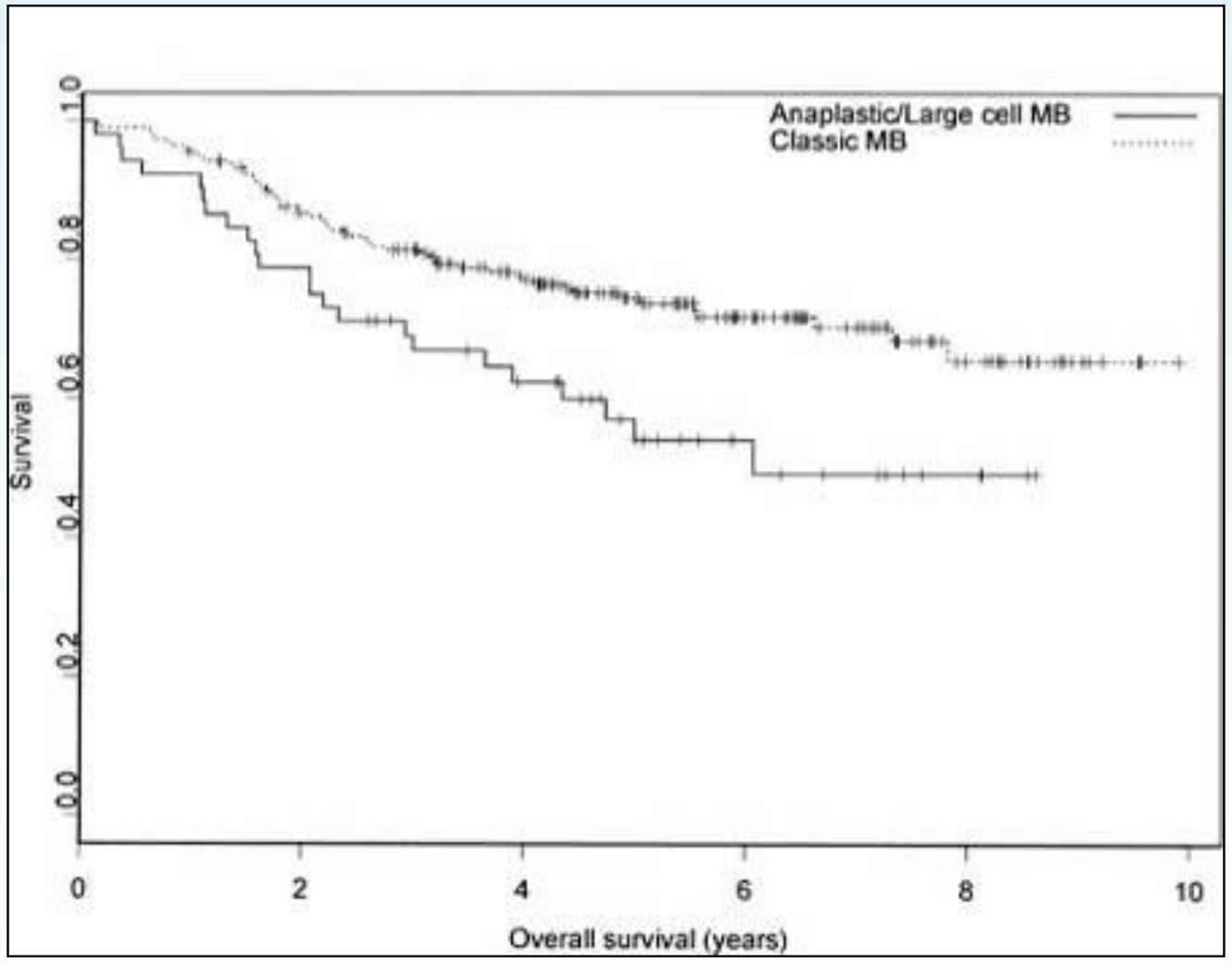
Nodule Formation and Desmoplasia in Medulloblastomas—Defining the Nodular/Desmoplastic Variant and Its Biological Behavior

Charles S. McManamy[1,2*]; Jane Pears[1,3*]; Claire L. Weston[4]; Zoltan Hanzely[5]; James W. Ironside[6]; Roger E. Taylor[7]; Richard G. Grundy[8]; Steven C. Clifford[1]; David W. Ellison[1,2,3,9]; on behalf of the Clinical Brain Tumour Group, Children's Cancer and Leukaemia Group (formerly the UK Children's Cancer Study Group), UK

Anaplastic and Large Cell Medulloblastoma



Anaplastic and large cell medulloblastoma carry a poor prognosis



Mc Nanamy *et al.* 2003 JNEN

Risk stratification-molecular subtyping

Molecular Subgroups of Medulloblastoma

CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: infant, child, adult

Gender: ♀ ♂

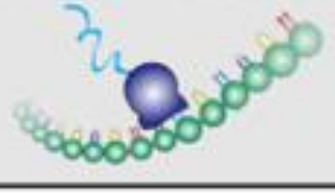
CLINICAL FEATURES

	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS

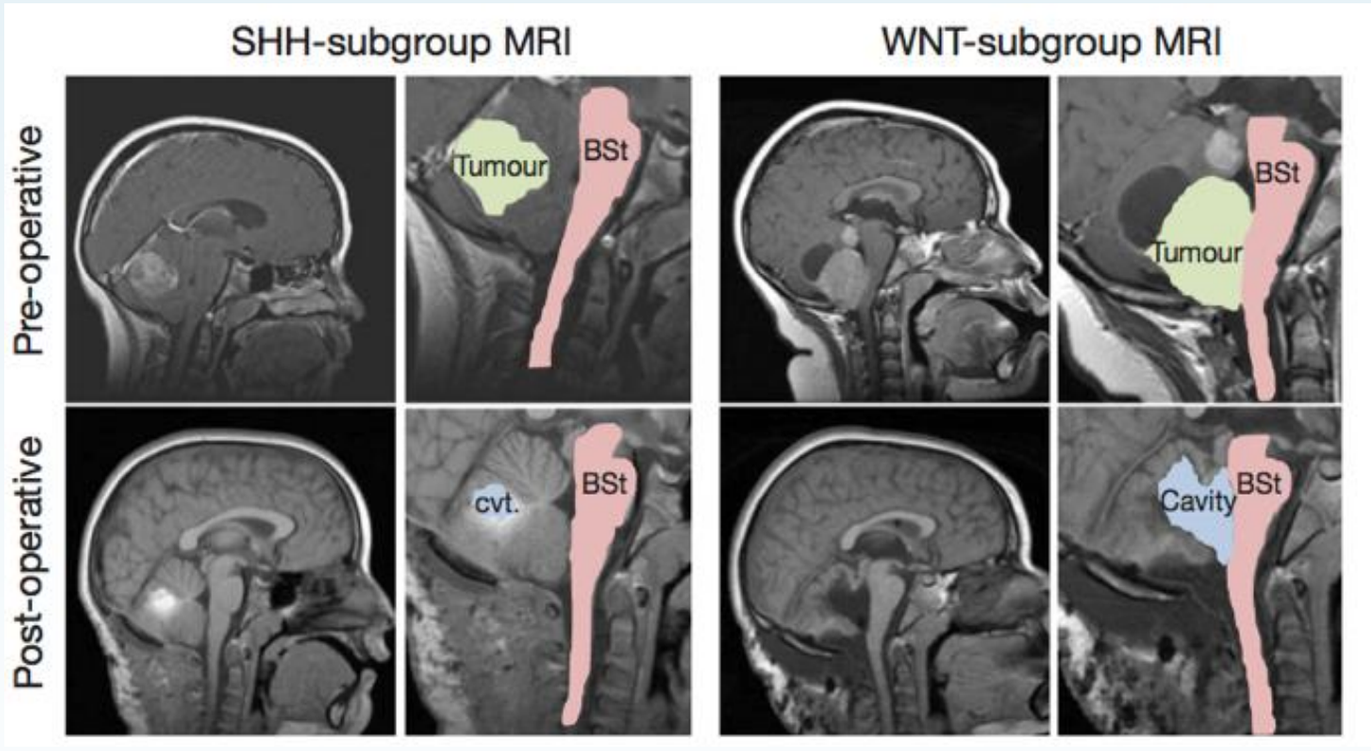
	WNT	SHH	Group 3	Group 4
	6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION



	WNT	SHH	Group 3	Group 4
	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

Different types medulloblastomas have different developmental origins



LETTER

doi:10.1038/nature09587

Subtypes of medulloblastoma have distinct developmental origins

Paul Gibson[1], Yiai Tong[1], Giles Robinson[1,2], Margaret C. Thompson[9], D. Spencer Currle[1], Christopher Eden[1], Tanya A. Kranenburg[1], Twala Hogg[1], Helen Poppleton[1], Julie Martin[1], David Finkelstein[3], Stanley Pounds[4], Aaron Weiss[10], Zoltan Patay[5], Matthew Scoggins[5], Robert Ogg[5], Yanxin Pei[11], Zeng-Jie Yang[11], Sonja Brun[11], Youngsoo Lee[6], Frederique Zindy[6], Janet C. Lindsey[12], Makoto M. Taketo[13], Frederick A. Boop[7], Robert A. Sanford[7], Amar Gajjar[2], Steven C. Clifford[12], Martine F. Roussel[6], Peter J. McKinnon[6], David H. Gutmann[14], David W. Ellison[8], Robert Wechsler-Reya[11] & Richard J. Gilbertson[1,2]

Classification by immunohistochemistry

Table 2 Immunophenotypes of SHH, WNT, and non-SHH/WNT molecular subgroups

Molecular group	Immunoreactivity			
	GAB1	β-catenin	Filamin A	YAP1
SHH	Cytoplasmic	Cytoplasmic	Cytoplasmic	Nuclear + cytoplasmic
WNT	Negative	Nuclear + cytoplasmic	Cytoplasmic	Nuclear + cytoplasmic
Non-SHH/WNT	Negative	Cytoplasmic	Negative	Negative

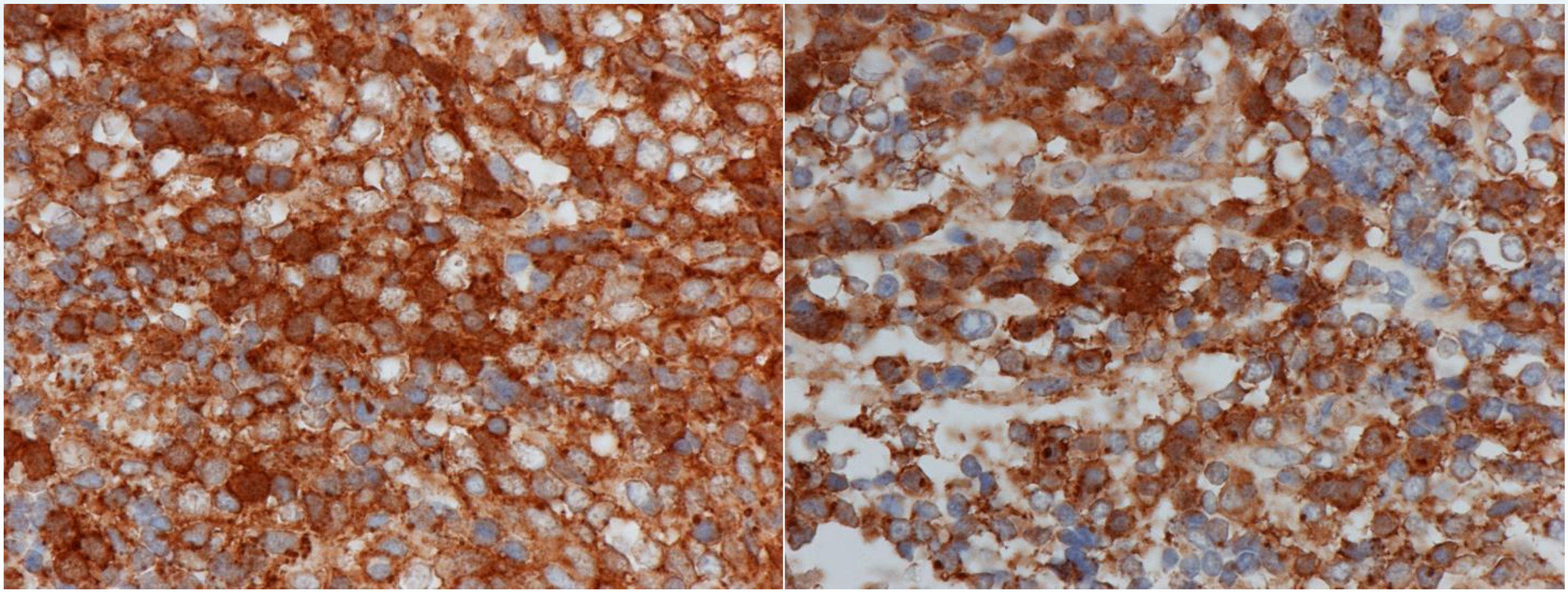
Acta Neuropathol (2011) 121:381–396
DOI 10.1007/s00401-011-0800-8

ORIGINAL PAPER

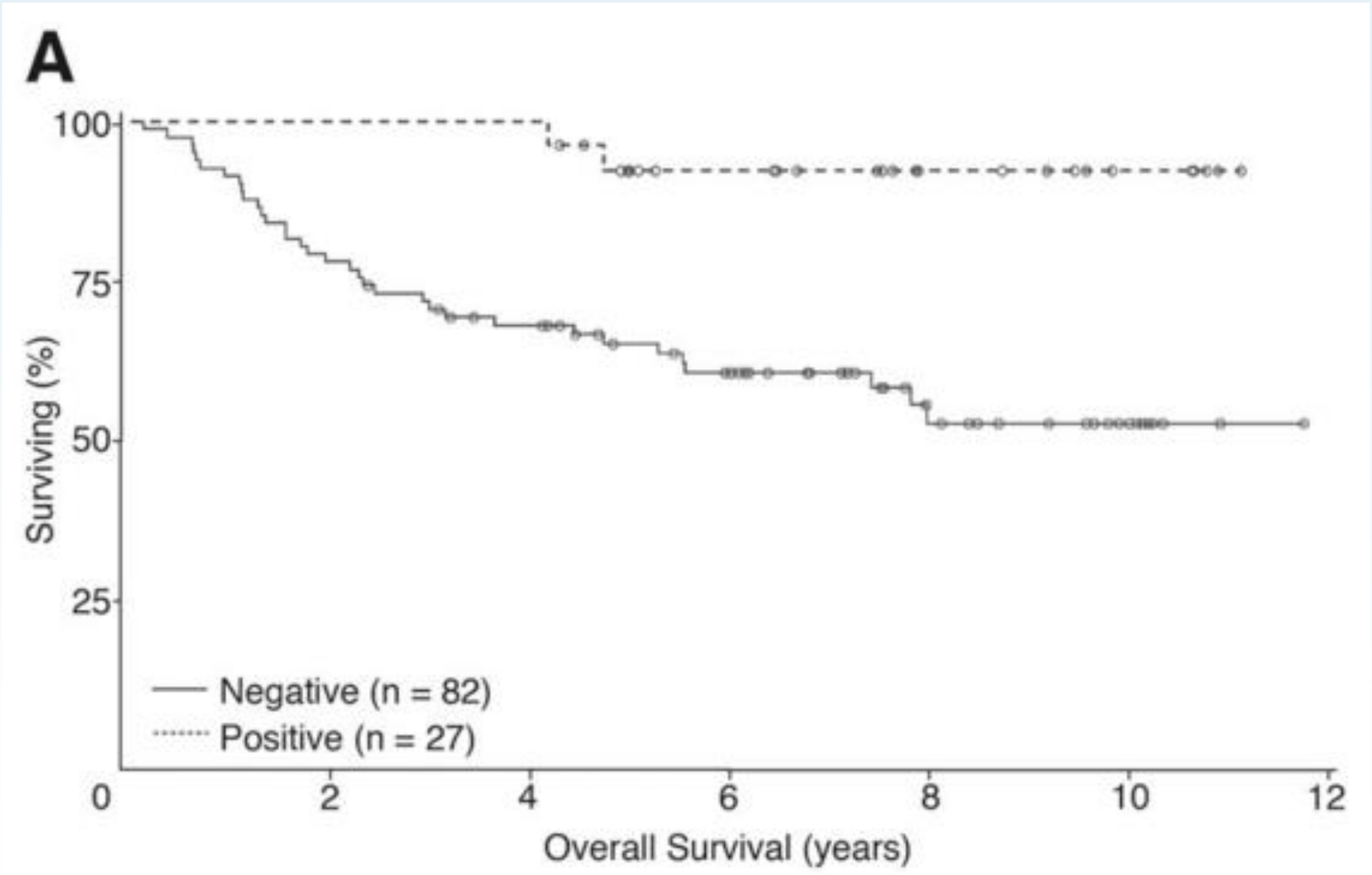
Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups

David W. Ellison · James Dalton · Mehmet Kocak · Sarah Leigh Nicholson · Charles Fraga · Geoff Neale · Anna M. Kenney · Dan J. Brat · Arie Perry · William H. Yong · Roger E. Taylor · Simon Bailey · Steven C. Clifford · Richard J. Gilbertson

Beta-catenin nuclear staining identifies WNT-subgroup medulloblastoma



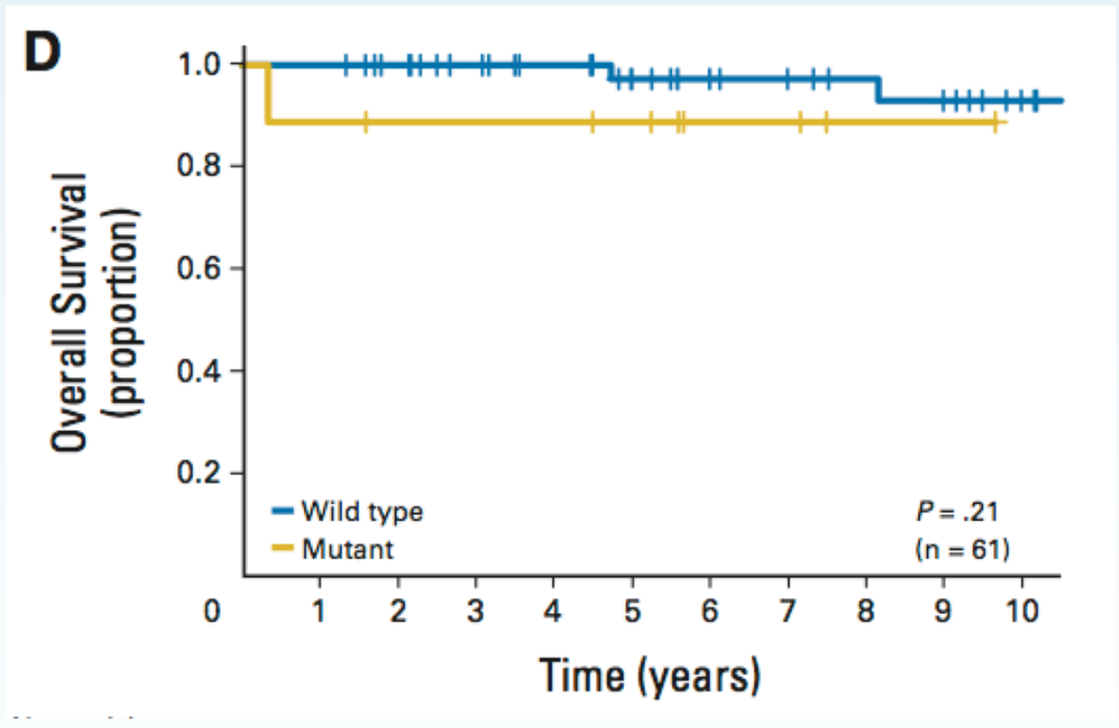
WNT-medulloblastoma have an excellent prognosis

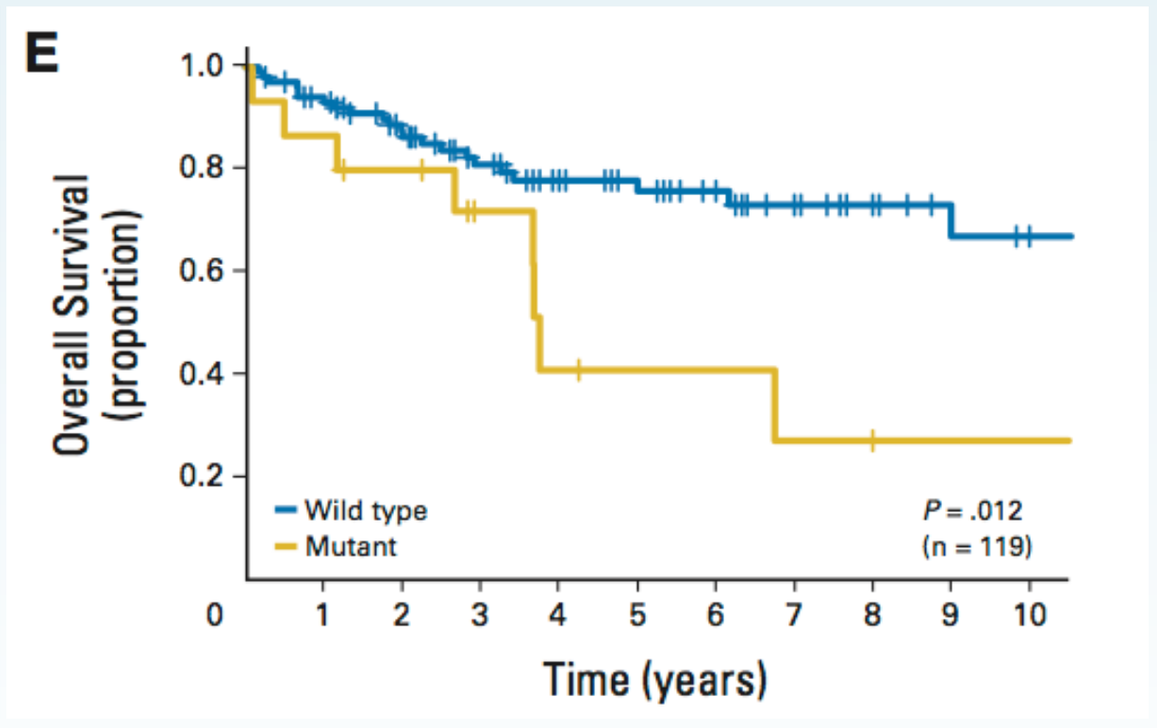


Ellison et al. 2005

MYC and *MYCN* amplification characterises poor prognosis medulloblastoma

TP53 mutations are a poor prognostic feature in the SHH-subtype of medulloblastoma





WNT-subtype

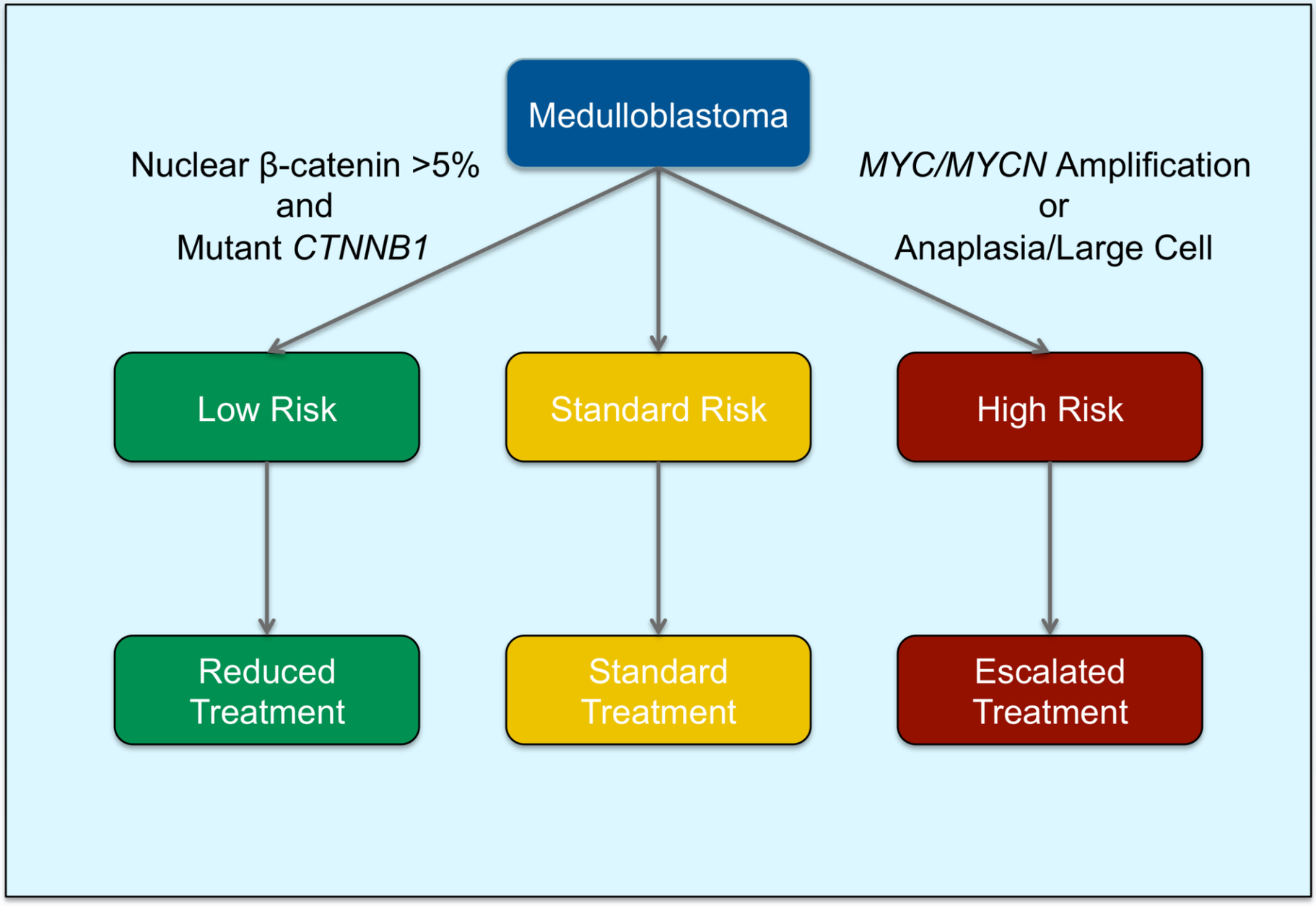
SHH-subtype

VOLUME 31 · NUMBER 23 · AUGUST 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Subgroup-Specific Prognostic Implications of *TP53* Mutation in Medulloblastoma



Neuropathology and Applied Neurobiology
BNS

Editorial

Medulloblastoma: selecting children for reduced treatment

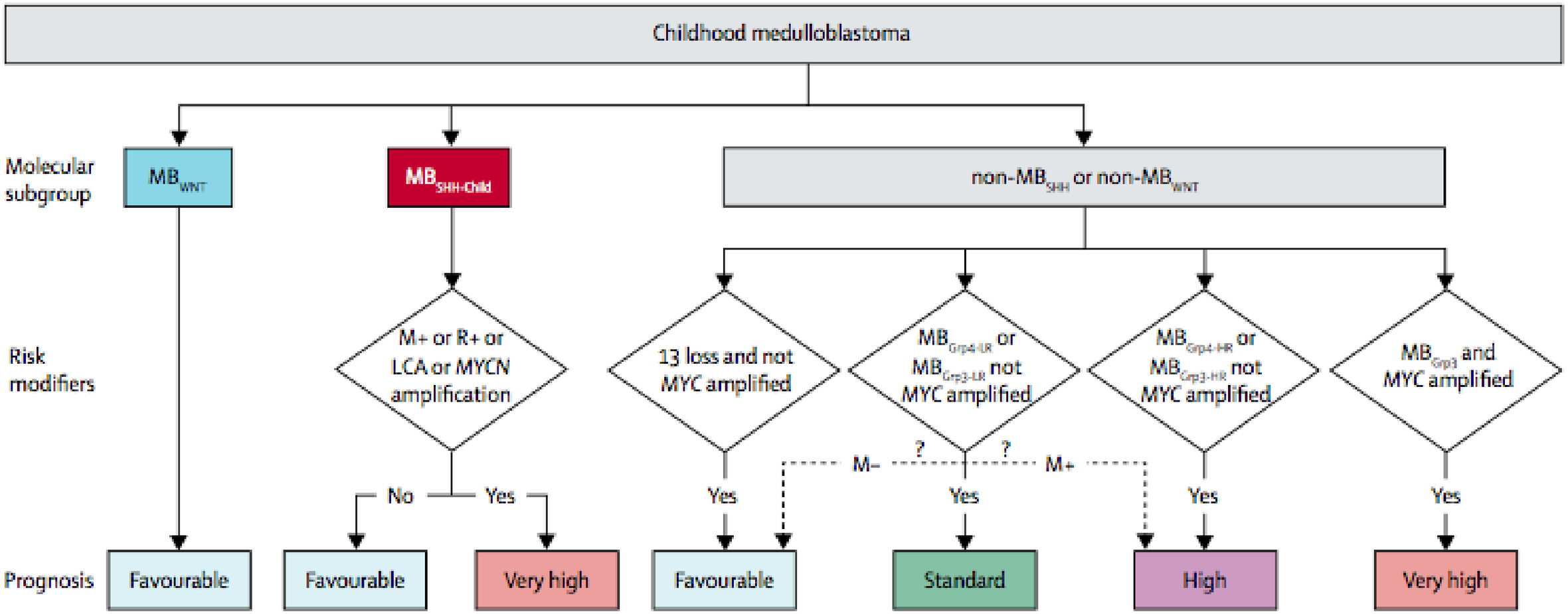
T. J. Stone, T. S. Jacques

Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study

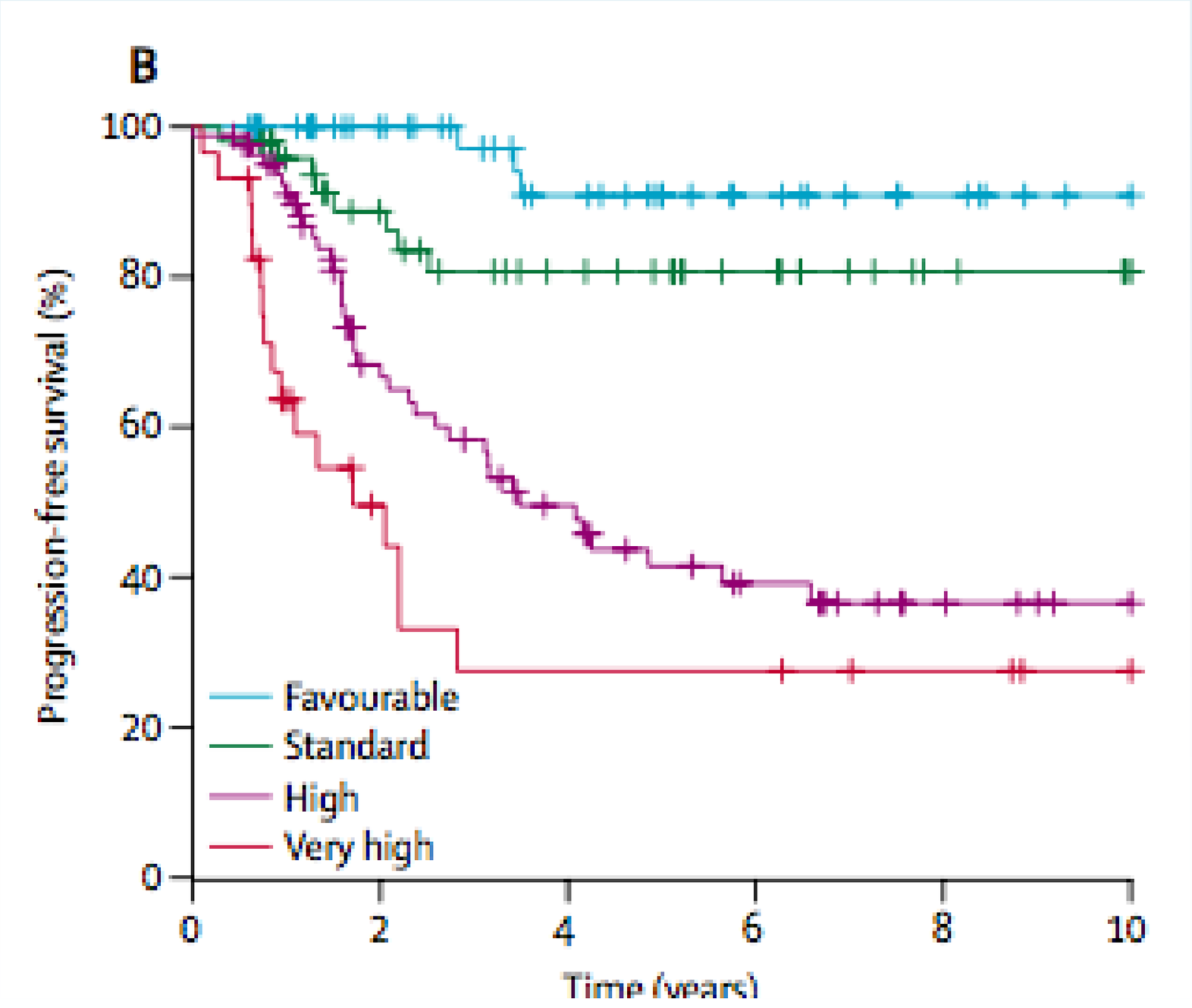
Edward C Schwalbe, Janet C Lindsey, Sirintra Nakjang, Stephen Crosier, Amanda J Smith, Debbie Hicks, Gholamreza Rafiee, Rebecca M Hill, Alice Iliasova, Thomas Stone, Barry Pizer, Antony Michalski, Abhijit Joshi, Stephen B Wharton, Thomas S Jacques, Simon Bailey, Daniel Williamson, Steven C Clifford

		WNT	$MB_{SHH-Child}$	$MB_{SHH-Infant}$	$MB_{Grp4-HR}$	$MB_{Grp4-LR}$	$MB_{Grp3-LR}$	$MB_{Grp3-HR}$
Demographics	Infant disease % (<3 years)	0	5	78	5	3	54	17
	Male %	48	63	55	67	66	68	77
	n	33	38	65	85	73	50	65
Clinical features	Histology (%) CLAS:DN:LCA	86:3:10	32:26:41	35:55:10	86:5:9	85:6:9	90:2:8	61:4:35
	Metastasis (%)	3	16	28	30	23	41	33
	Sub-total resection (%)	10	17	26	35	28	24	25
	10 year overall survival (95% CI)	72% (66–100)	48% (29–80)	58% (46–75)	36% (22–59)	72% (59–88)	69% (55–87)	22% (10–46)
Molecular features	Mutation	*CTNNB1, TP53*	*TP53, TP53 GL, TERT, SUFU, PTCH1*	*SUFU, PTCH1*				*GFI1*
	Cytogenetics	6–	9p+ 17p– 9q– *MYCN, GLI2* amplification	9q–	i17q	17p+ 7+ 18+ i17q 8– 11– 16q– *MYCN* amplification	7+ 14+ 18+ 4– 8– 10– 11– 13– 15– 16– 21–	5+ 8+ 13+ i17q 16q– *MYC* amplification
	Gene expression*		↑*RUNX3, HCAR1, HCAR2, FOXG1*	↑*TRABD2A, TTC9, SLFN11, CHRM2*	↑*ESYT2, WDR60, DAPK2, PRDM6*	↑*BMP5, SPTLC3, COL9A3, ZIC5*	↑*FGD6, BRMS1L, FAM122B, REV3L*	↑*PVT1, TRAP1, NMRAL1, CNTLN* Ribosome biogenesis genes
DNA methylation	Global	↓*vs* CB	↓*vs* CB ↑*vs* $MB_{SHH-Infant}$	↓*vs* CB ↓*vs* $MB_{SHH-Child}$	↓*vs* CB ↓*vs* $MB_{Grp4-LR}$	↓*vs* CB ↑*vs* $MB_{Grp4-HR}$	↓*vs* CB ↑*vs* $MB_{Grp3-HR}$	↓*vs* CB ↓*vs* $MB_{Grp3-LR}$
	Probe level*	PI3K-Akt, Ras signalling pathways	Ras signalling pathway	Hippo signalling pathway	PI3K-Akt signalling pathway			PI3K-Akt signalling pathway
	Gene level*		↑*vs* $MB_{SHH-Infant}$, CB *DLX6–AS1, ACTA1, GCM2, FEZF2*			↑*vs* $MB_{Grp4-HR}$, CB *HLA-DRB5, NXK2-5, ABLIM1, HOXC6*	↑*vs* $MB_{Grp3-HR}$, CB *PRKCZ, MCF2L, MIR662*	↑*vs* $MB_{Grp3-LR}$, CB *GALNT9, MIR662*

A


Childhood medulloblastoma
Molecular subgroup
MB WNT
MB SHH-Child
non-MB SHH or non-MB WNT
Risk modifiers
M+ or R+ or LCA or MYCN amplification
13 loss and not MYC amplified
MB Grp4-LR or MB Grp3-LR not MYC amplified
MB Grp4-HR or MB Grp3-HR not MYC amplified
MB Grp3 and MYC amplified
No
Yes
Yes
M–
?
?
M+
Yes
Yes
Yes
Prognosis
Favourable
Favourable
Very high
Favourable
Standard
High
Very high

Improved risk stratification



CHAPTER 8

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Embryonal tumour with multilayered rosettes, NOS

Medulloepithelioma

CNS neuroblastoma

CNS ganglioneuroblastoma

CNS embryonal tumour, NOS

Atypical teratoid/rhabdoid tumour

CNS embryonal tumour with rhabdoid features

Non-Medulloblastoma Embryonal Tumours

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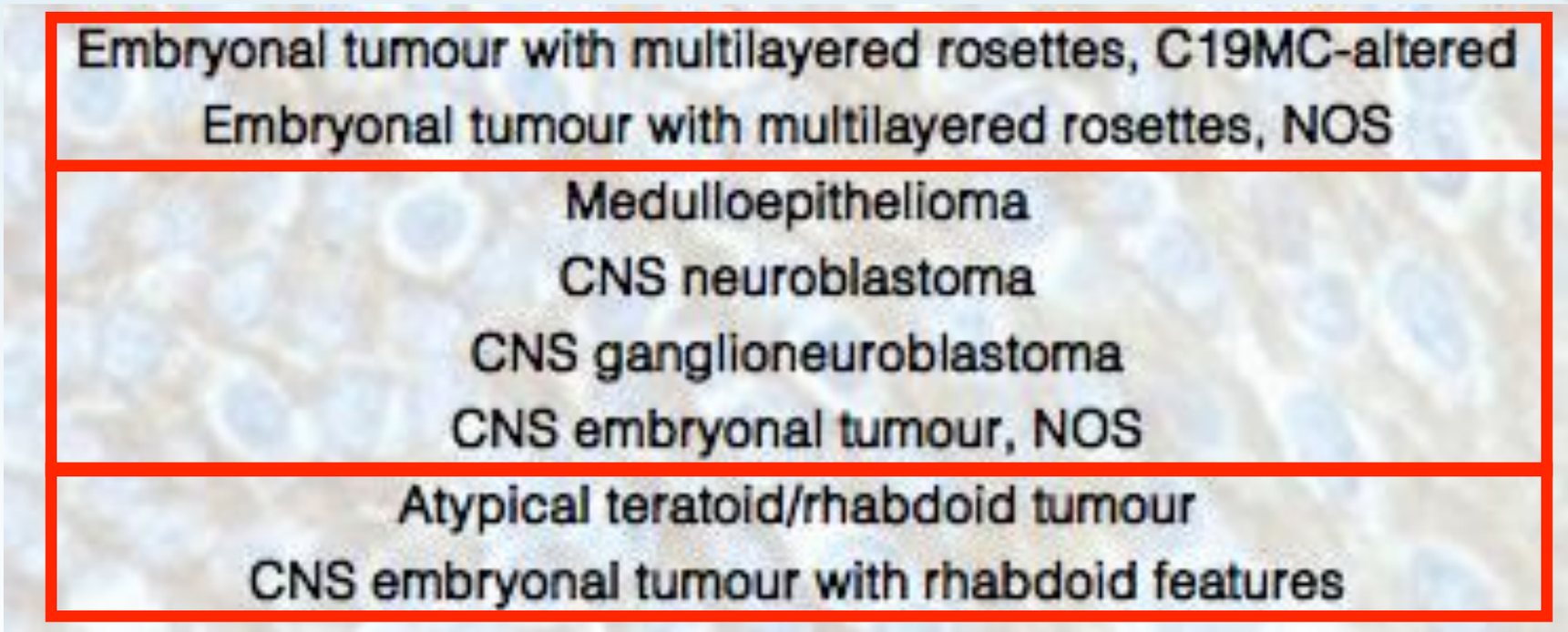
CNS embryonal tumour, NOS
Atypical teratoid/rhabdoid tumour
CNS embryonal tumour with rhabdoid features

Non-Medulloblastoma Embryonal Tumours

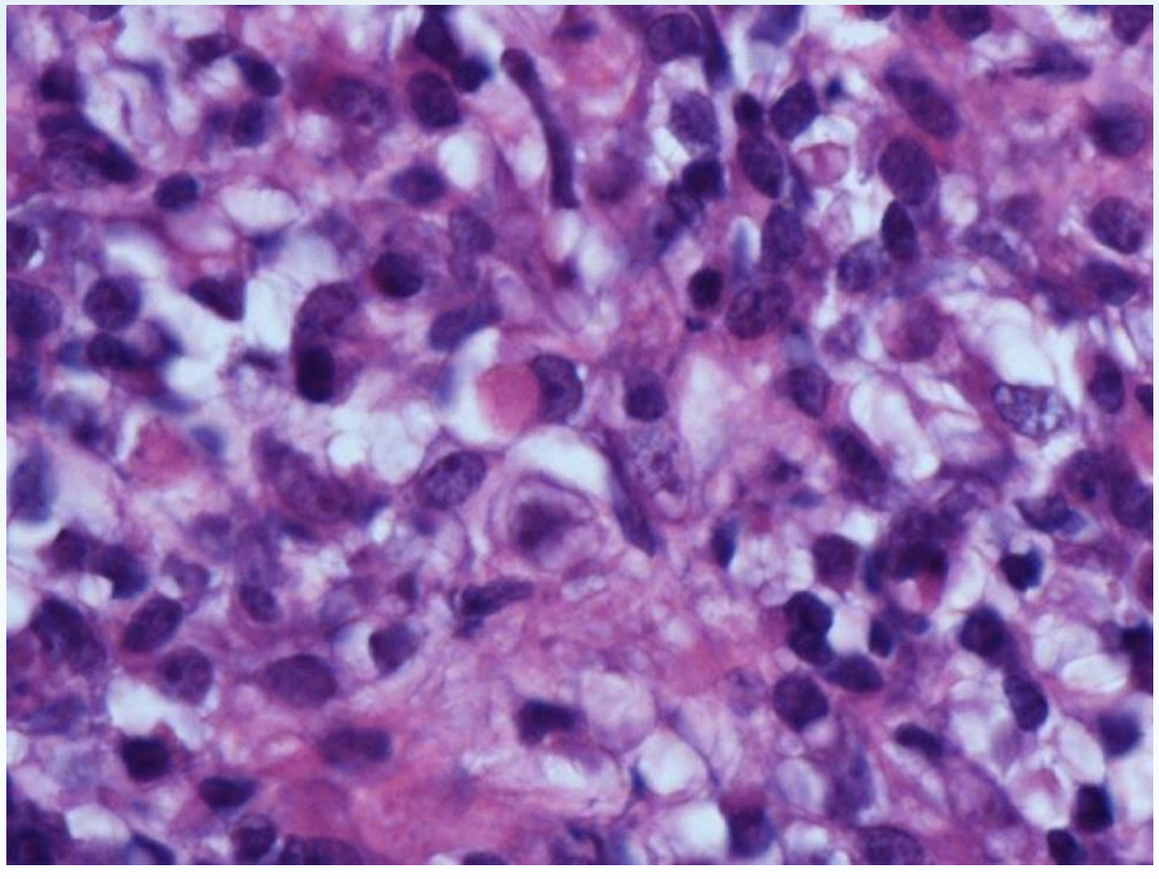


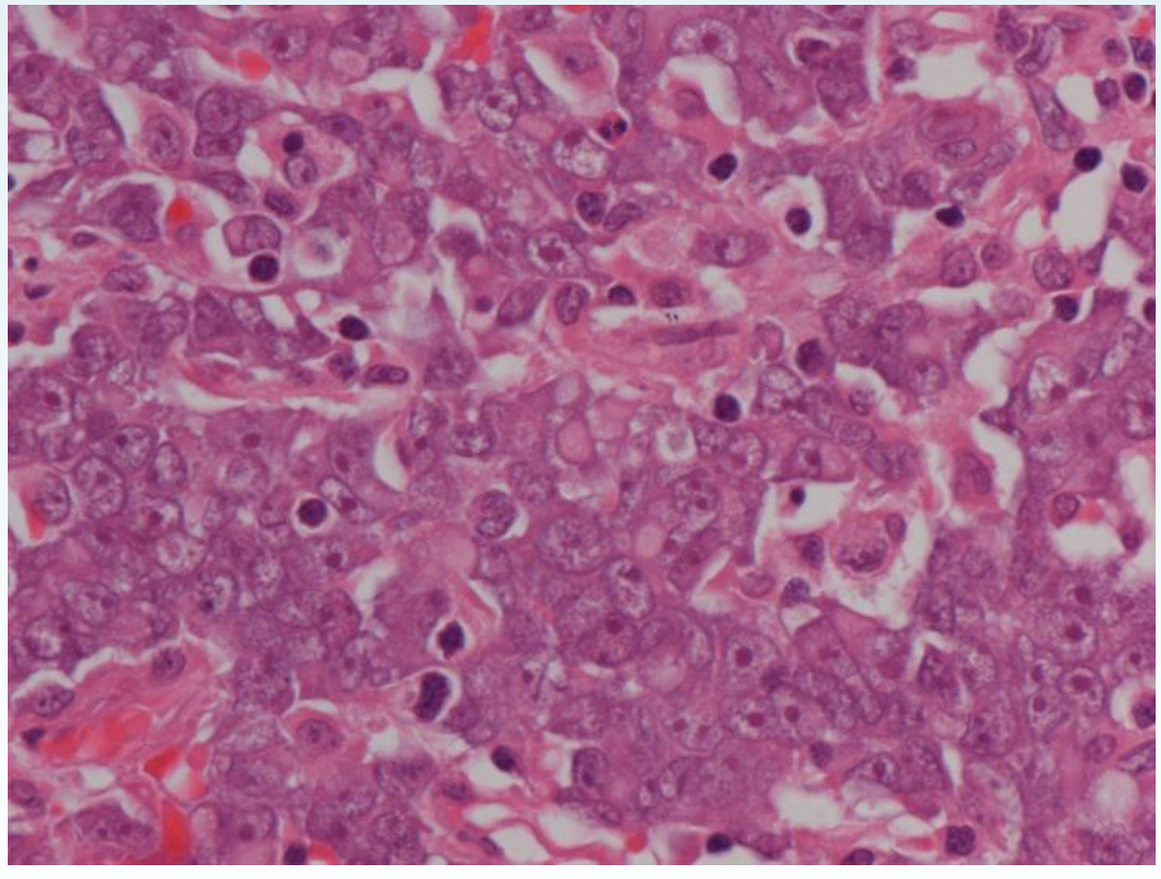
ETMR

CNS Embryonal Tumours

Rhabdoid Tumours

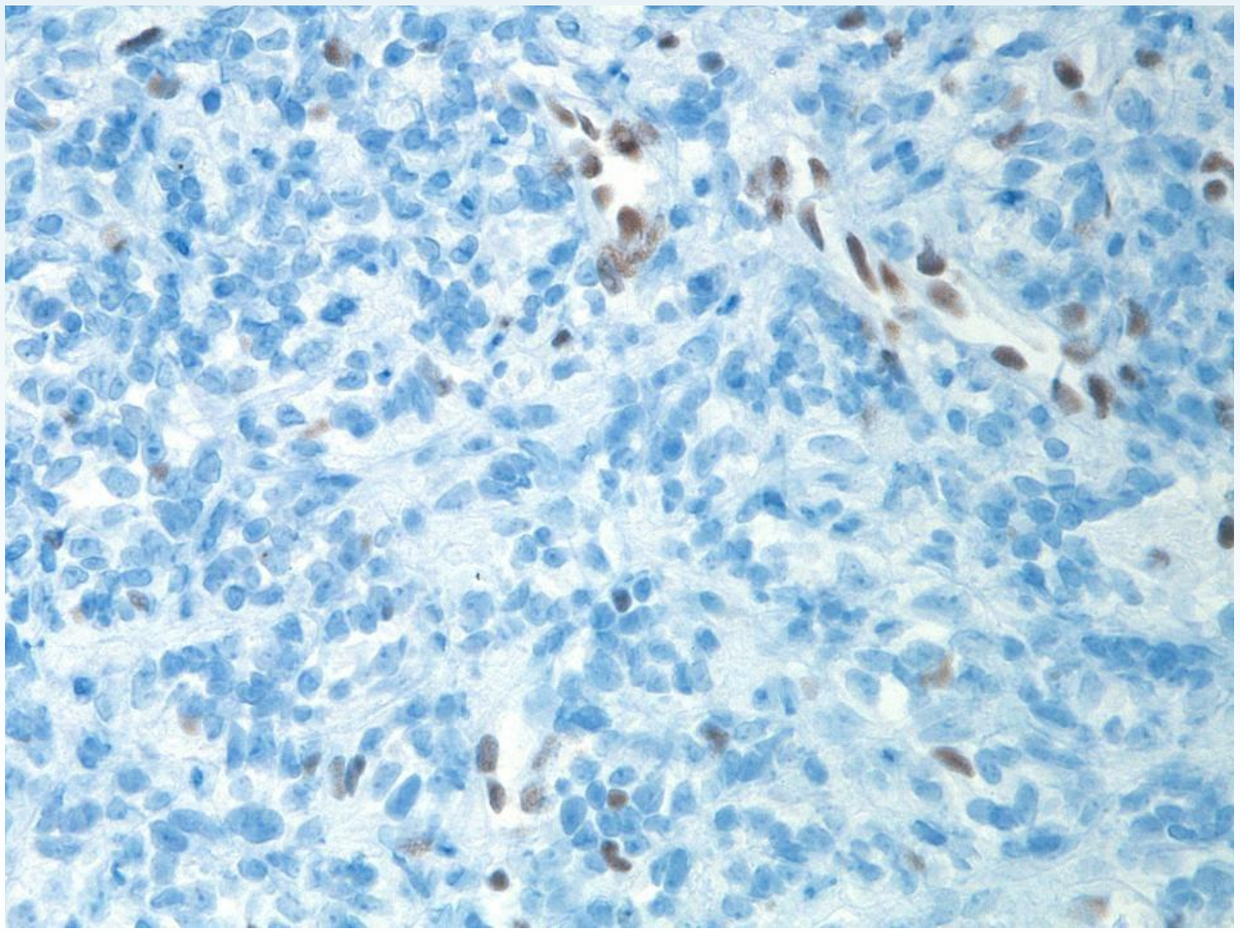
Atypical Teratoid / Rhabdoid Tumour



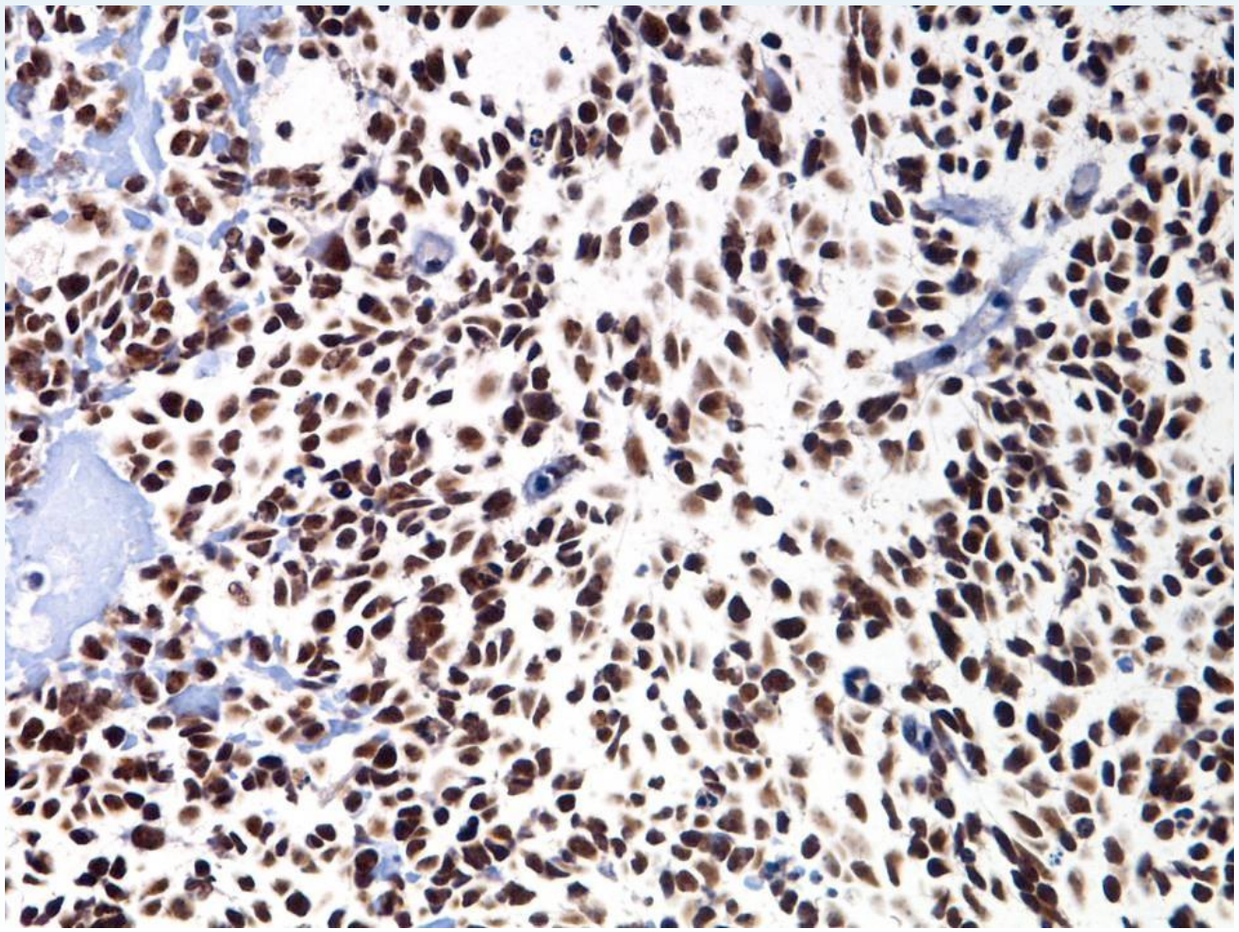


Atypical Teratoid / Rhabdoid Tumour

INI-1 (=SMARCB1)

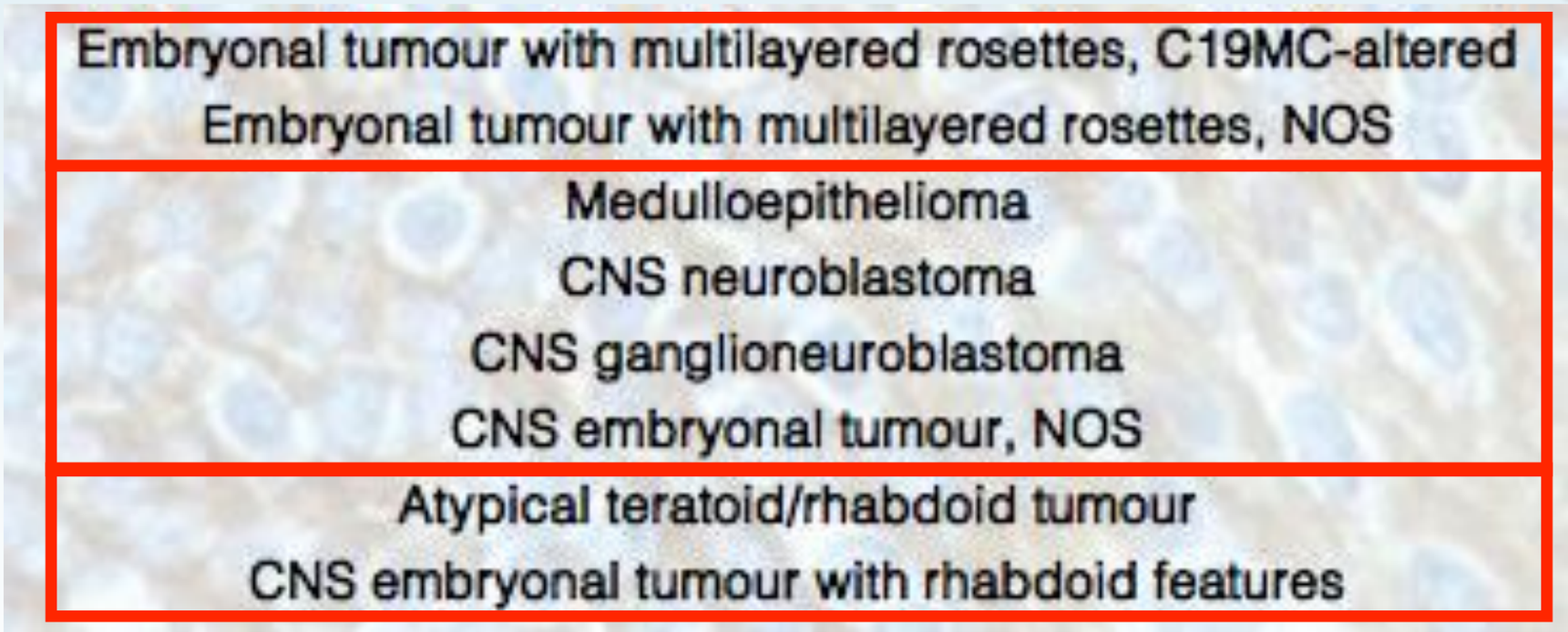


ATRT



Medulloblastoma

Non-Medulloblastoma Embryonal Tumours

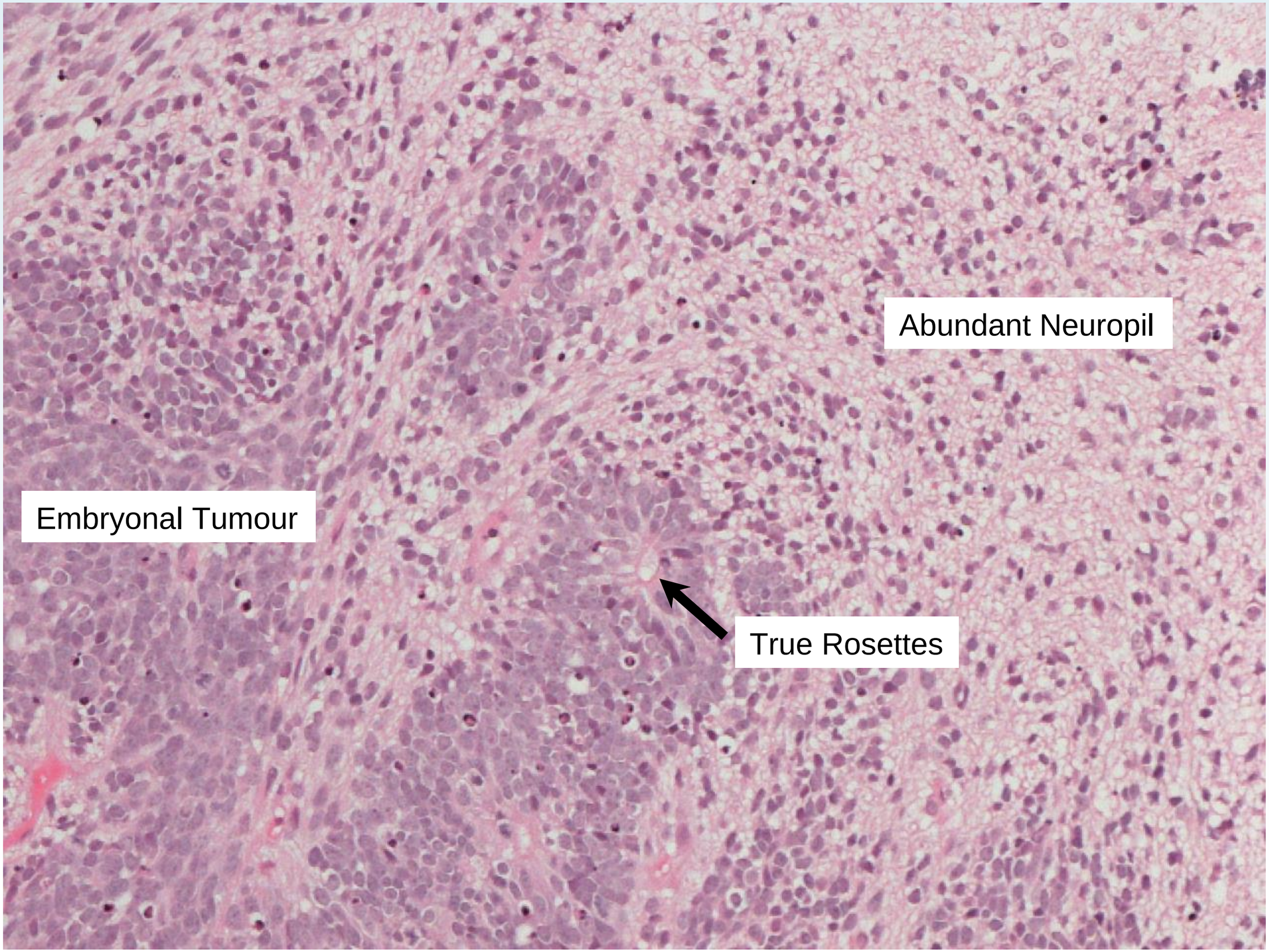


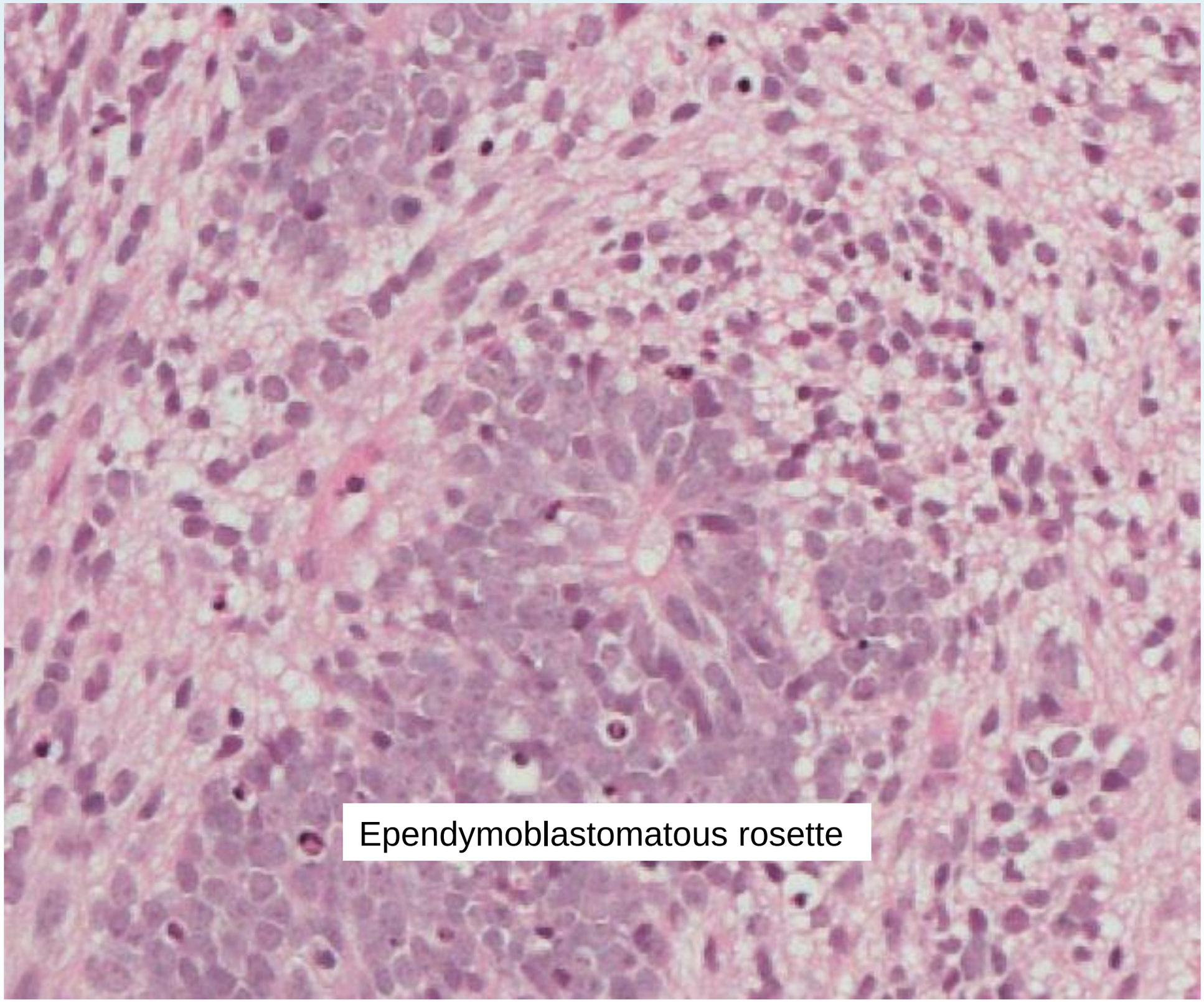
ETMR

CNS Embryonal Tumours

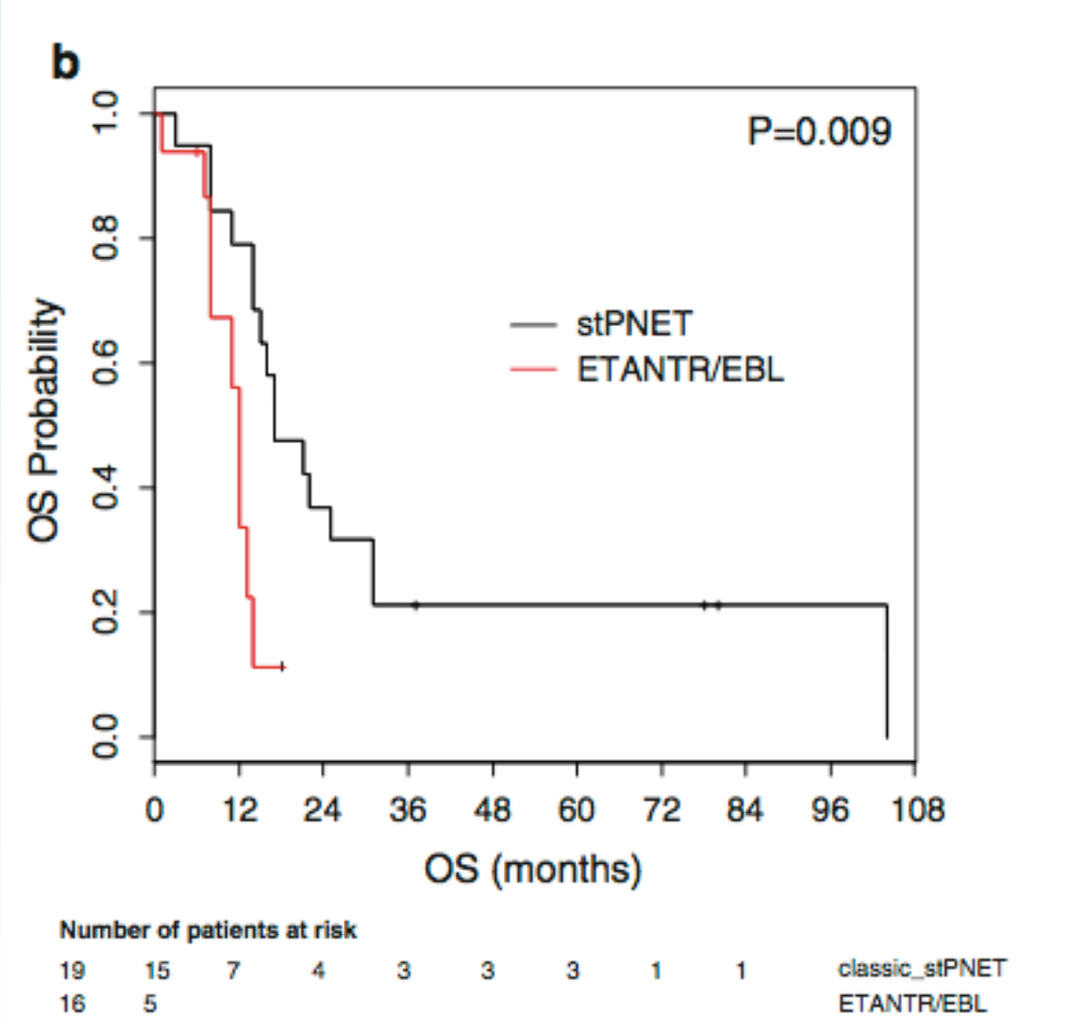
Rhabdoid Tumours

Embryonal Tumour with Multilayered Rosettes (ETMR), *C19MC*-altered


Abundant Neuropil
Embryonal Tumour
True Rosettes


Ependymoblastomatous rosette

ETMR have a very poor prognosis



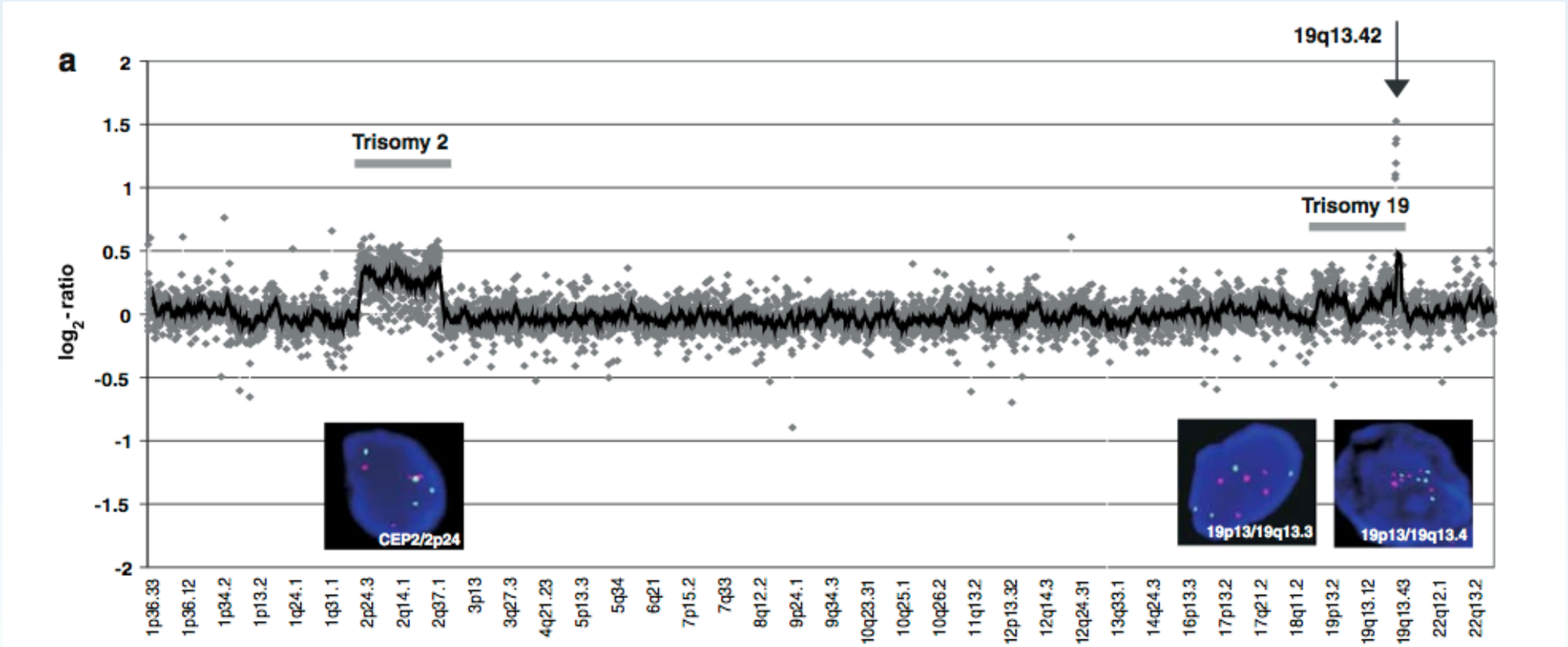
Acta Neuropathol
DOI 10.1007/s00401-010-0688-8

ORIGINAL PAPER

Focal genomic amplification at 19q13.42 comprises a powerful diagnostic marker for embryonal tumors with ependymoblastic rosettes

Andrey Korshunov · Marc Remke · Marco Gessi · Marina Ryzhova · Thomas Hielscher · Hendrik Witt · Vivienne Tobias · Anna Maria Buccoliero · Iacopo Sardi · Marina Paola Gardiman · Jose Bonnin · Bernd Scheithauer · Andreas E. Kulozik · Olaf Witt · Sverre Mork · Andreas von Deimling · Otmar D. Wiestler · Felice Giangaspero · Marc Rosenblum · Torsten Pietsch · Peter Lichter · Stefan M. Pfister

ETMR is defined by amplification of *C19MC*

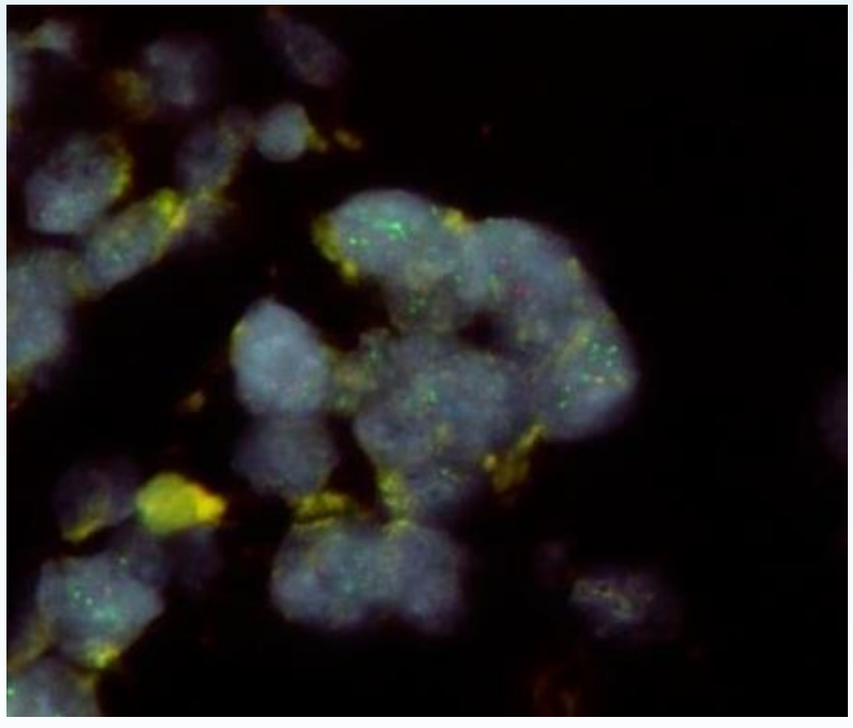


Acta Neuropathol (2009) 117:457–464
DOI 10.1007/s00401-008-0467-y

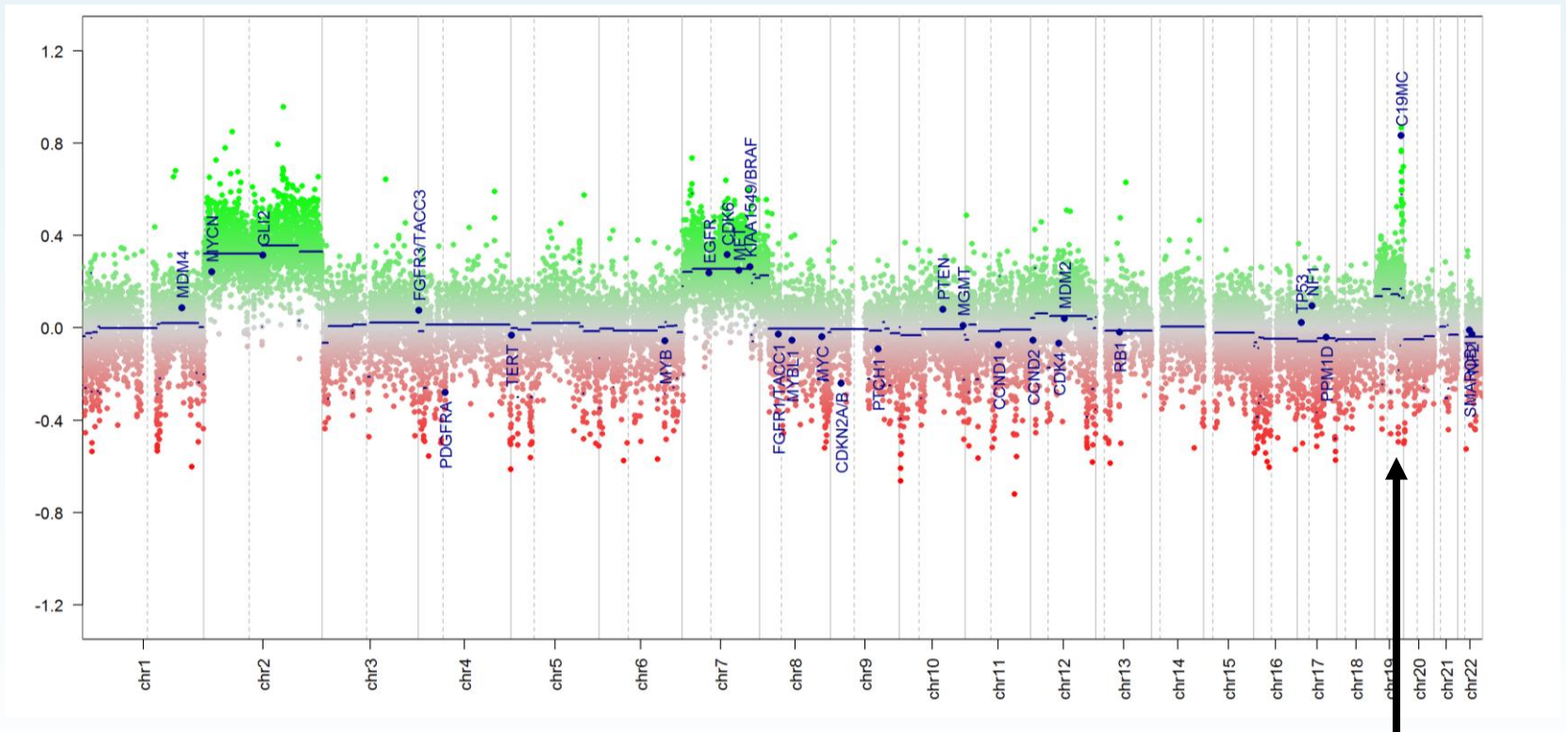
CASE REPORT

Novel genomic amplification targeting the microRNA cluster at 19q13.42 in a pediatric embryonal tumor with abundant neuropil and true rosettes

Diagnostic tests for *C19MC* amplification

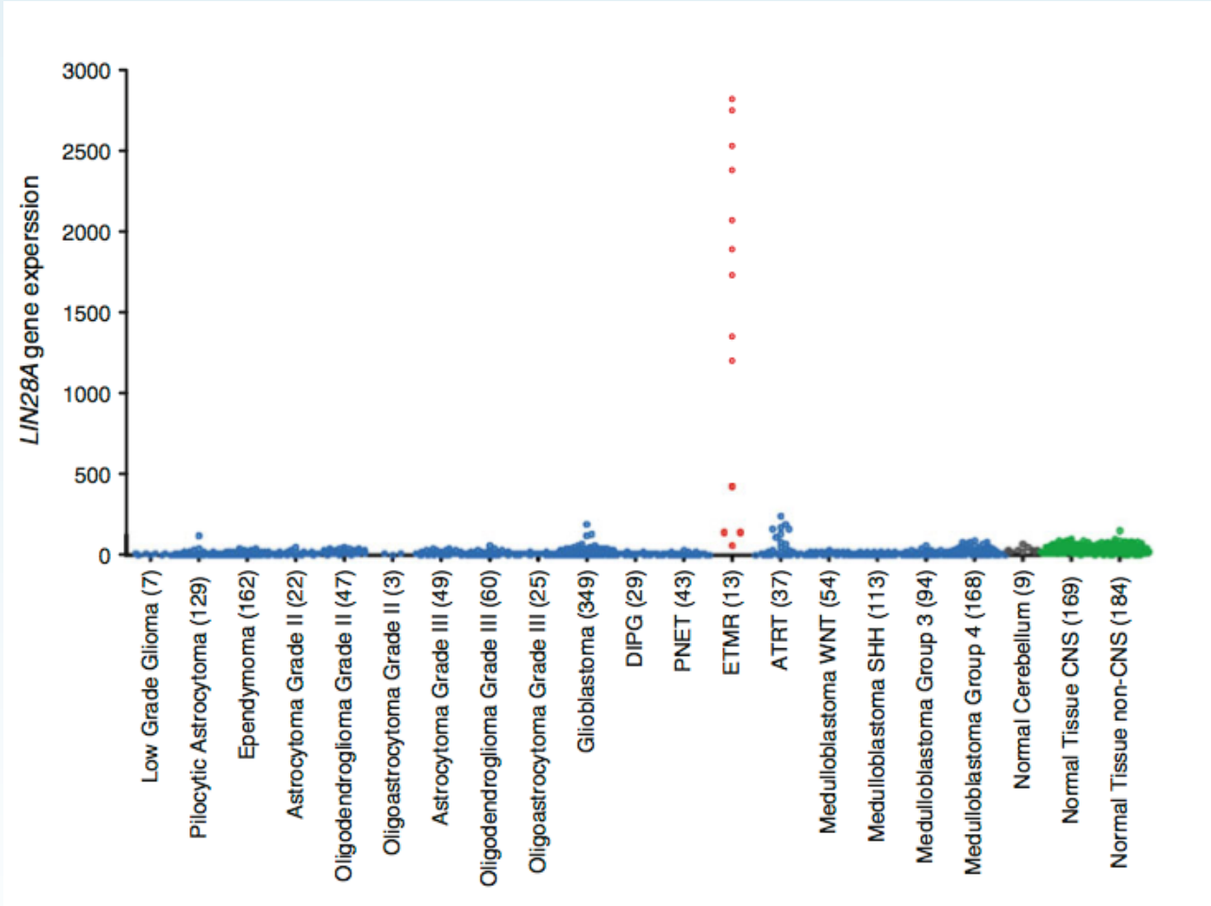


FISH



Methylation array

LIN28A is a marker for ETMR

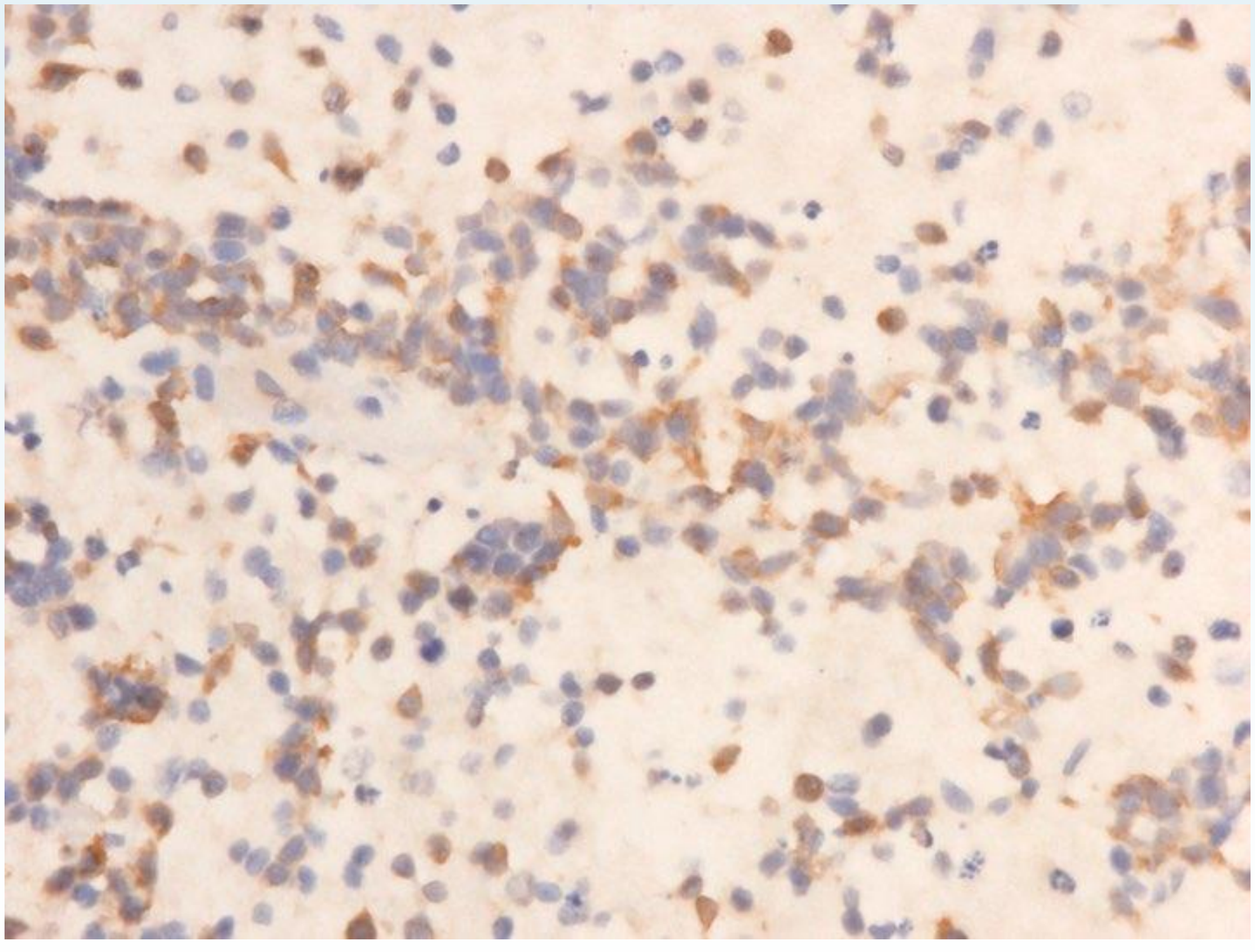


Acta Neuropathol (2012) 124:875–881
DOI 10.1007/s00401-012-1068-3

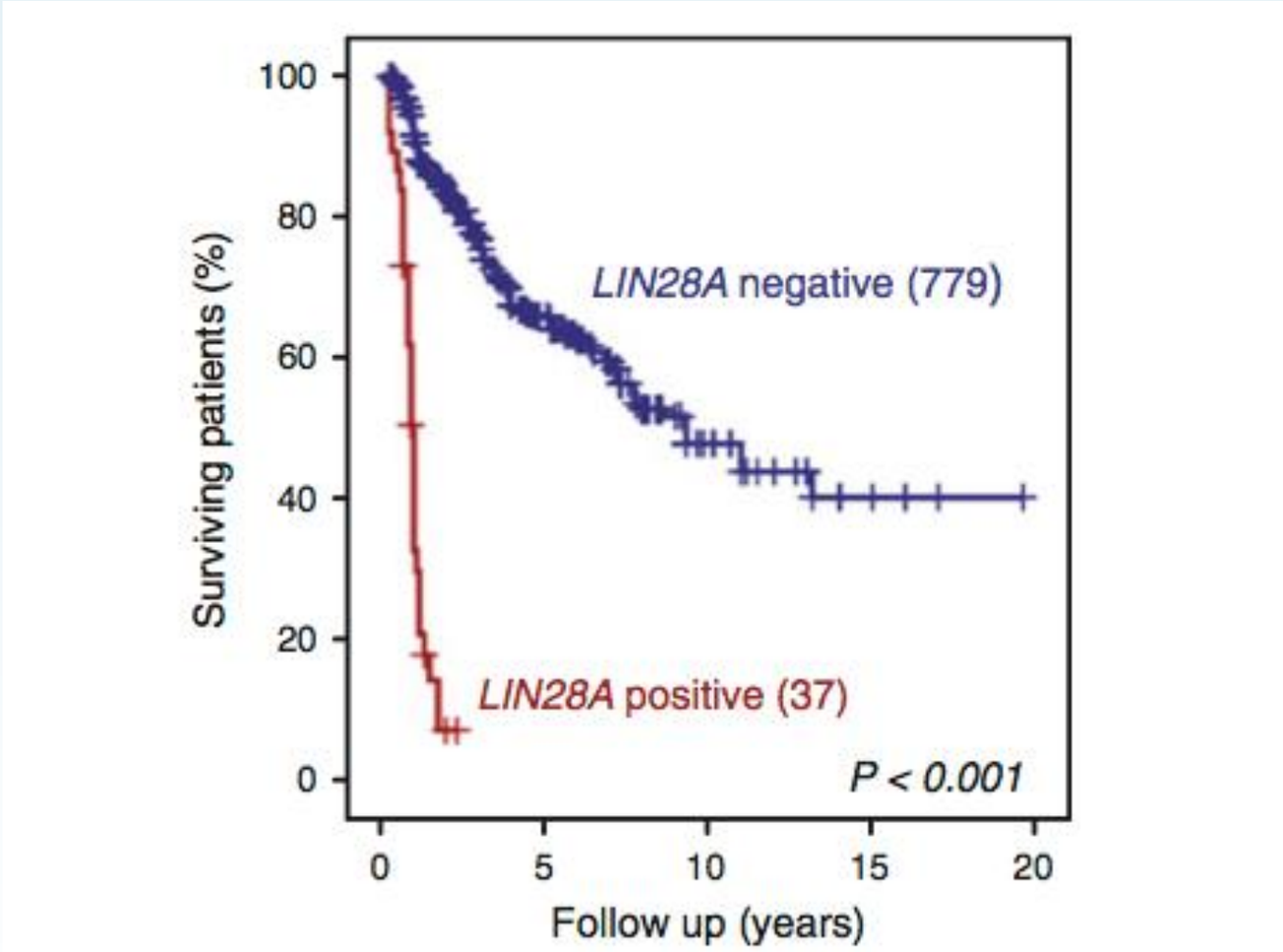
ORIGINAL PAPER

LIN28A immunoreactivity is a potent diagnostic marker of embryonal tumor with multilayered rosettes (ETMR)

LIN28A Immunohistochemistry



LIN28A tumours have a poor prognosis



Acta Neuropathol (2012) 124:875–881
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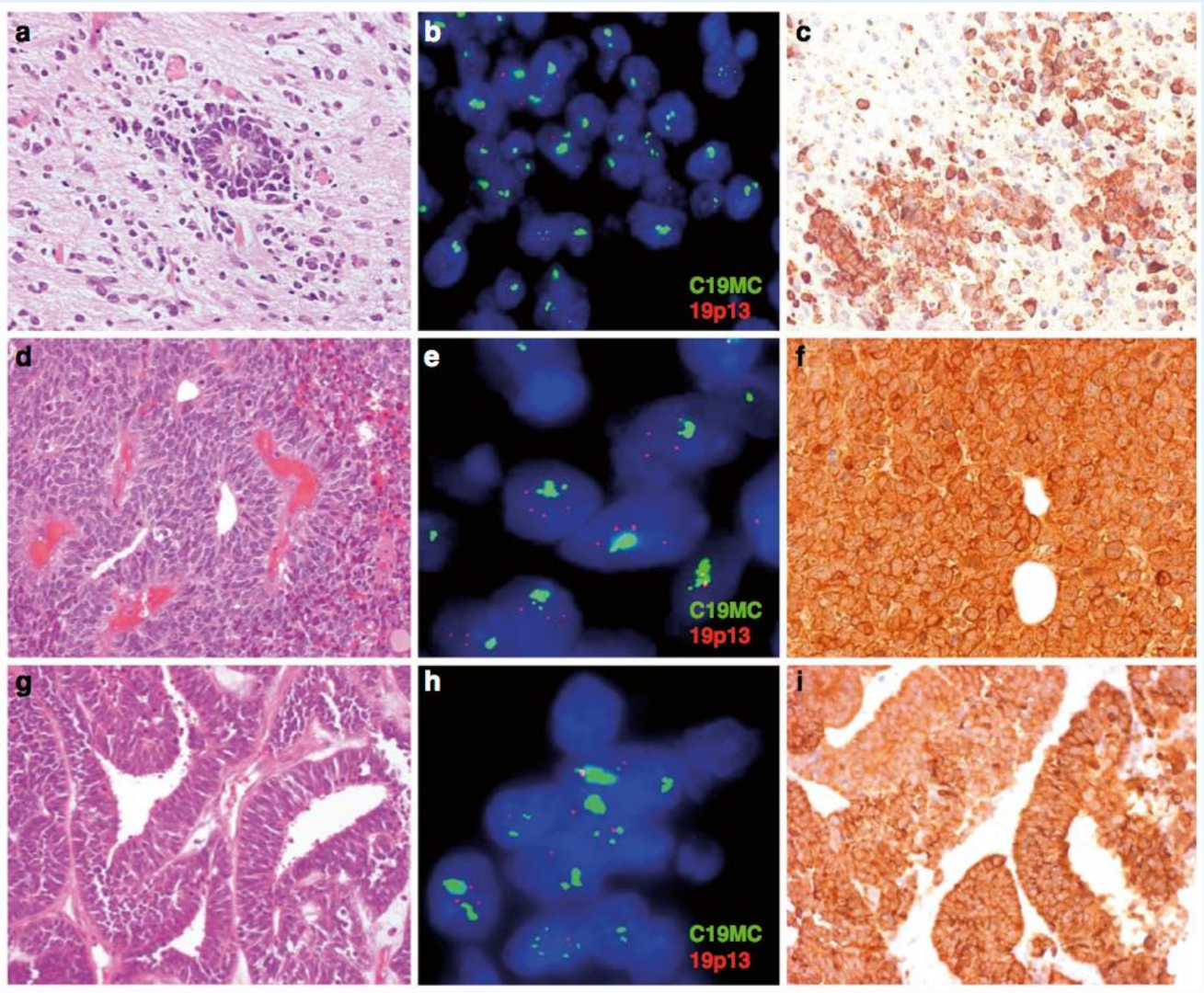
ORIGINAL PAPER

LIN28A immunoreactivity is a potent diagnostic marker of embryonal tumor with multilayered rosettes (ETMR)

Andrey Korshunov · Marina Ryzhova · David T. W. Jones · Paul A. Northcott · Peter van Sluis · Richard Volckmann · Jan Koster · Rogier Versteeg · Cynthia Cowdrey · Arie Perry · Daniel Picard · Marc Rosenblum · Felice Giangaspero · Eleonora Aronica · Ulrich Schüller · Martin Hasselblatt · V. Peter Collins · Andreas von Deimling · Peter Lichter · Annie Huang · Stefan M. Pfister · Marcel Kool

ETMR replaces multiple tumour types

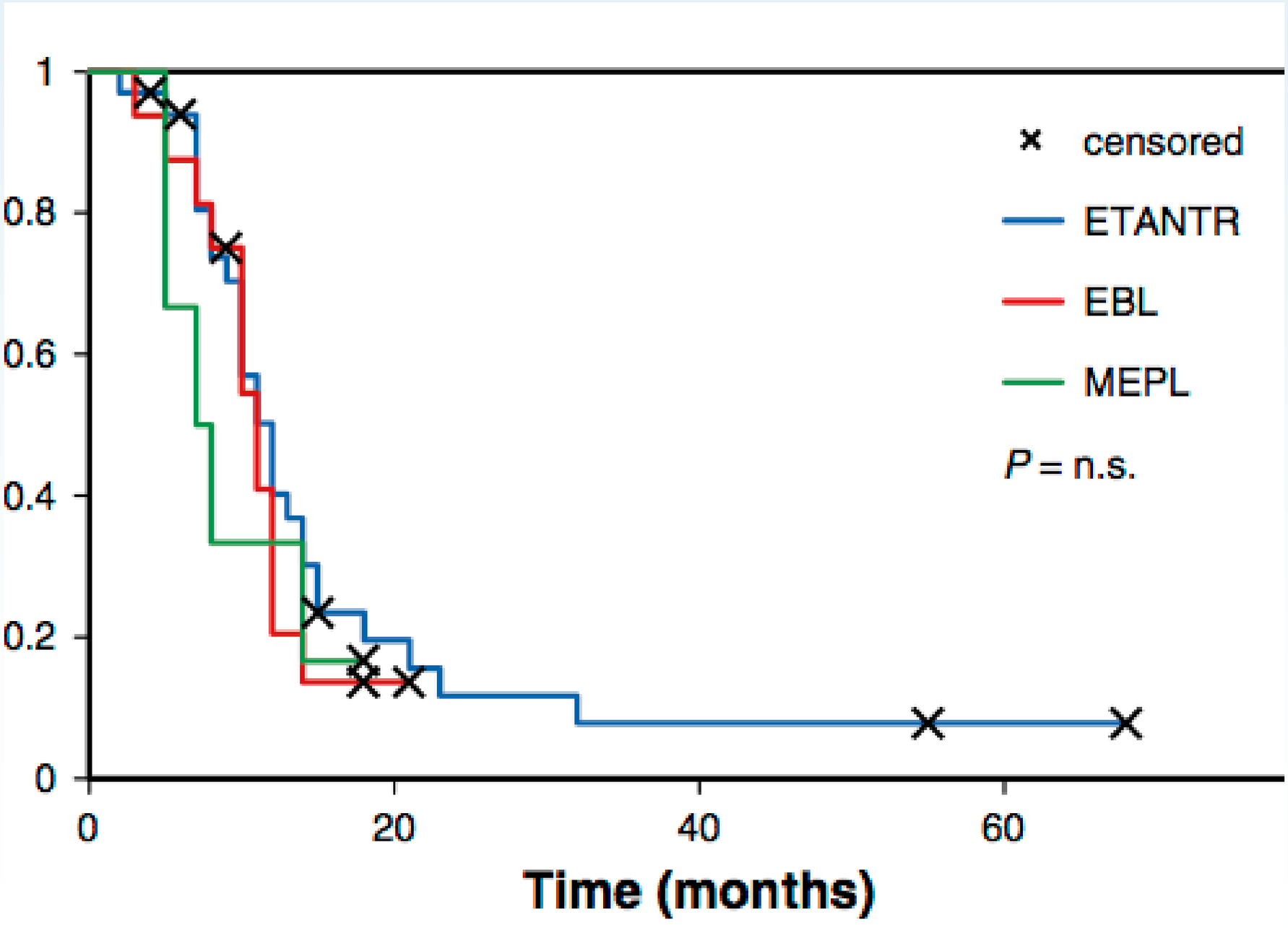


Acta Neuropathol (2014) 128:279–289
DOI 10.1007/s00401-013-1228-0

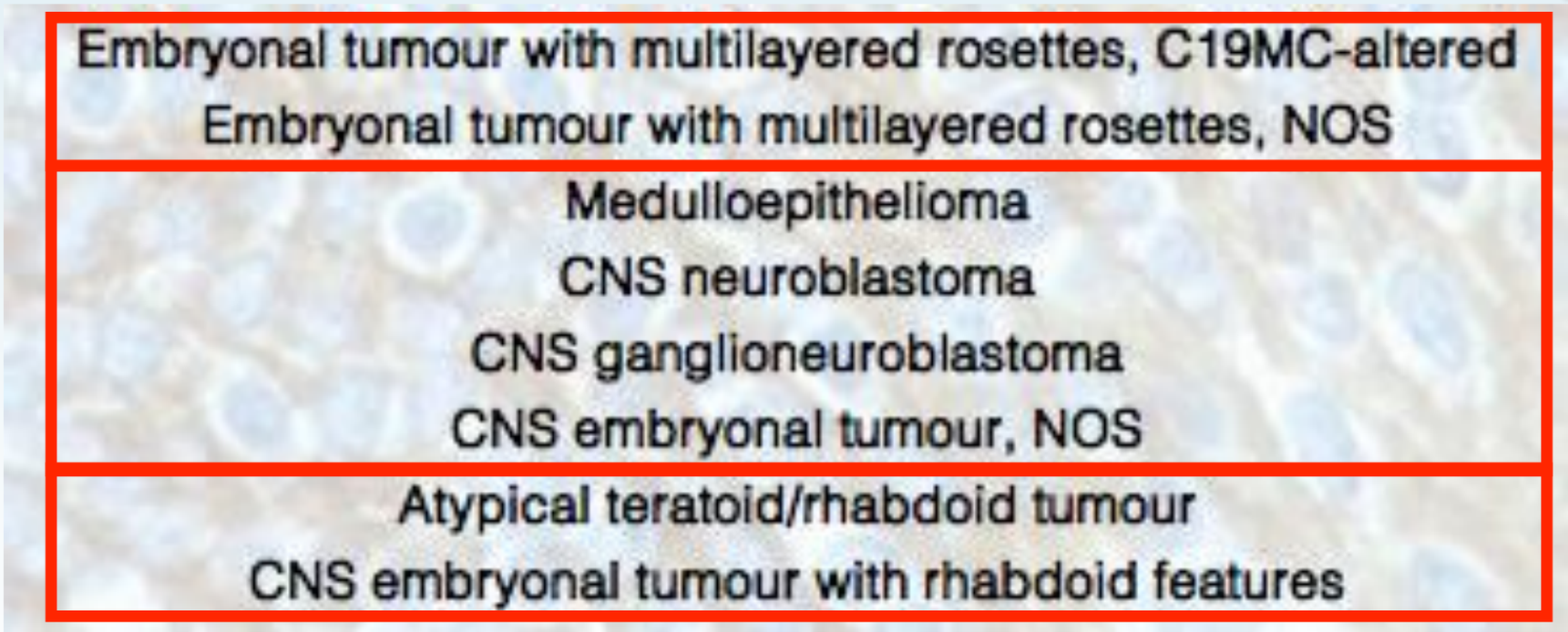
ORIGINAL PAPER

Embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma share molecular similarity and comprise a single clinicopathological entity

ETMR replaces multiple tumour types



Non-Medulloblastoma Embryonal Tumours

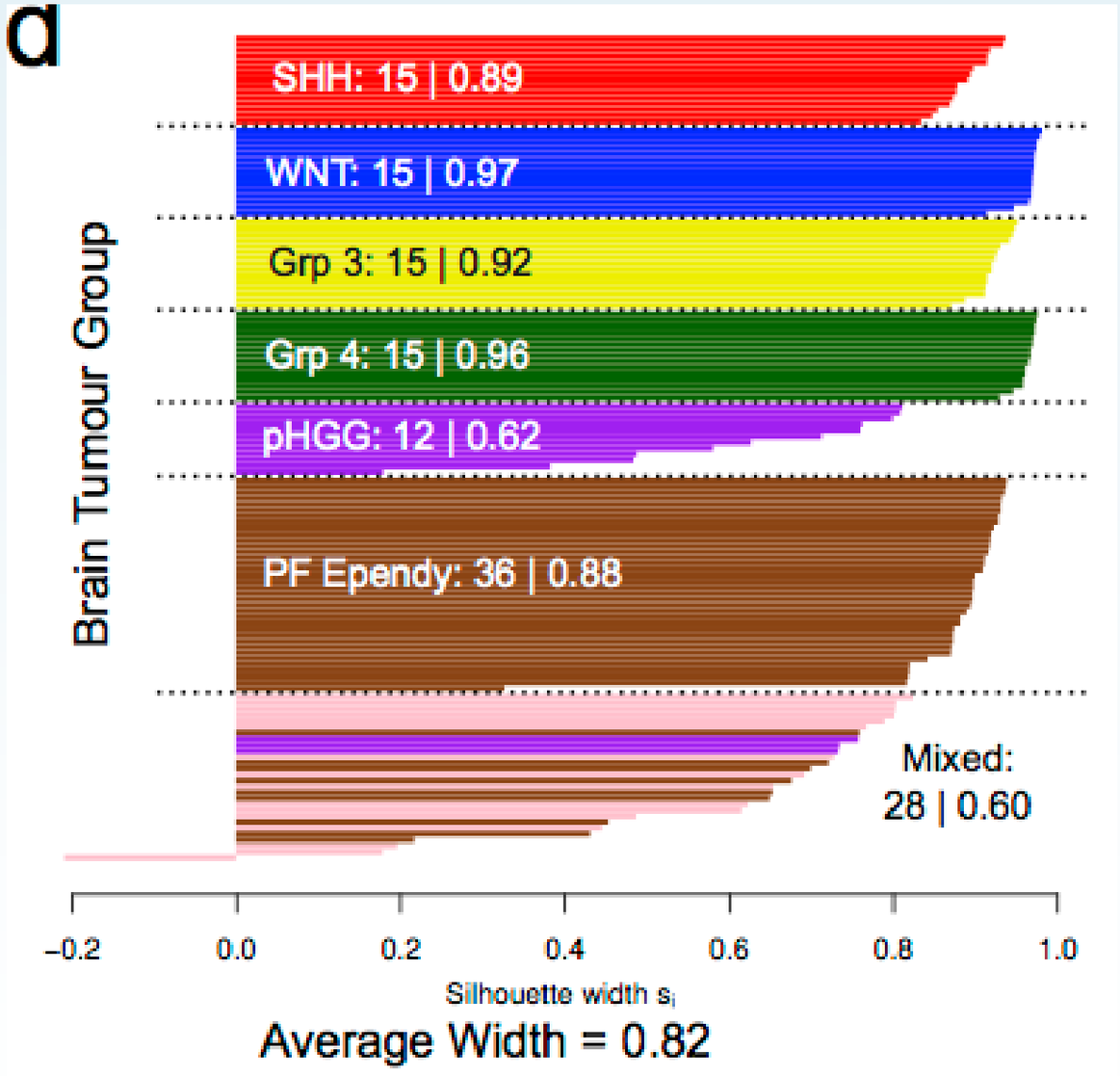


ETMR

CNS Embryonal Tumours

Rhabdoid Tumours

What other tumour are there?



Acta Neuropathol (2013) 126:943–946
DOI 10.1007/s00401-013-1206-6

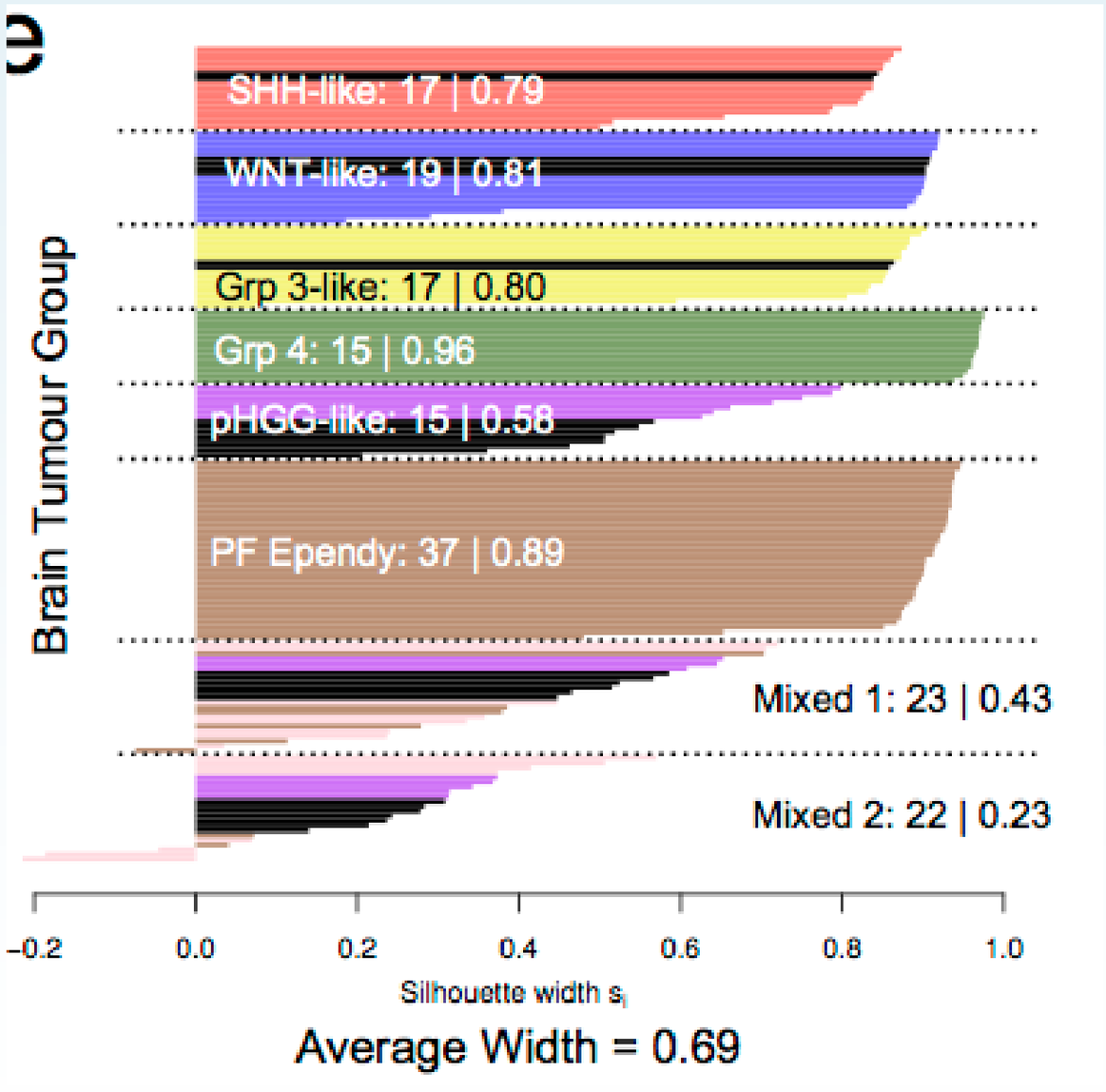
CORRESPONDENCE

Histologically defined central nervous system primitive neuro-ectodermal tumours (CNS-PNETs) display heterogeneous DNA methylation profiles and show relationships to other paediatric brain tumour types

Ed. C. Schwalbe · James T. Hayden · Hazel A. Rogers · Suzanne Miller · Janet C. Lindsey · Rebecca M. Hill · Sarah-Leigh Nicholson · John-Paul Kilday · Martyna Adamowicz-Brice · Lisa Storer · Thomas S. Jacques · Keith Robson · Jim Lowe · Daniel Williamson · Richard G. Grundy · Simon Bailey · Steven C. Clifford

Received: 29 October 2013 / Accepted: 1 November 2013 / Published online: 9 November 2013

What other tumour are there?



Acta Neuropathol (2013) 126:943–946
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CORRESPONDENCE

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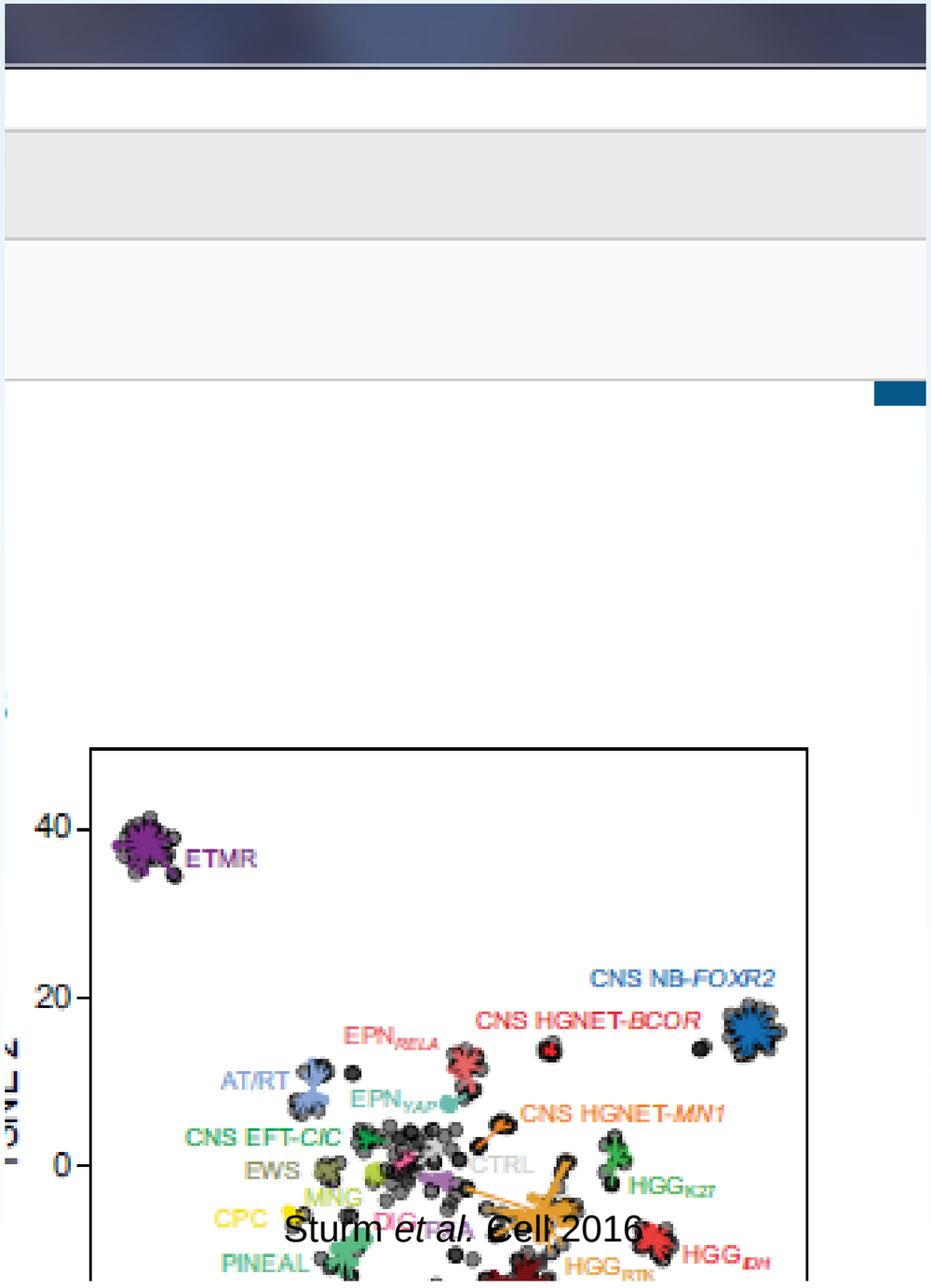
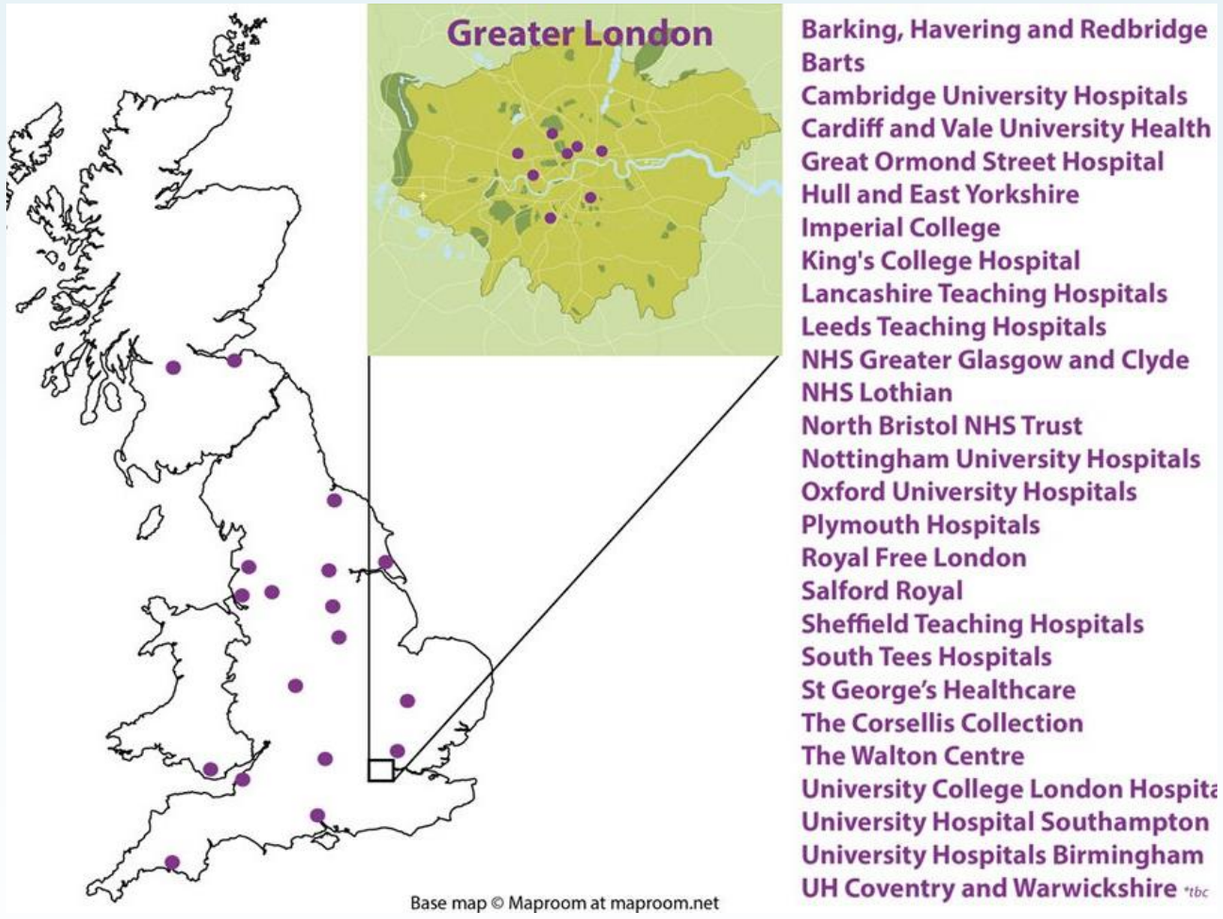
Received: 29 October 2013 / Accepted: 1 November 2013 / Published online: 9 November 2013

Identification of novel tumour types



Sturm *et al.* Cell 2016

Classification of embryonal and other rare CNS tumours in the UK



Jess Pickles

Amy Fairchild

Sherry Yasin

INSTINCT

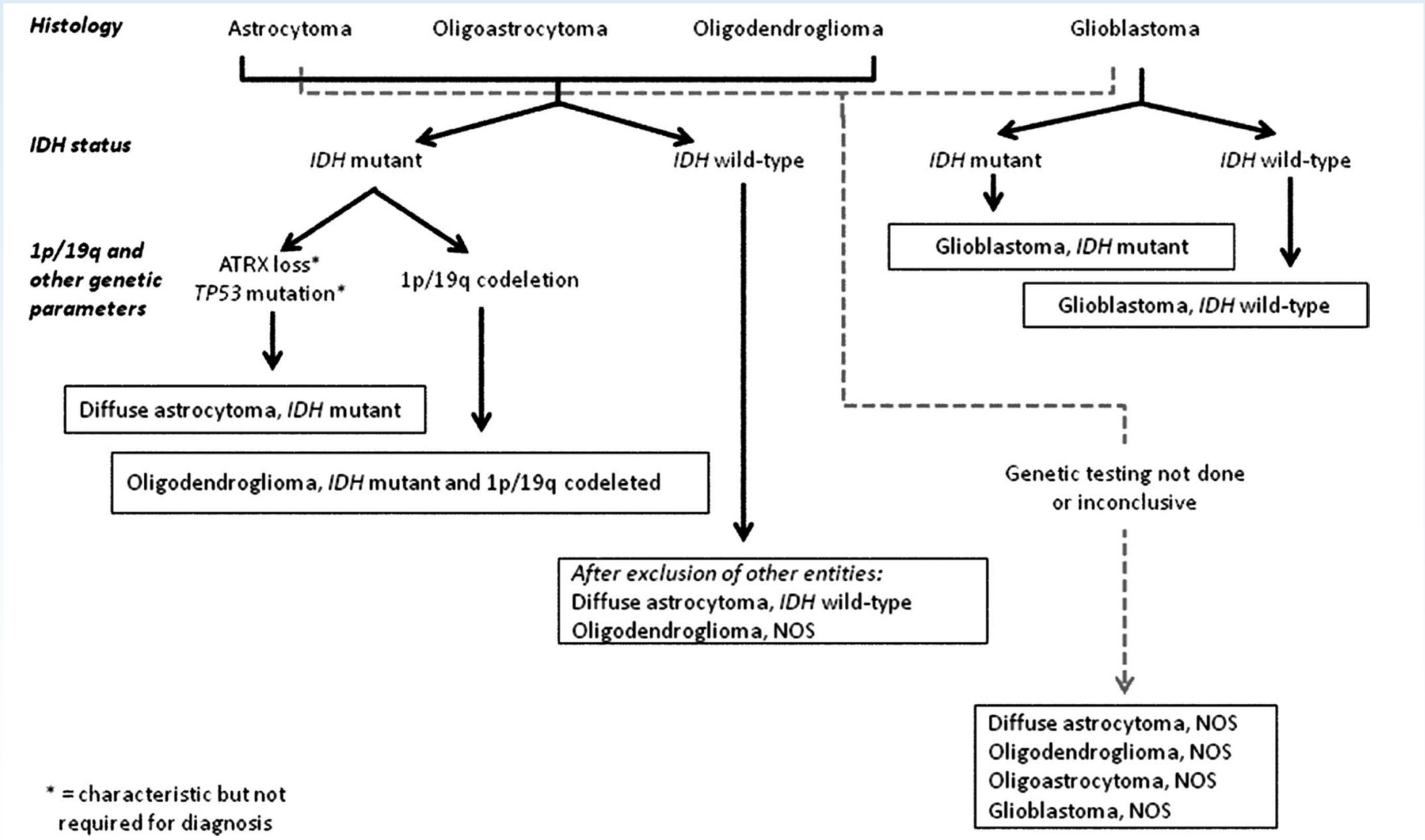
Childhood Astrocytoma

Classification of gliomas

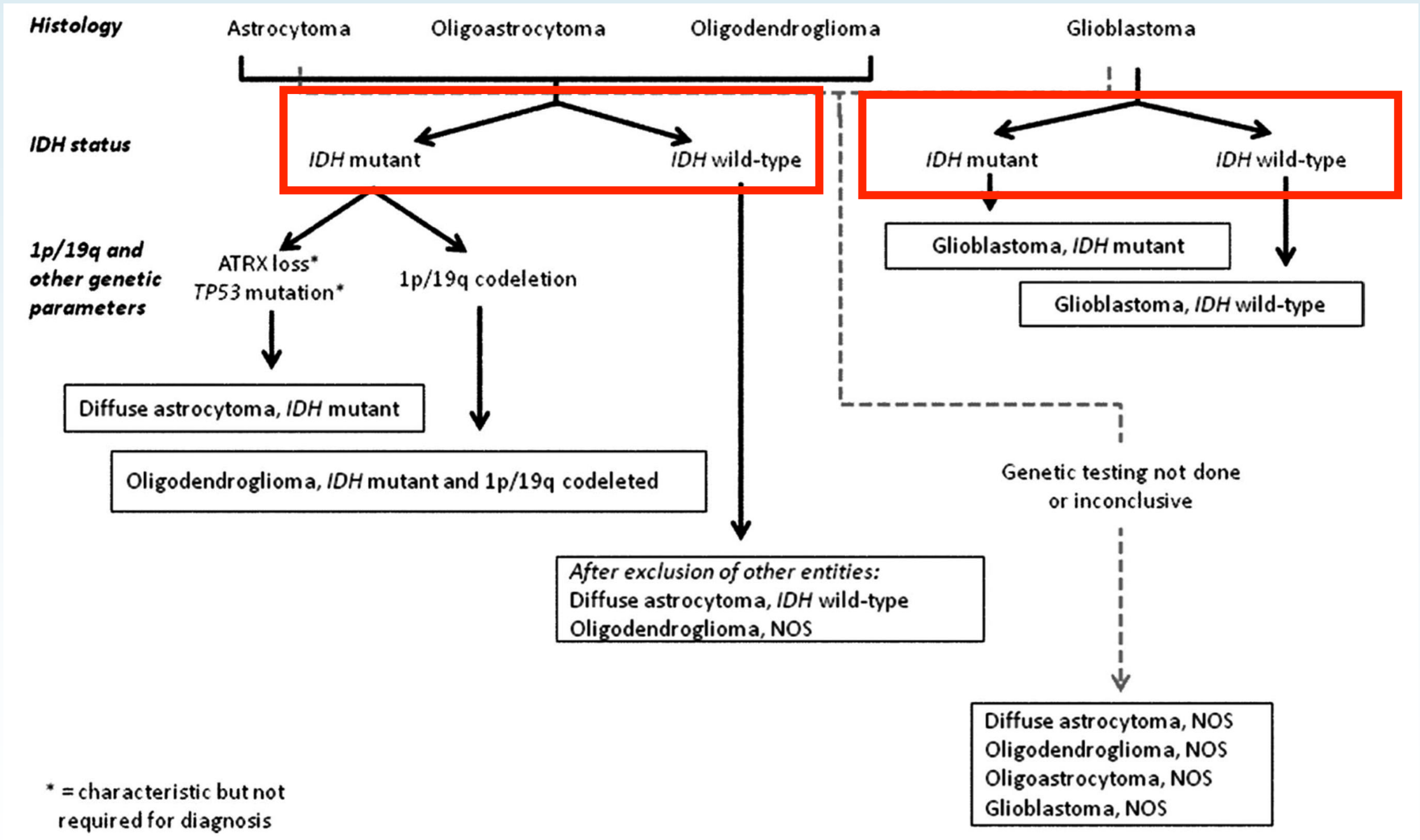
Diffuse astrocytoma/oligodendrogolioma

Other astrocytomas

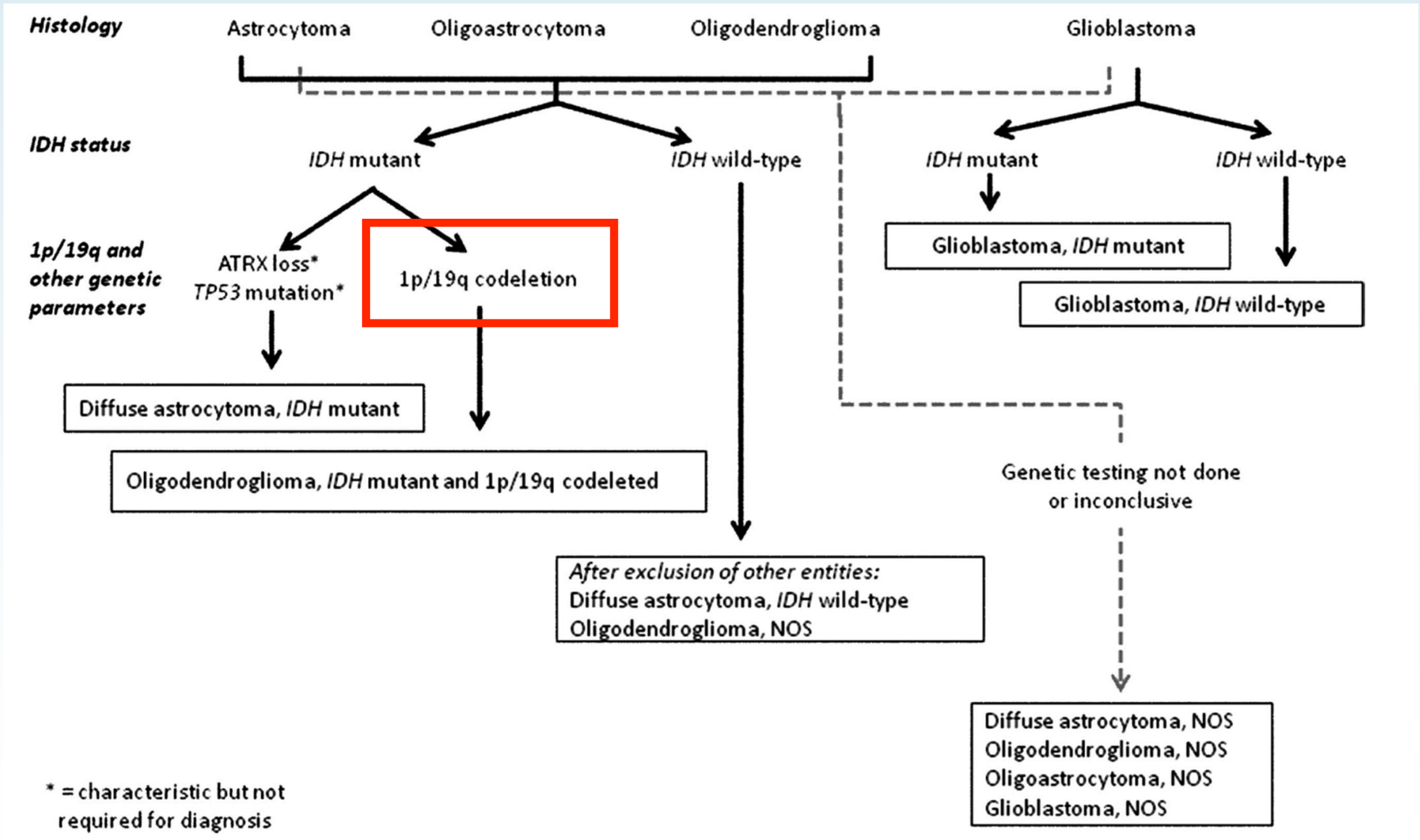
Adult gliomas



Adult gliomas: IDH1/2 mutations



Adult gliomas: 1p19q codeletion



Paediatric tumours are genetically distinct

Acta Neuropathol (2011) 121:753–761
DOI 10.1007/s00401-011-0810-6

ORIGINAL PAPER

Adult grade II diffuse astrocytomas are genetically distinct from and more aggressive than their paediatric counterparts

David T. W. Jones · Shani A. Mulholland · Danita M. Pearson ·
Deborah S. Malley · Samuel W. S. Openshaw · Sally R. Lambert ·
Lu Liu · L. Magnus Bäcklund · Koichi Ichimura · V. Peter Collins

Acta Neuropathol (2005) 109: 387–392
DOI 10.1007/s00401-004-0976-2

REGULAR PAPER

Portia A. Kreiger · Yoshifumi Okada · Scott Simon
Lucy B. Rorke · David N. Louis · Jeffrey A. Golden

Losses of chromosomes 1p and 19q are rare in pediatric oligodendrogliomas

Paediatric diffuse tumours in the WHO

Paediatric diffuse astrocytoma

Although the histopathology of paediatric diffuse astrocytoma resembles that of adult diffuse astrocytoma, there are many important distinctions between the disease in children and in adults.

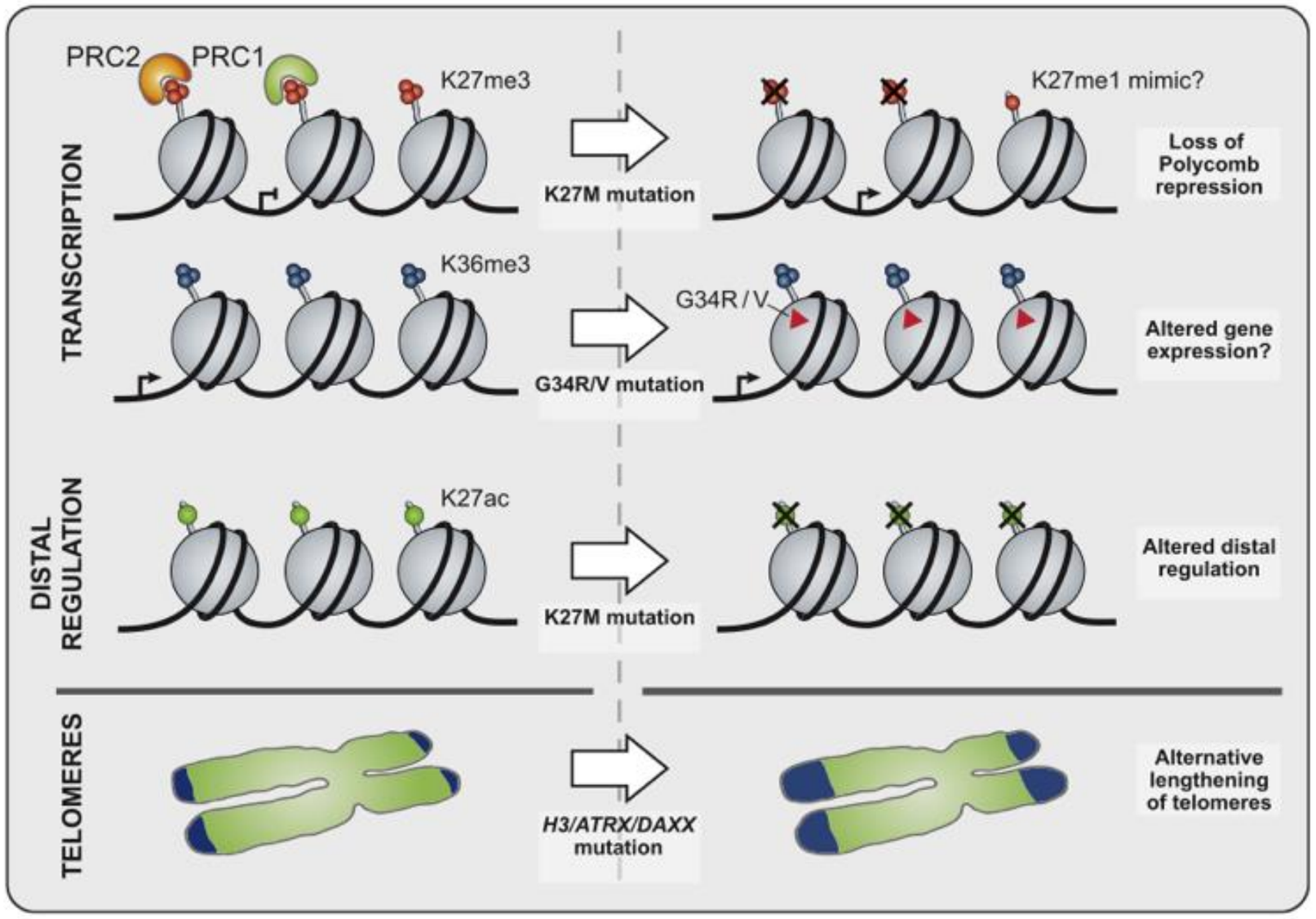
Clinicopathological aspects

The annual incidence of paediatric diffuse astrocytoma (defined by patient age < 20 years at diagnosis) is 0.27 cases per 100 000 population; lower than that of adult diffuse astrocytoma, which is 0.58 per 100 000 {1863}. Most paediatric diffuse astrocytomas are located in the cerebral hemispheres, but a significant proportion present in the thalamus, which is an unusual site for adult diffuse astrocytoma. Anaplastic progression occurs in approximately 75% of adult lesions, but is rare in paediatric tumours {284}.

Genetic aspects

Diffuse astrocytomas in children and adults have distinct genetic profiles. However, diffuse astrocytomas with genetically defined so-called adult-type disease can present in adolescents, and so-called paediatric-type disease can present in young adults. Paediatric diffuse astrocytomas are characterized mainly by alterations in *MYB* and *BRAF*. Amplification or rearrangements of *MYB* are detected in approximately 25% of paediatric diffuse astrocytomas {2518, 2855}. Rearrangements of *MYBL1* have also been described {2068}. Other paediatric diffuse astrocytomas harbour *BRAF* V600E mutations, *FGFR1* alterations, or *KRAS* mutations {2855}. Rare paediatric diffuse astrocytomas contain the H3 K27M mutation usually found in paediatric high-grade gliomas {2855}. The mutations in *IDH1*, *IDH2*, *TP53*, and *ATRX* that are frequently found in adult diffuse astrocytomas are not present in the paediatric tumours {2443}.

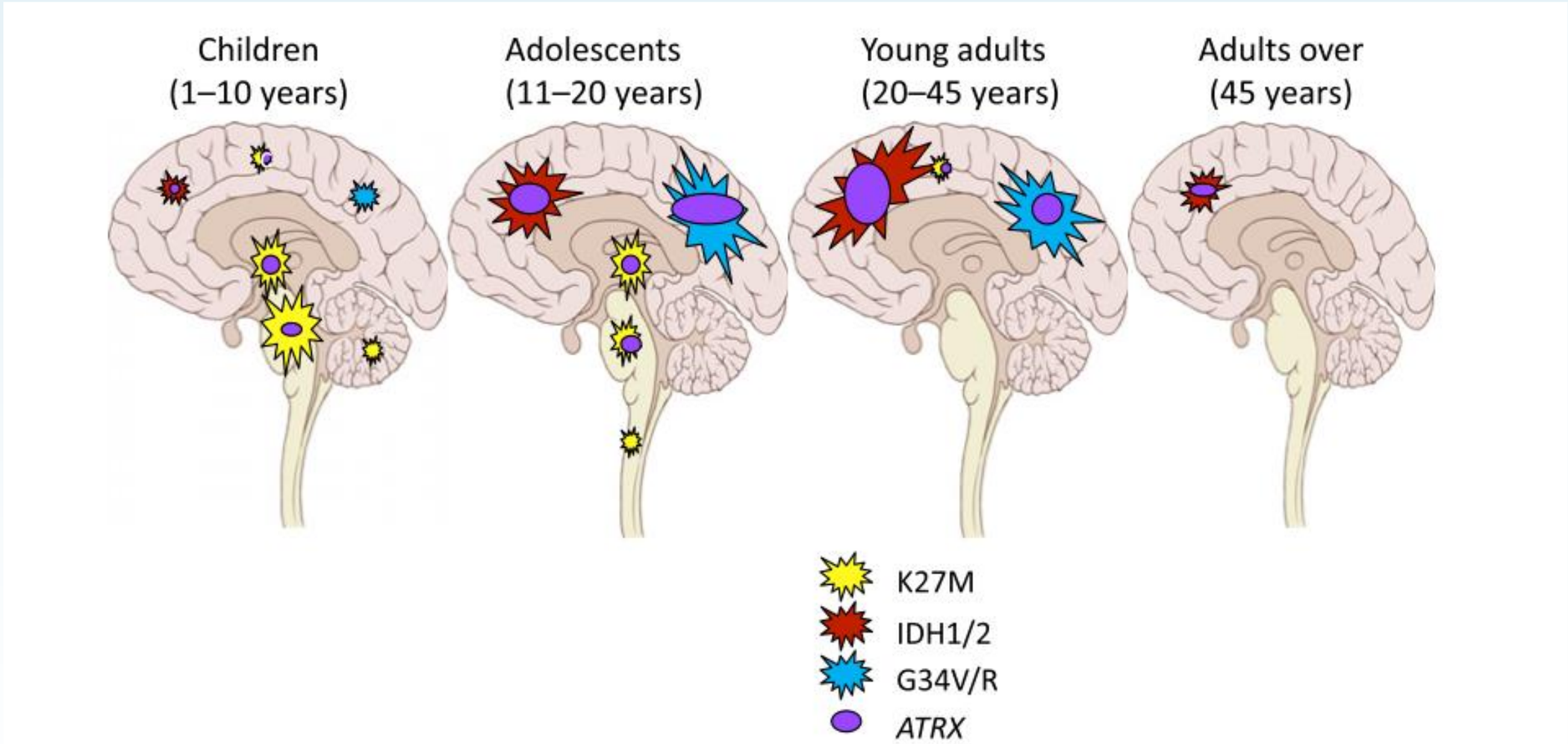
Paediatric high grade gliomas have mutations in histone genes



A Tell-Tail Sign of Chromatin: Histone Mutations Drive Pediatric Glioblastoma

Esther Rheinbay,[1,2,3,4] David N. Louis,[2] Bradley E. Bernstein,[1,2,3,*] and Mario L. Suvà[1,2,3]
[1]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[2]Department of Pathology, Center for Cancer Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[3]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
[4]Bioinformatics Program, Boston University, Boston, MA 02215, USA
*Correspondence: bernstein.bradley@mgh.harvard.edu
DOI 10.1016/j.ccr.2012.03.001

Mutations in paediatric glioma relate to location and age

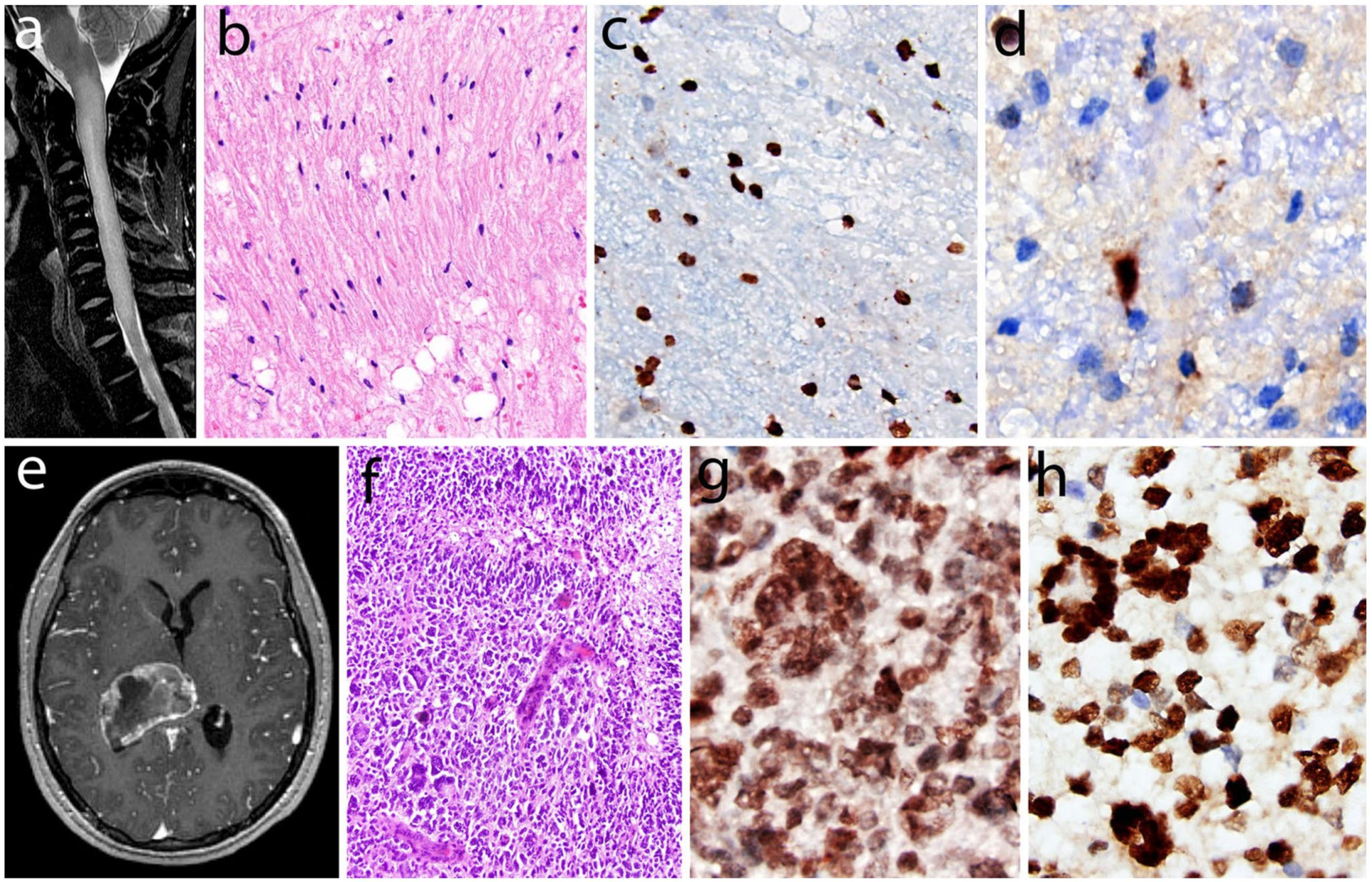


MINI-SYMPOSIUM: When Genetics Meets Epigenetics—A New Option for Therapeutic Intervention in Brain Tumors?

Chromatin Remodeling Defects in Pediatric and Young Adult Glioblastoma: A Tale of a Variant Histone 3 Tail

Adam M. Fontebasso[1]; Xiao-Yang Liu[2]; Dominik Sturm[3]; Nada Jabado[1,2,4]

Diffuse midline glioma, H3 K27M-mutant

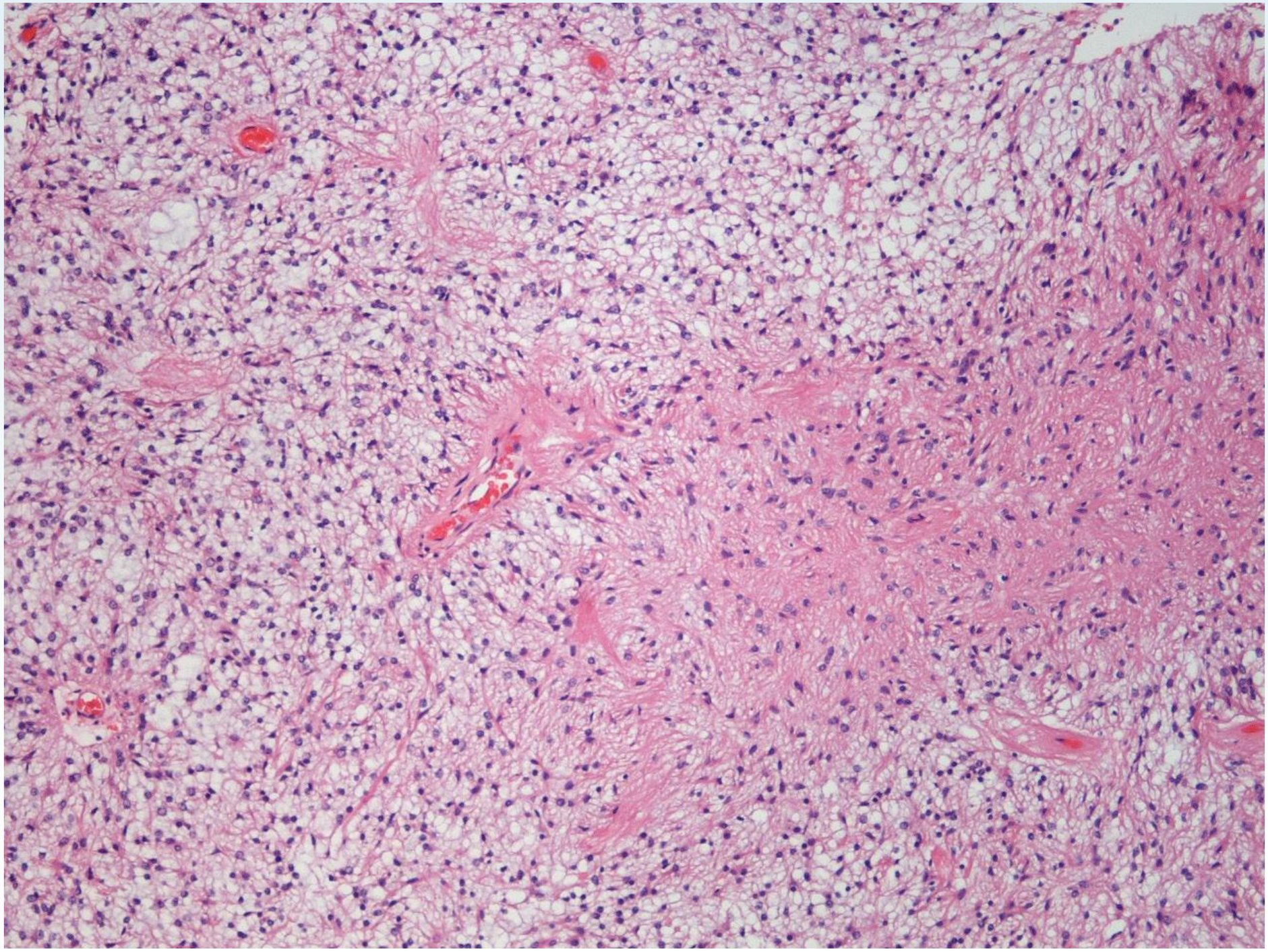


Classification of gliomas

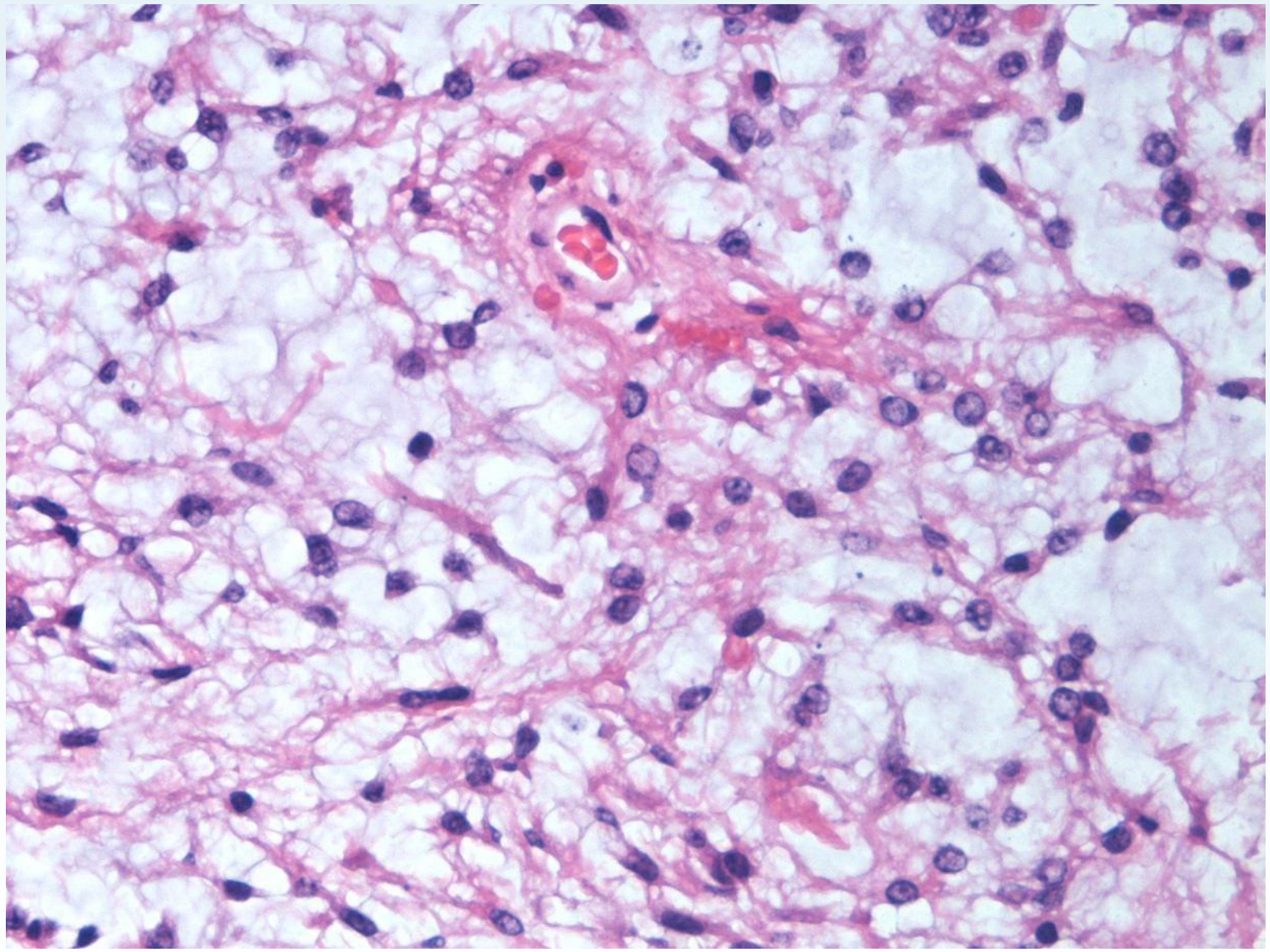
Diffuse astrocytoma/oligodendrogolioma

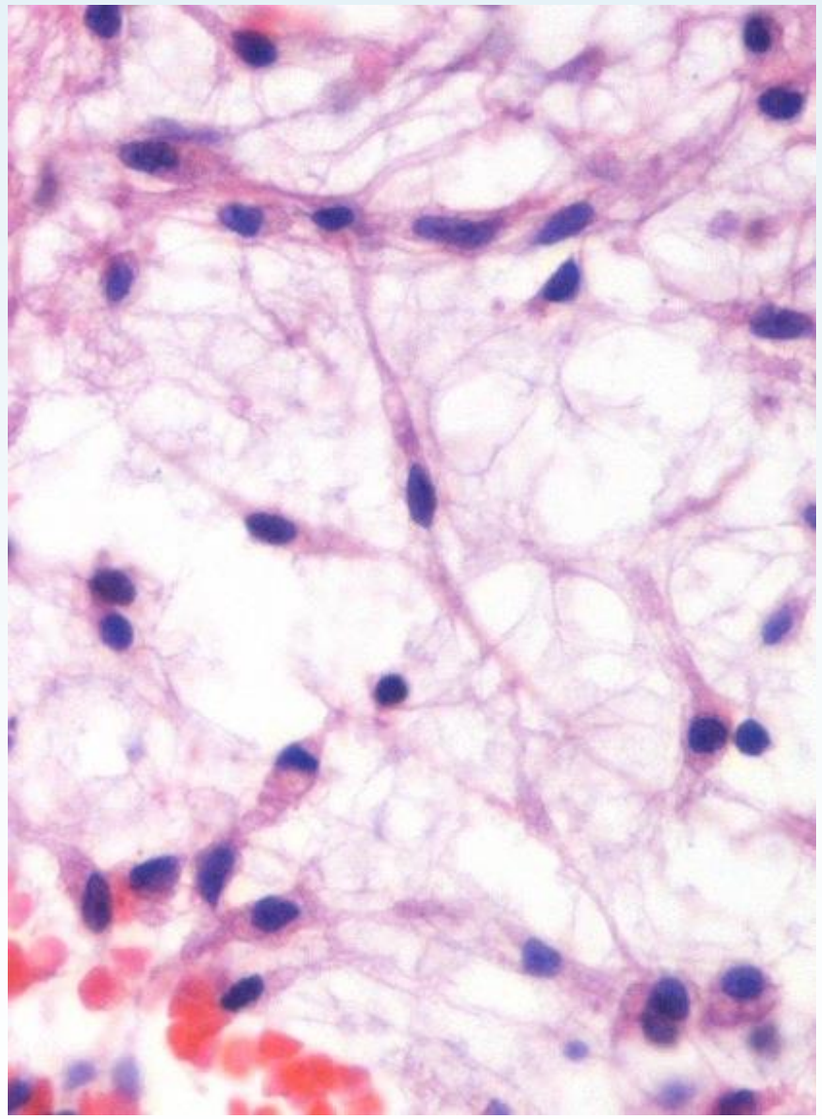
Other astrocytomas

Pilocytic astrocytoma: Architecture

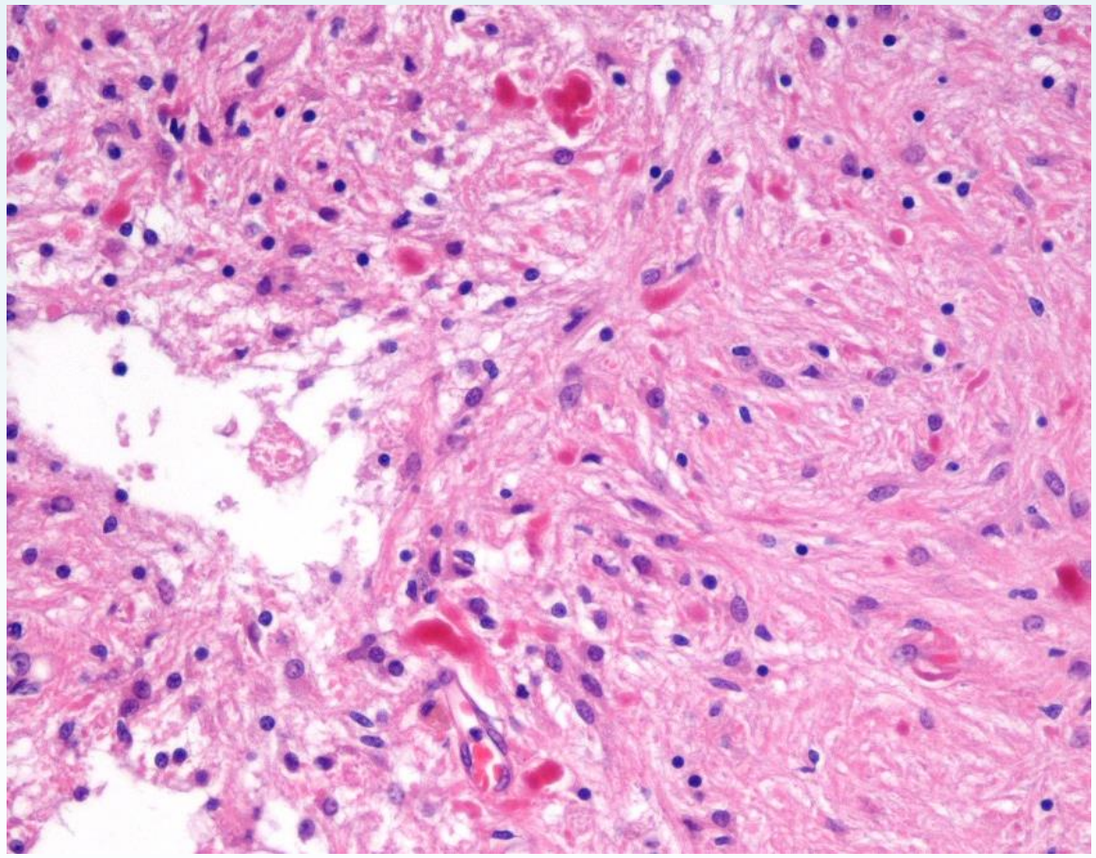


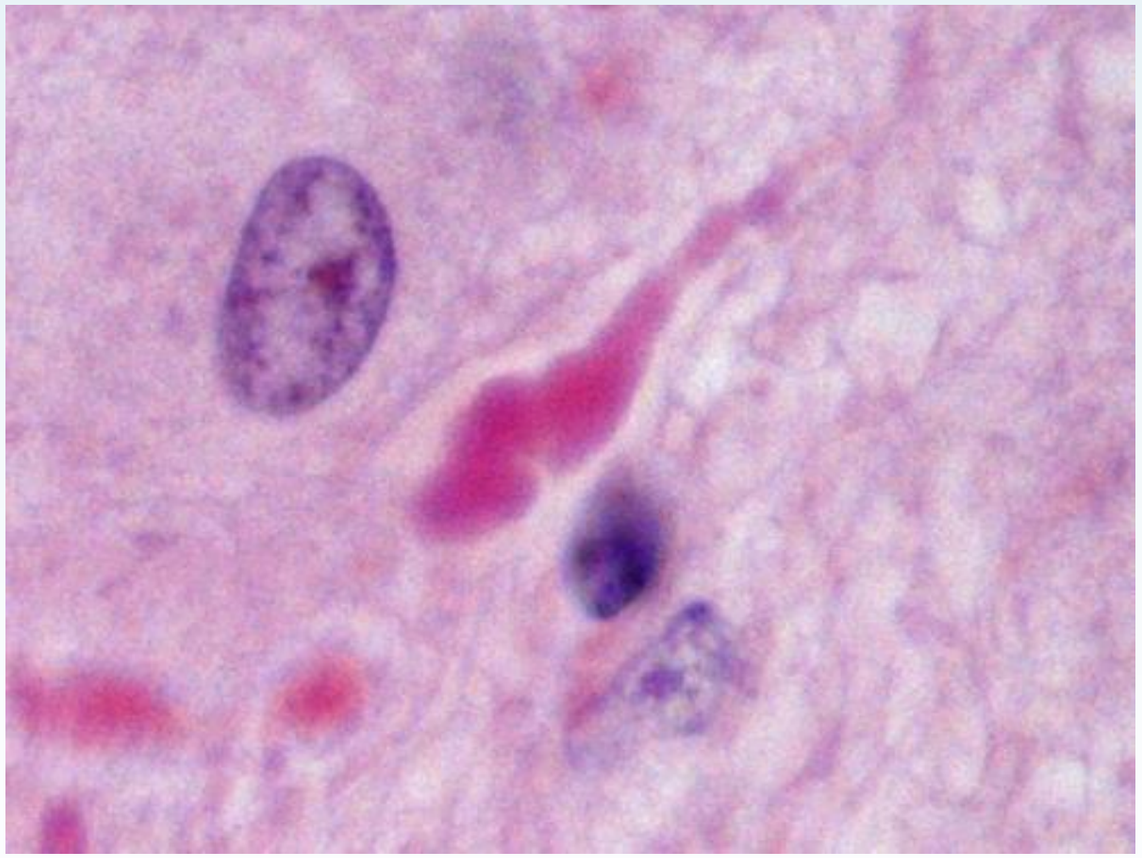
Pilocytic astrocytoma: Cytology



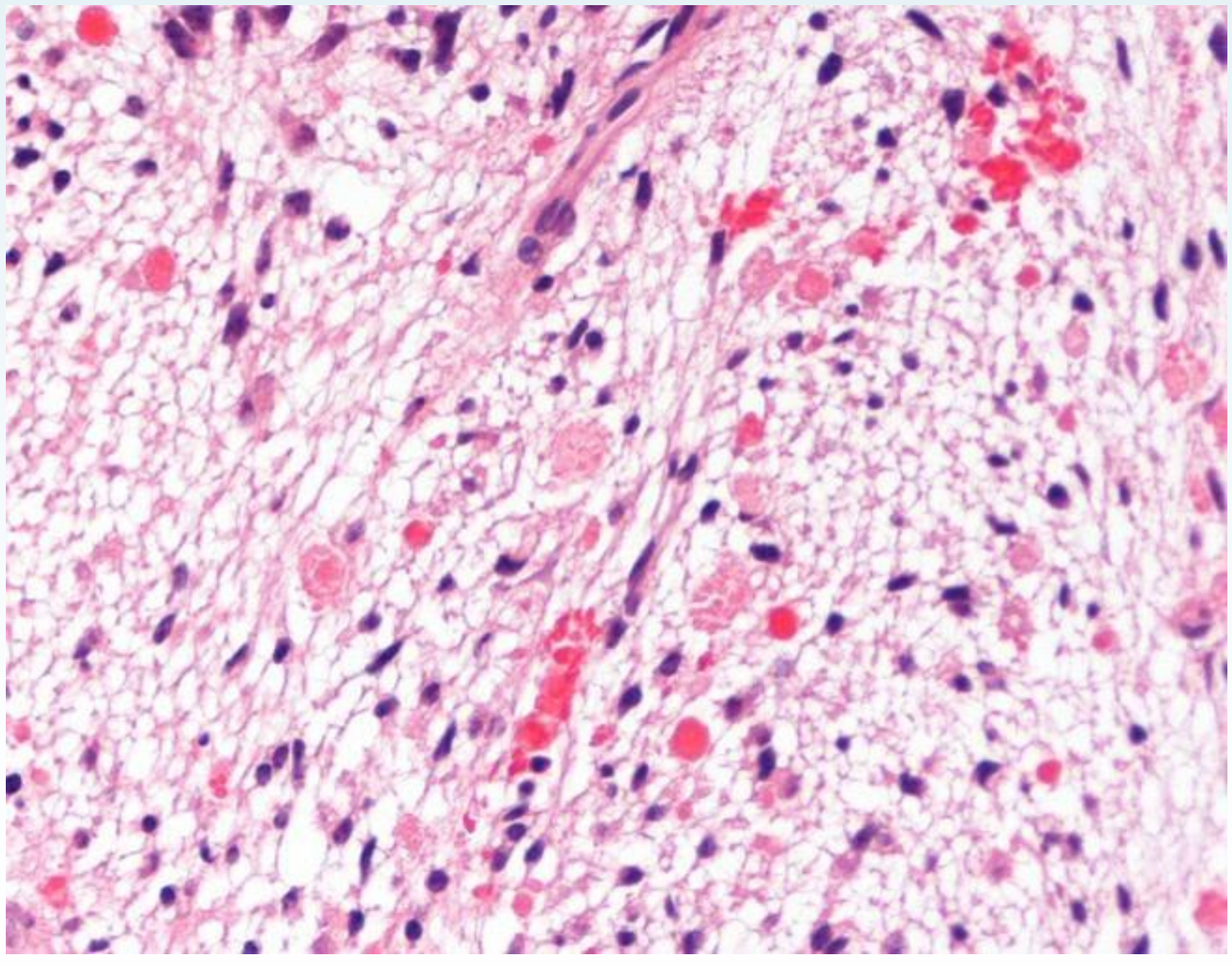


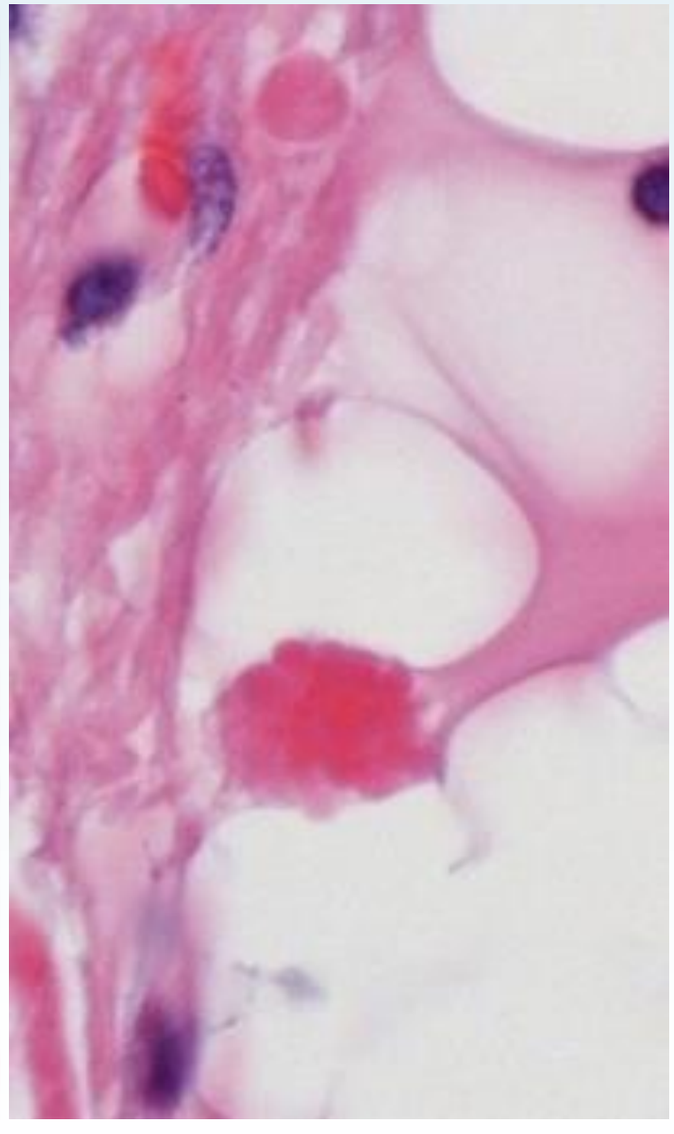
Pilocytic astrocytoma: Rosenthal fibres



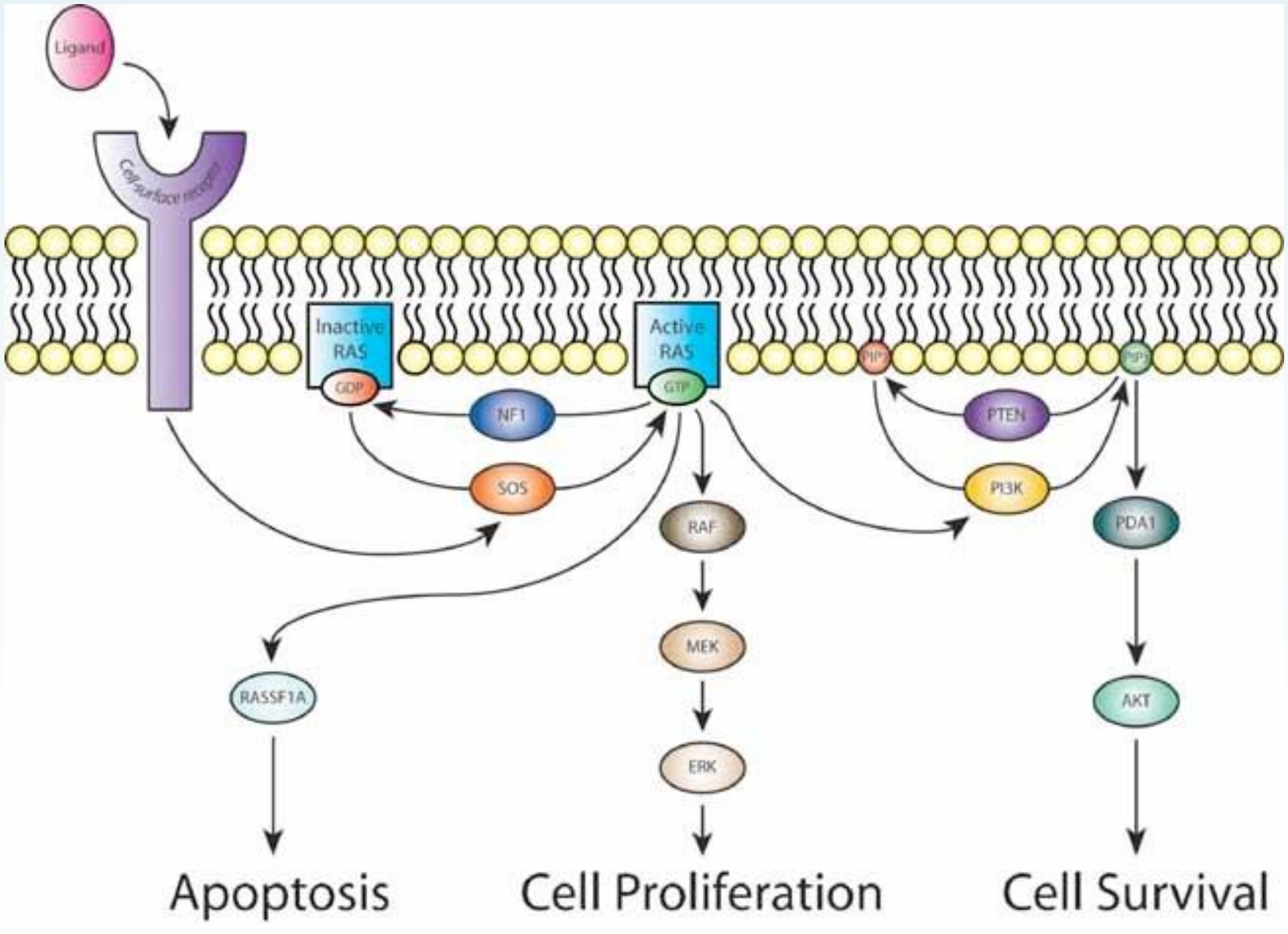


Pilocytic astrocytoma: Eosinophilic Granular Bodies (EGBs)

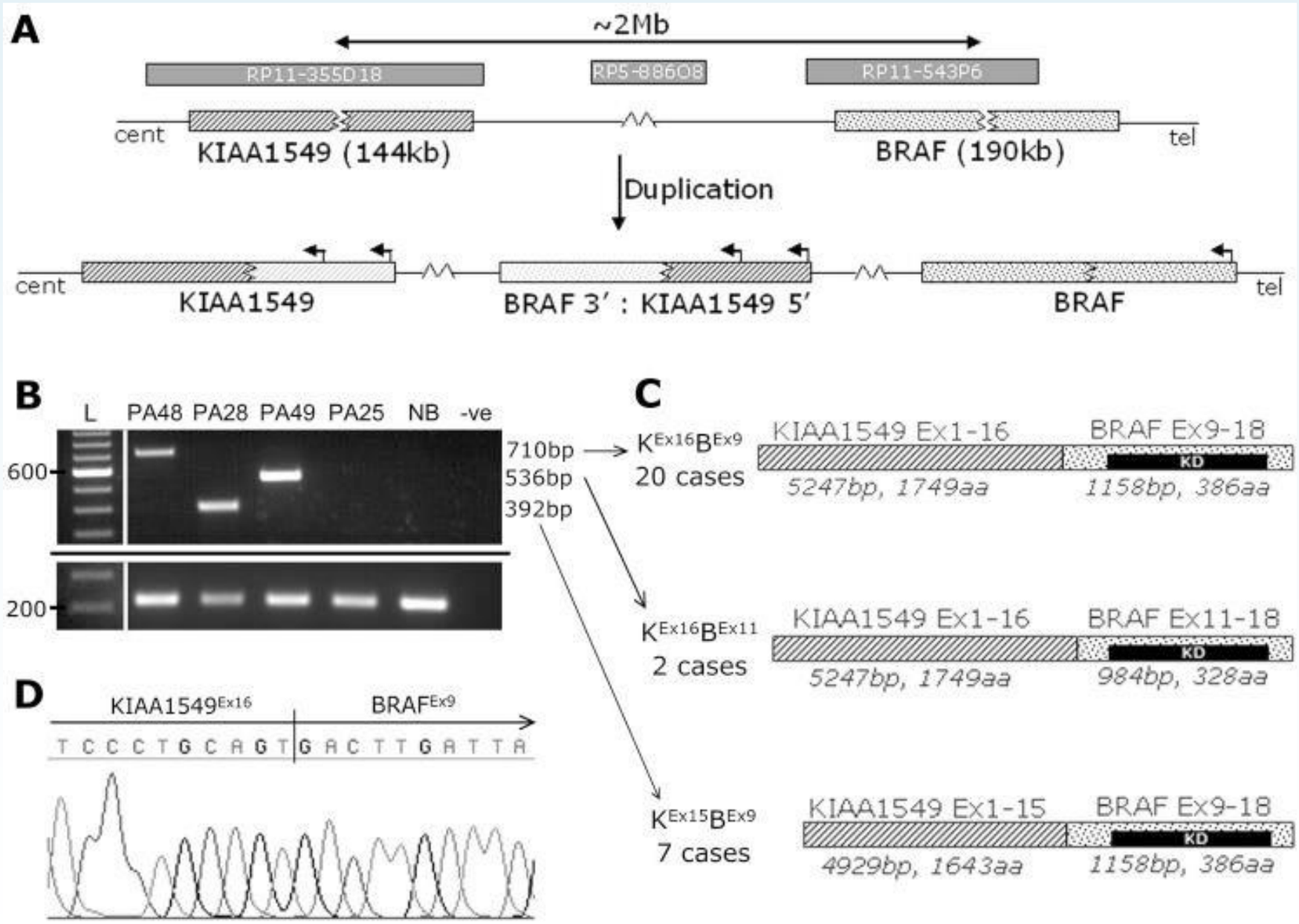




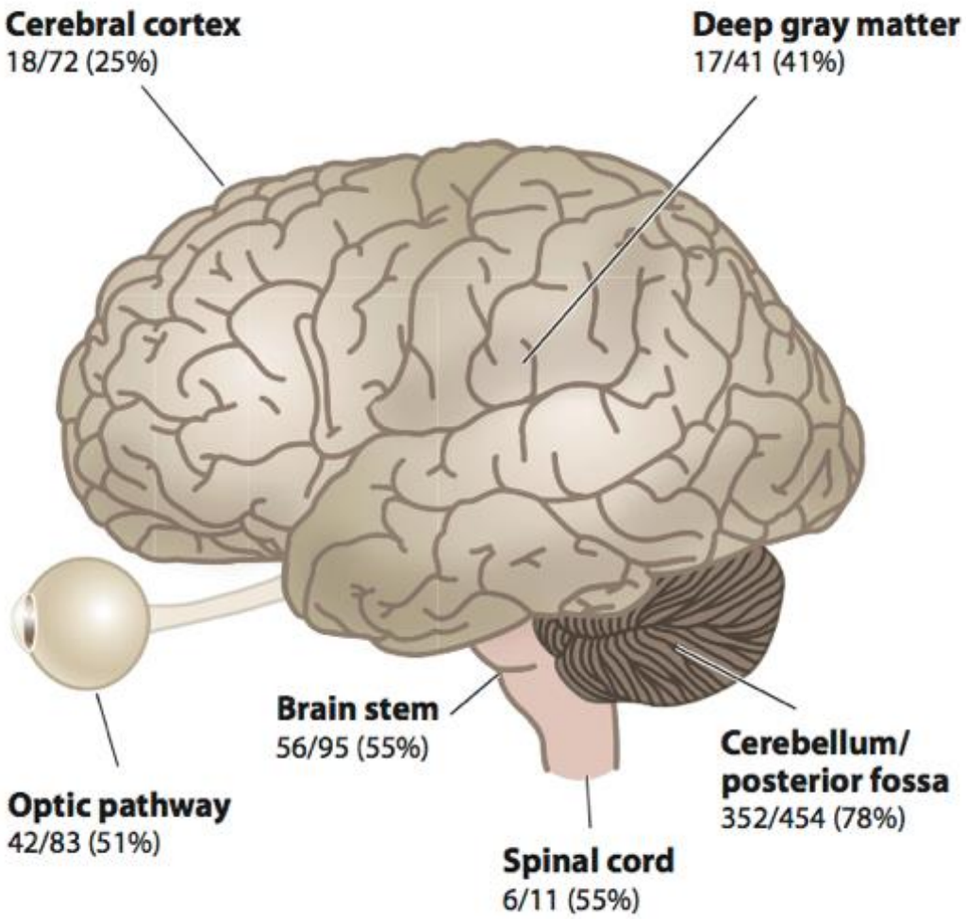
Abnormalities of the MAPK pathway characterise pilocytic astrocytoma



BRAF fusions are characteristic of pilocytic astrocytoma



The frequency of *BRAF* fusions vary with anatomical site

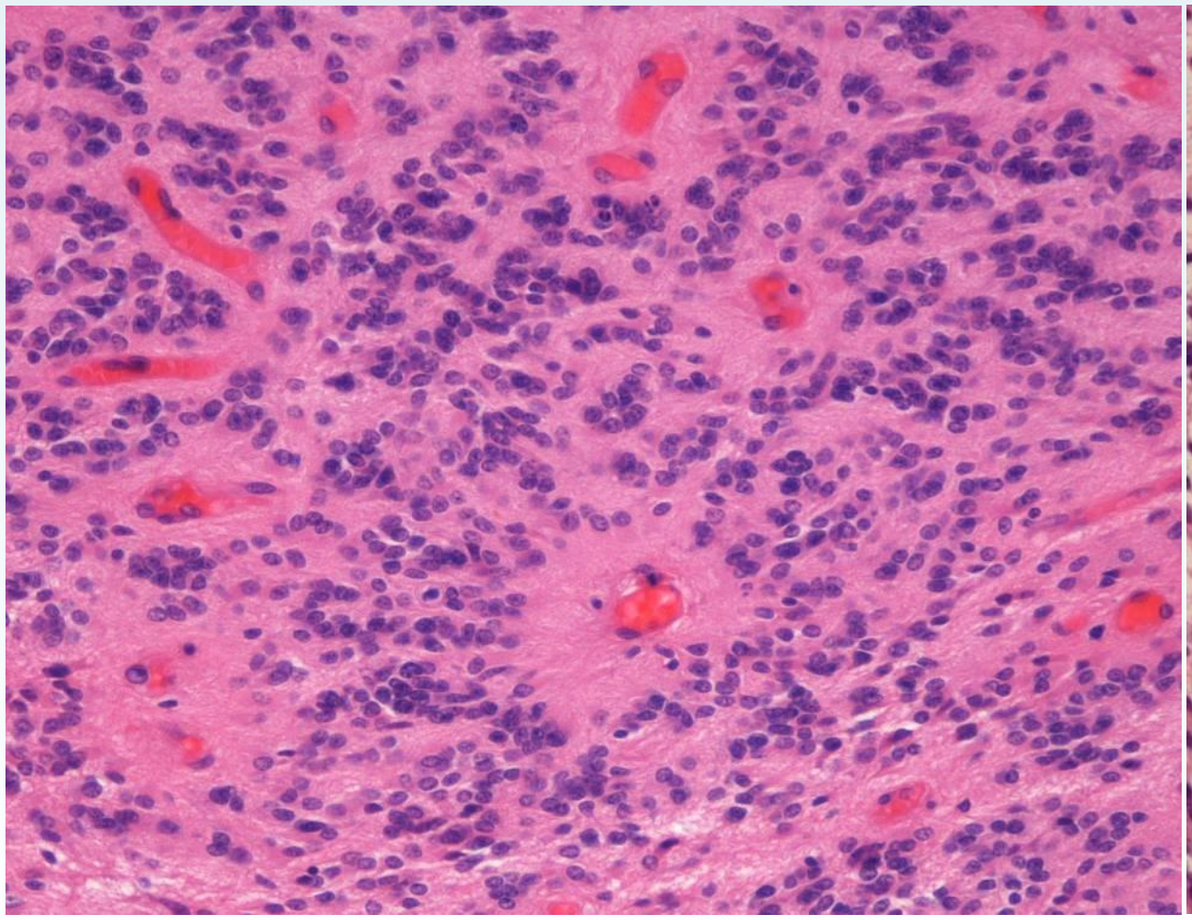


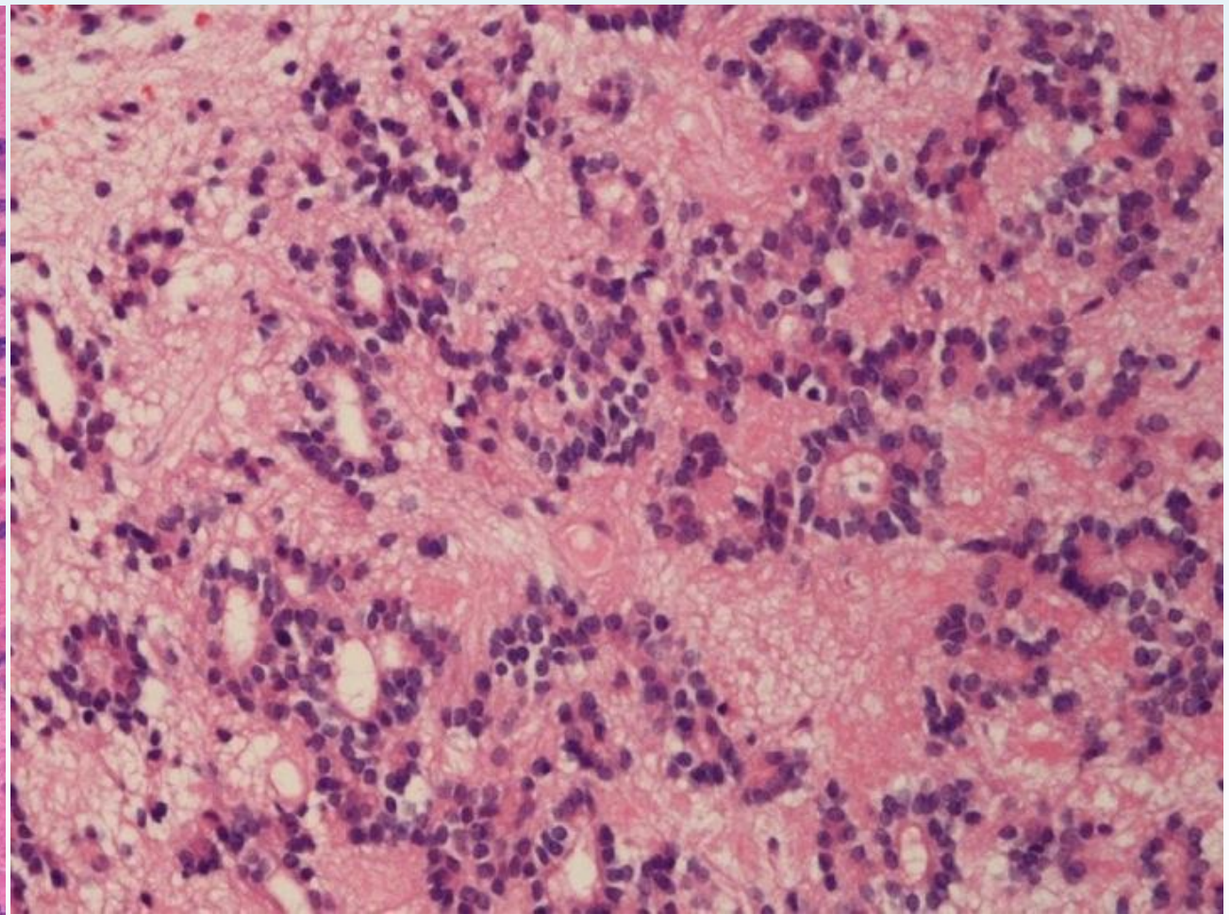
Pathological and Molecular Advances in Pediatric Low-Grade Astrocytoma

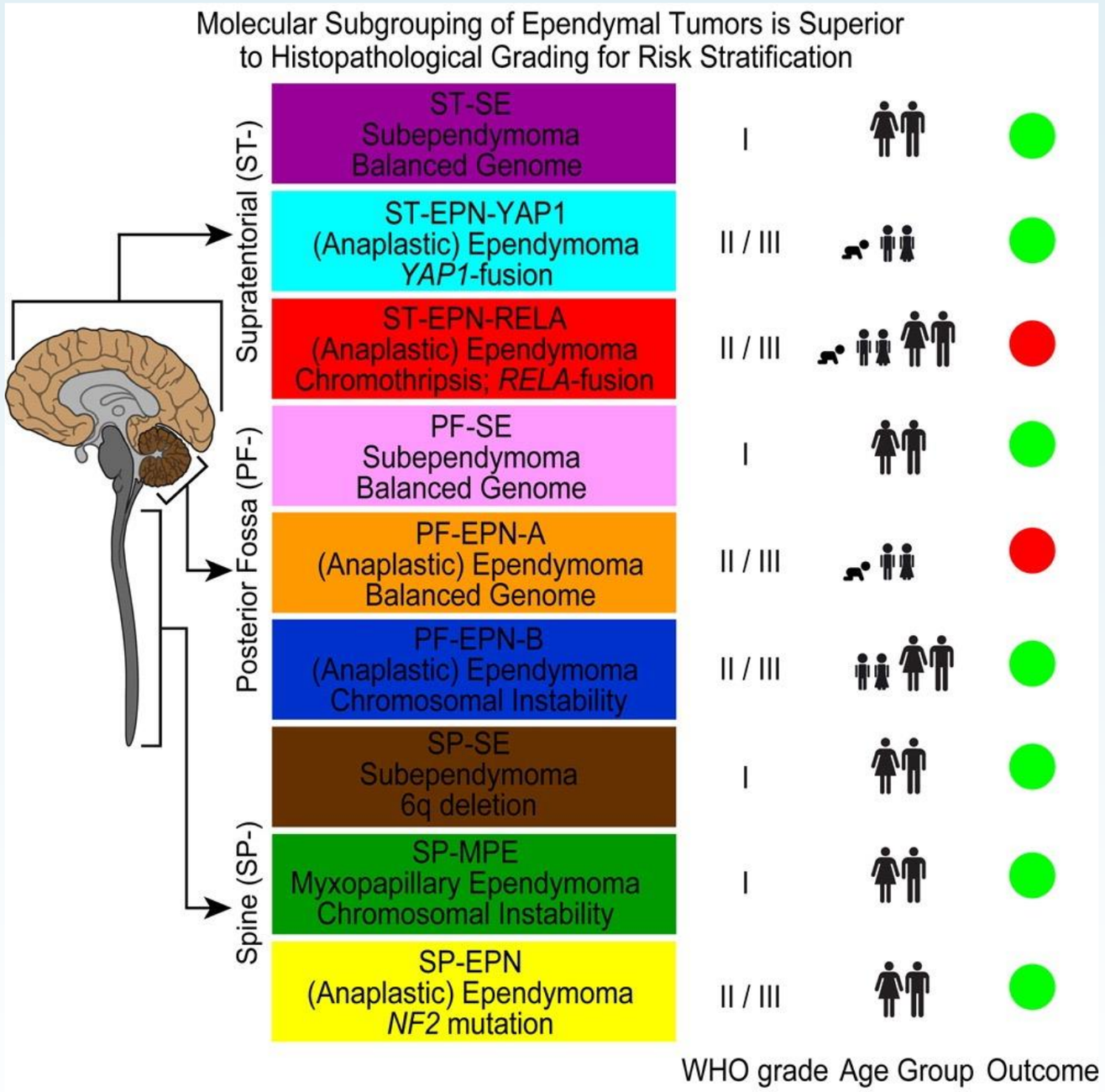
Fausto J. Rodriguez,[1] Kah Suan Lim,[1]
Daniel Bowers,[4] and Charles G. Eberhart[1,2,3]

Ependymoma

Ependymoma







Article

Cancer Cell

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Ependymoma, *RELA* fusion-positive

Ependymoma, *RELA* fusion–positive

Ellison D.W.
Korshunov A.
Witt H.

Definition

A supratentorial ependymoma characterized by a RELA *fusion gene.*

The genetically defined *RELA* fusion–positive ependymoma accounts for approximately 70% of all childhood supratentorial tumours {1891} and a lower proportion of such ependymomas in adult patients {1880}. Ependymomas in the posterior fossa and spinal compartments do not harbour this fusion gene. *RELA* fusion–positive ependymomas exhibit a range of histopathological features, with or without anaplasia.

ICD-O code 9396/3

Grading

RELA fusion-positive ependymomas are classified according to their histopathological features into WHO grade II or grade III. No grade I ependymoma has been recorded as containing this genetic alteration.

Microscopy

RELA fusion–positive ependymomas do not have a specified morphology {1891}. They exhibit the standard range of architectural and cytological features found in supratentorial ependymomas, but they often have a distinctive vascular pattern of branching capillaries or clear-cell change. Uncommon variants of ependymoma (e.g. tanycytic ependymoma) do not tend to be *RELA* fusion–positive.

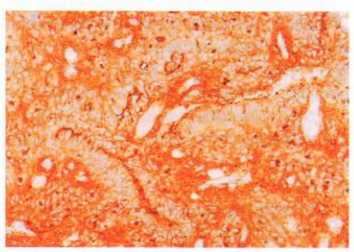


Fig. 3.15 *RELA* fusion–positive ependymoma. L1CAM protein expression correlates well with the presence of a *RELA* fusion gene.

Immunophenotype

RELA fusion–positive ependymomas demonstrate the immunoreactivities for GFAP and EMA described in other ependymomas. Expression of L1CAM correlates well with the presence of a *RELA* fusion in supratentorial ependymomas {1891}, but L1CAM can also be expressed by other types of brain tumours.

Genetic profile

The *C11orf95-RELA* fusion is the most common structural variant found in ependymomas {1880,1891,1974}. It forms in the context of chromothripsis, a shattering and reassembly of the genome that rearranges genes and produces oncogenic gene products {2852}. *RELA* fusion–positive ependymomas show constitutive activation of the NF-kappaB pathway, the *RELA*-encoded transcription factor p65 being a key effector in this pathway. Rarely, *C11orf95* or *RELA* can be fused with other genes as a result of chromothripsis {1891}.

The presence of a *C11orf95-RELA* fusion gene can be detected by various methods, but a simple approach using formalin-fixed, paraffin-embedded tissue is interphase FISH with break-apart probes around both genes. Rearrangement in the context of chromothripsis splits the dual-colour signals in probe sets for *C11orf95* and *RELA* {1891}.

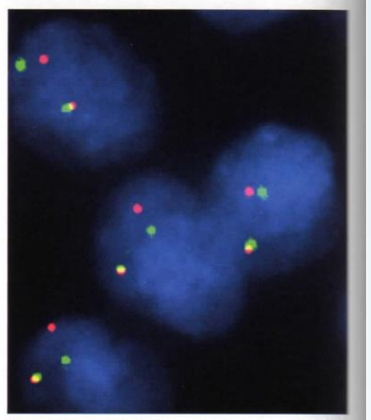
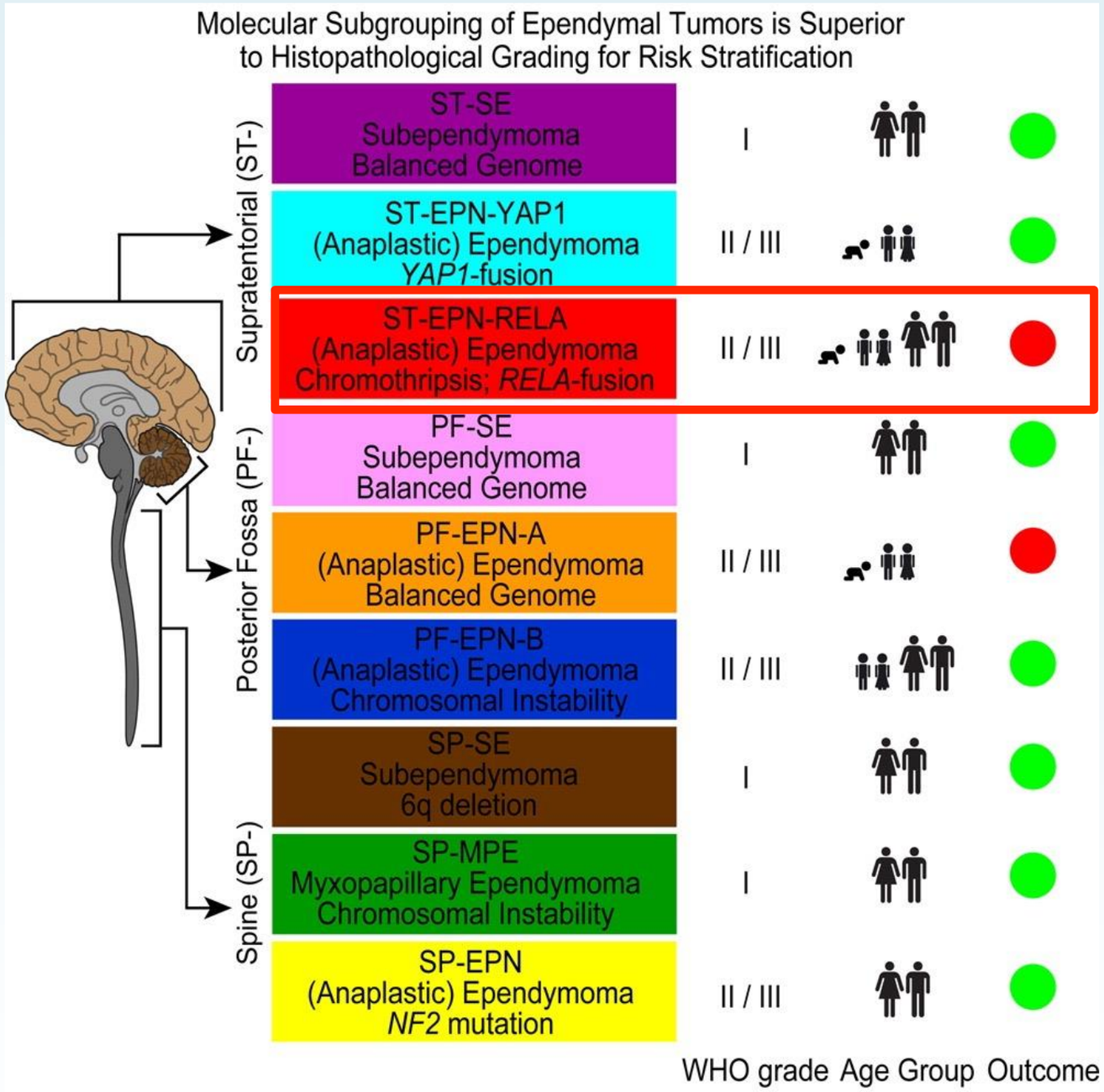


Fig. 3.16 *RELA* fusion–positive ependymoma. Interphase FISH with break-apart probes around the *RELA* gene. Overlapping probes (yellow) indicate an intact *RELA* gene, but probe separation (red/green) occurs with rearrangement of the *RELA* gene.

Prognosis and predictive factors

The data available to date (which come from only a single study) suggest that *RELA* fusion–positive ependymomas have the worst outcome of the three supratentorial molecular groups {1880}.



Article

Cancer Cell

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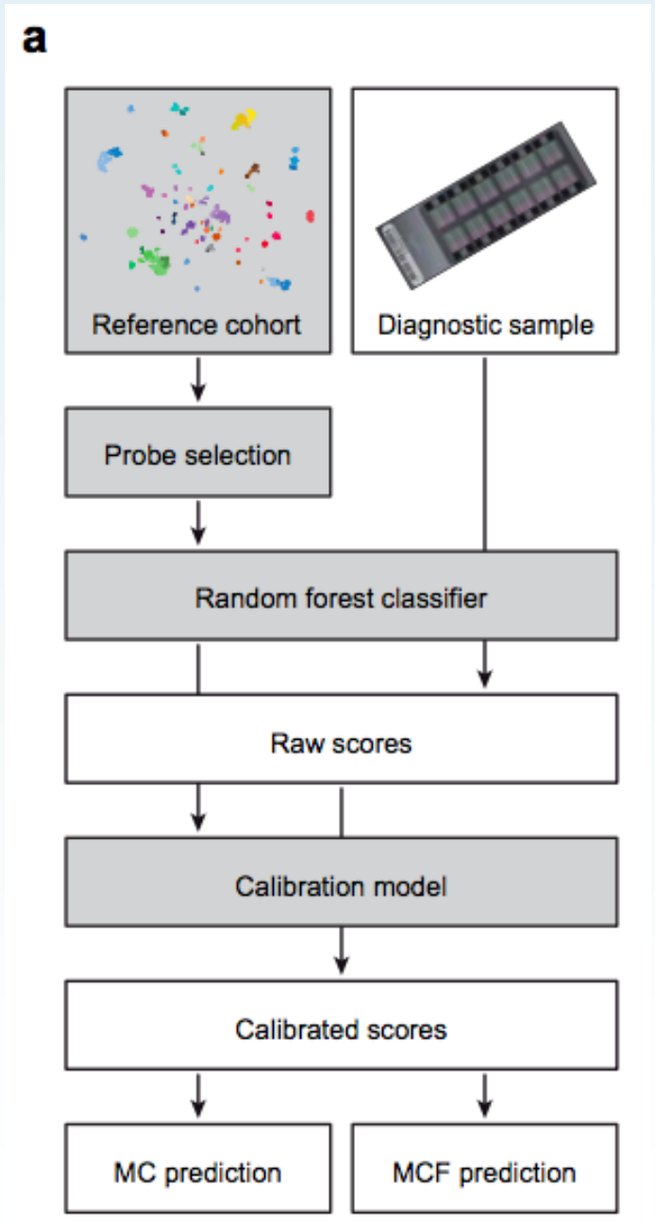
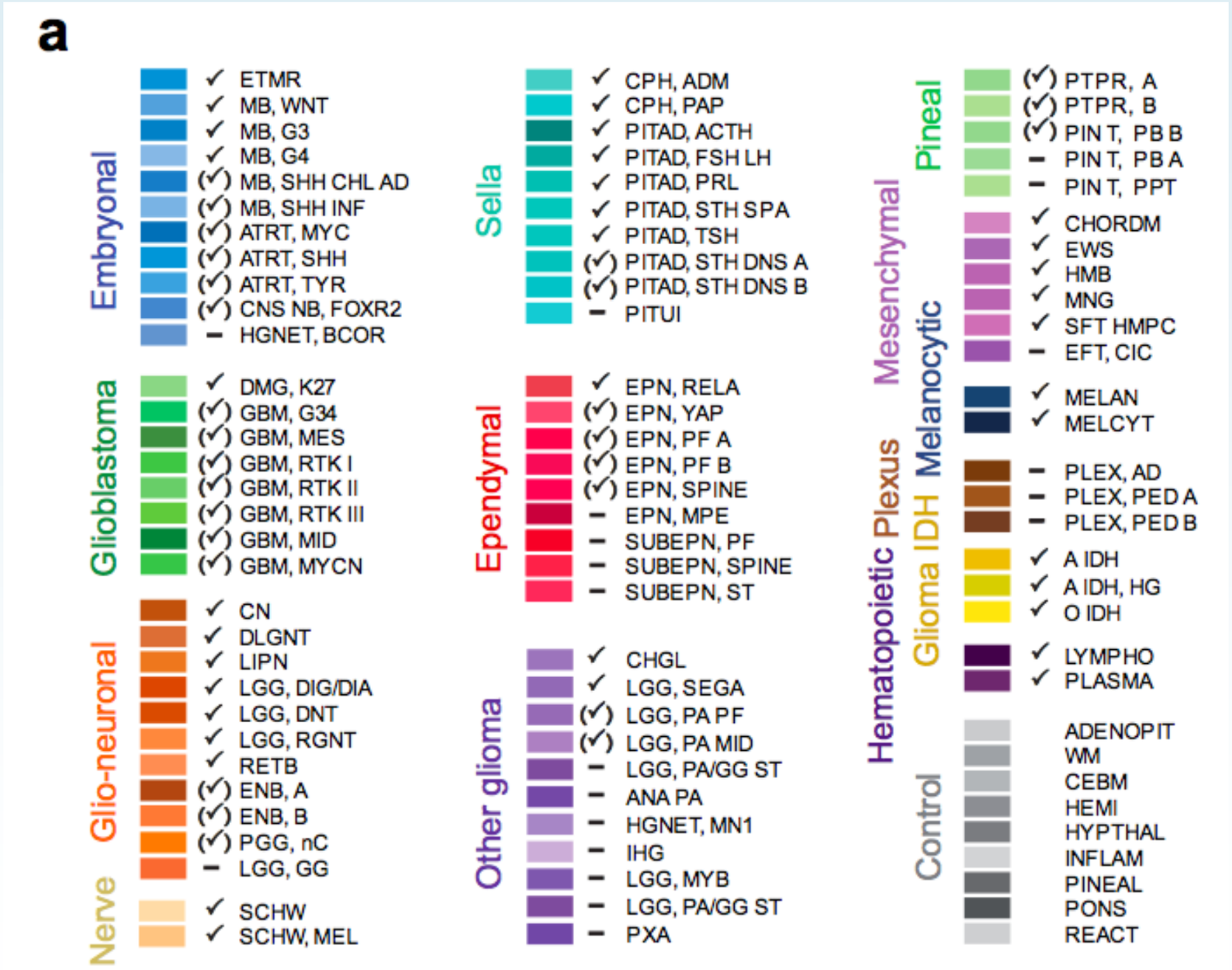
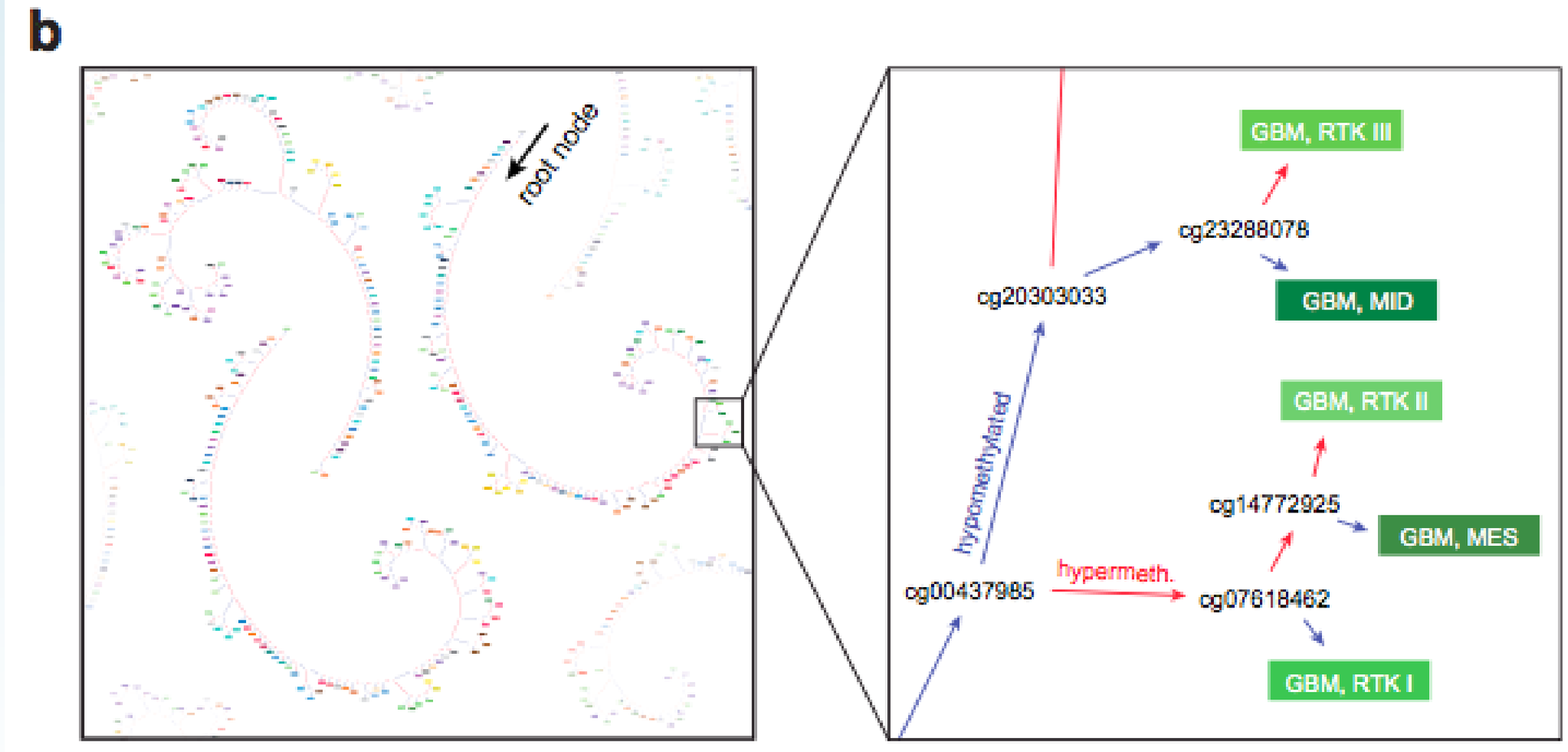
Methylation profiling



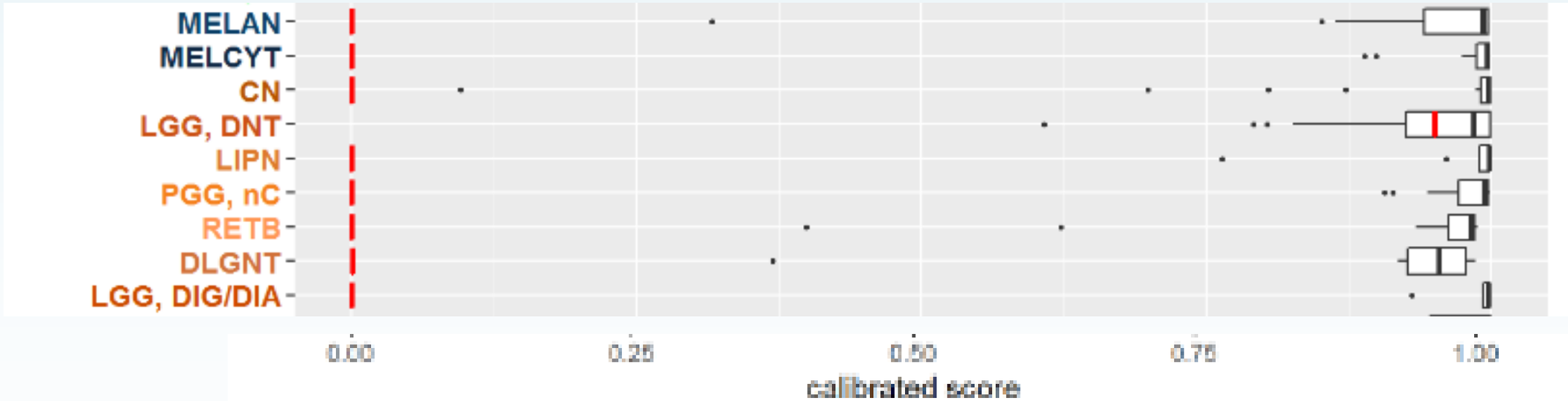
Training a computer to make a diagnosis



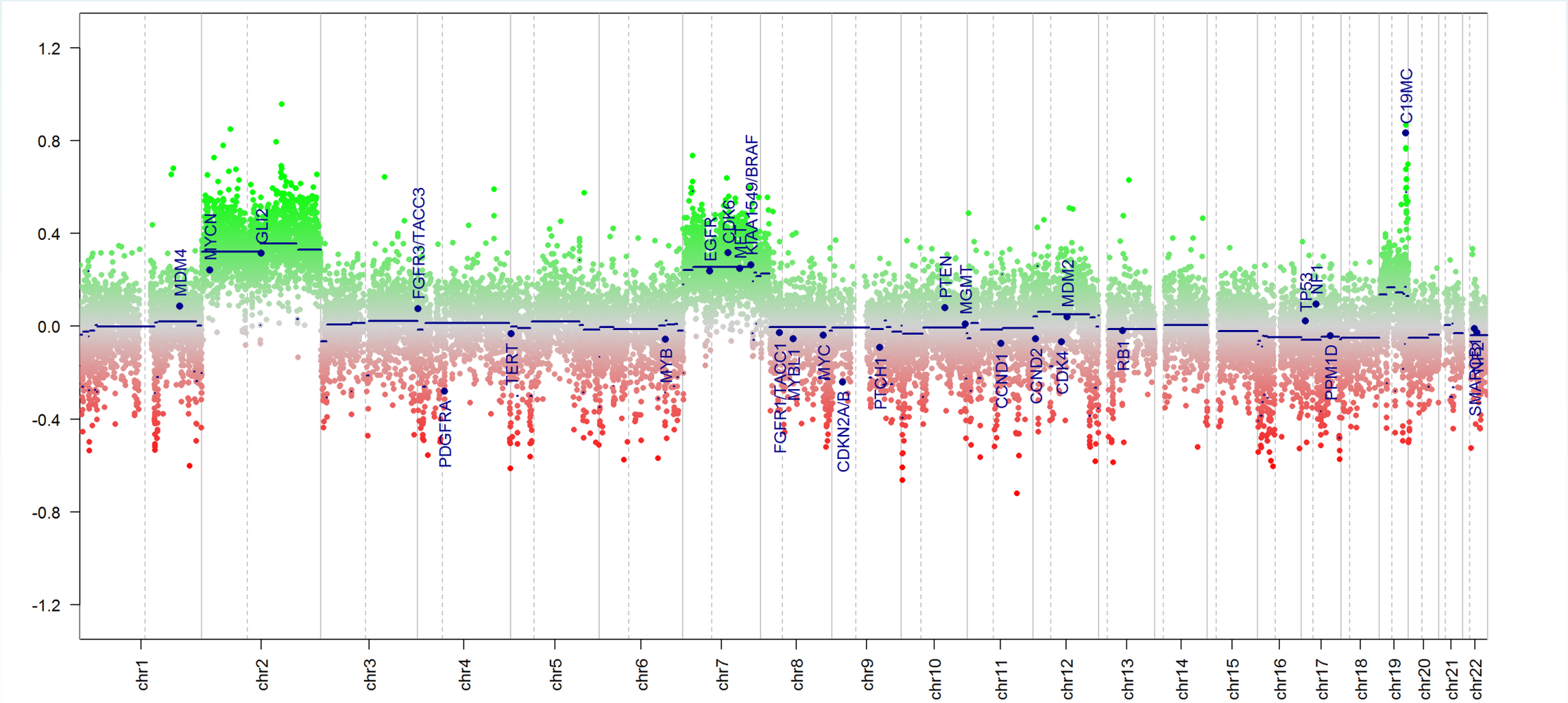
The classifier votes for a diagnosis



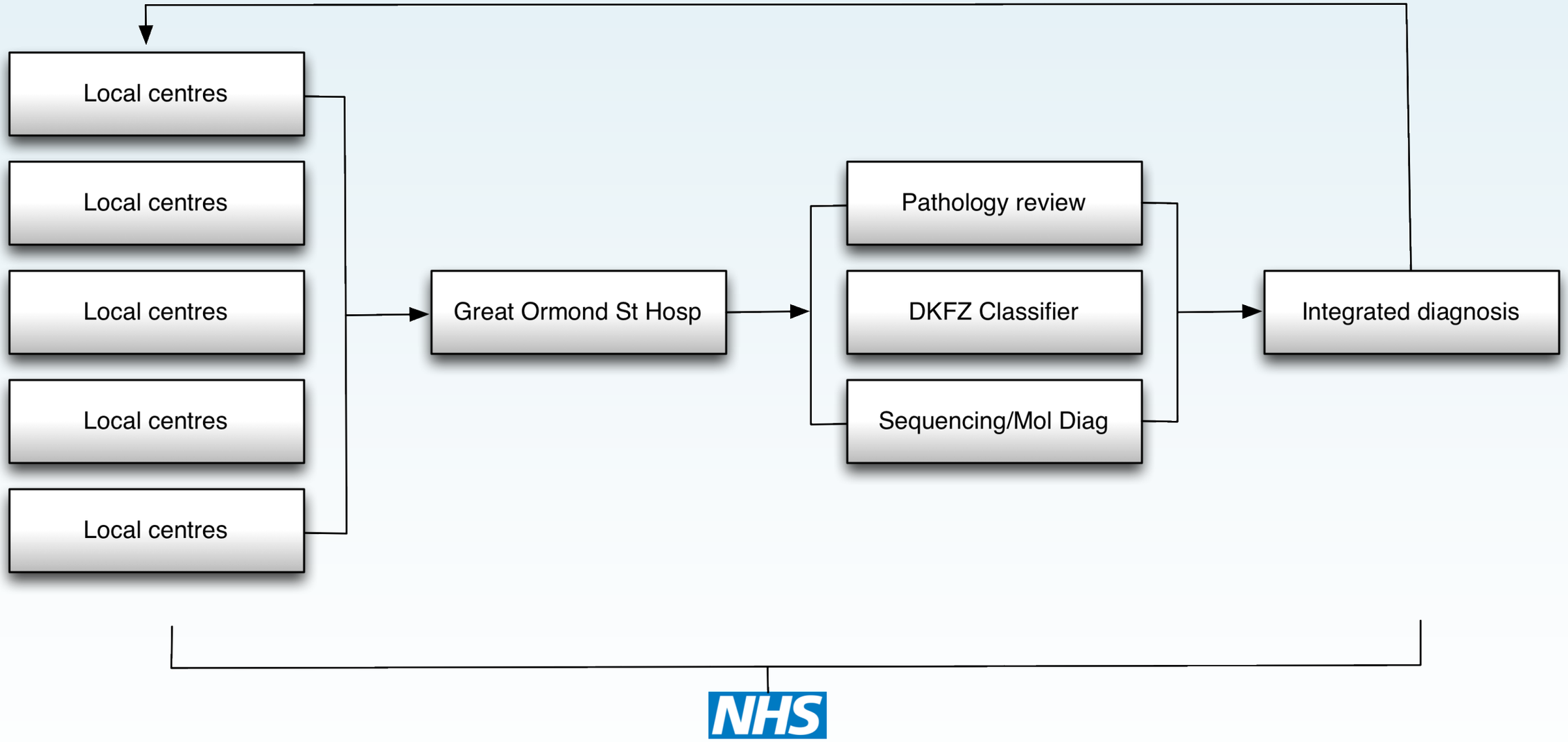
The votes for each diagnosis are added together



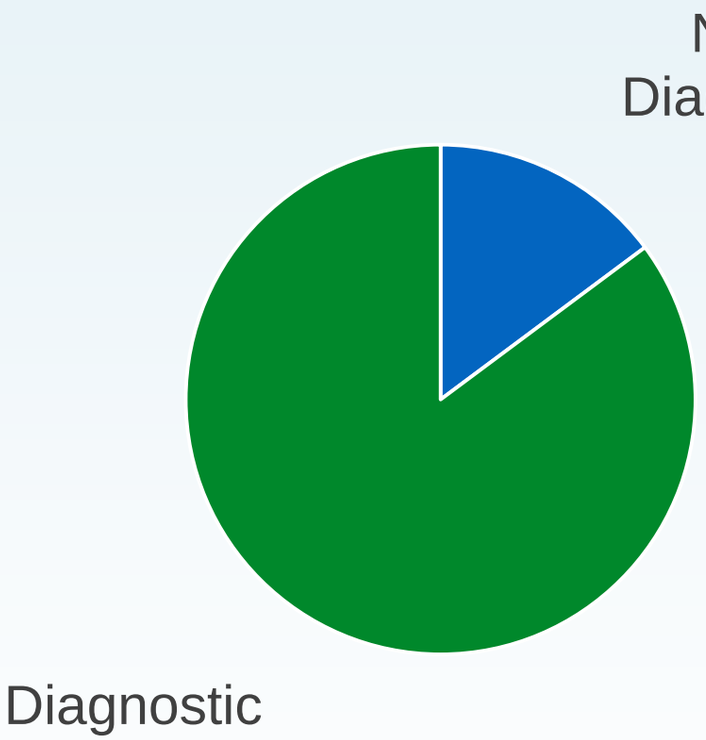
Copy number data for the methylation arrays



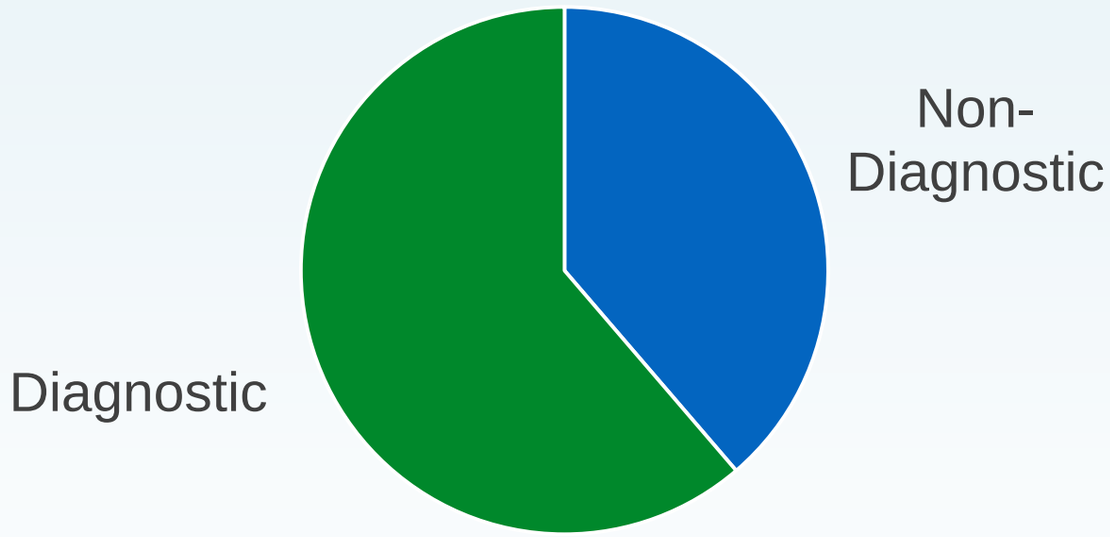
Translation into NHS practice



Impact on diagnosis in the NHS

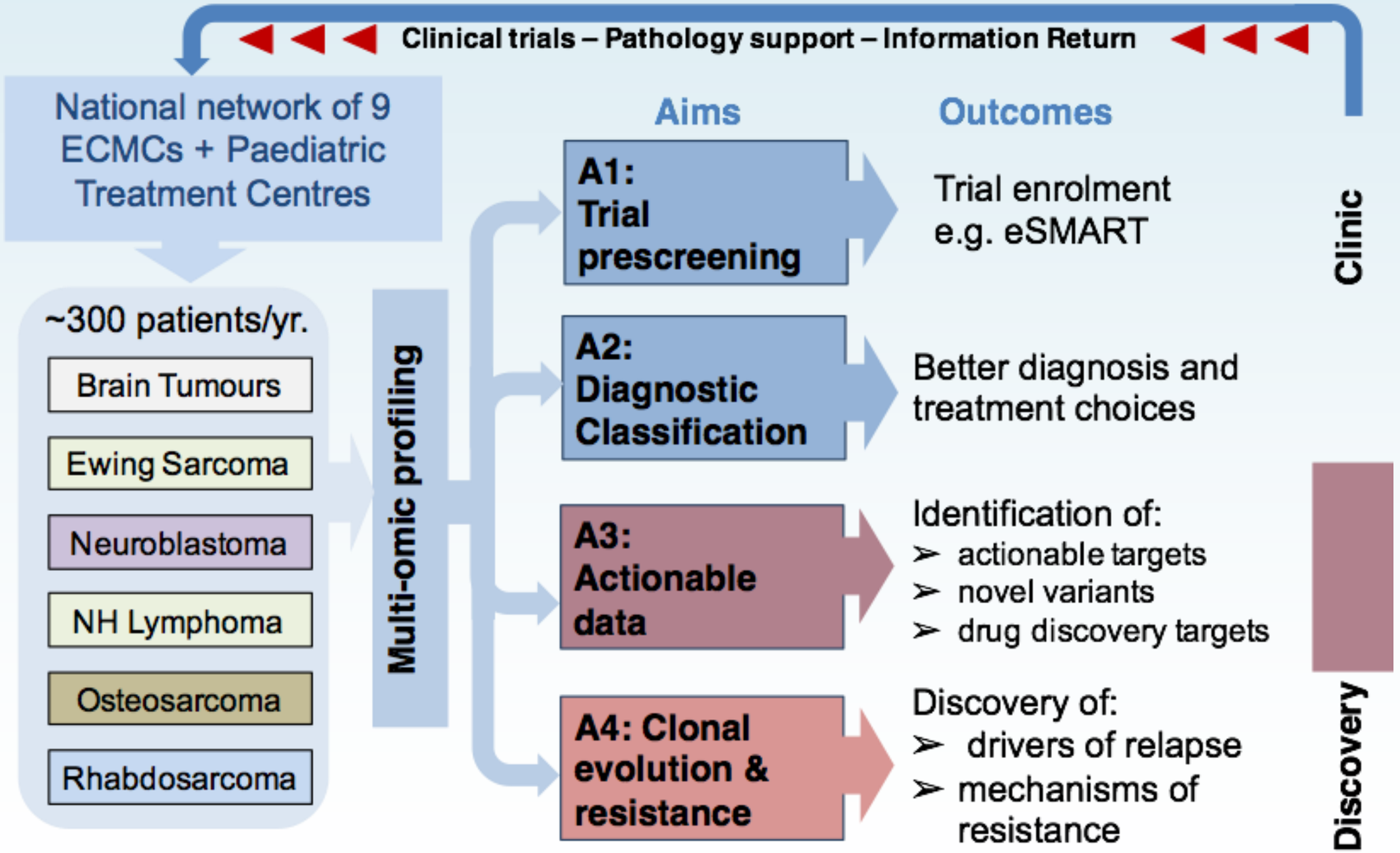


Known cases



Difficult cases

National initiatives: SMPaeds



Jacques Lab


Aimee Avery

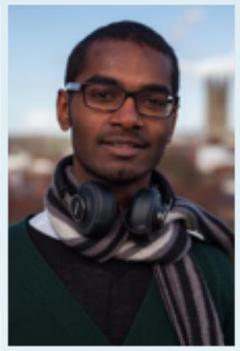

Barbora Benova


Amy Fairchild


Derek Li


Jess Pickles


Tom Stone


Alex Virasami


Sherry Yasin

Collaborators


John Anderson UCL-ICH


David Capper Berlin


Lou Chesler ICR

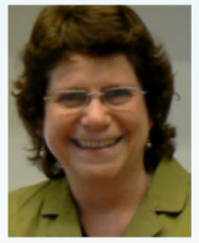

Steve Clifford Newcastle


Darren Hargrave GOSH


Mike Hubank ICR


David Jones Heidelberg


JP Martinez-Barbera UCL-ICH


Denise Sheer QMUL

CANCER RESEARCH UK

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children with cancer uk
fighting the UK's biggest child killer

Great Ormond Street Hospital Charity

NHS
National Institute for Health Research