Update on molecular diagnostics in CNS cancers

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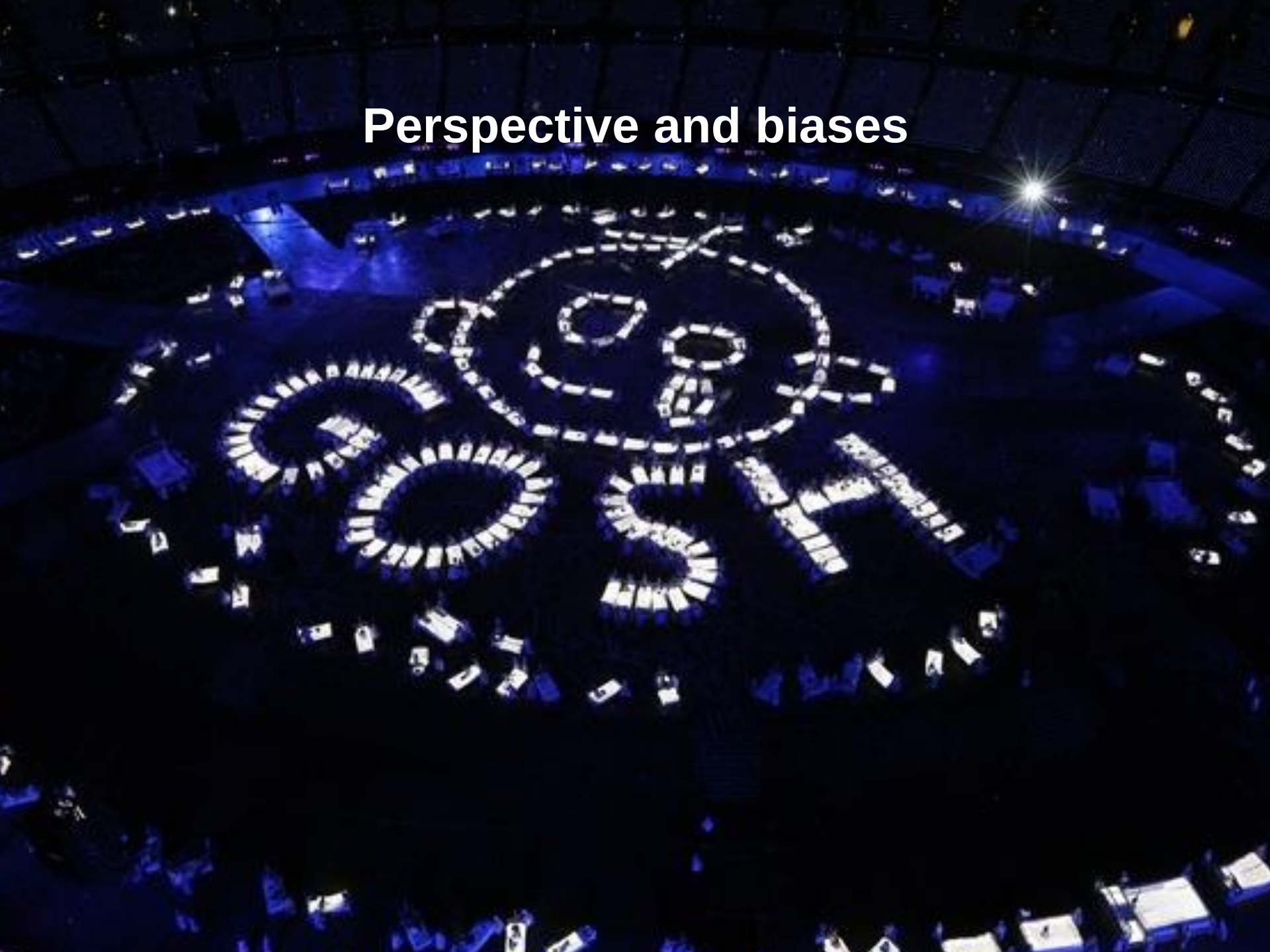
Objectives

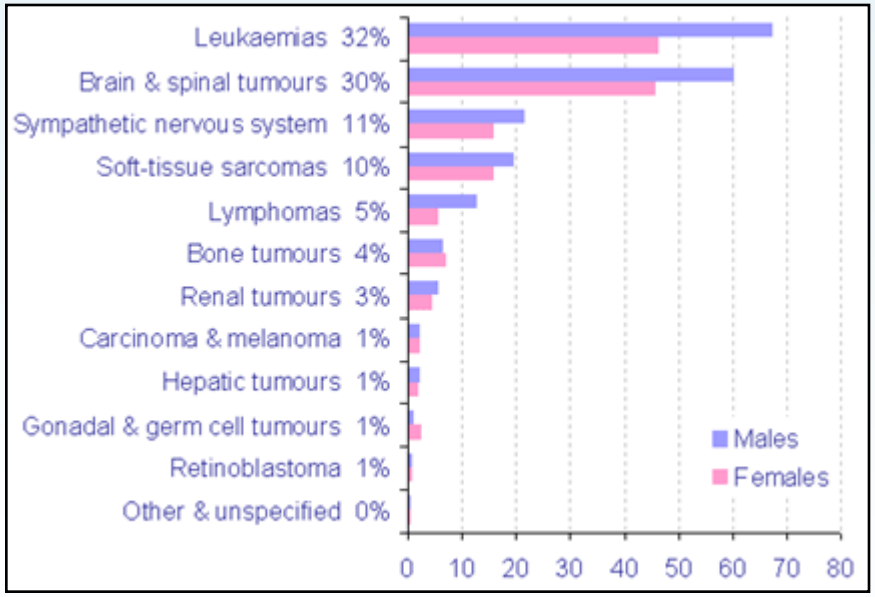
- To describe the current landscape of molecular diagnosis in brain tumours, focussing on:
  - Tests that are currently available
  - Tests that alter clinical management or prognosis
  - The incorporation of the tests in to more traditional pathology

Perspective and biases



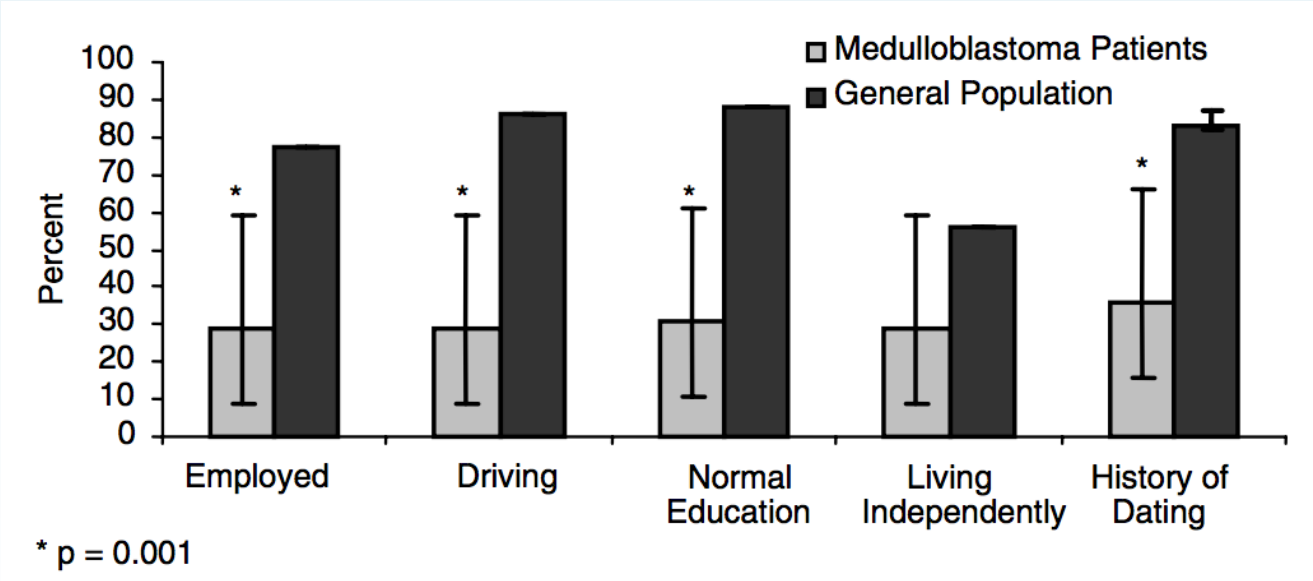
What distinguishes neuropathology for children?

Distinctive clinical features of childhood brain tumours



- CNS tumours are the commonest solid tumours of childhood and the commonest fatal tumours in childhood
- Paediatric brain tumours are often amenable to curative treatment
- ...but significant morbidity may be associated with treatment
- Complete surgical resection is often critical for curative treatment.
- Many patients will be on trials with up-front molecular pathology for stratification

Survival is at the cost of long-term complications

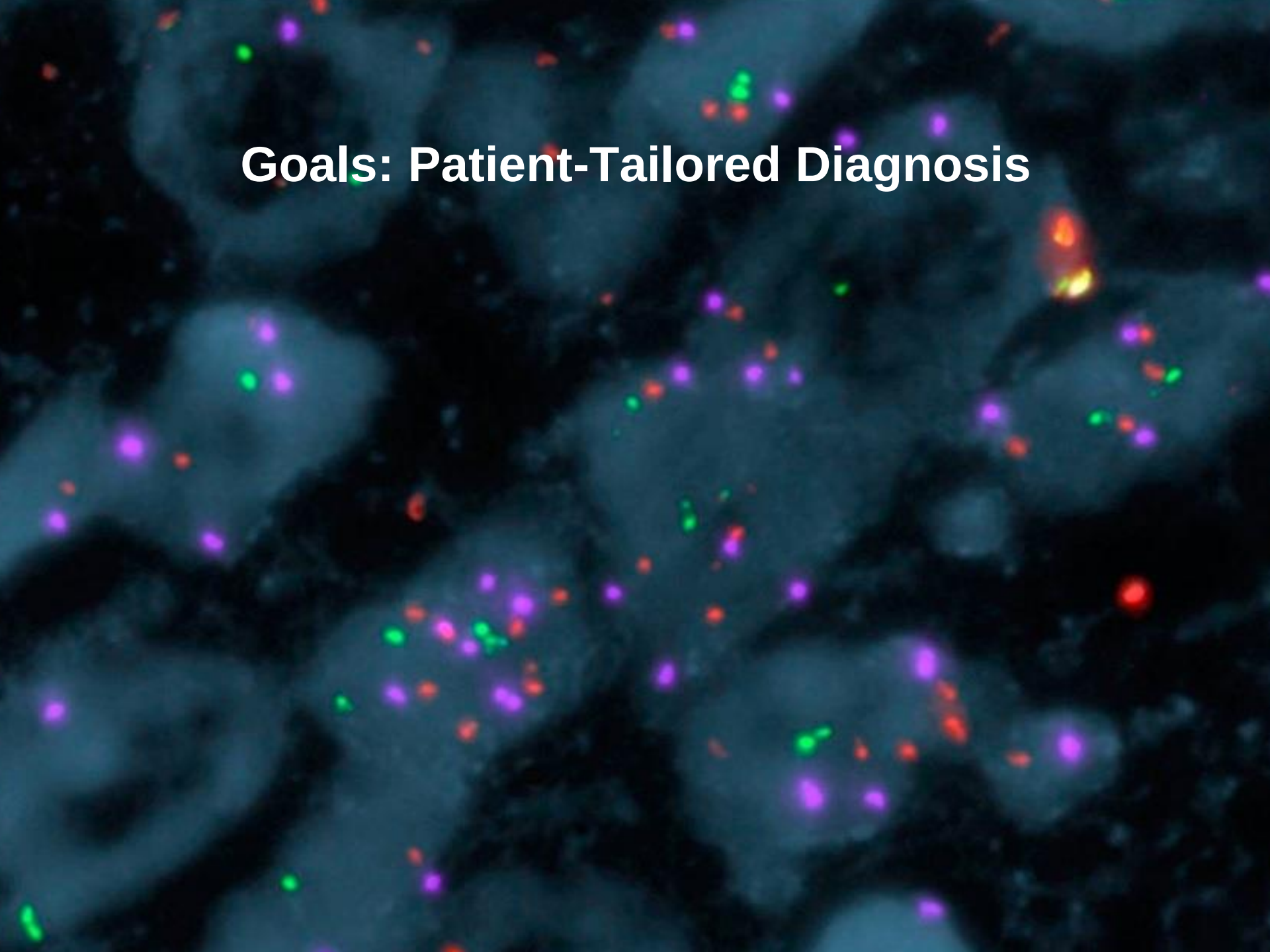


Maddgrey et al. 2005

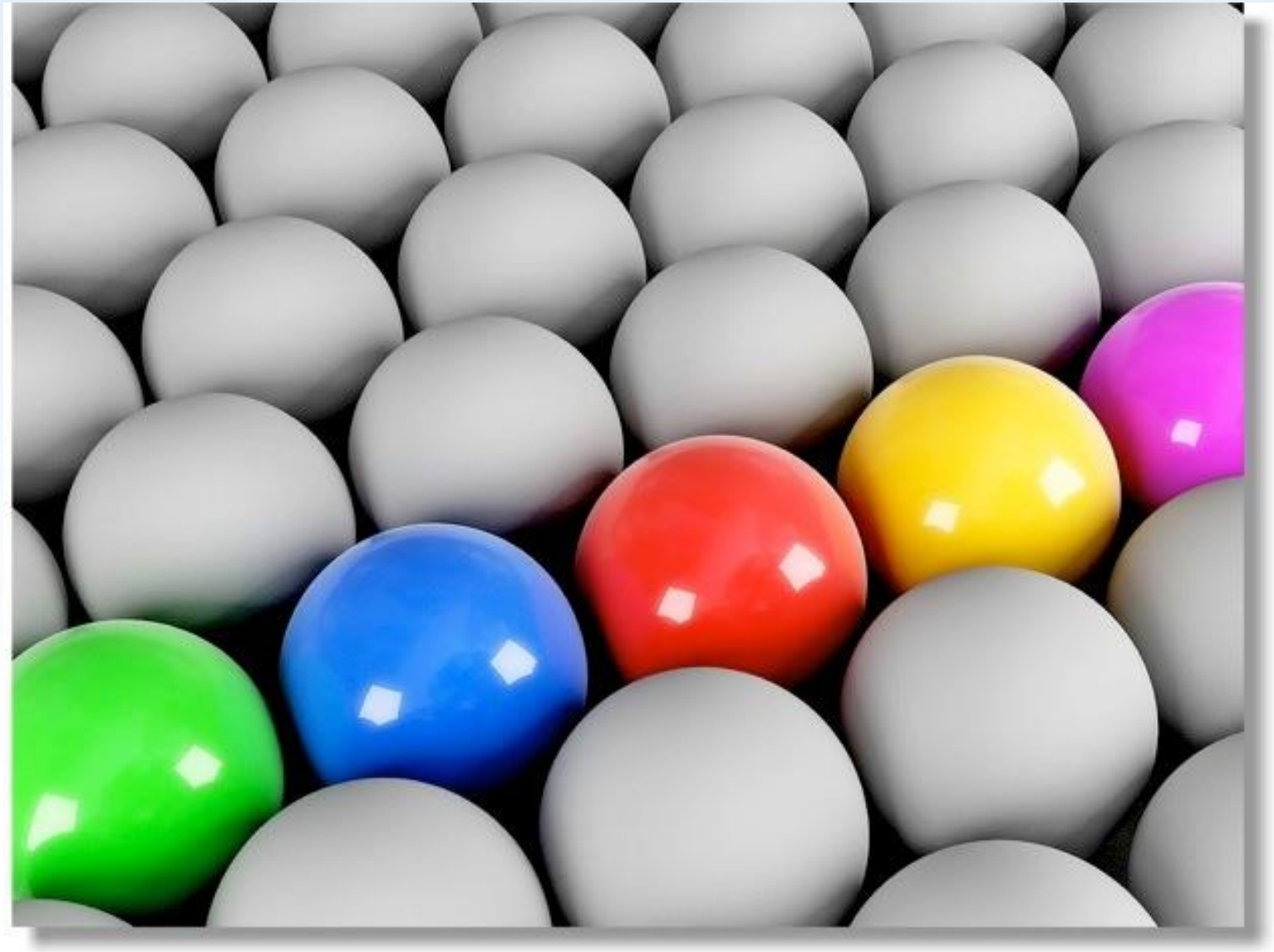
Late effects

Long term cure

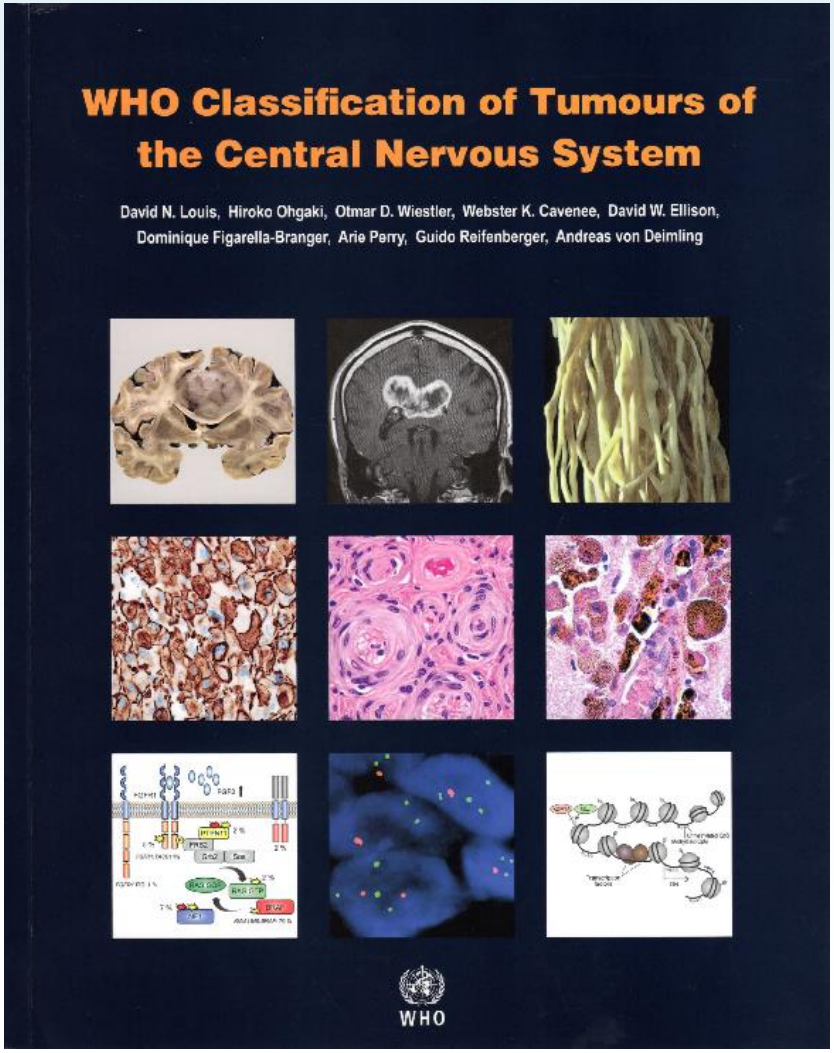
Goals: Patient-Tailored Diagnosis



The challenges of the numbers



The revised WHO classification



For the first time: 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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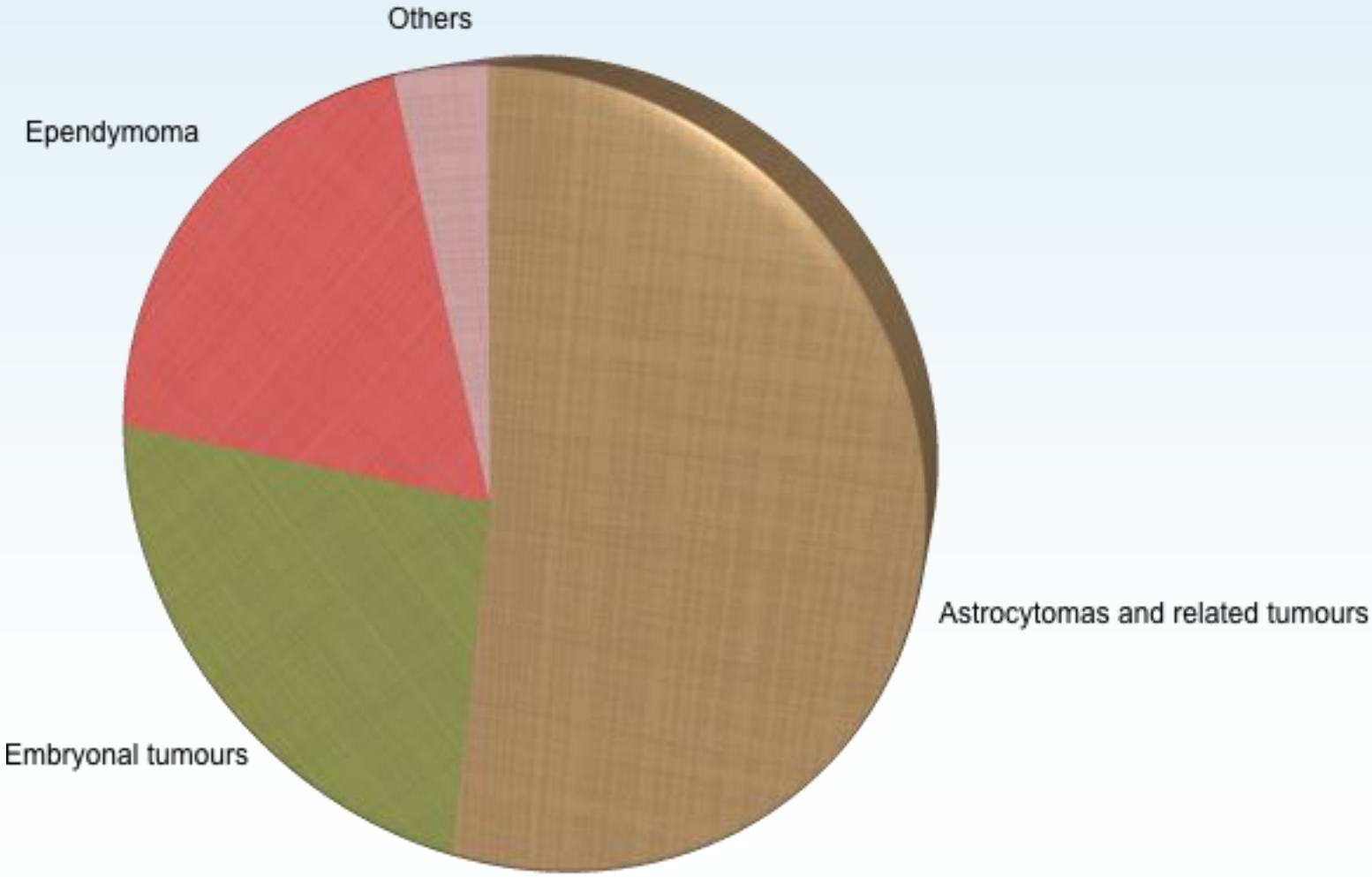
INTEGRATED DIAGNOSIS

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



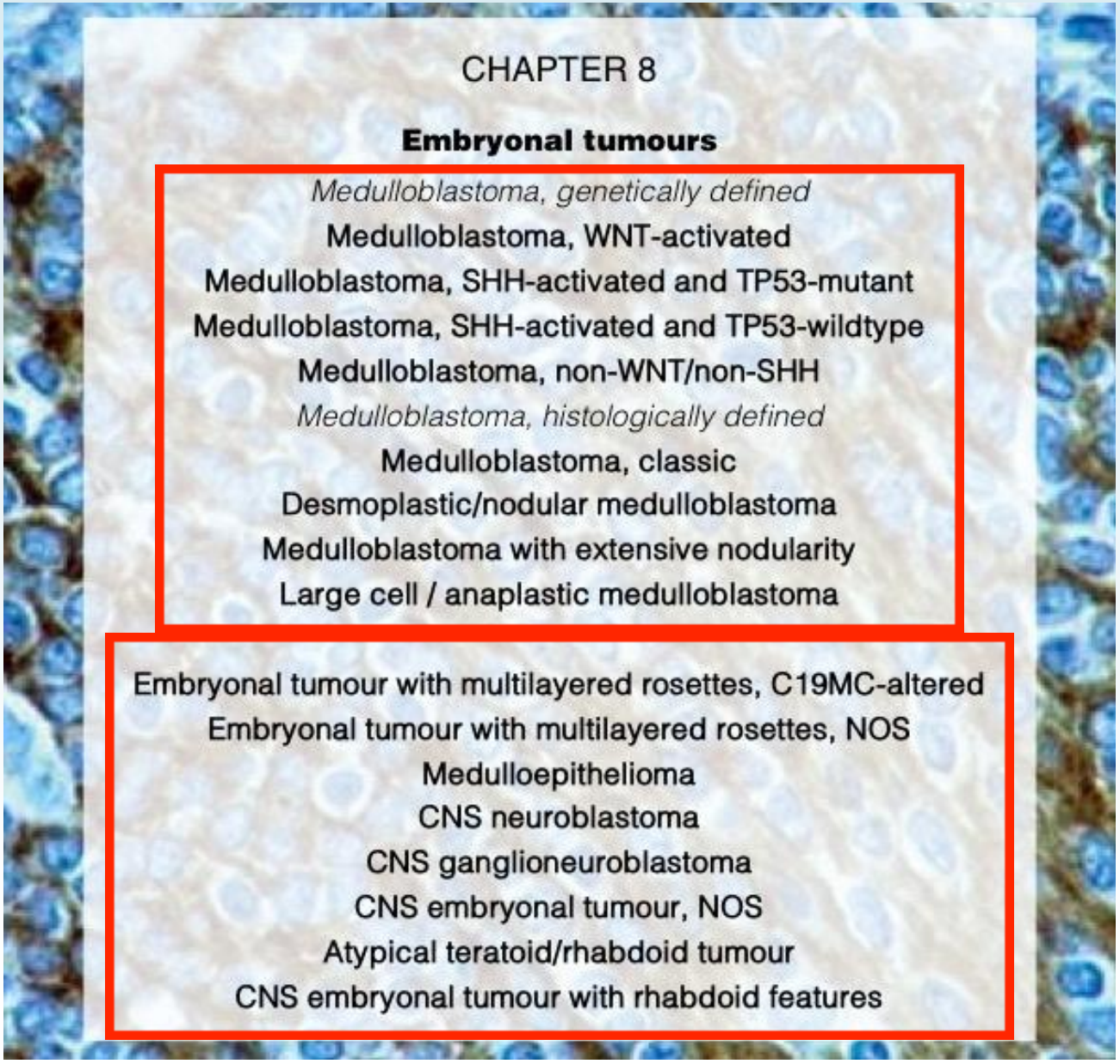
Embryonal Tumours

Terminology

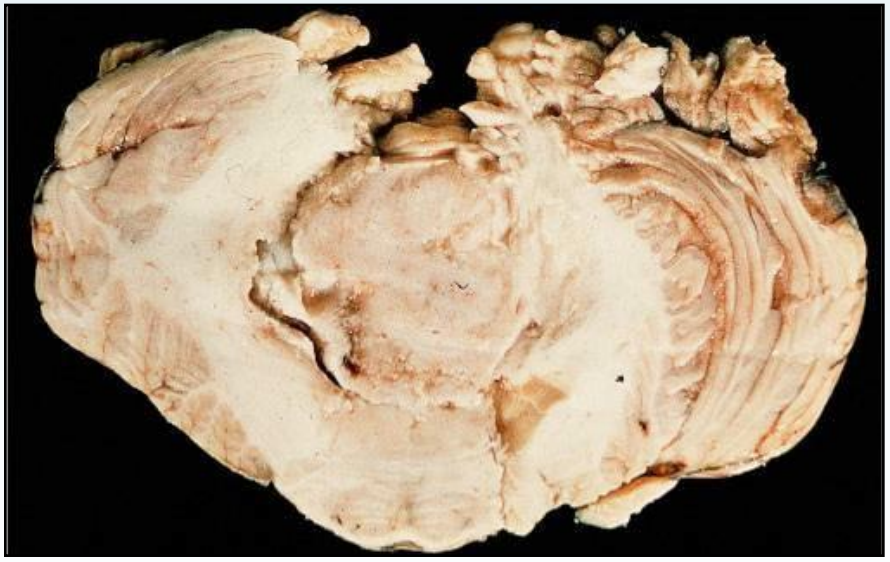
- Embryonal tumours
- Primitive Neuro-ectodermal Tumours (PNET)
  - In essence primary small round blue cell tumours of the brain

Embryonal Tumour classification

- Embryonal Tumour in the cerebellum=Medulloblastoma
- Everything else

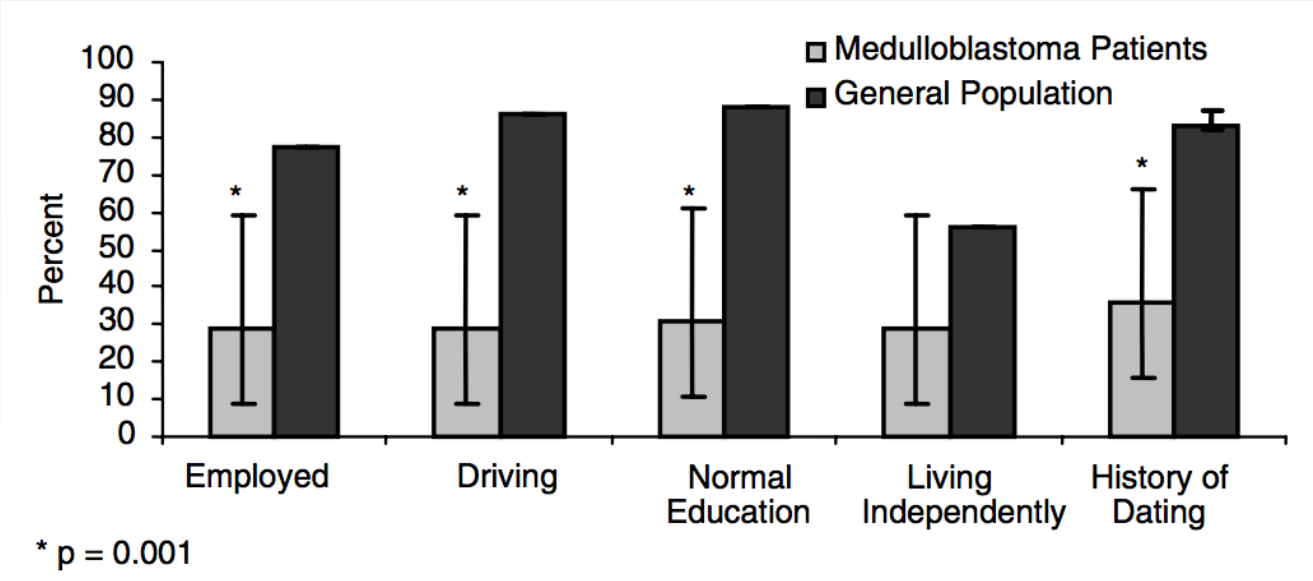

CHAPTER 8
Embryonal tumours
Medulloblastoma, genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, SHH-activated and TP53-wildtype
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, histologically defined
Medulloblastoma, classic
Desmoplastic/nodular 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



- Definition-embyronal tumour of the posterior fossa
- Peak age of onset 7 years
- 5-yr survival >70%

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

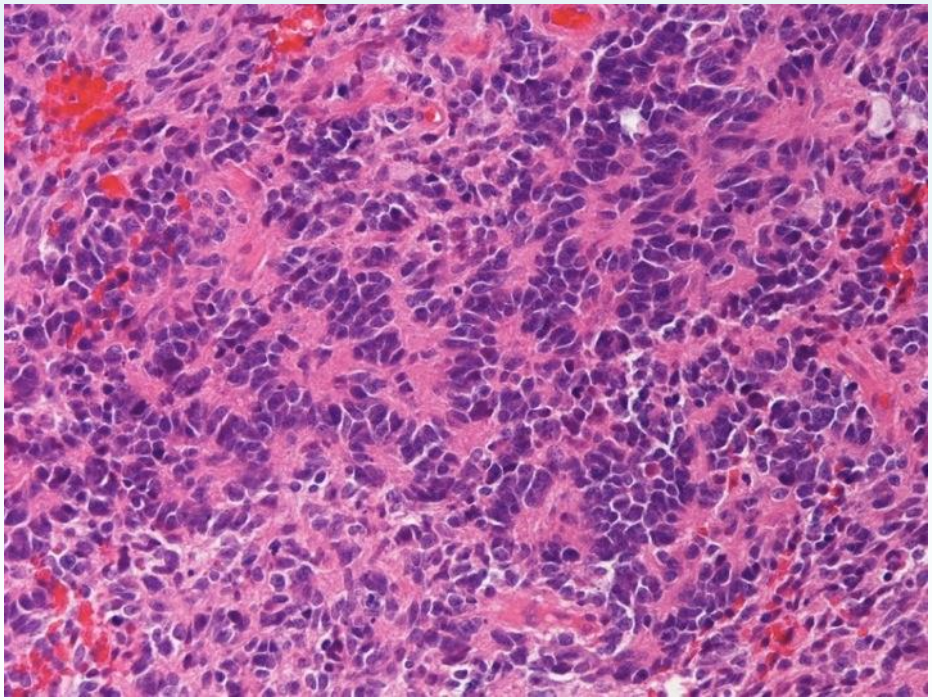
Desmoplastic/nodular medulloblastoma

Medulloblastoma with extensive nodularity

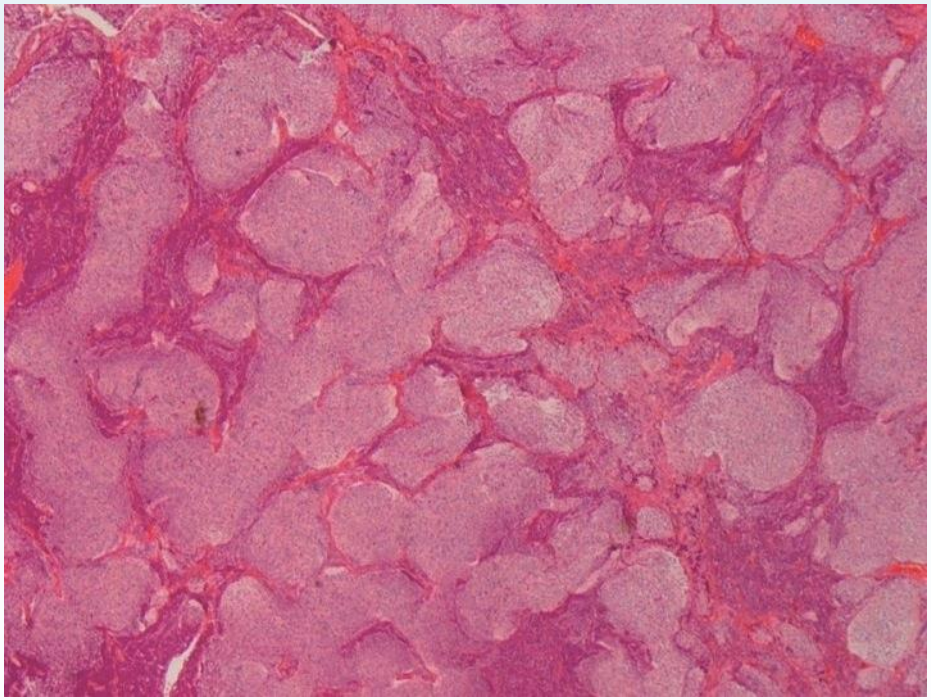
Large cell / anaplastic medulloblastoma

Risk stratification-conventional histology

Medulloblastoma-Architecture

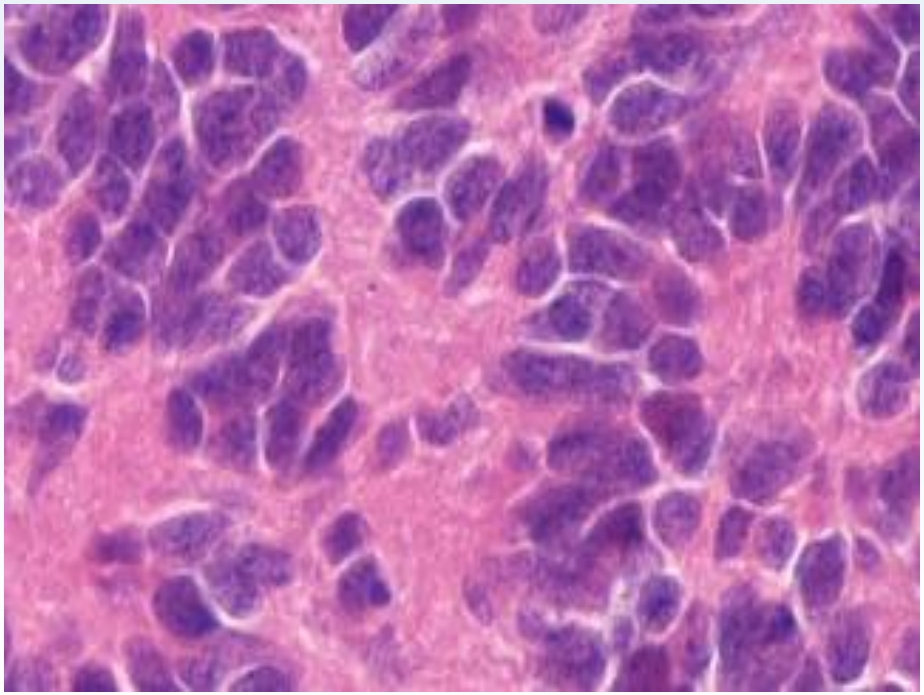


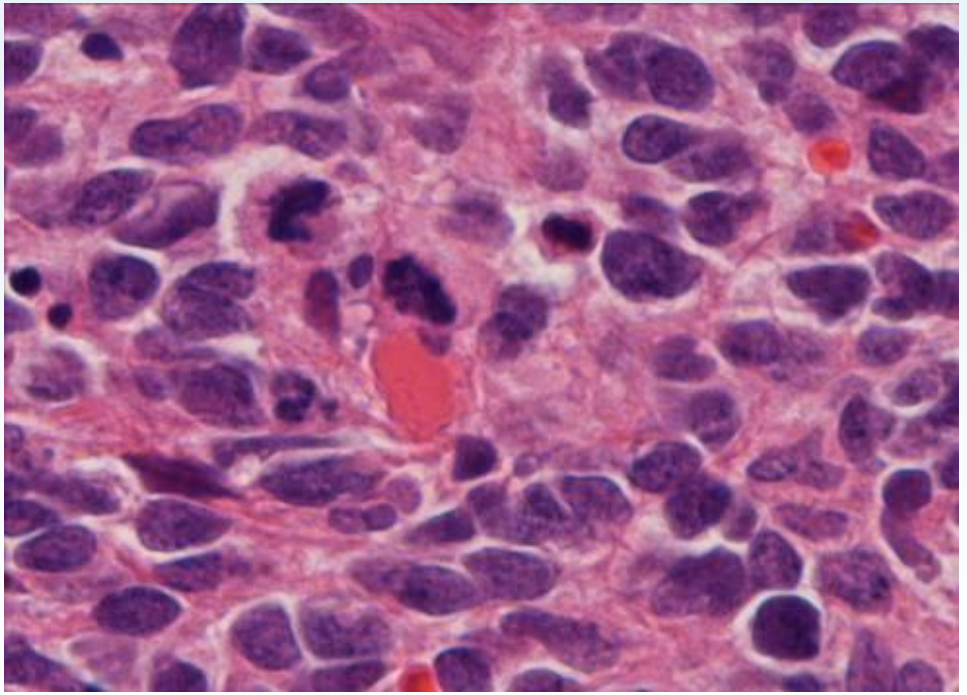
Diffuse



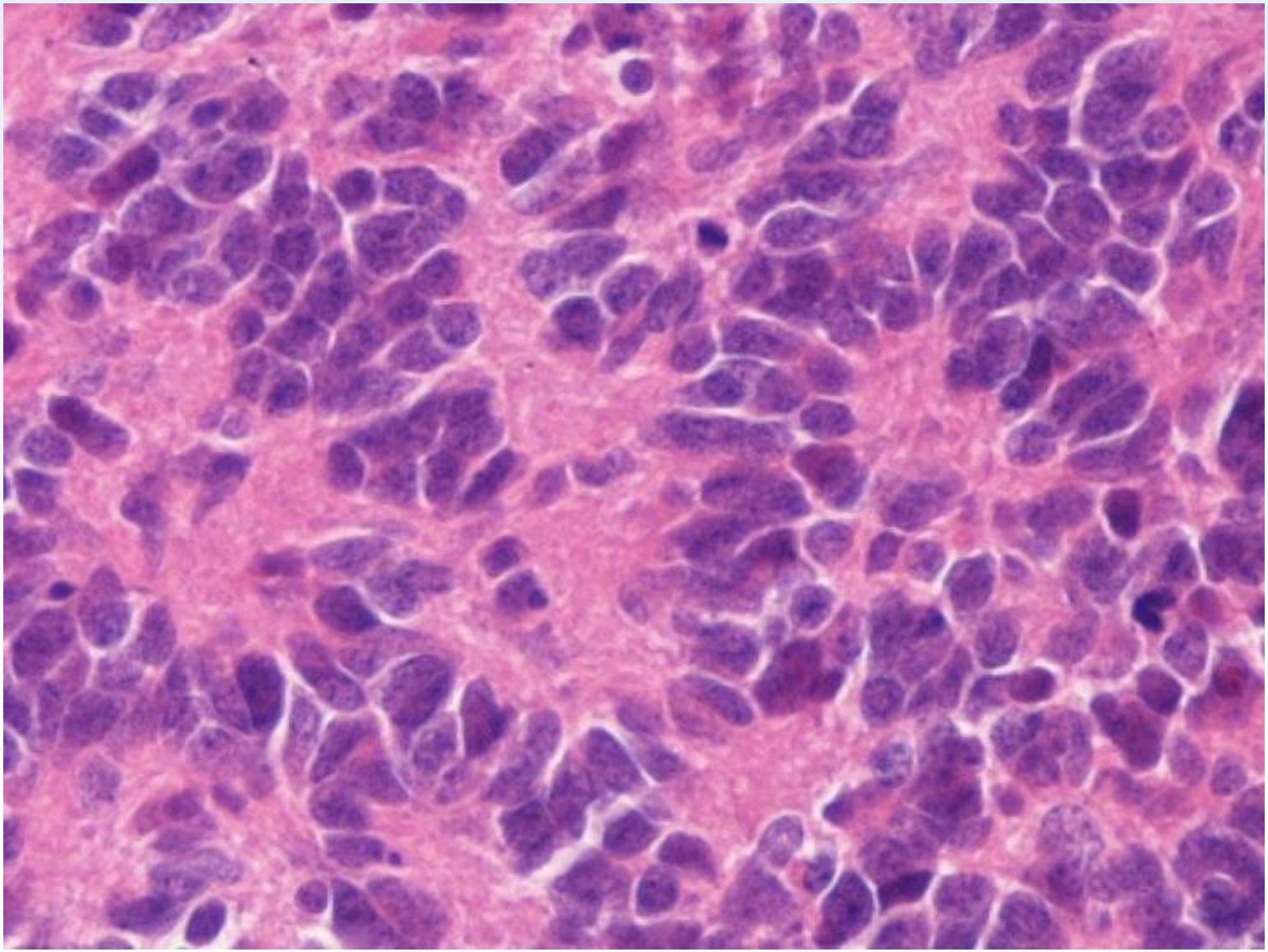
Nodular

Medulloblastoma-Cytology

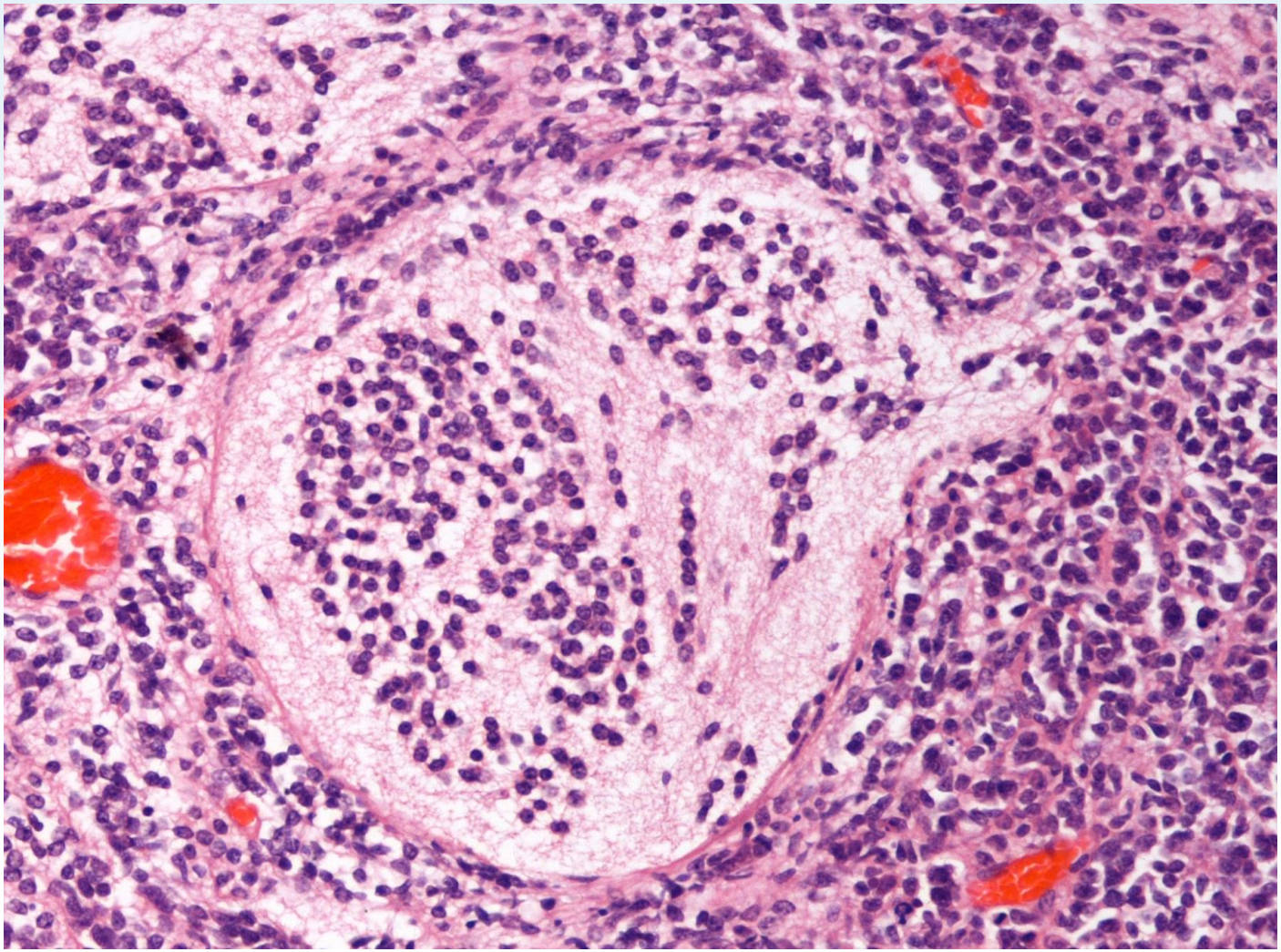




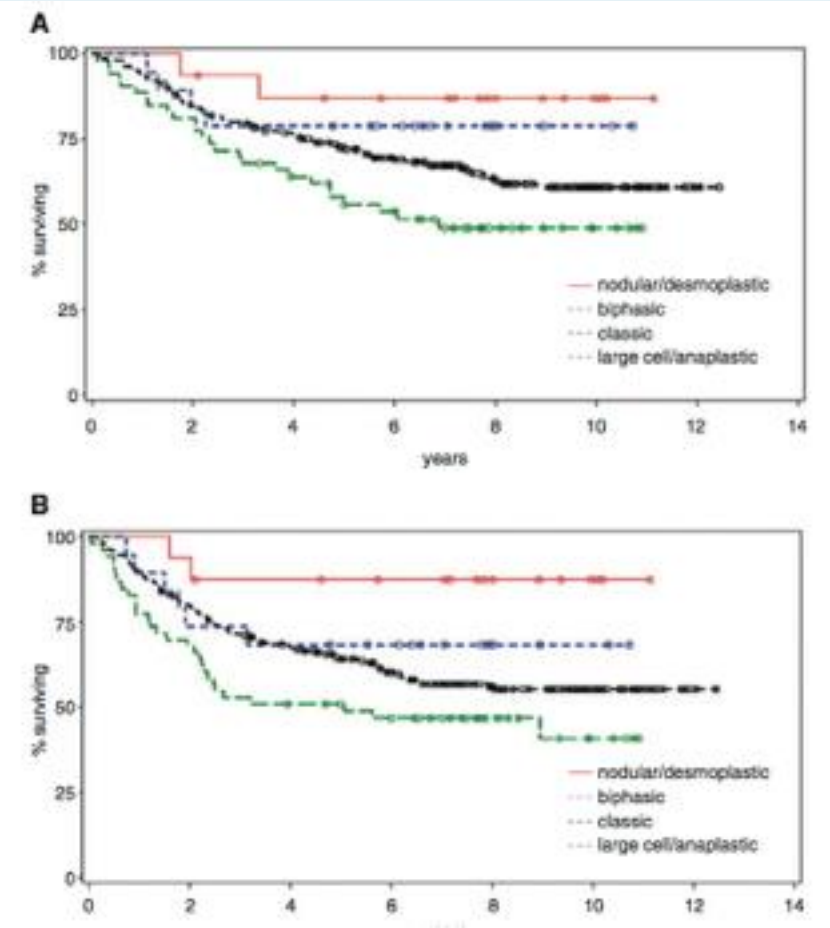
Medulloblastoma-Homer Wright rosettes



Variants-Nodular Medulloblastoma



Nodularity is associated with a better prognosis



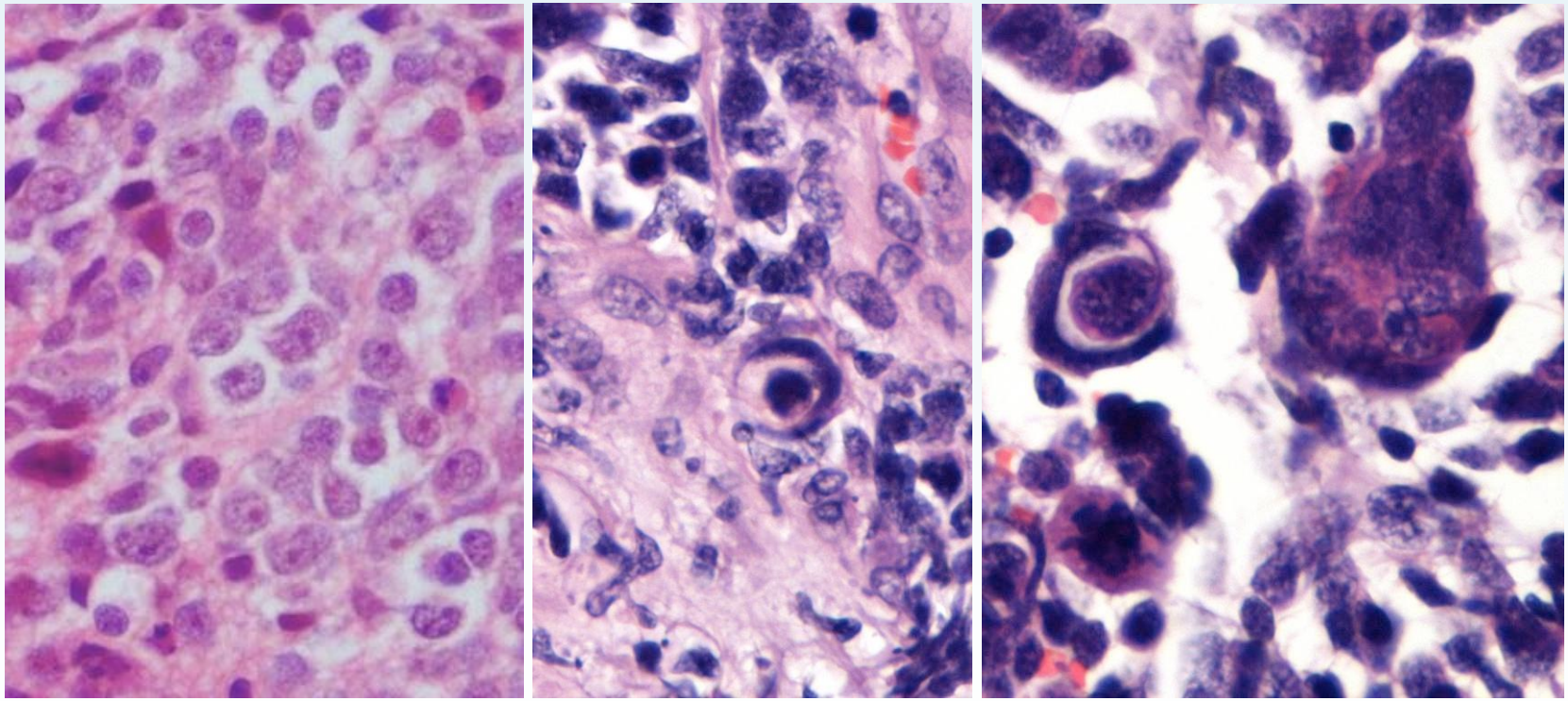
RESEARCH ARTICLE

DOI 10.1111/j.1750-3639.2007.00058.x

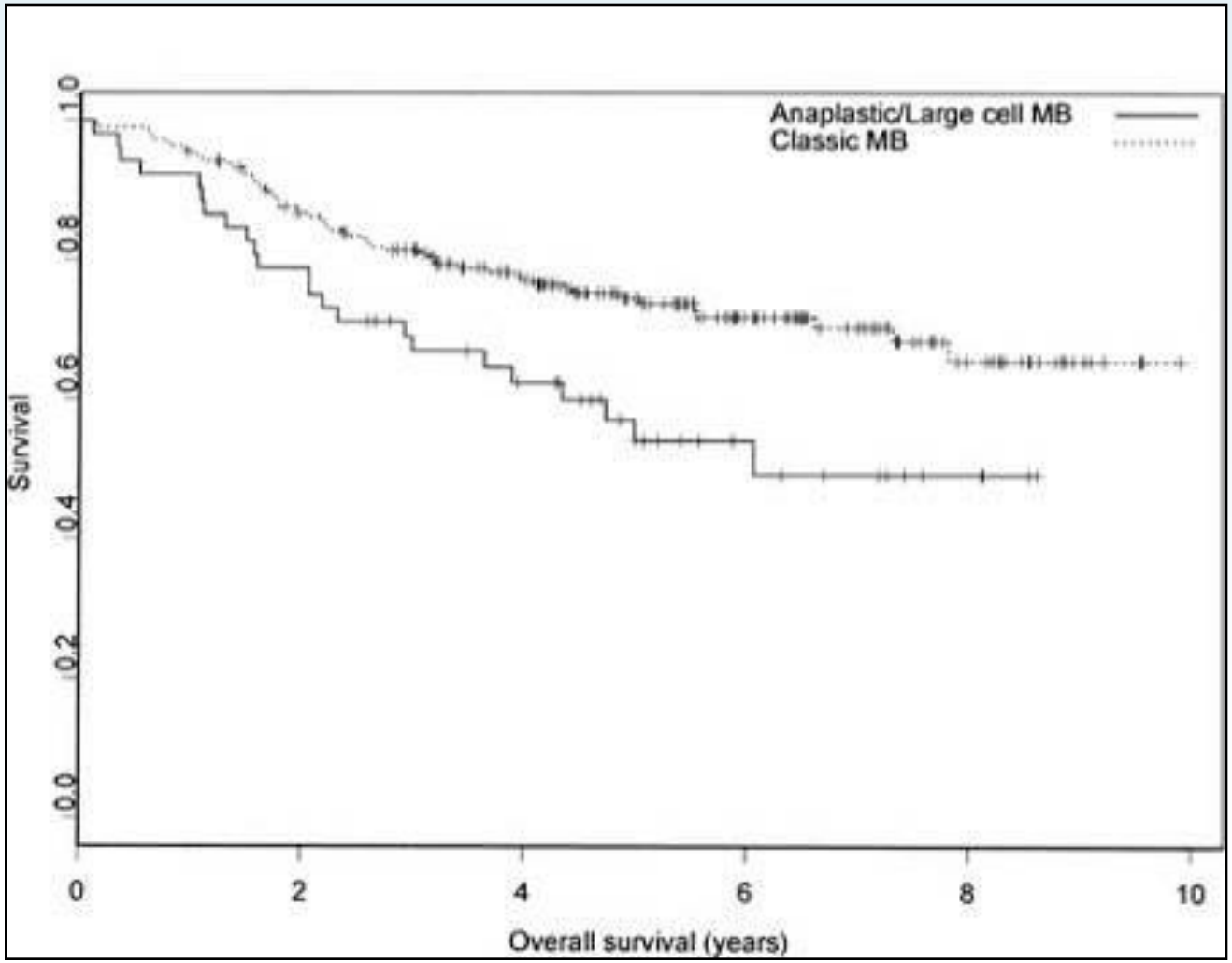
Nodule Formation and Desmoplasia in Medulloblastomas—Defining the Nodular/Desmoplastic Variant and Its Biological Behavior

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

Prognostic Factors: Anaplastic and Large Cell Medulloblastoma

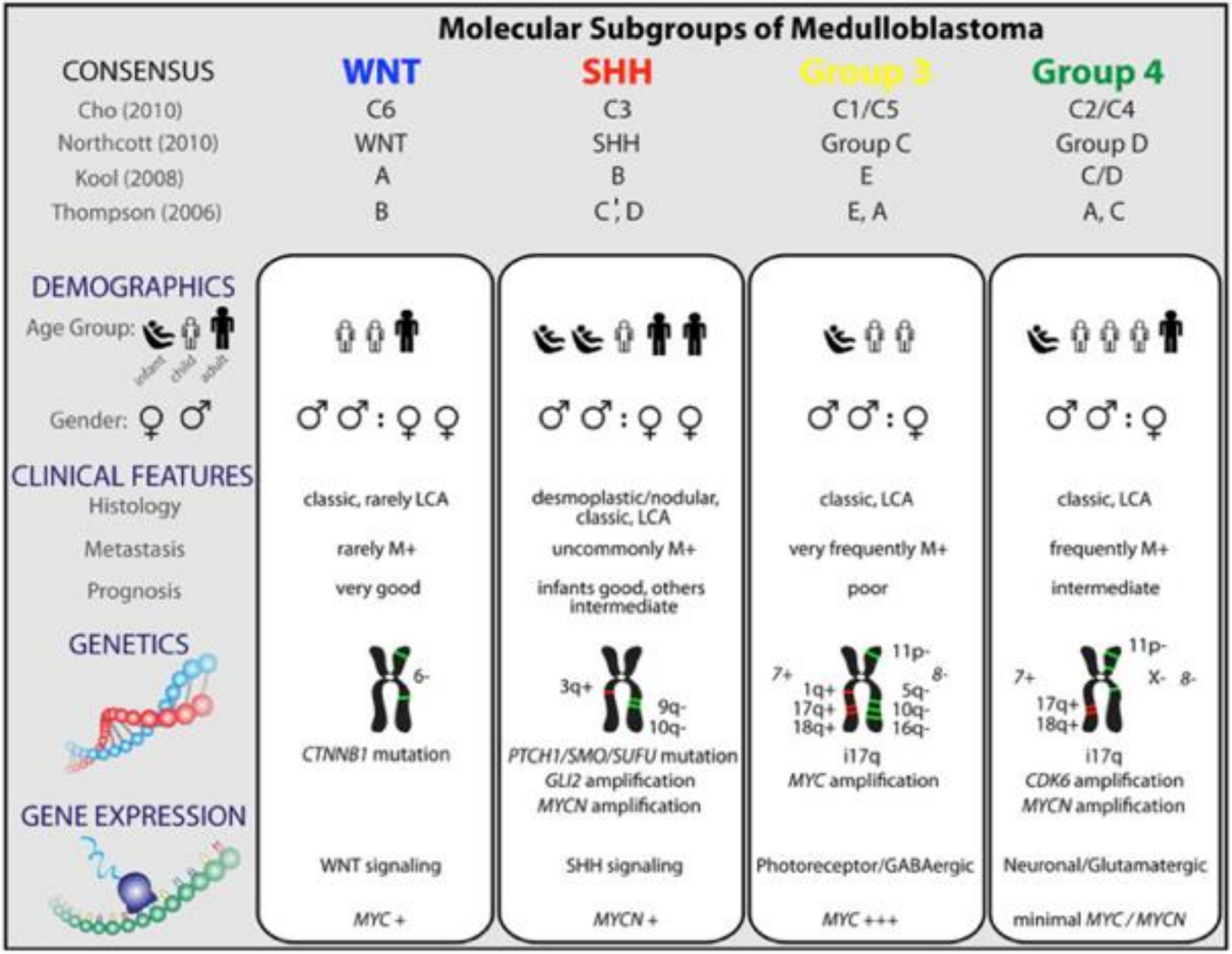


Anaplastic and large cell medulloblastoma carry a worse prognosis



Mc Nanamy *et al.* 2003 JNEN

Risk stratification-molecular subtyping

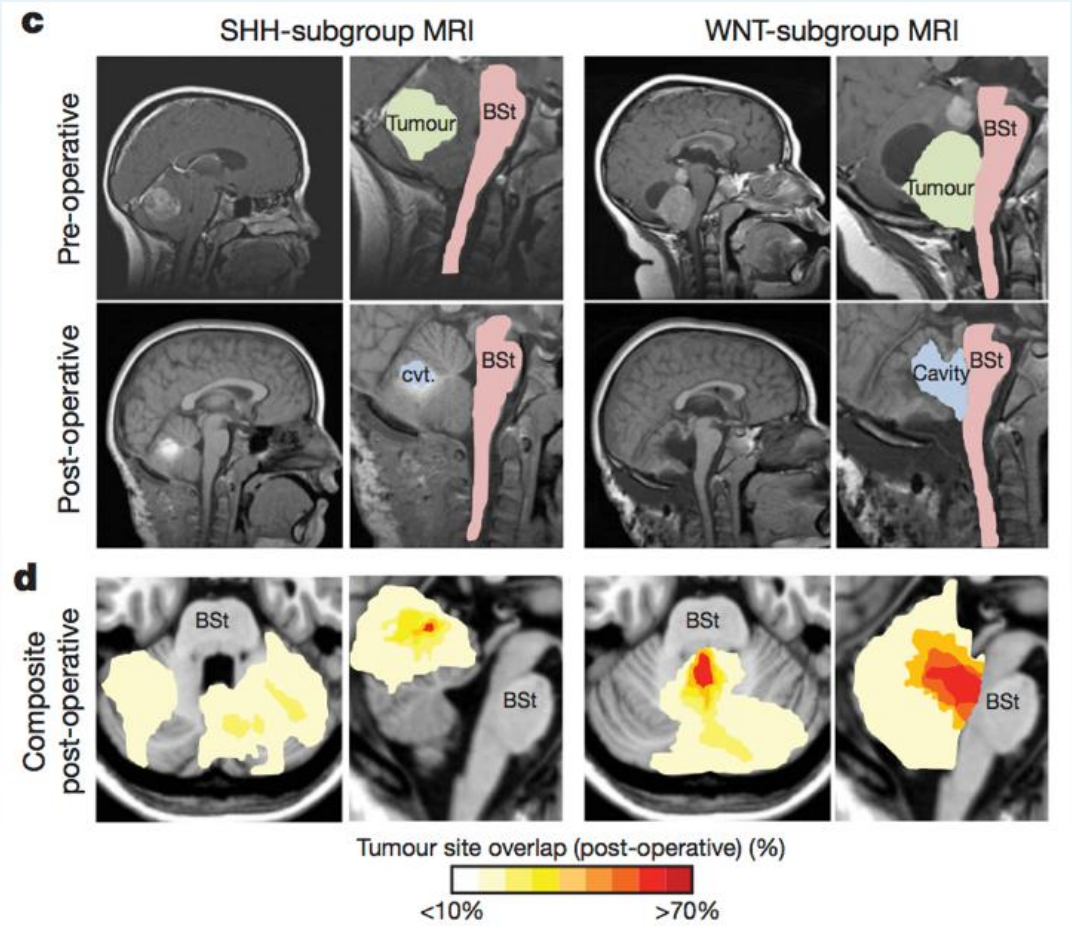

Molecular Subgroups of Medulloblastoma
CONSENSUS
WNT
SHH
Group 3
Group 4
Cho (2010)
C6
C3
C1/C5
C2/C4
Northcott (2010)
WNT
SHH
Group C
Group D
Kool (2008)
A
B
E
C/D
Thompson (2006)
B
C, D
E, A
A, C
DEMOGRAPHICS
Age Group:
infant
child
adult
Gender:
CLINICAL FEATURES
Histology
Metastasis
Prognosis
GENETICS
GENE EXPRESSION
classic, rarely LCA
rarely M+
very good
6-
CTNNB1 mutation
WNT signaling
MYC +
desmoplastic/nodular, classic, LCA
uncommonly M+
infants good, others intermediate
3q+
9q-
10q-
PTCH1/SMO/SUFU mutation
GLI2 amplification
MYCN amplification
SHH signaling
MYCN +
classic, LCA
very frequently M+
poor
7+
1q+
17q+
18q+
11p-
8-
5q-
10q-
16q-
i17q
MYC amplification
Photoreceptor/GABAergic
MYC +++
classic, LCA
frequently M+
intermediate
7+
17q+
18q+
11p-
X-
8-
i17q
CDK6 amplification
MYCN amplification
Neuronal/Glutamatergic
minimal MYC / MYCN

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]



Diagnostic molecular classification

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

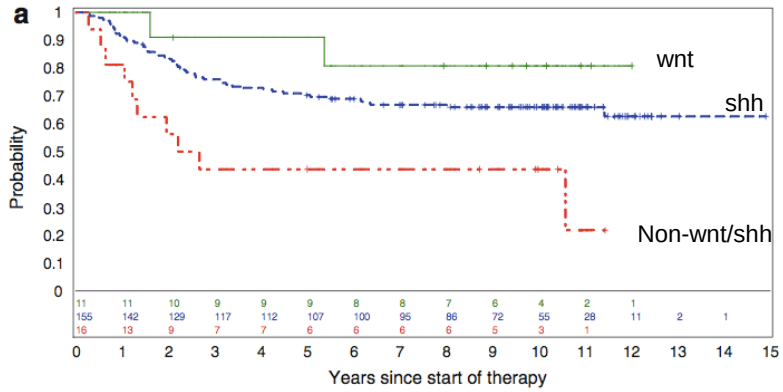
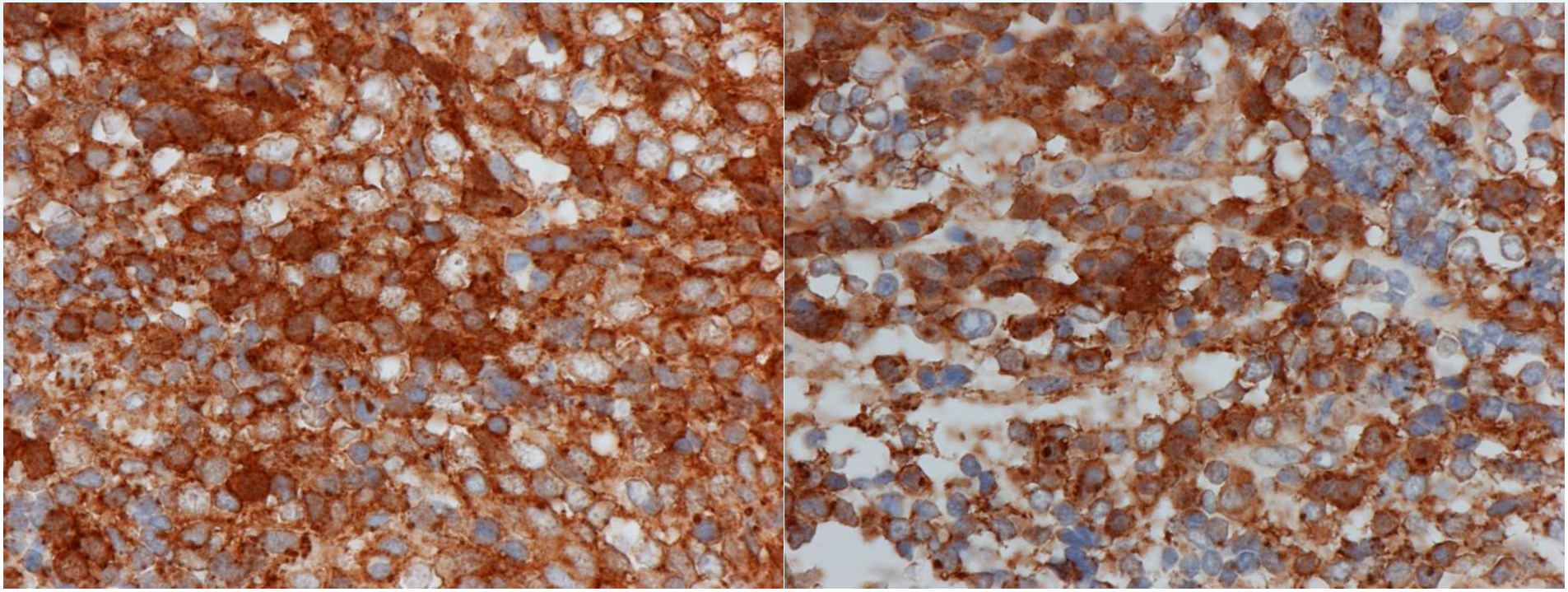


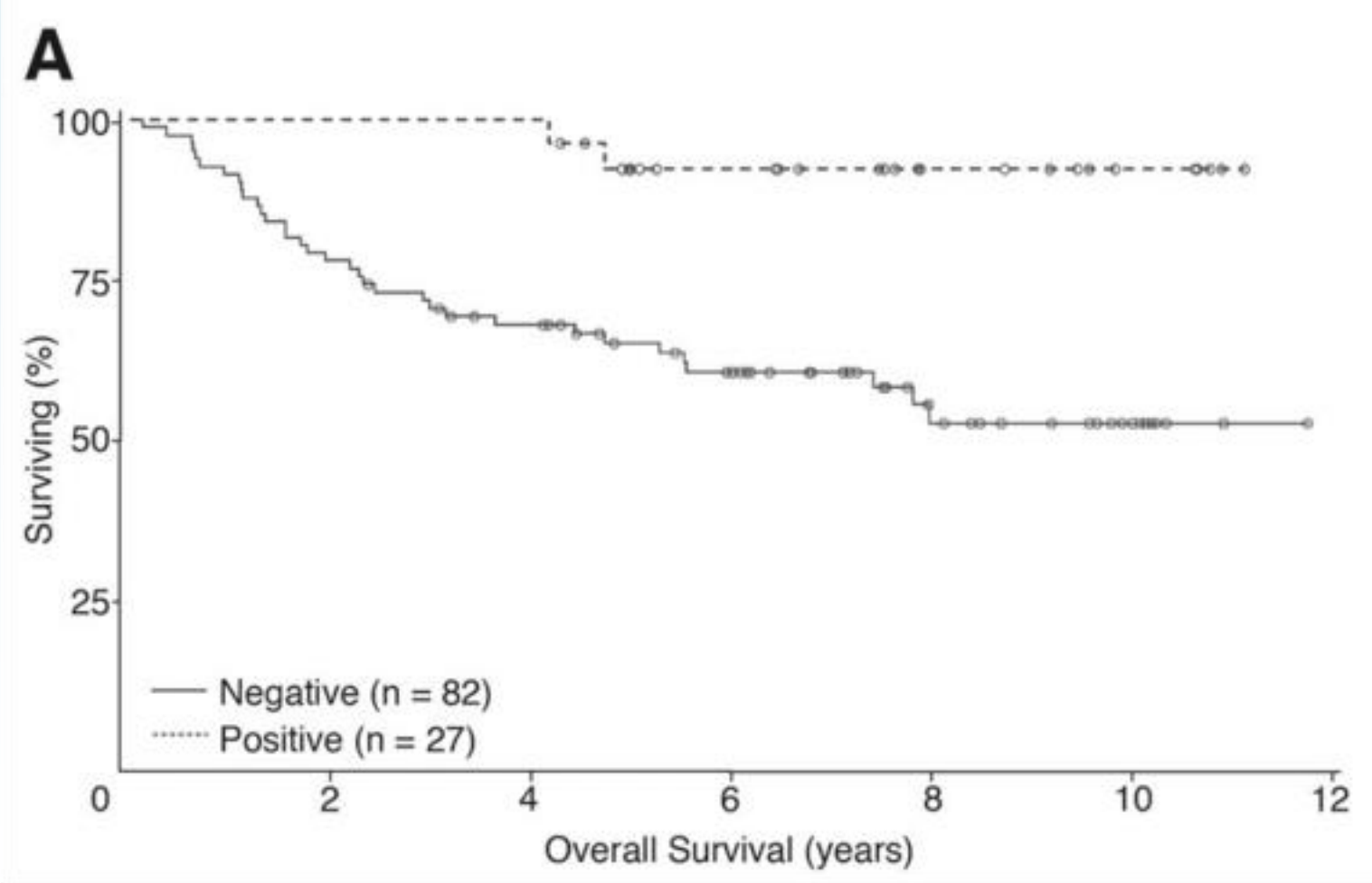
Table 2 Immunophenotypes of SHH, WNT, and non-SHH/WNT molecular subgroups

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

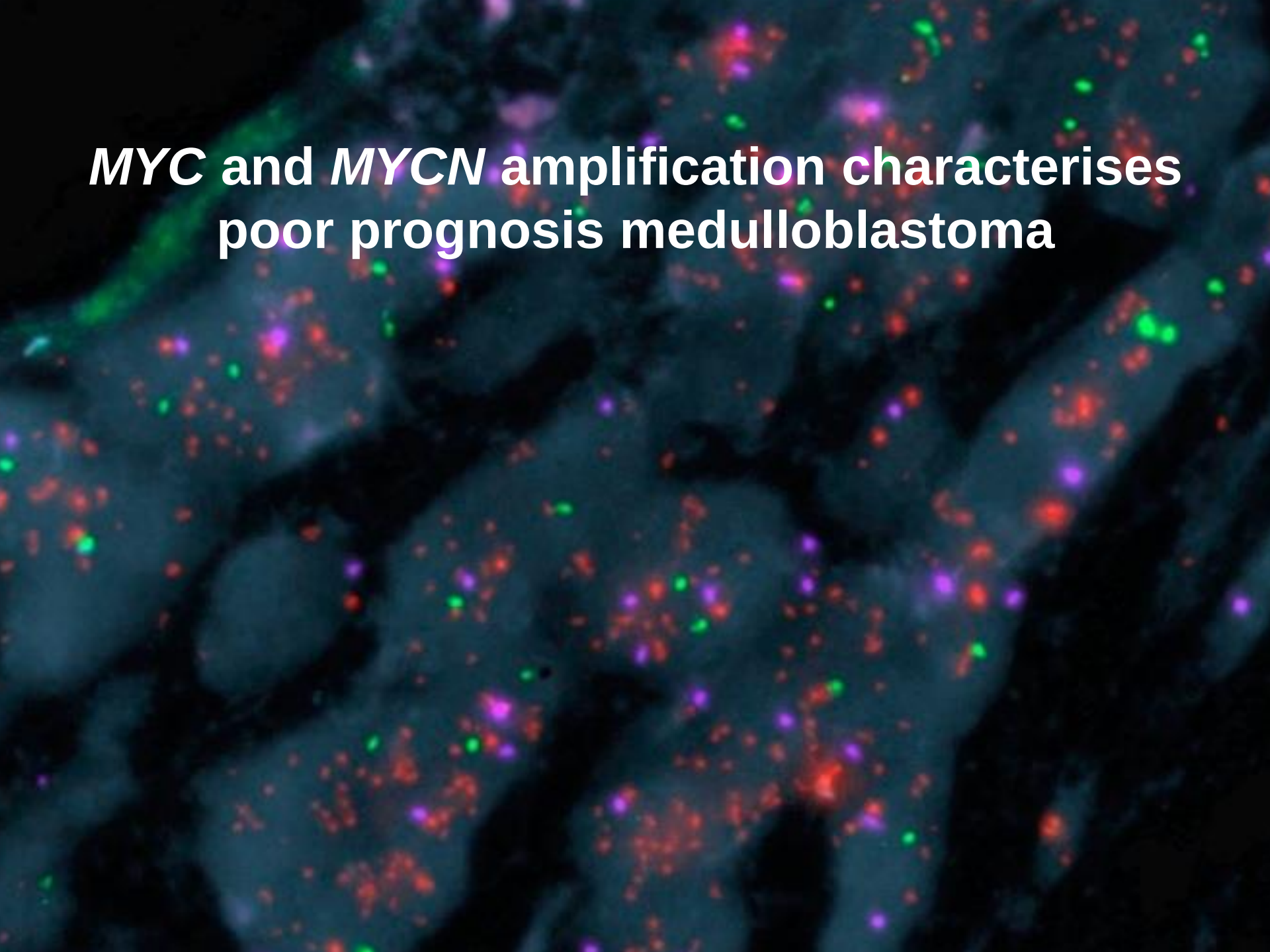
Beta-catenin nuclear staining identifies WNT-subgroup medulloblastoma



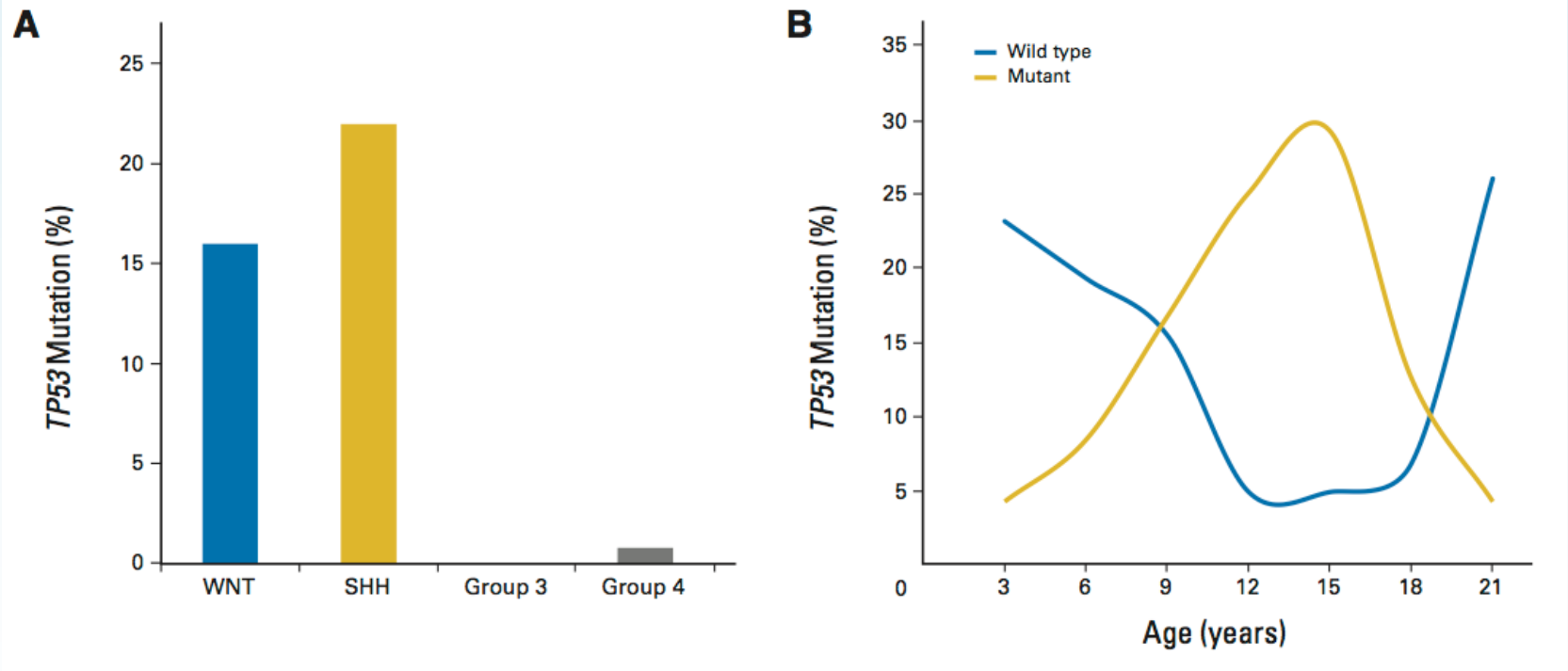
Nuclear beta-catenin expression is associated with an excellent prognosis



Ellison et al. 2005


MYC and *MYCN* amplification characterises poor prognosis medulloblastoma

TP53 mutations occur in specific subtypes of medulloblastoma

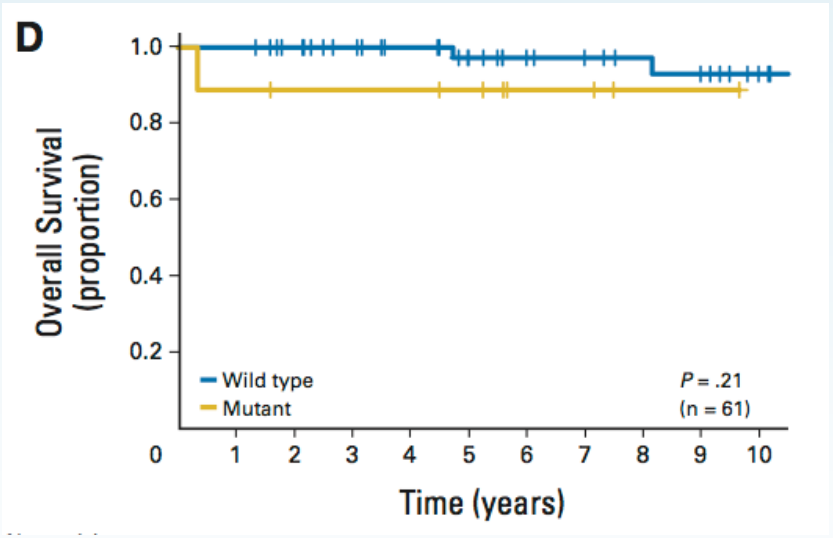


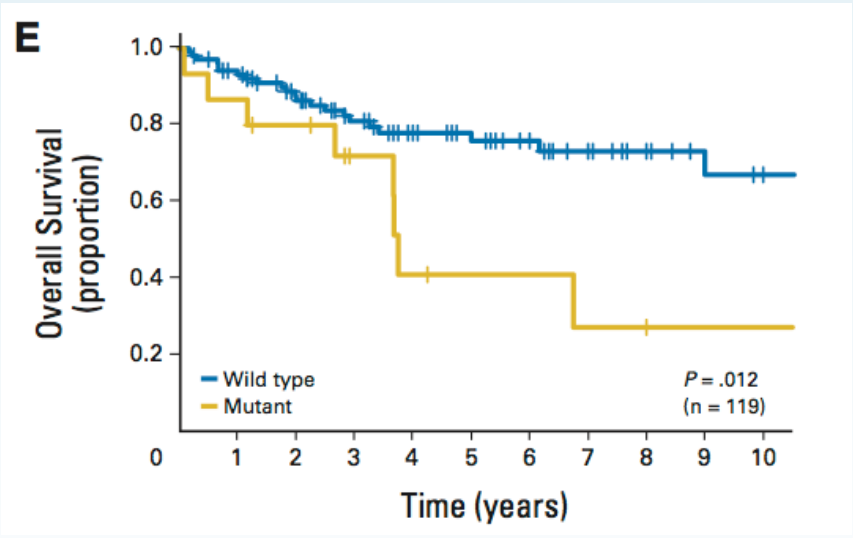
VOLUME 31 · NUMBER 23 · AUGUST 10 2013
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

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

Nataliya Zhukova, Vijay Ramaswamy, Marc Remke, Elke Pfaff, David J.H. Shih, Dianna C. Martin, Pedro Castelo-Branco, Berivan Baskin, Peter N. Ray, Eric Bouffet, André O. von Bueren, David T.W. Jones, Paul A. Northcott, Marcel Kool, Dominik Sturm, Trevor J. Pugh, Scott L. Pomeroy, Yoon-Jae Cho, Torsten Pietsch, Marco Gessi, Stefan Rutkowski, Laszlo Bognar, Almos Klekner, Byung-Kyu Cho, Seung-Ki Kim, Kyu-Chang Wang, Charles G. Eberhart, Michelle Fevre-Montange, Maryam Fouladi, Pim J. French, Max Kros, Wieslawa A. Grajkowska, Nalin Gupta, William A. Weiss, Peter Hauser, Nada Jabado, Anne Jouvet, Shin Jung, Toshihiro Kumabe, Boleslaw Lach, Jeffrey R. Leonard, Joshua B. Rubin, Linda M. Liau, Luca Massimi, Ian F. Pollack, Young Shin Ra, Erwin G. Van Meir, Karel Zitterbart, Ulrich Schüller, Rebecca M. Hill, Janet C. Lindsey, Ed C. Schwalbe, Simon Bailey, David W. Ellison, Cynthia Hawkins, David Malkin, Steven C. Clifford, Andrey Korshunov, Stefan Pfister, Michael D. Taylor, and Uri Tabori

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





WNT-subtype

SHH-subtype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Risk stratification for medulloblastoma

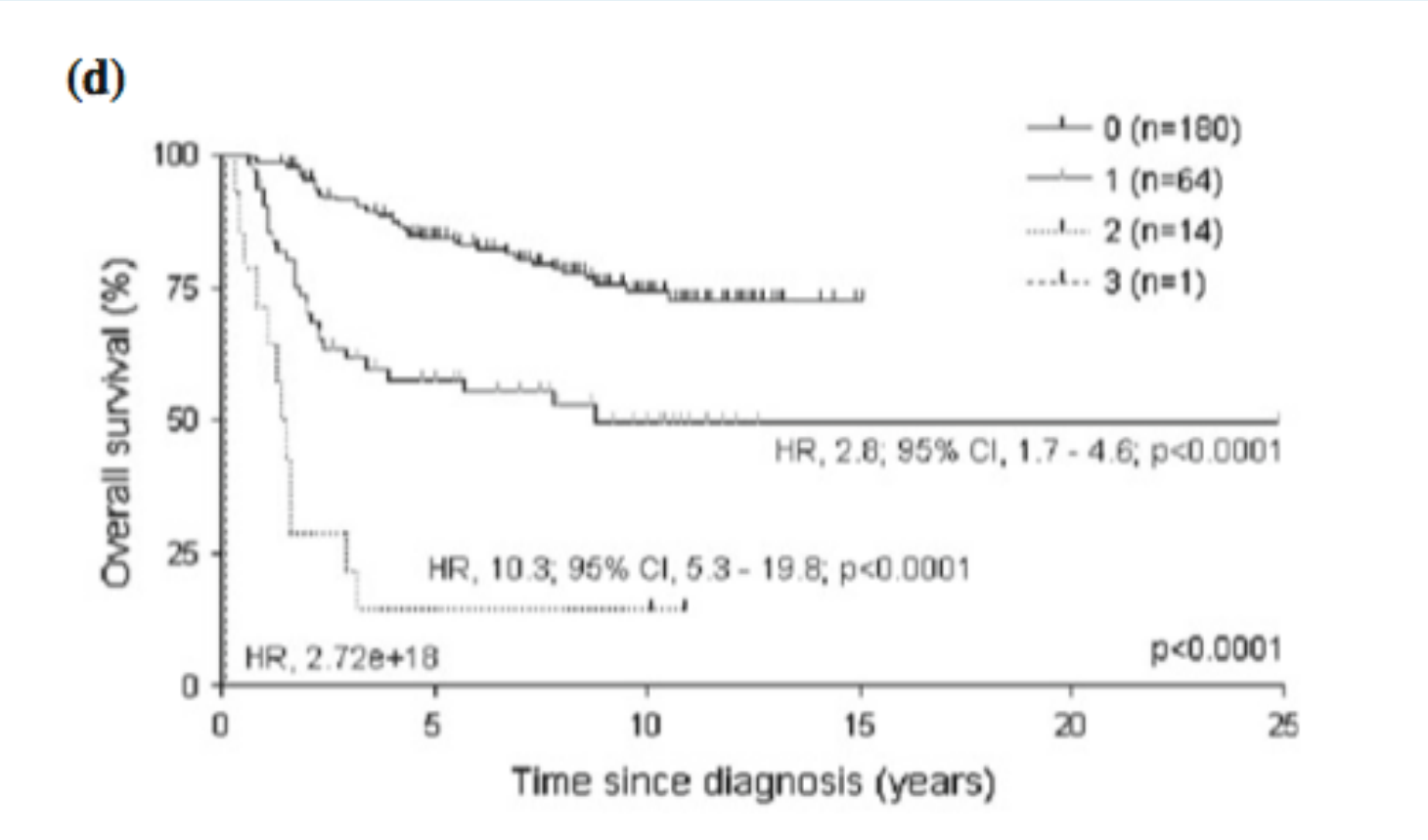
Adverse prognosis

- *MYC* and *MYCN* amplification
- Large Cell/Anaplastic
- *TP53*-mutant, SHH-activated

Good prognosis

- Nodular/Desmoplastic
- WNT-activated

Poor prognostic factors are additive



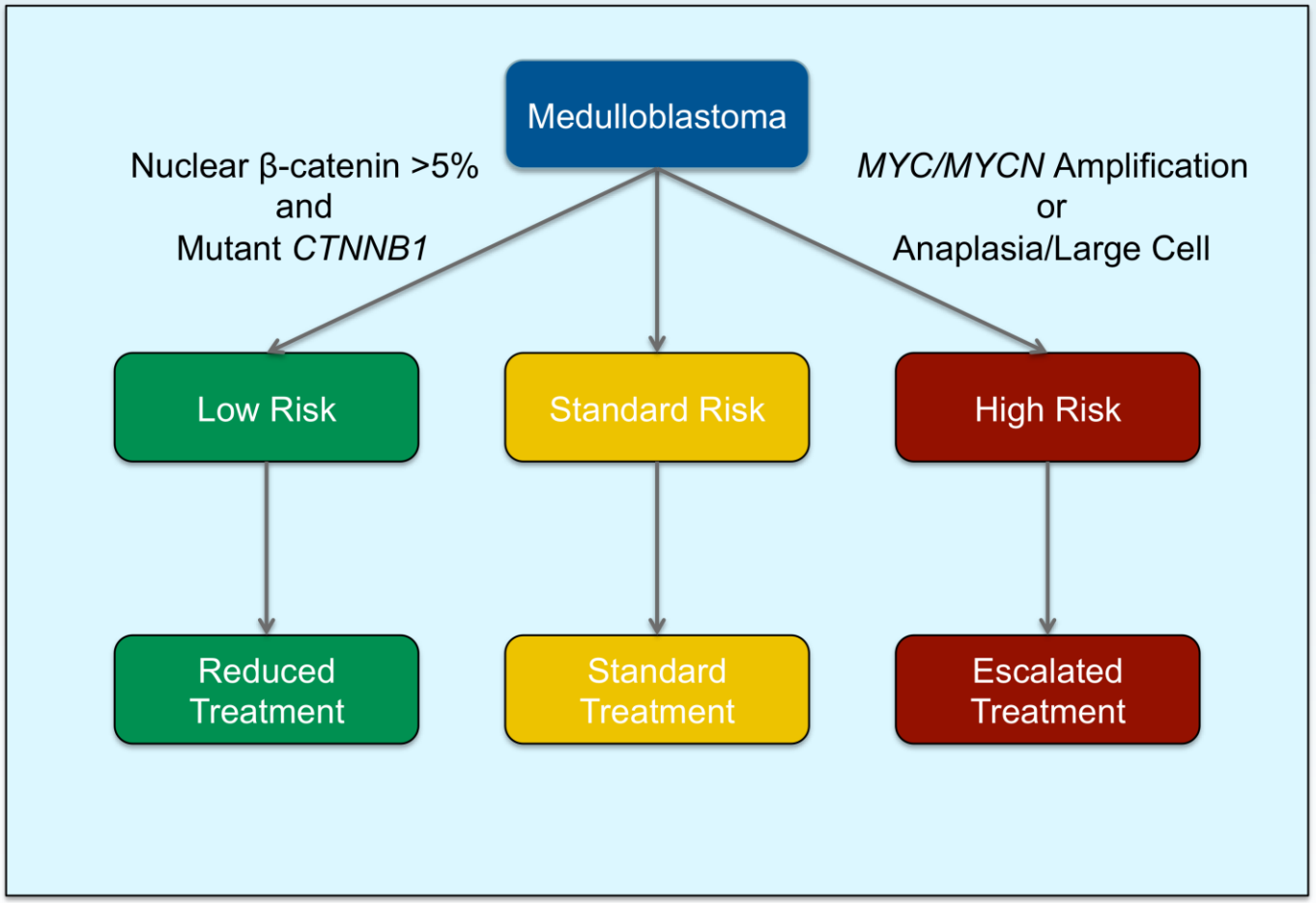
Acta Neuropathol (2012) 123:501–513
DOI 10.1007/s00401-011-0923-y

ORIGINAL PAPER

***MYC* family amplification and clinical risk-factors interact to predict an extremely poor prognosis in childhood medulloblastoma**

Sarra L. Ryan · Ed C. Schwalbe · Michael Cole · Yuan Lu · Meryl E. Lusher · Hisham Megahed · Kieran O'Toole · Sarah Leigh Nicholson · Laszlo Bognar · Miklos Garami · Peter Hauser · Andrey Korshunov · Stefan M. Pfister · Daniel Williamson · Roger E. Taylor · David W. Ellison · Simon Bailey · Steven C. Clifford

Received: 4 October 2011 / Revised: 16 November 2011 / Accepted: 22 November 2011 / Published online: 3 December 2011



Neuropathology and Applied Neurobiology
BNS

Editorial

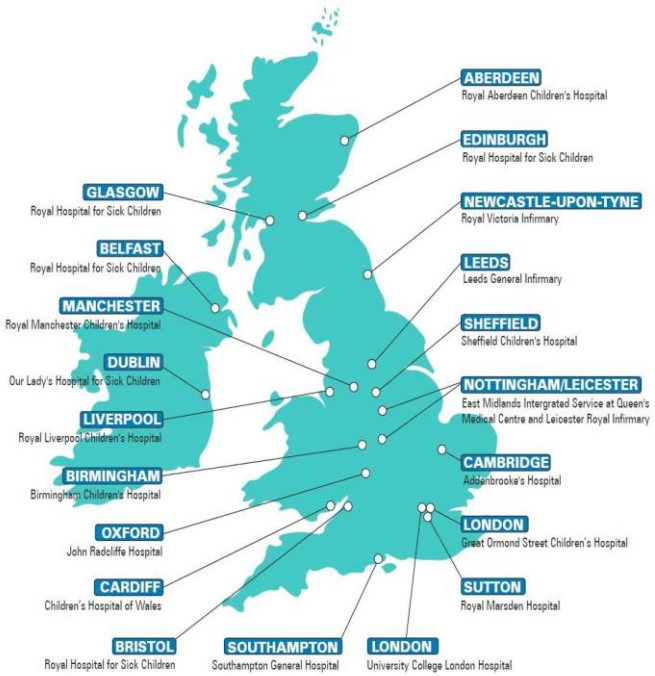
Medulloblastoma: selecting children for reduced treatment

T. J. Stone, T. S. Jacques

First published: 29 January 2015 Full publication history

Volume 41, Issue 2
February 2015
Pages 106–108

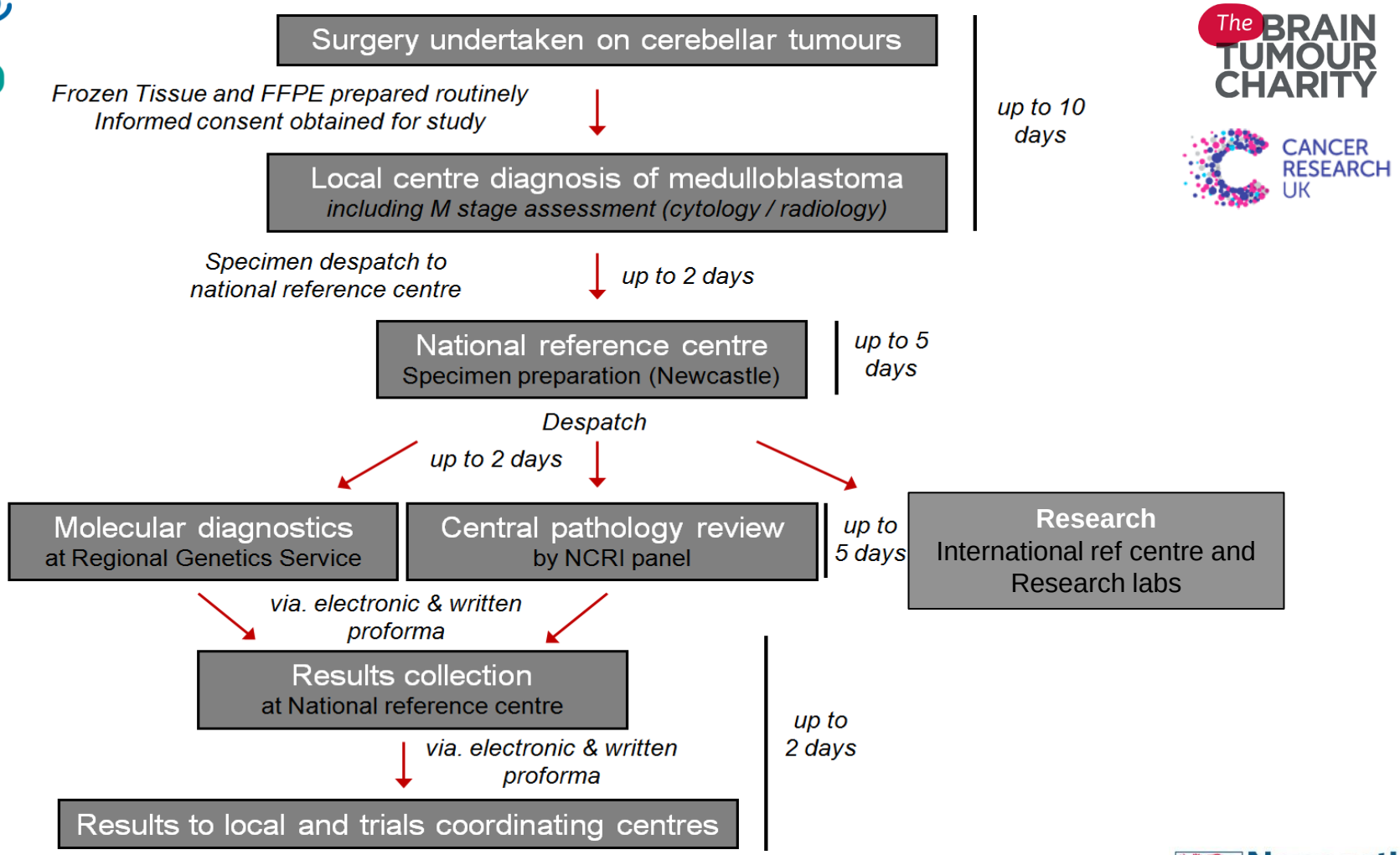
UK feasibility study



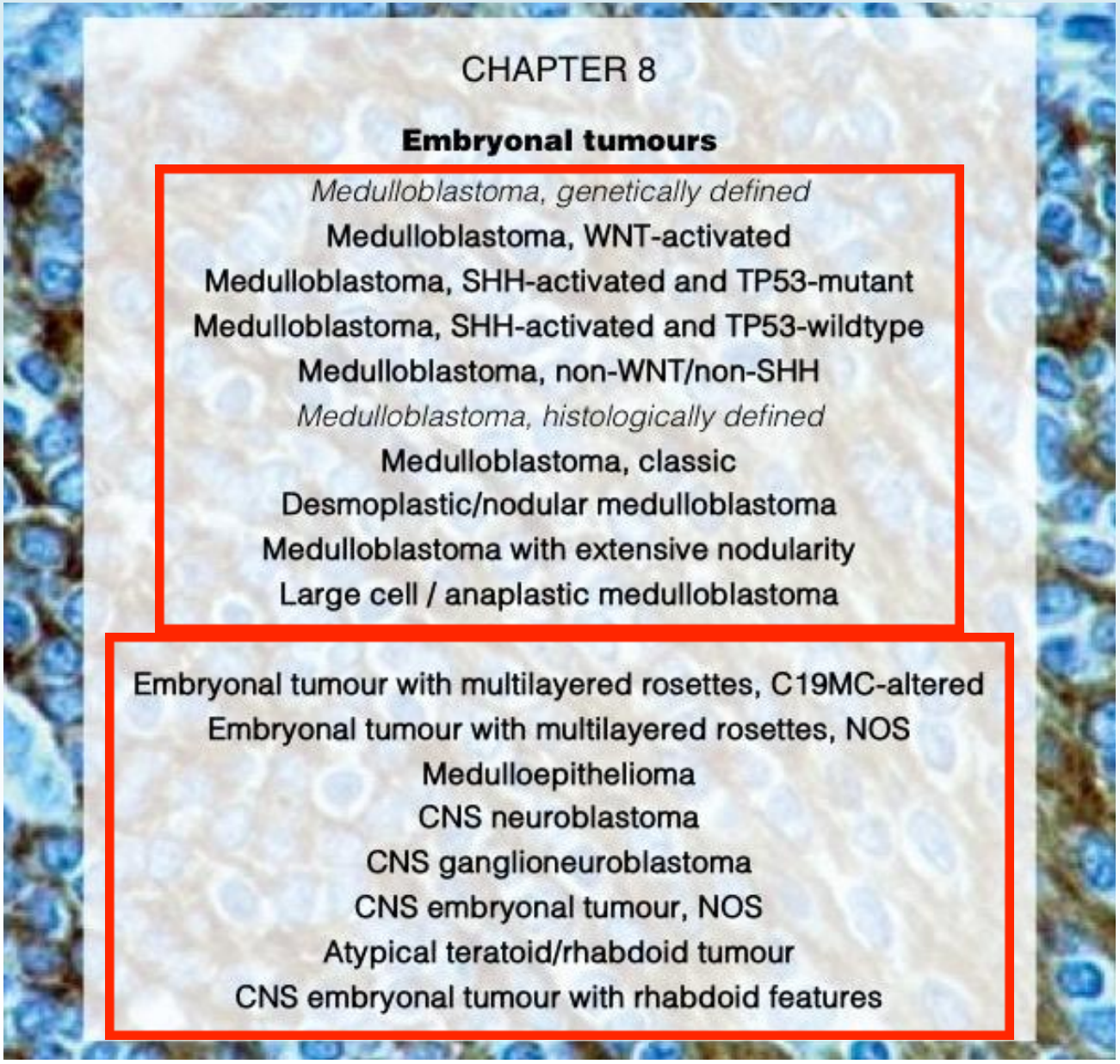
22 centres

- Commenced February 2009
- Study information packs circulated
  Lead pathologists, oncologists, centre coordinators
- Frozen tissue
  MYC, MYCN amplification status
- FFPE tissue:
  Central pathology review
  WNT (®-catenin) status

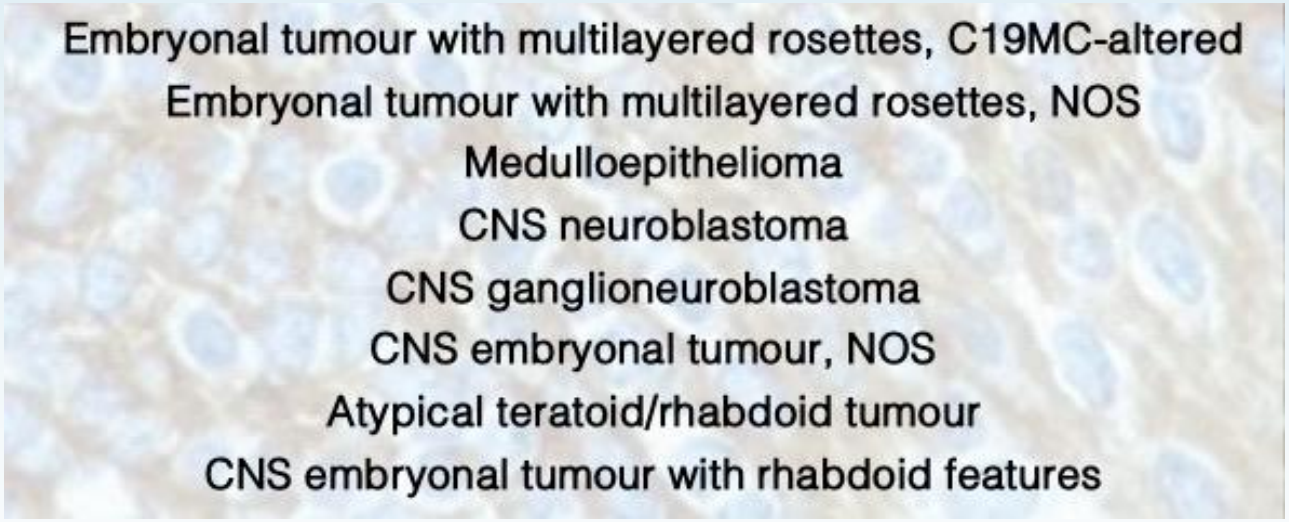
Centralised medulloblastoma molecular diagnostics and central pathology review



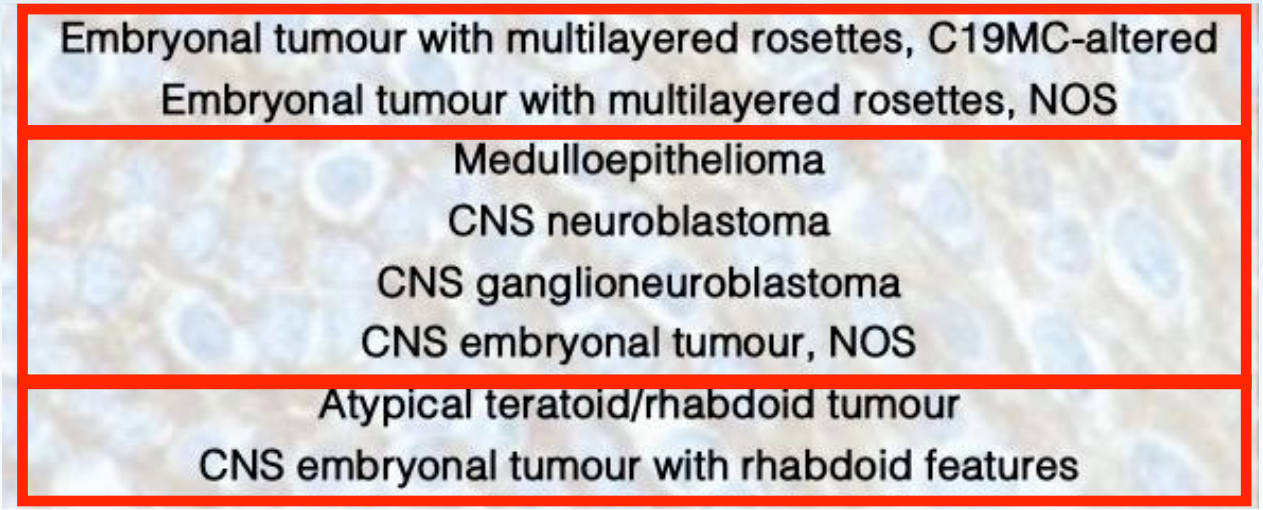
Does not influence therapy


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

Non-Medullo Embryonal Tumours



Non-Medullo Embryonal Tumours

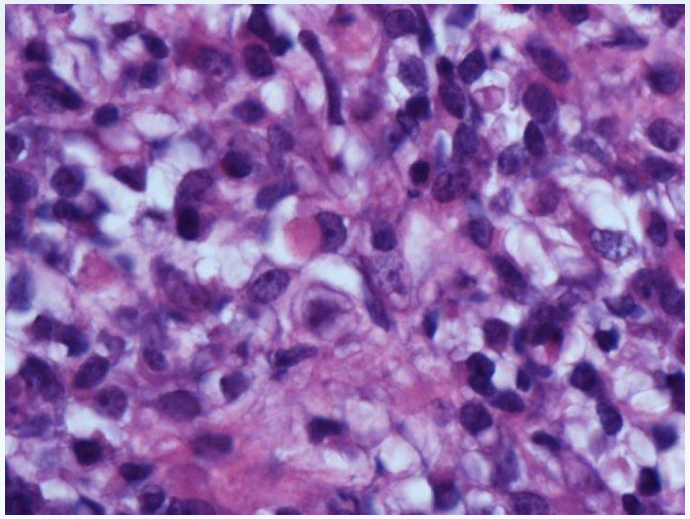


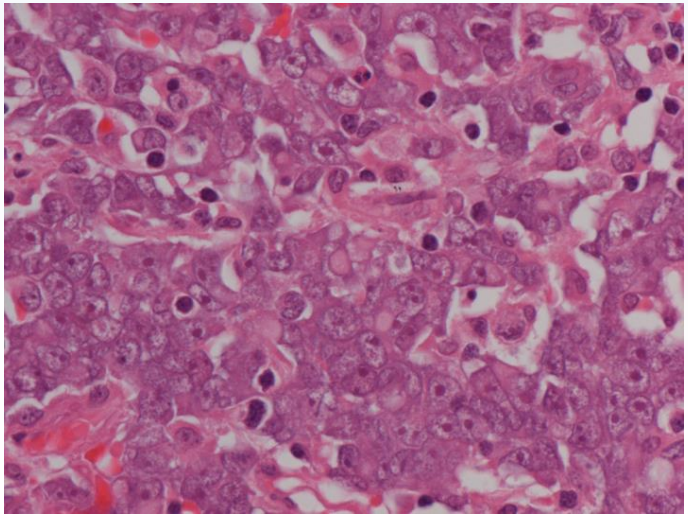
ETMR/ETANTR
Ependymoblastoma
Medulloepithlioma

CNS-PNET and variants

ATRT

Atypical Teratoid/Rhabdoid Tumour

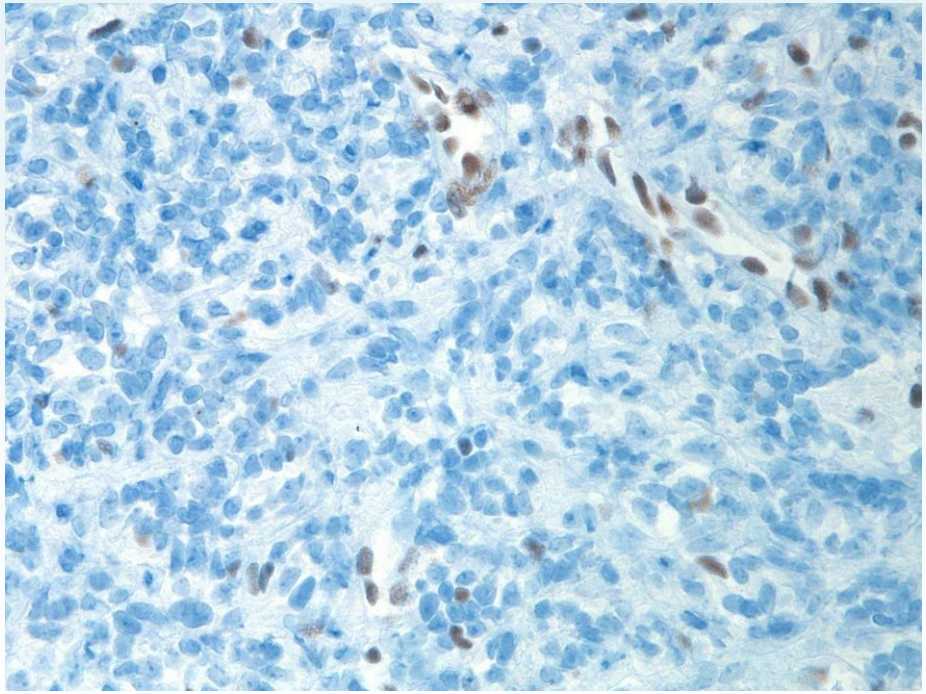




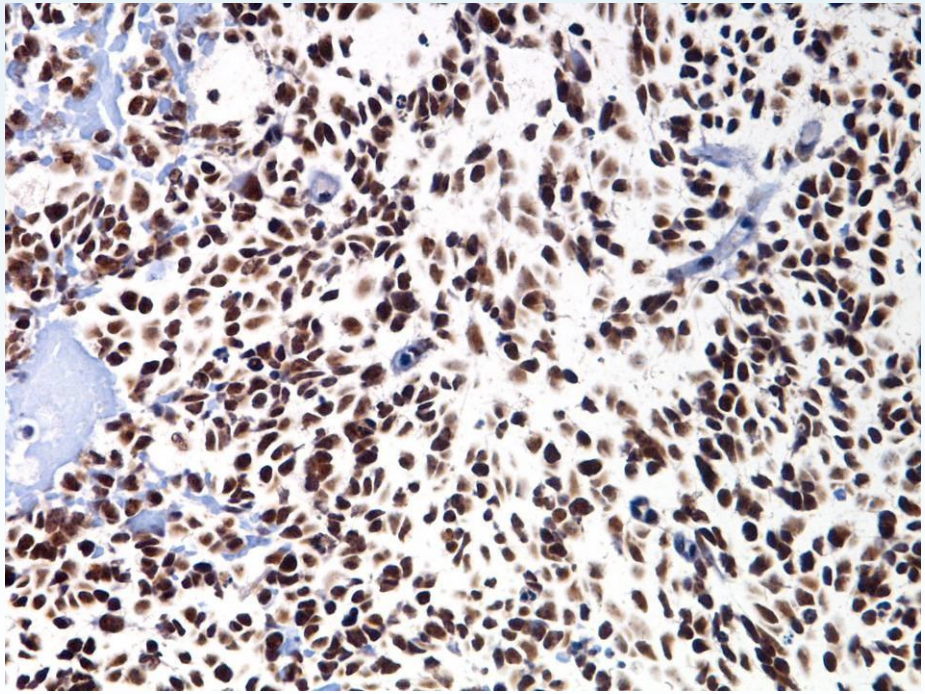
- Age usually <6 years old
- May have typical ‘rhabdoid’ cytology but usually very unpredictable morphology
- Protean immunohistochemistry
- Associated with mutations in *SMARCB1* (INI1) gene
- Rarely *SMARCA4* (BRG1) mutation
- Median survival typically short
- Germline predisposition

Atypical Teratoid/Rhabdoid Tumour

INI-1

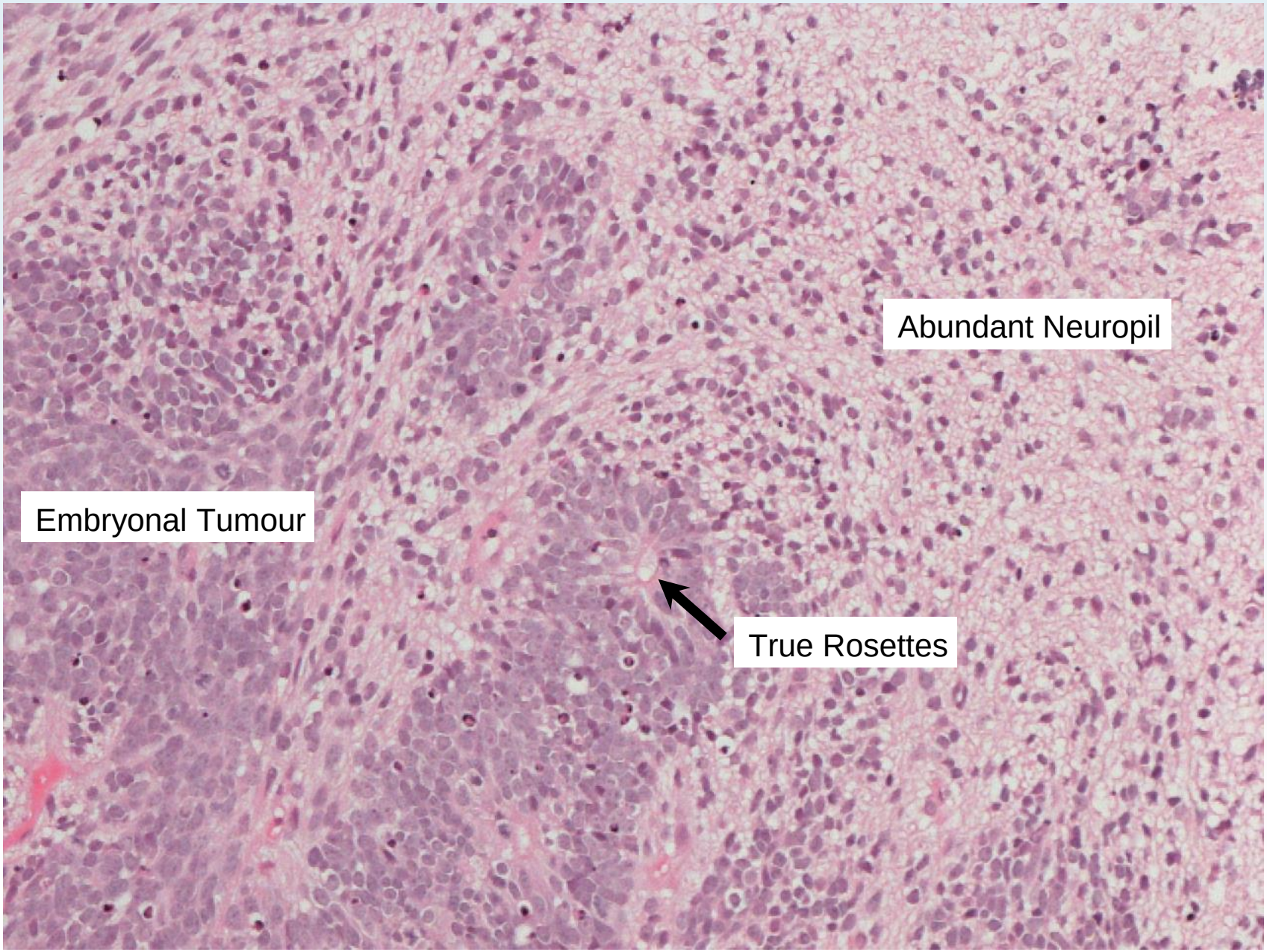


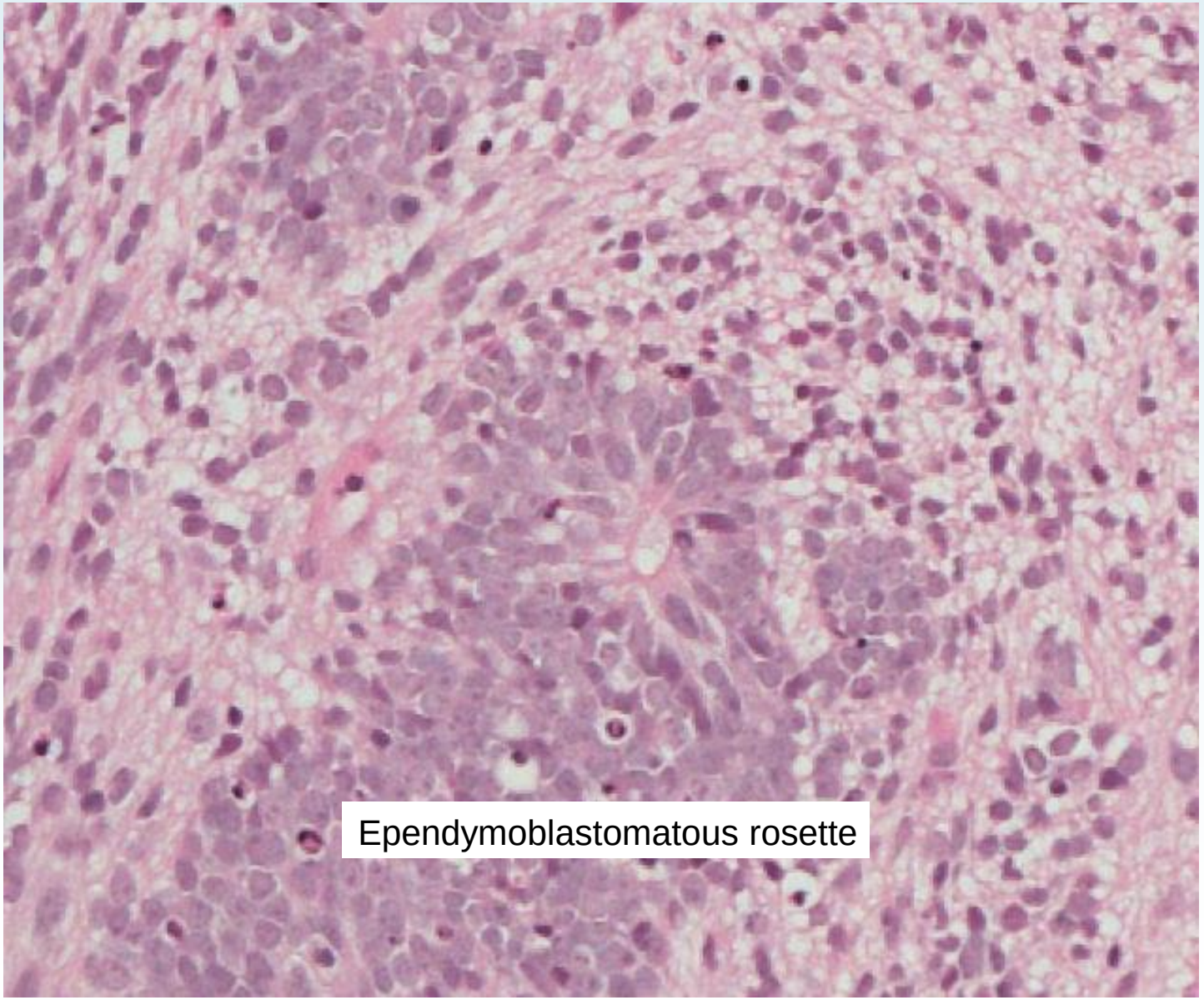
ATRT



Medulloblastoma

Embryonal Tumour with Multilayered Rosettes (ETMR), C19MC altered


Abundant Neuropil
Embryonal Tumour
True Rosettes

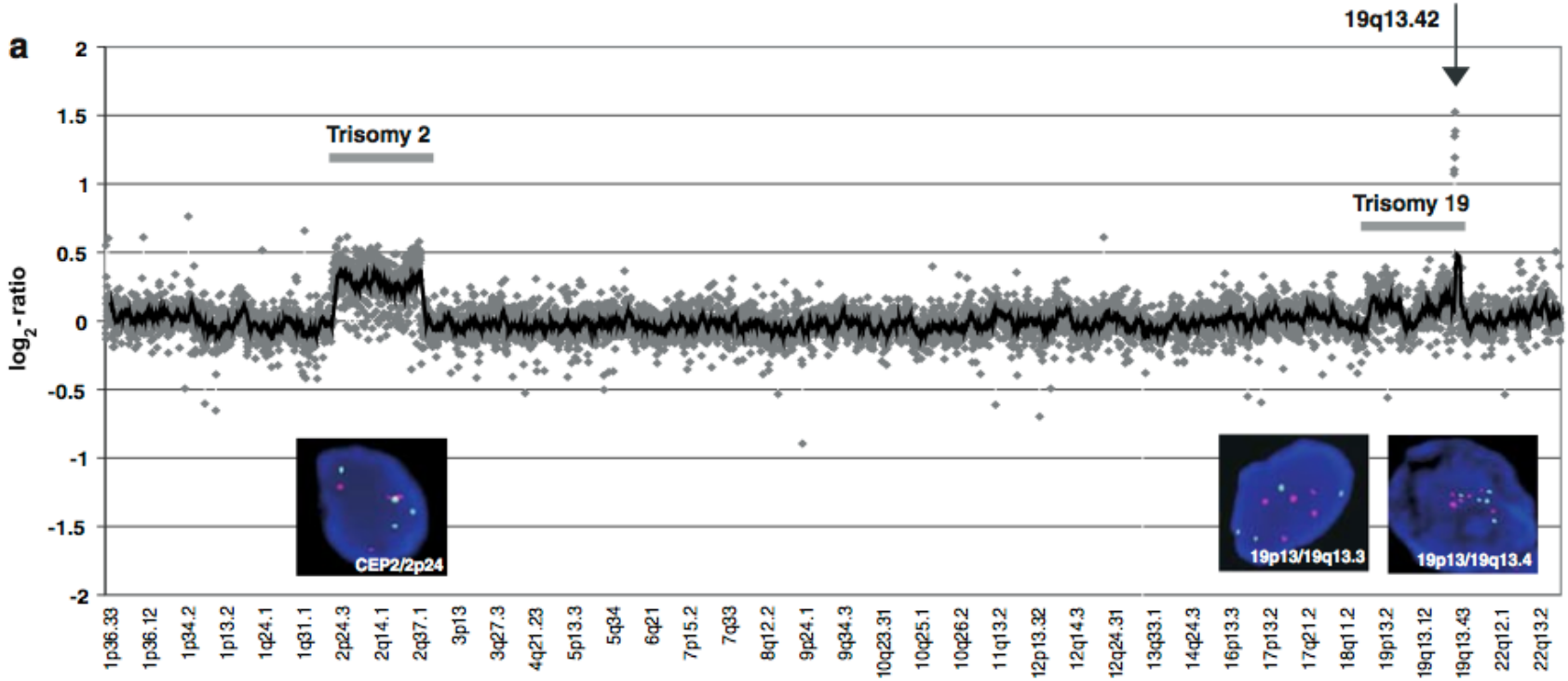

Ependymoblastomatous rosette

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

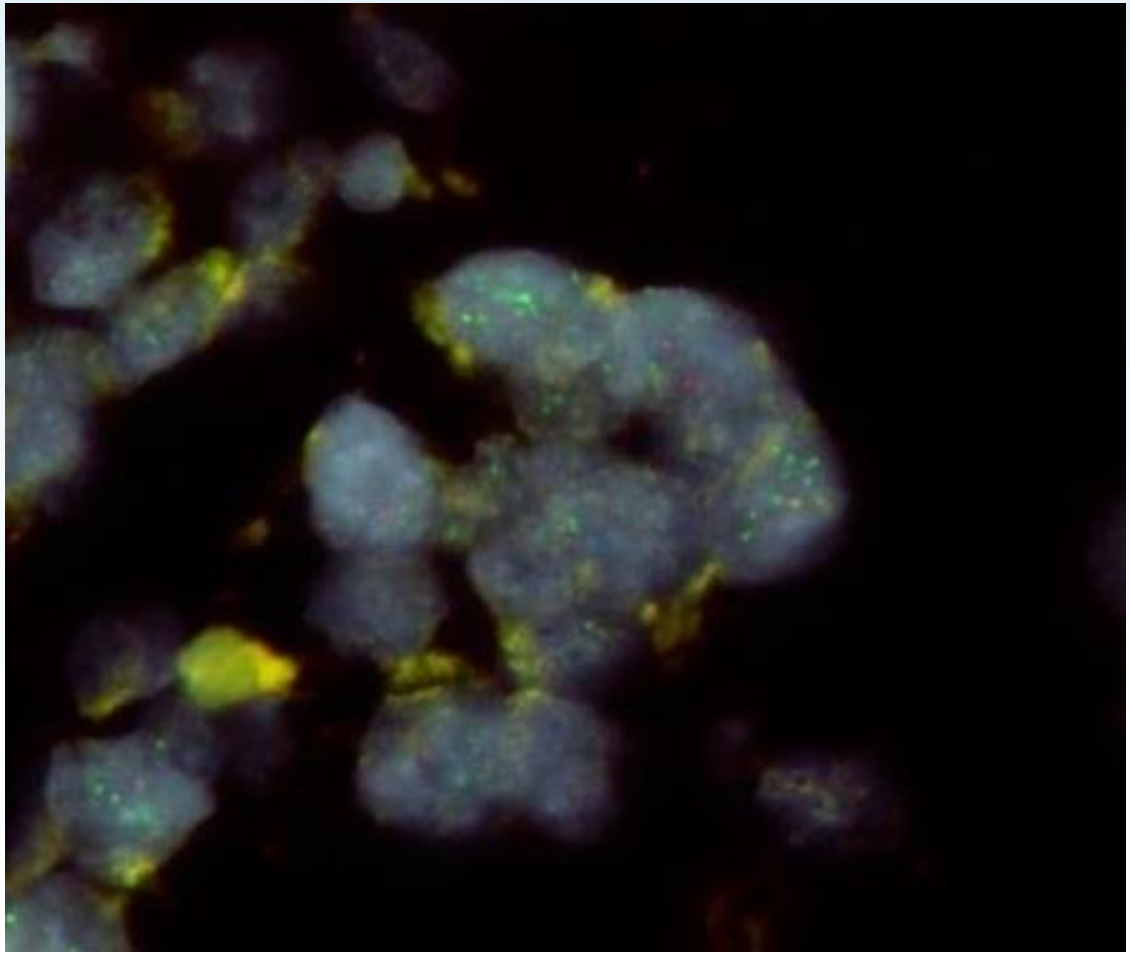
CASE REPORT

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

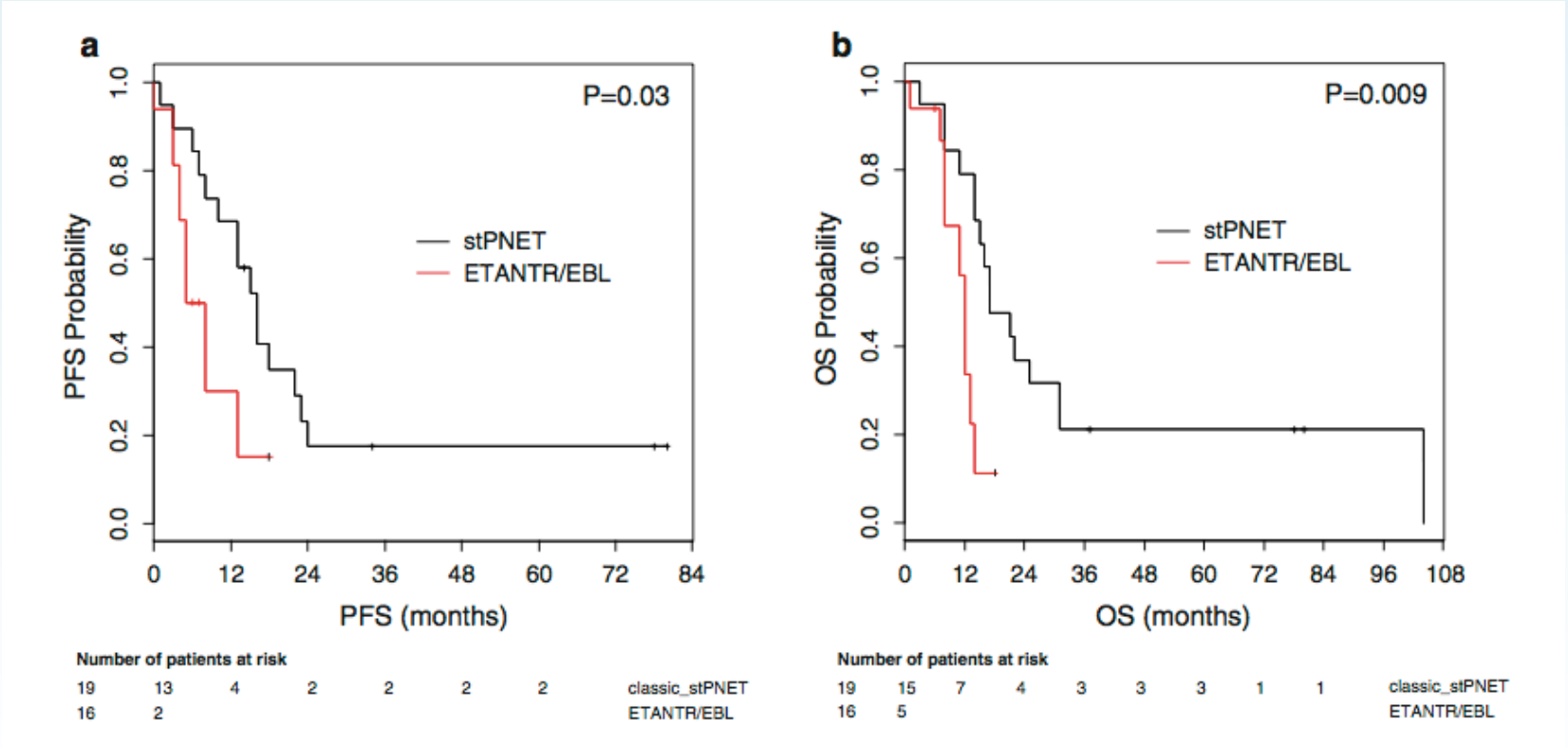
Stefan Pfister · Marc Remke · Mirco Castoldi · Alfa H. C. Bai · Martina U. Muckenthaler · Andreas Kulozik · Andreas von Deimling · Armin Pscherer · Peter Lichter · Andrey Korshunov



FISH for 19q amplification



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

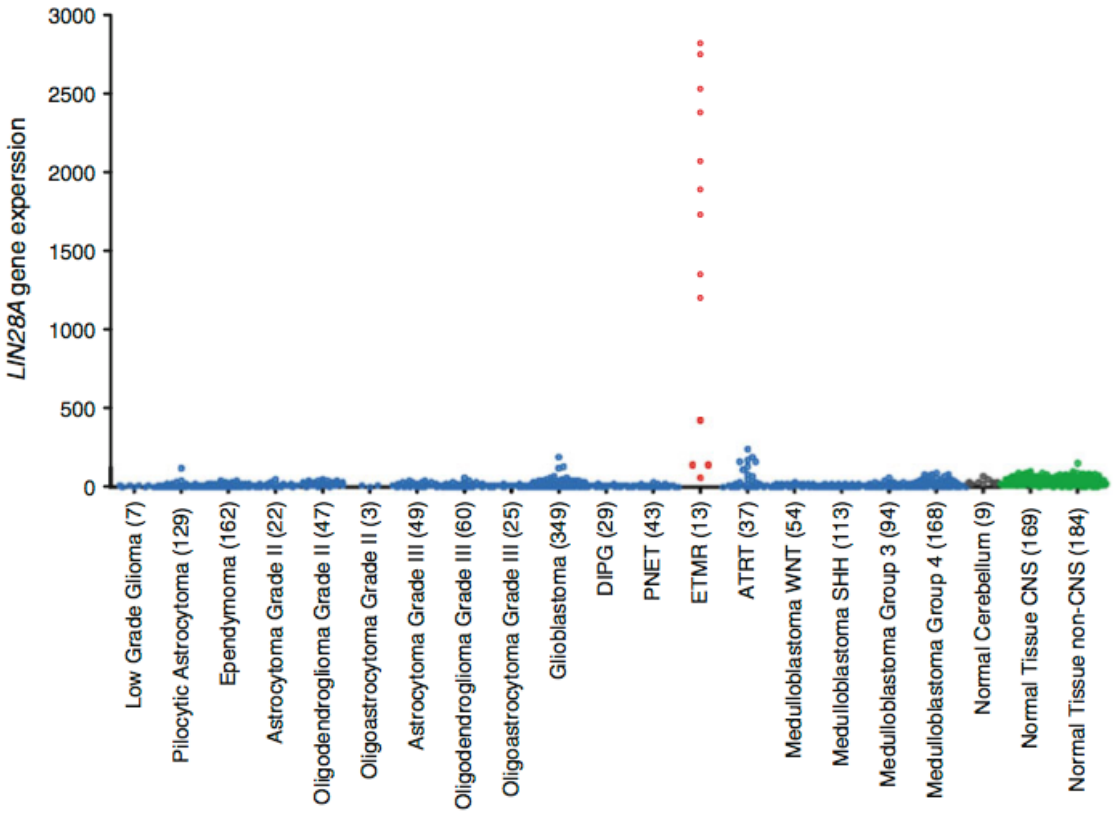
Andrey Korshunov · Marc Remke · Marco Gessi · Marina Ryzhova · Thomas Hielscher · Hendrik Witt · Vivienne Tobias · Anna Maria Buccoliero · Iacopo Sardi · Marina Paola Gardiman · Jose Bonnin · Bernd Scheithauer · Andreas E. Kulozik · Olaf Witt · Sverre Mork · Andreas von Deimling · Otmar D. Wiestler ·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

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

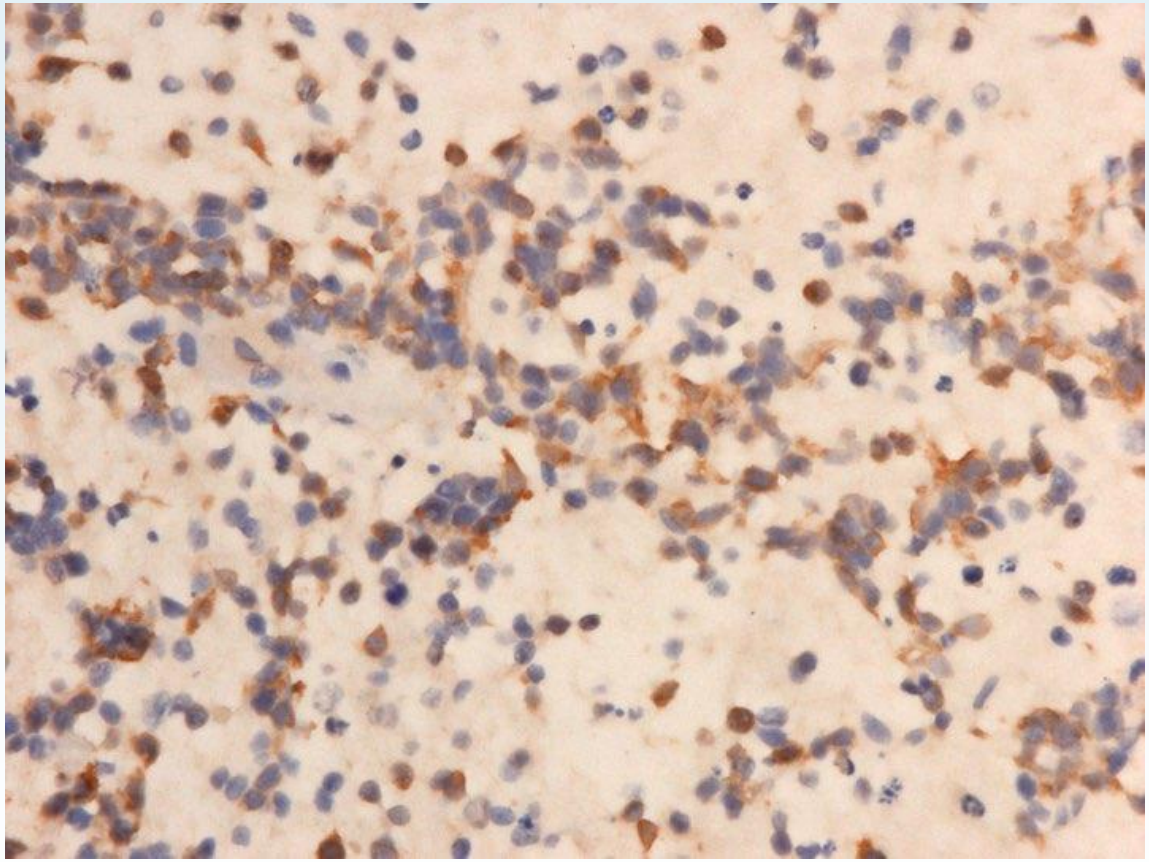
ORIGINAL PAPER

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

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

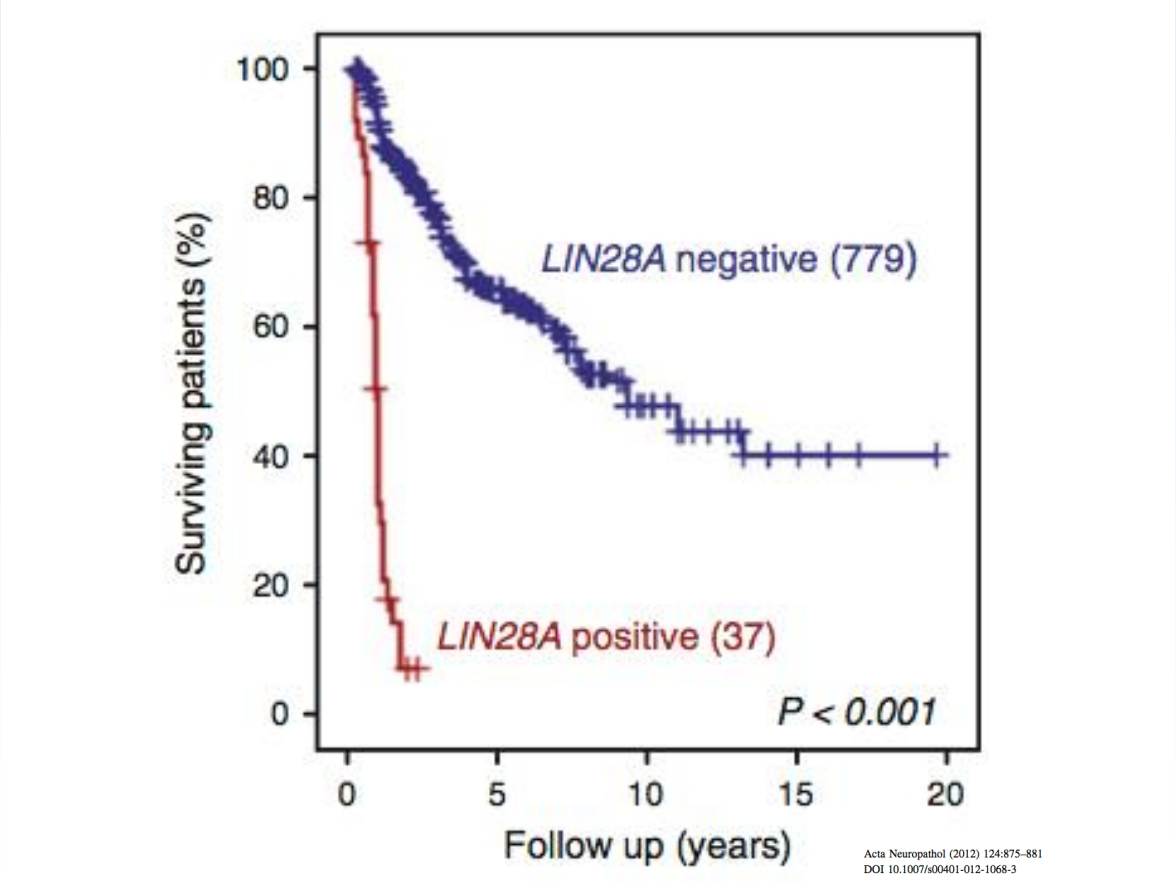


ETMR: Immunohistochemistry



LIN28a

LIN28A tumours have a poor prognosis



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)

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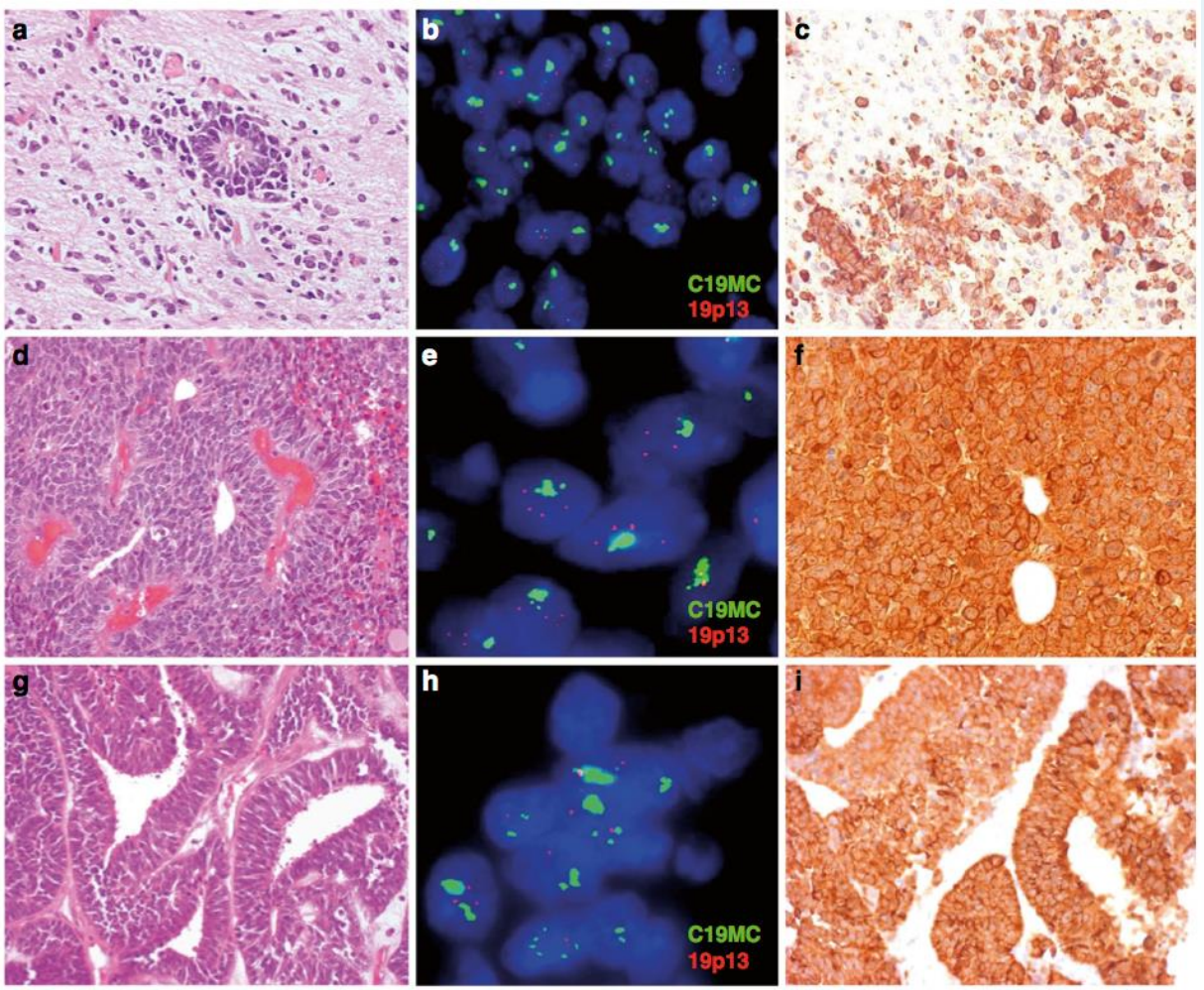
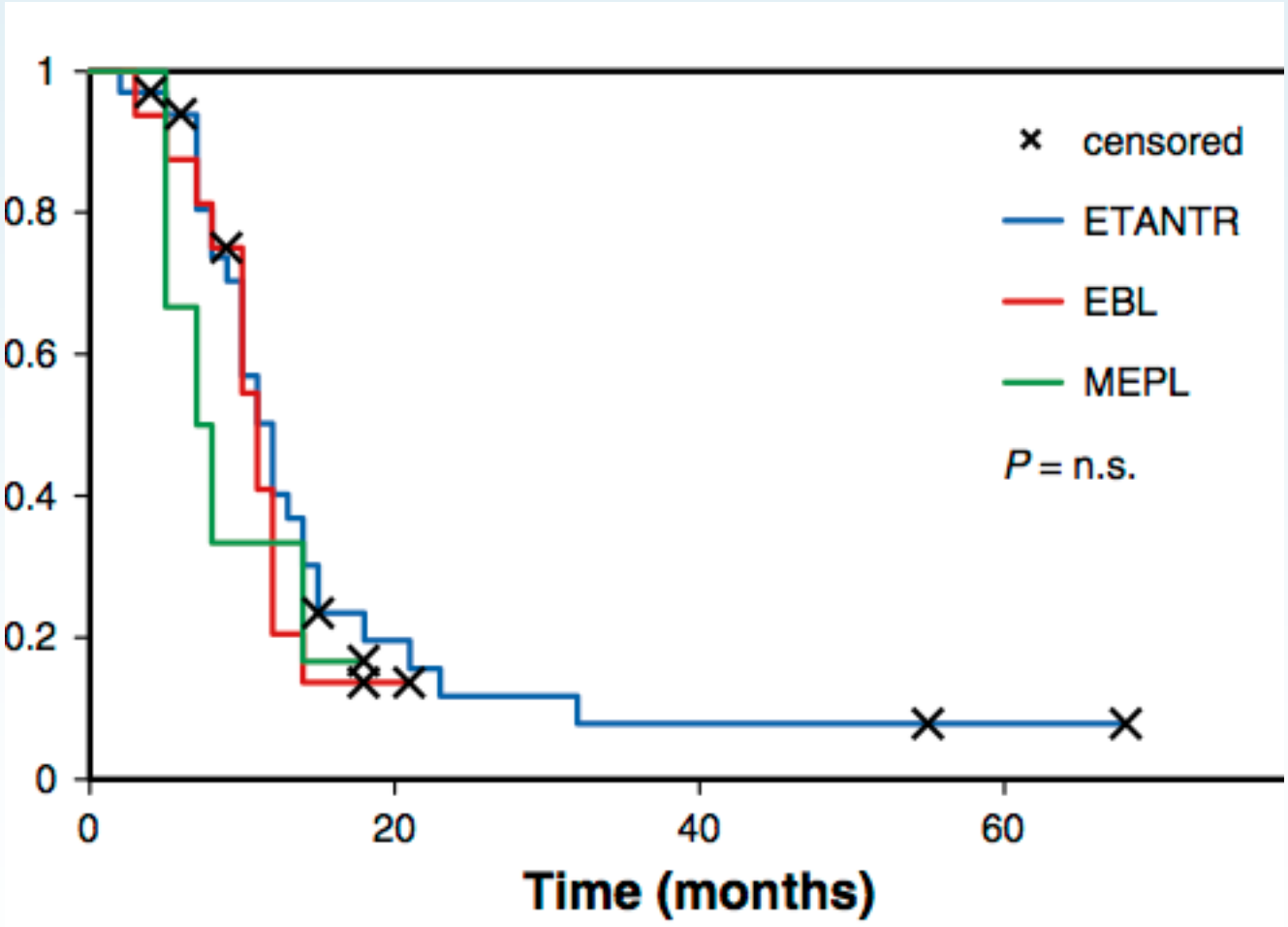
Acta Neuropathol (2014) 128:279–289
DOI 10.1007/s00401-013-1228-0

ORIGINAL PAPER

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




1
0.8
0.6
0.4
0.2
0
0
20
40
60
Time (months)
censored
ETANTR
EBL
MEPL
P = n.s.

nature genetics

Fusion of *TTYH1* with the C19MC microRNA cluster drives expression of a brain-specific *DNMT3B* isoform in the embryonal brain tumor ETMR

Claudia L Kleinman[1,2,17], Noha Gerges[2,17], Simon Papillon-Cavanagh[1], Patrick Sin-Chan[3], Albena Pramatarova[1], Dong-Anh Khuong Quang[2], Véronique Adoue[1], Stephan Busche[1], Maxime Caron[1], Haig Djambazian[1], Amandine Bemmo[1], Adam M Fontebasso[4], Tara Spence[3], Jeremy Schwartzentruber[1], Steffen Albrecht[5], Peter Hauser[6], Miklos Garami[6], Almos Klekner[7], Laszlo Bognar[7], Jose-Luis Montes[8], Alfredo Staffa[1], Alexandre Montpetit[1], Pierre Berube[1], Magdalena Zakrzewska[9], Krzysztof Zakrzewski[10], Pawel P Liberski[9], Zhifeng Dong[11], Peter M Siegel[11], Thomas Duchaine[12], Christian Perotti[13], Adam Fleming[14], Damien Faury[14], Marc Remke[15], Marco Gallo[15], Peter Dirks[15], Michael D Taylor[15], Robert Sladek[1,2], Tomi Pastinen[1], Jennifer A Chan[13], Annie Huang[3,16,18], Jacek Majewski[1,2,18] & Nada Jabado[2,4,18]

What other tumour are there?

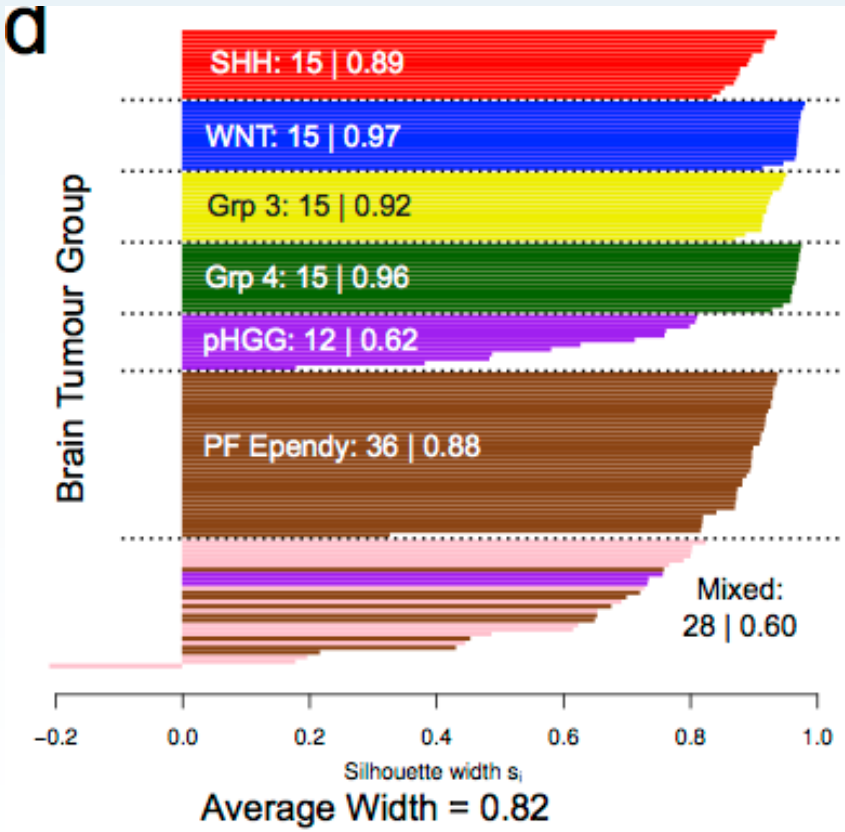
Acta Neuropathol (2013) 126:943–946
DOI 10.1007/s00401-013-1206-6

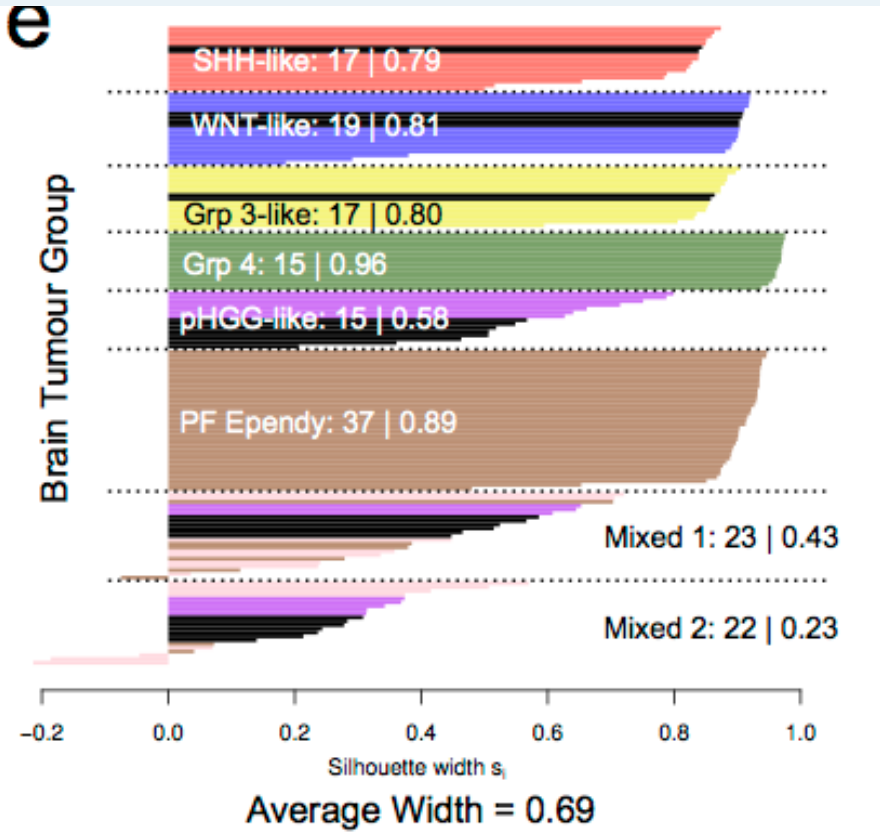
CORRESPONDENCE

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

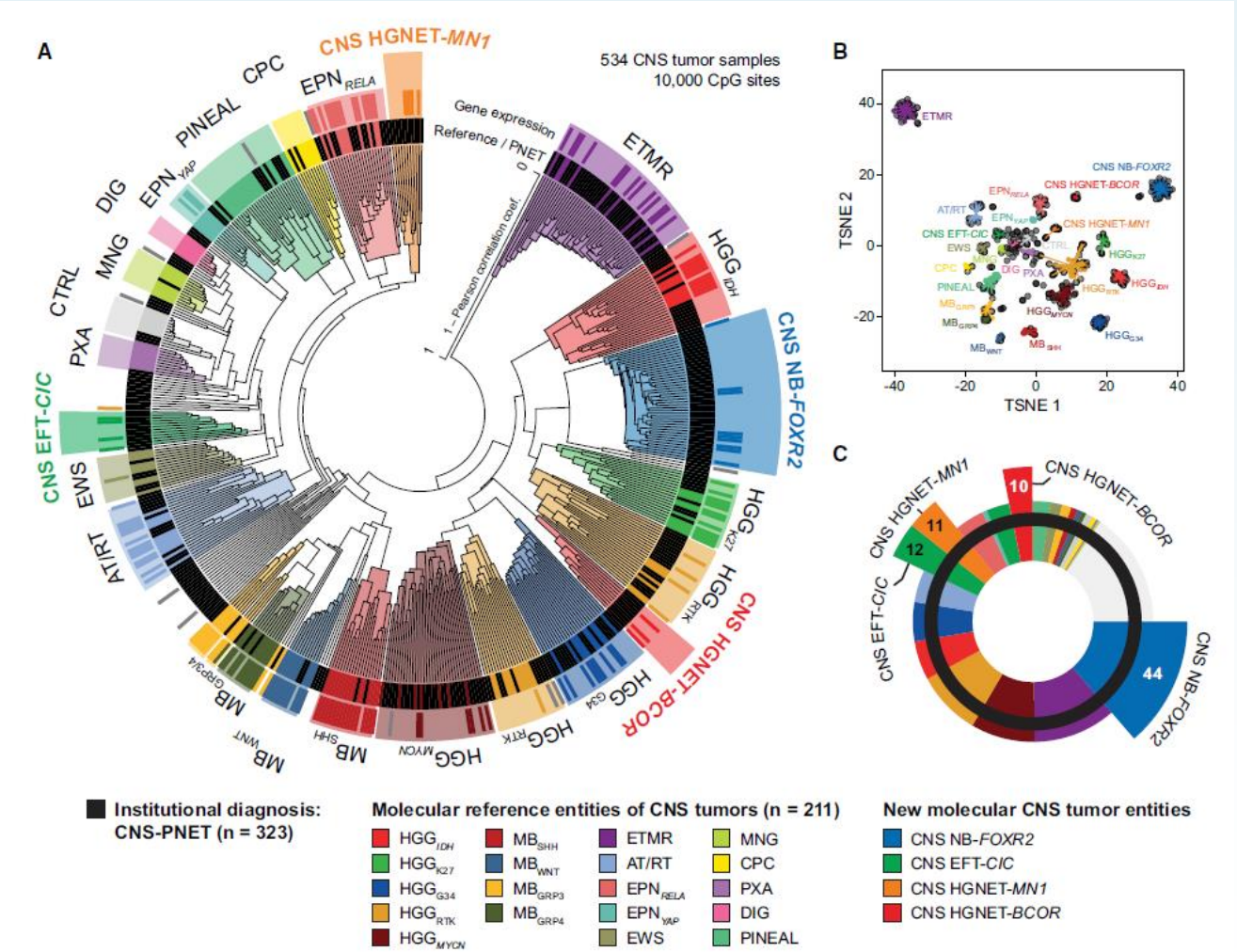
Ed. C. Schwalbe · James T. Hayden · Hazel A. Rogers · Suzanne Miller · Janet C. Lindsey · Rebecca M. Hill · Sarah-Leigh Nicholson · John-Paul Kilday · Martyna Adamowicz-Brice · Lisa Storer · Thomas S. Jacques · Keith Robson · Jim Lowe · Daniel Williamson · Richard G. Grundy · Simon Bailey · Steven C.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

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



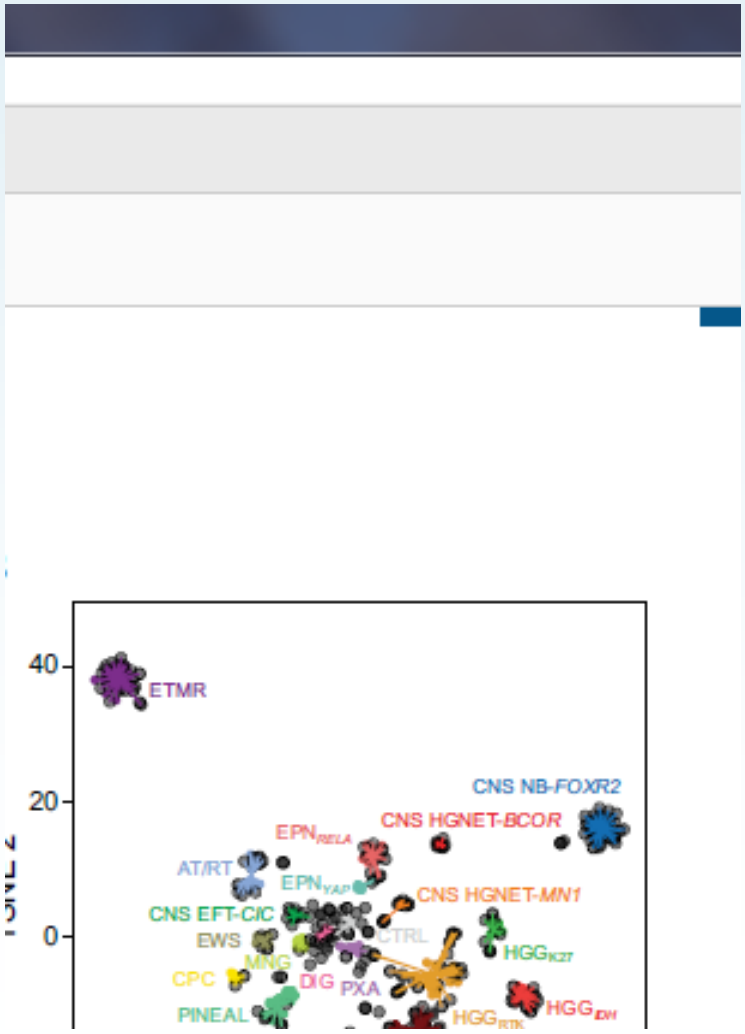


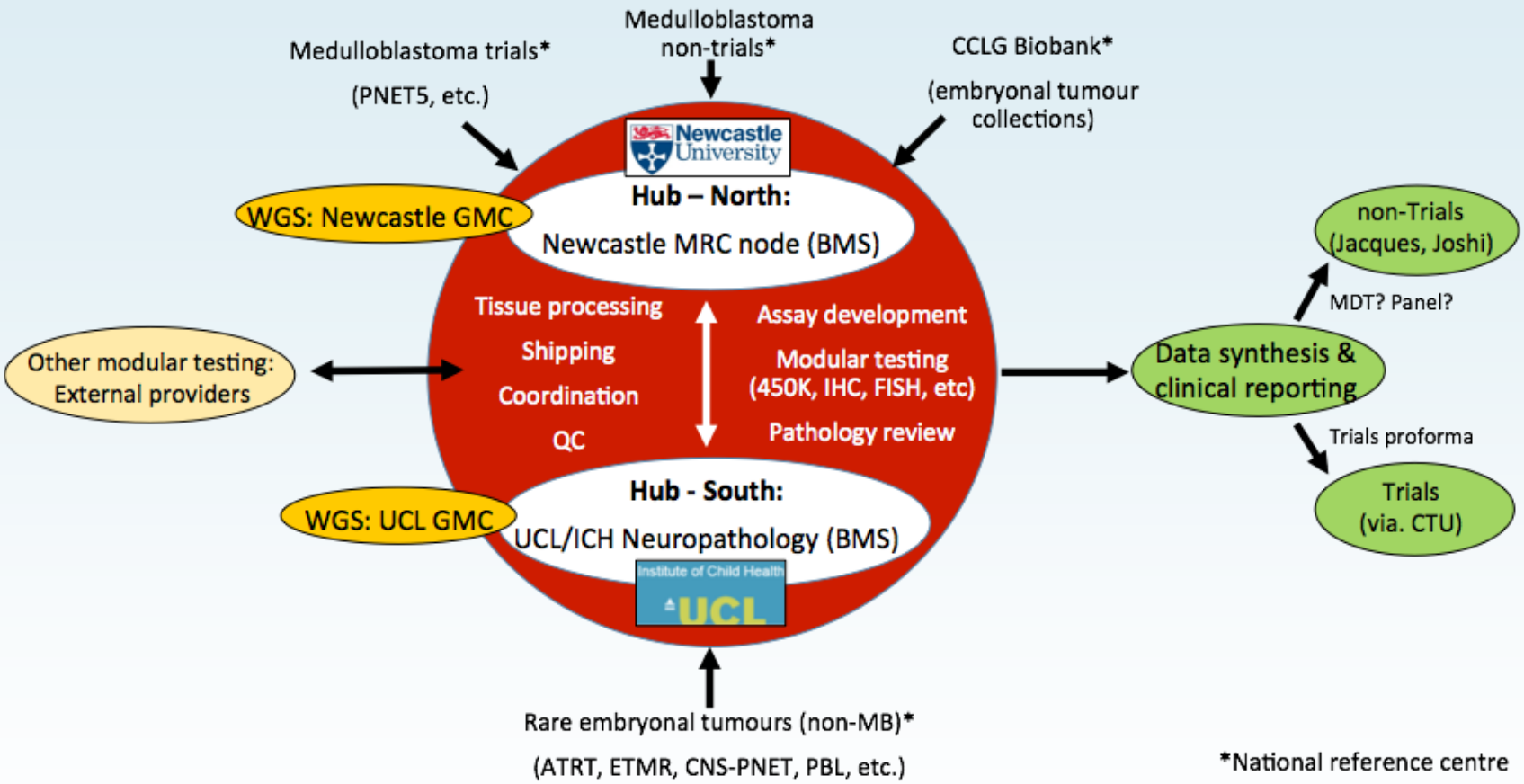
Novel tumour types



Sturm *et al.* Cell 2016

Novel tumour types




Medulloblastoma trials*
(PNET5, etc.)
Medulloblastoma non-trials*
CCLG Biobank*
(embryonal tumour collections)
Newcastle University
Hub – North:
Newcastle MRC node (BMS)
WGS: Newcastle GMC
Other modular testing: External providers
Tissue processing
Shipping
Coordination
QC
Assay development
Modular testing (450K, IHC, FISH, etc)
Pathology review
Hub - South:
UCL/ICH Neuropathology (BMS)
Institute of Child Health
UCL
WGS: UCL GMC
Rare embryonal tumours (non-MB)*
(ATRT, ETMR, CNS-PNET, PBL, etc.)
Data synthesis & clinical reporting
non-Trials (Jacques, Joshi)
MDT? Panel?
Trials proforma
Trials (via. CTU)
*National reference centre

Astrocytomas in childhood

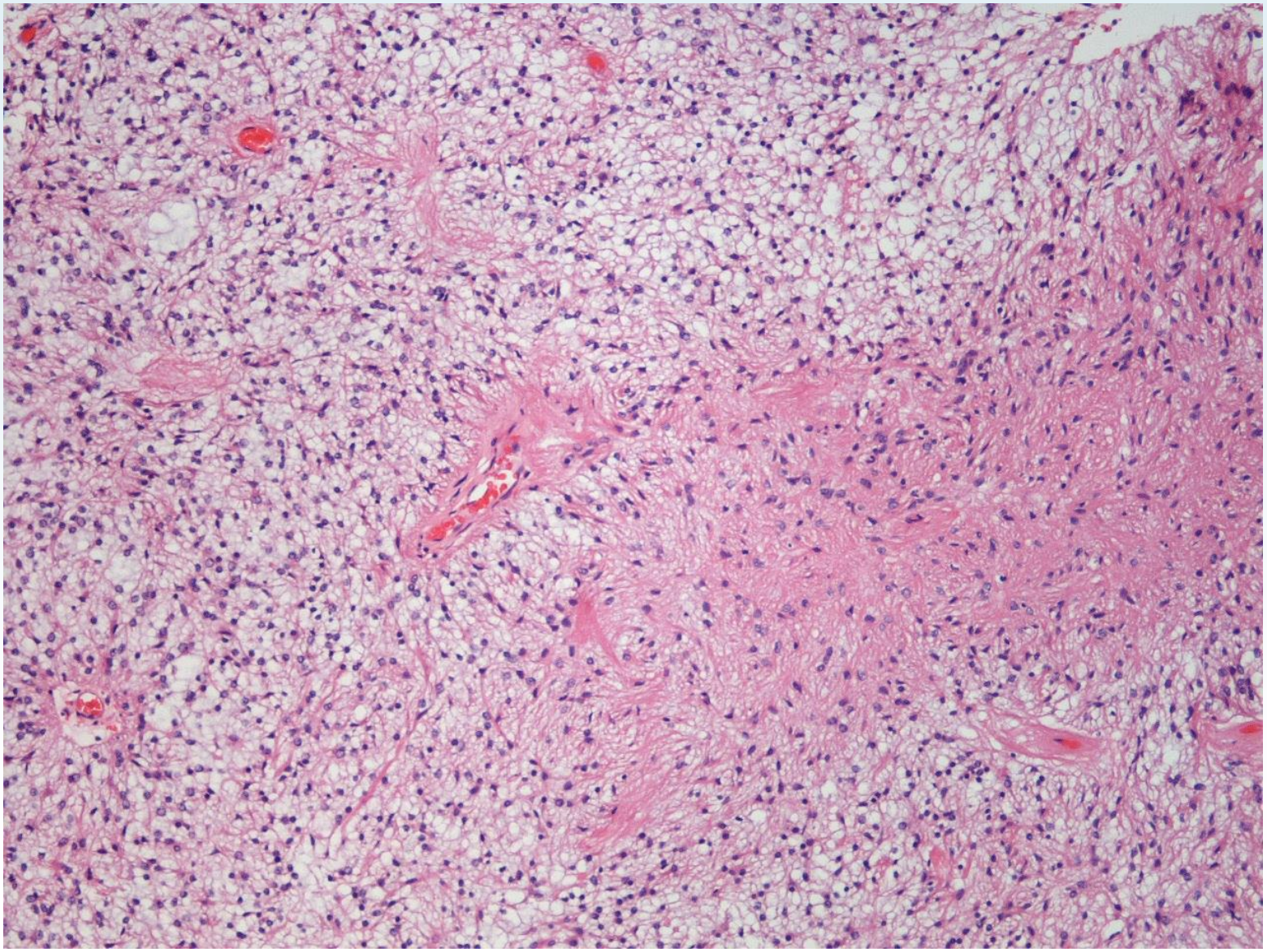
Gliomas

Diffuse astrocytic and oligodendroglial tumours

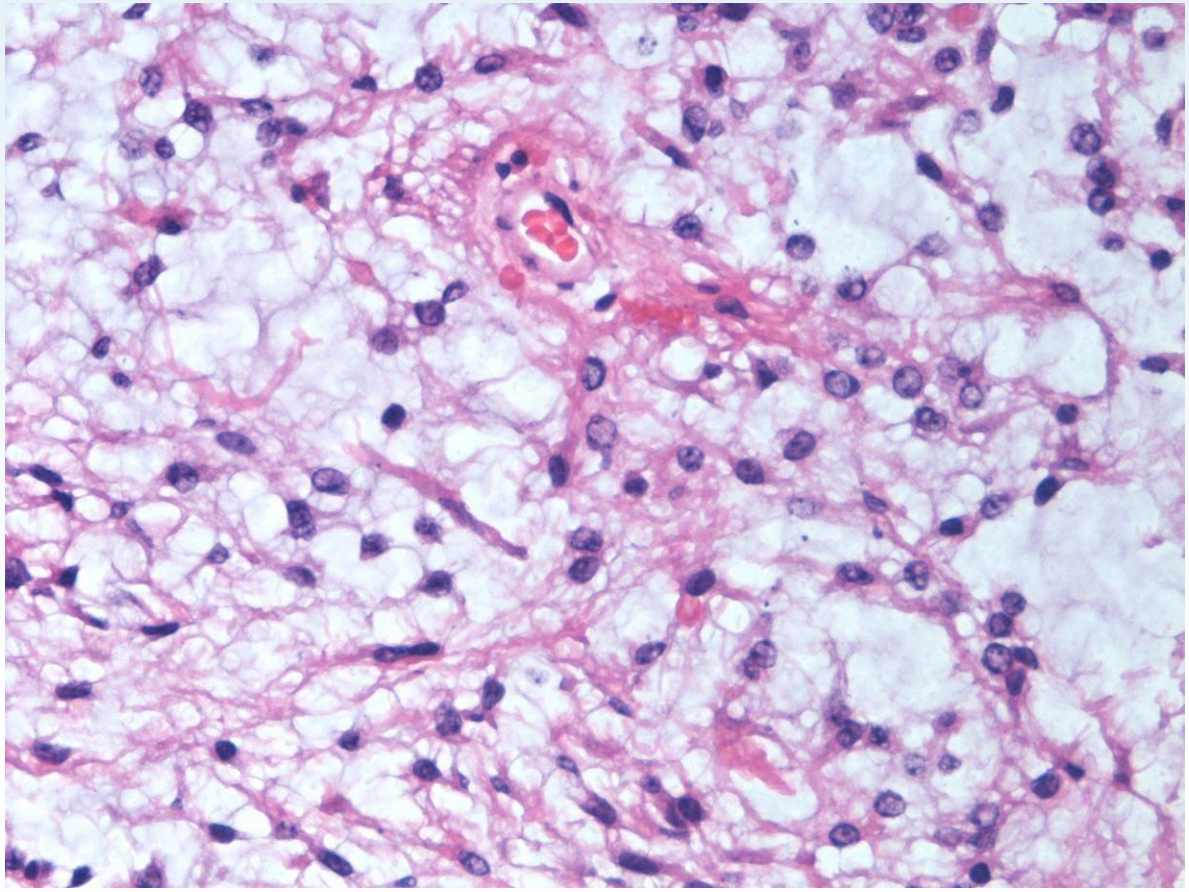
Other astrocytic tumours

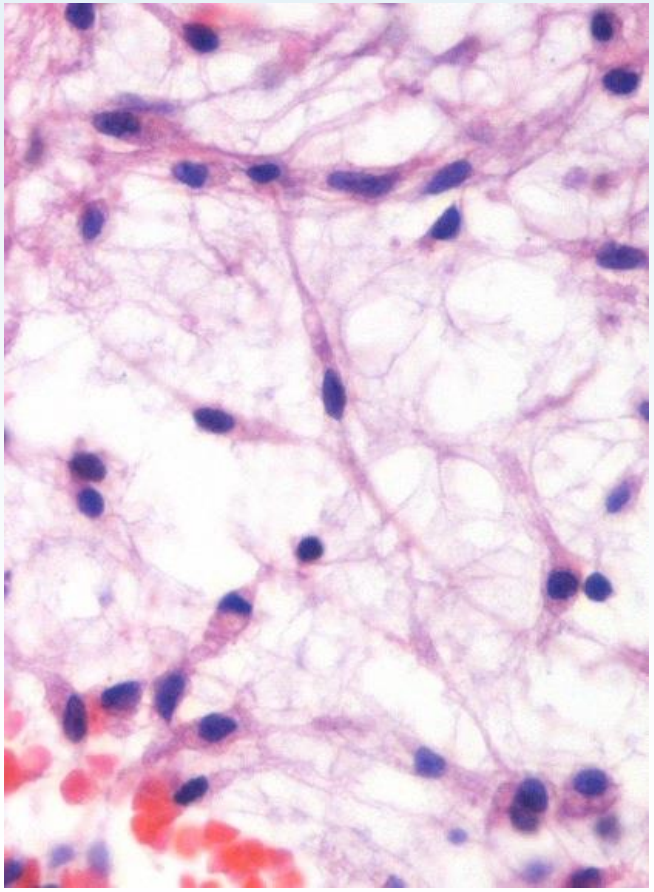
- Pilocytic astrocytoma
- Pilomyxoid astrocytoma
- SEGA
- PXA
- Anaplastic PXA

Pilocytic astrocytoma-Architecture

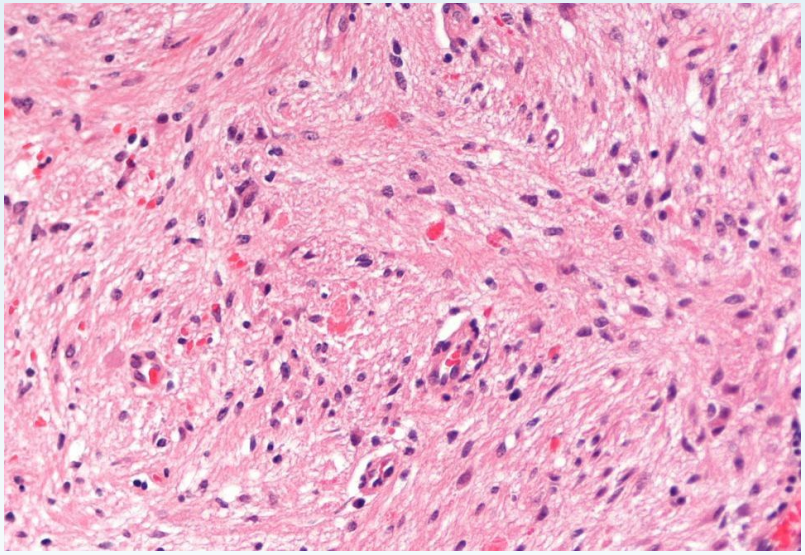


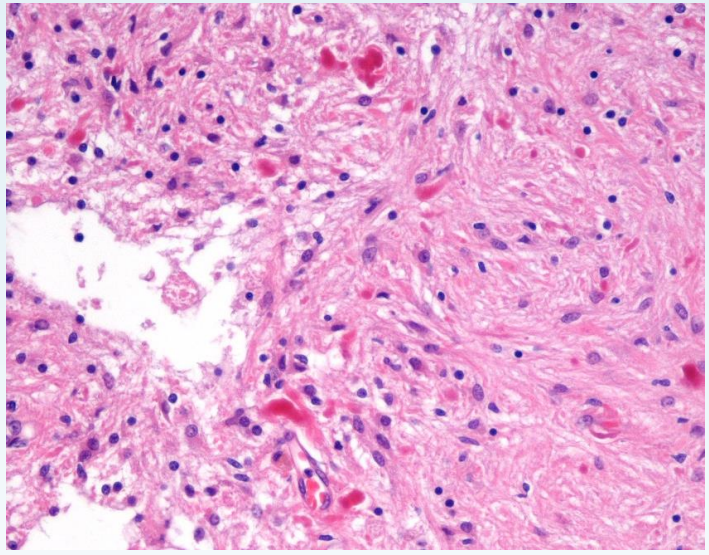
Pilocytic astrocytoma-Cytology

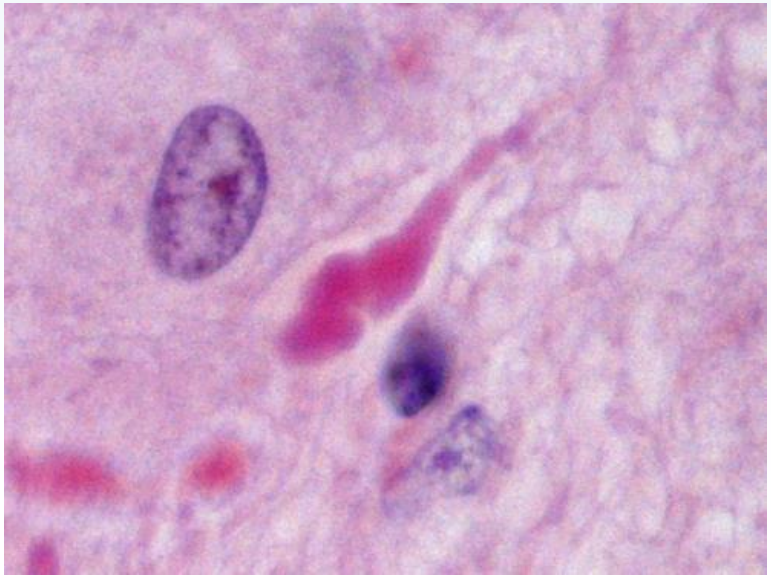




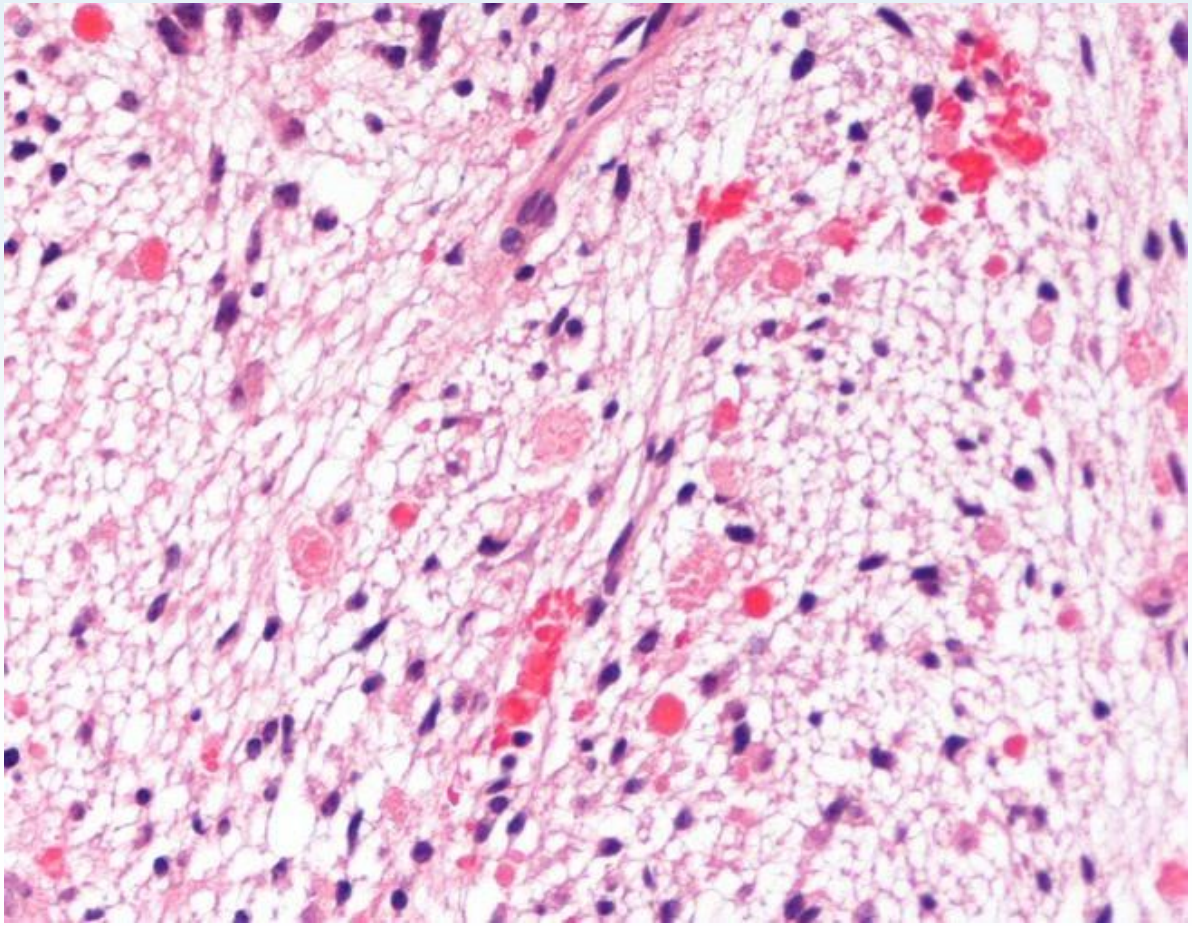
Pilocytic astrocytoma: Rosenthal fibres



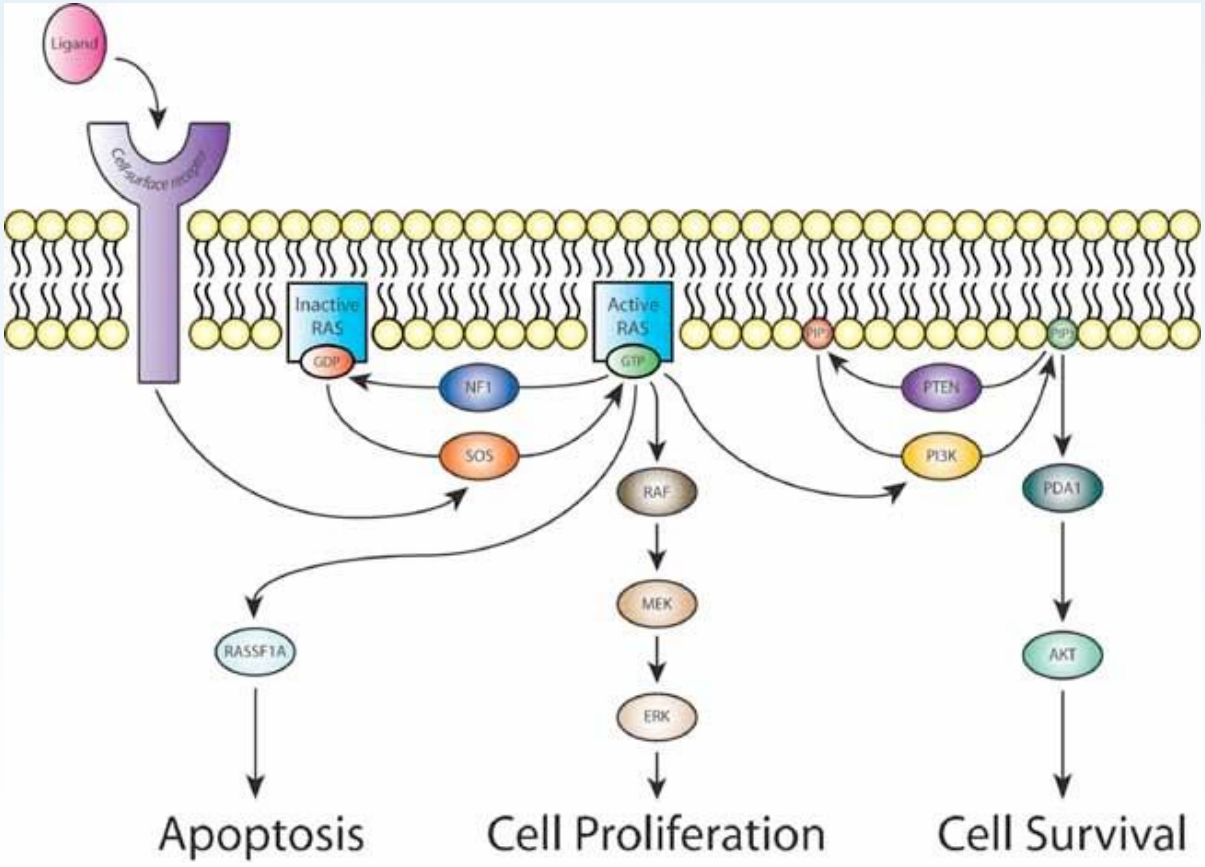




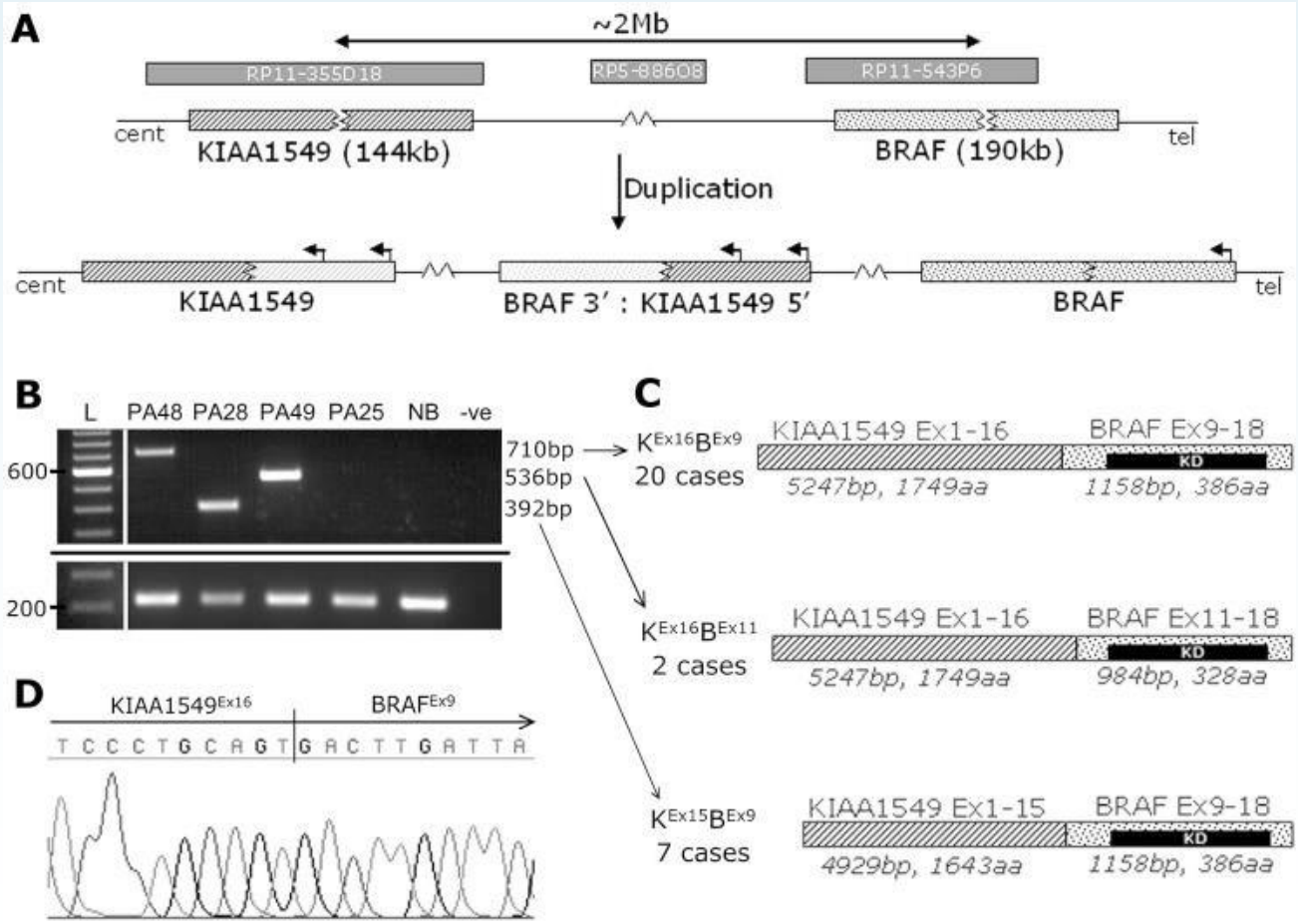
Pilocytic astrocytoma: Eosinophilic Granular Bodies (EGBs)



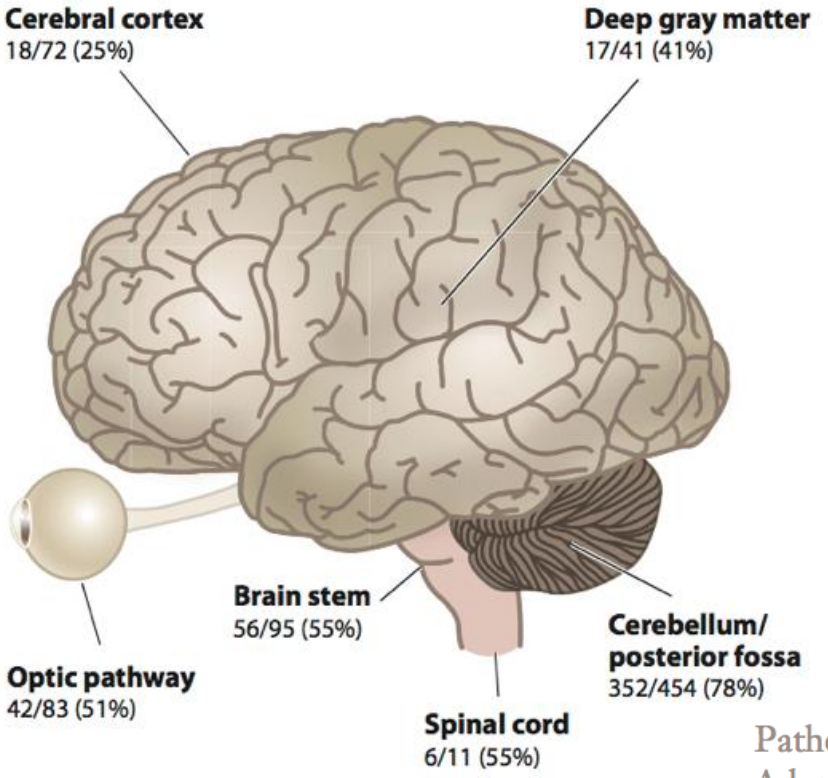
Abnormalities of the MAPK pathway characterise pilocytic astrocytoma



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]

Departments of [1]Pathology, [2]Ophthalmology, and [3]Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205; email: ceberha@jhmi.edu

[4]Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, Texas 75390

BRAF genetics are diagnostically useful

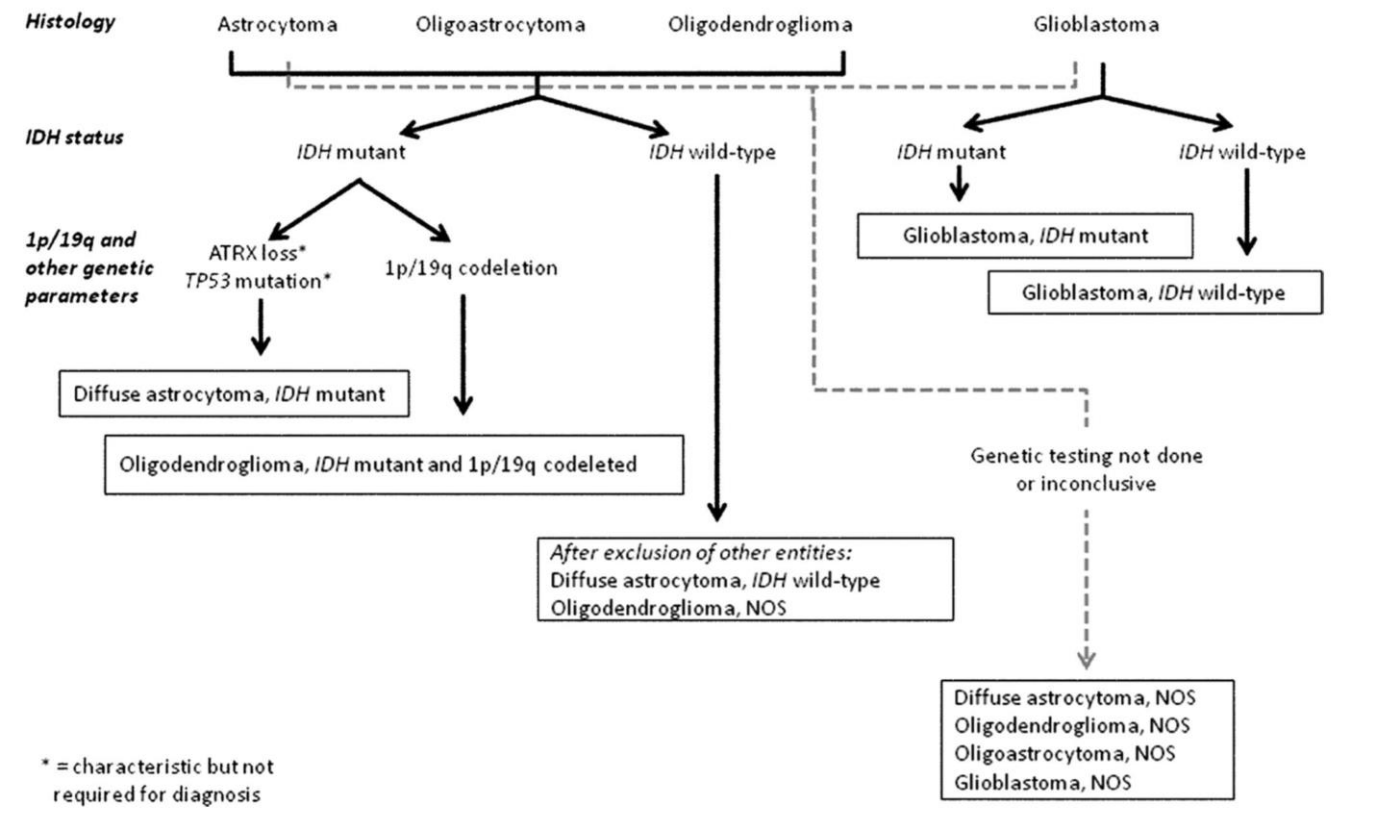
Acta Neuropathol (2010) 120:271–273
DOI 10.1007/s00401-010-0693-y

CORRESPONDENCE

RAF gene fusions are specific to pilocytic astrocytoma in a broad paediatric brain tumour cohort

Andrew R. J. Lawson · Ruth G. Tatevossian · Kim P. Phipps · Simon R. Picker · Antony Michalski · Denise Sheer · Thomas S. Jacques · Tim Forshew

Diffuse gliomas in the WHO are defined by IDH mutations and 1p19q co-deletion



..but they are different tumours

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.

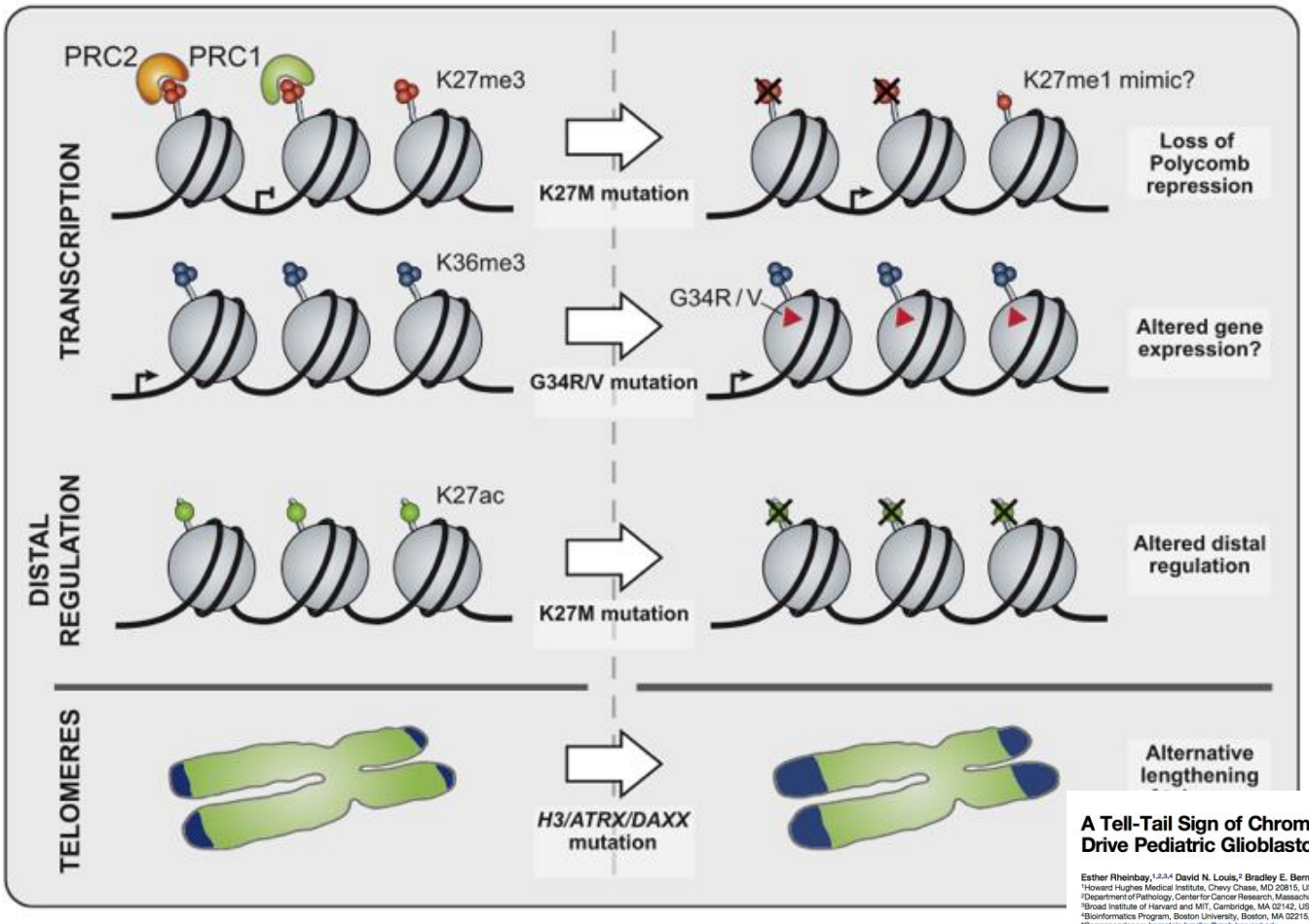
Clinicopathological aspects

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]
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[2]Department of Pathology, Center for Cancer Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
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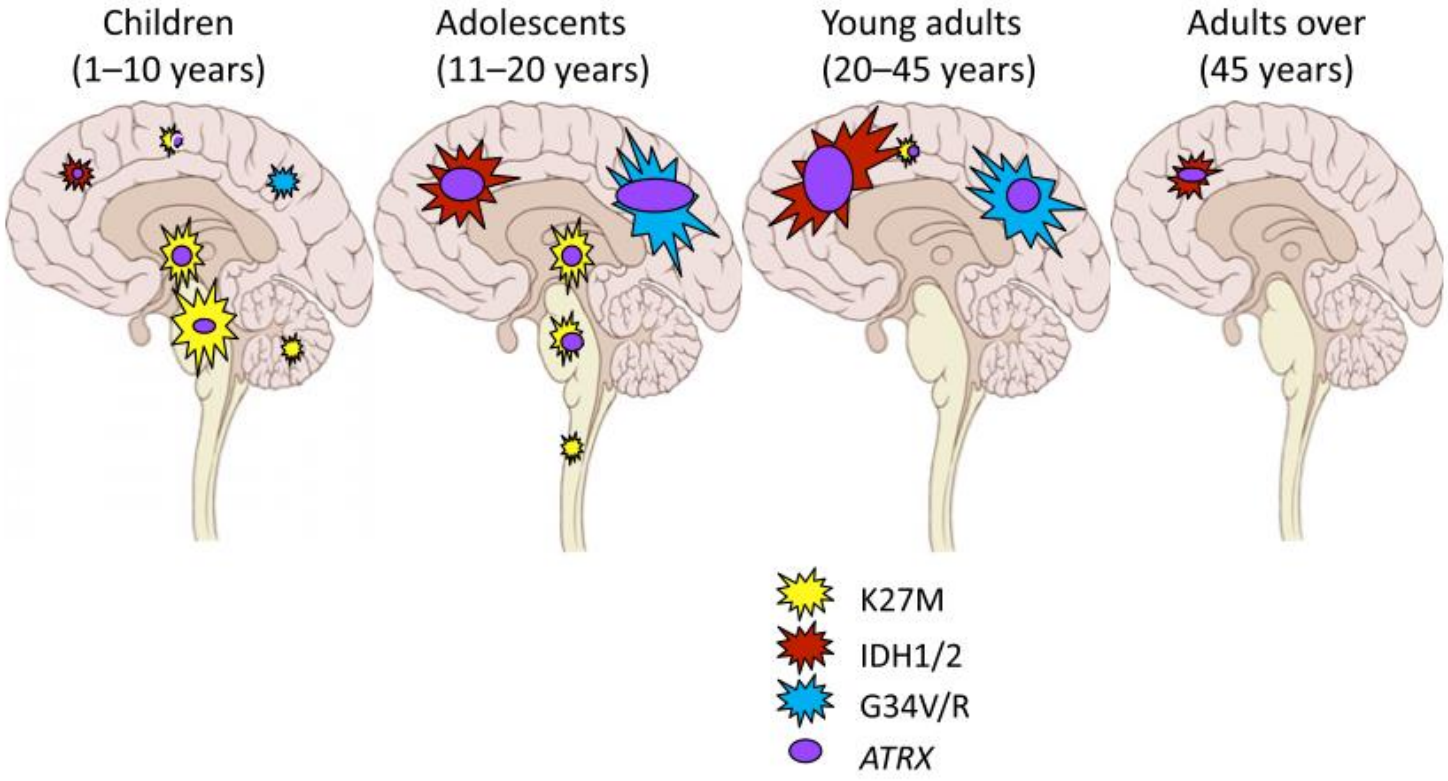
DOI 10.1016/j.ccr.2012.03.001

Mutations in paediatric glioma relate to location and age



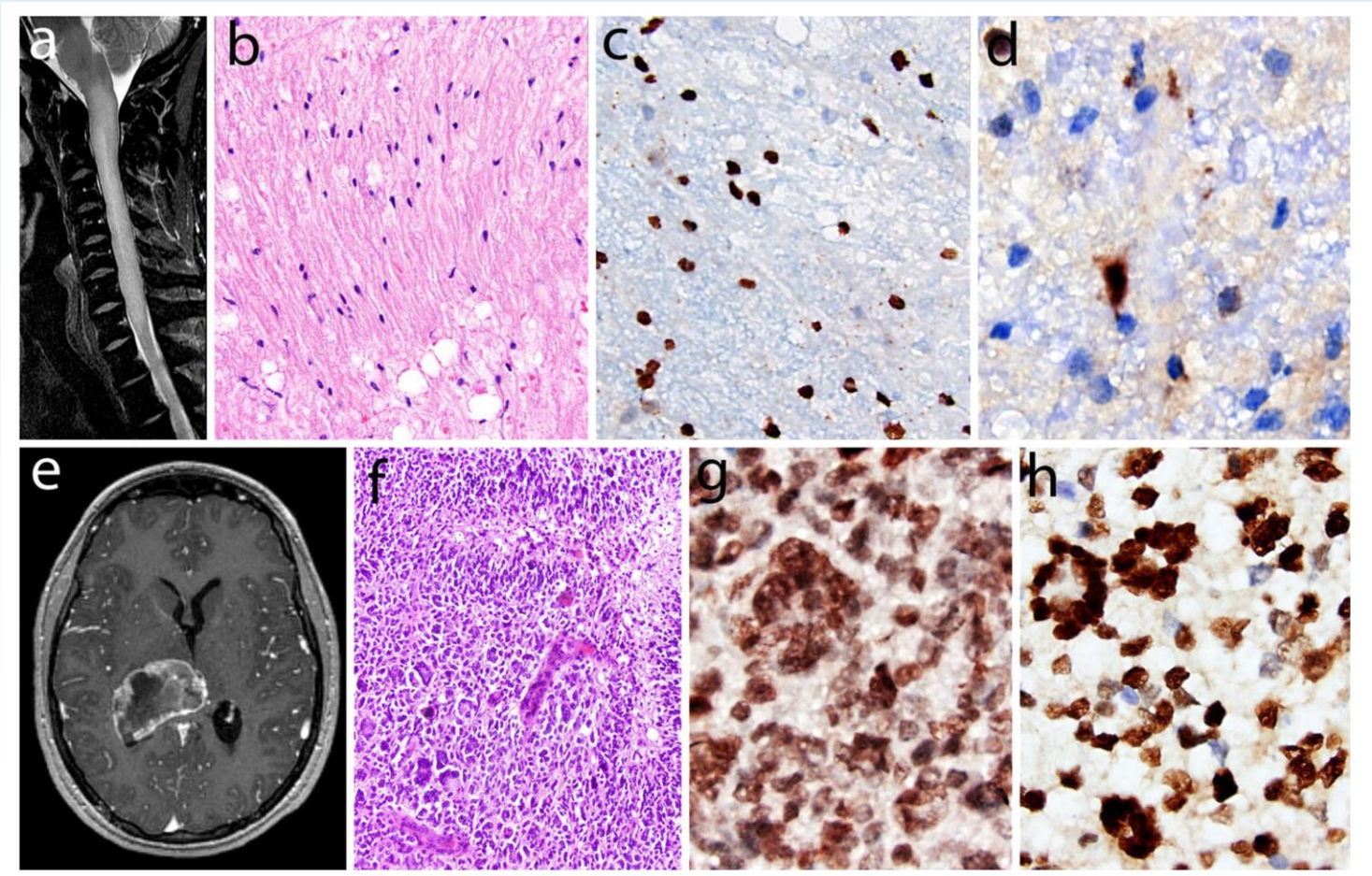
Therapeutic Intervention in Brain Tumors?

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]

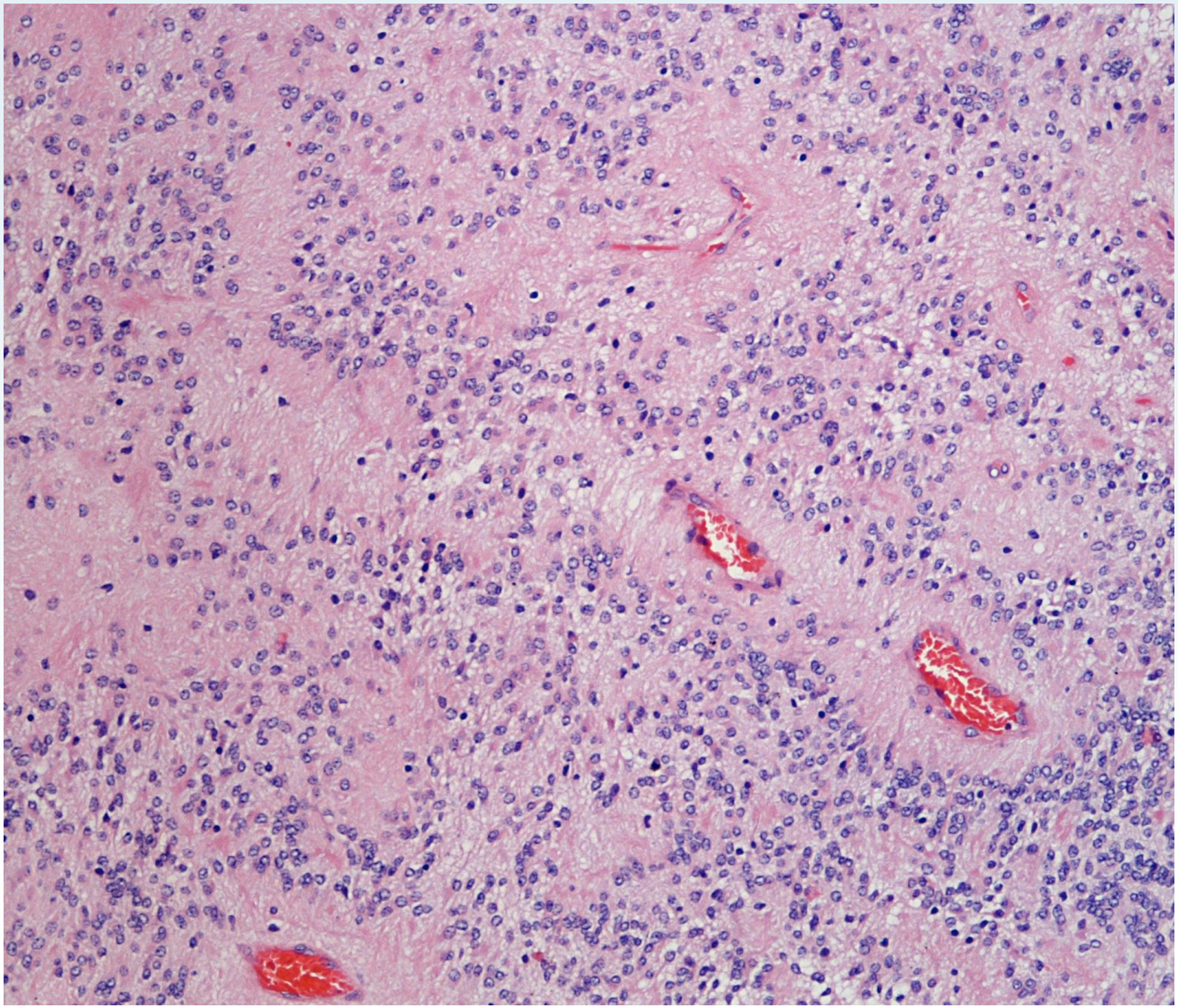
[1] Division of Experimental Medicine, McGill University and McGill University Health Centre, Montreal, QC, Canada.
[2] Department of Human Genetics, McGill University and McGill University Health Centre, Montreal, QC, Canada.
[3] Division of Pediatric Neuro-oncology, German Cancer Research Centre (DKFZ), Heidelberg, Germany.
[4] Department of Pediatrics, McGill University and the McGill University Health Centre Research Institute, Montreal, QC, Canada.

New entity: Diffuse midline glioma, H3 K27M-mutant

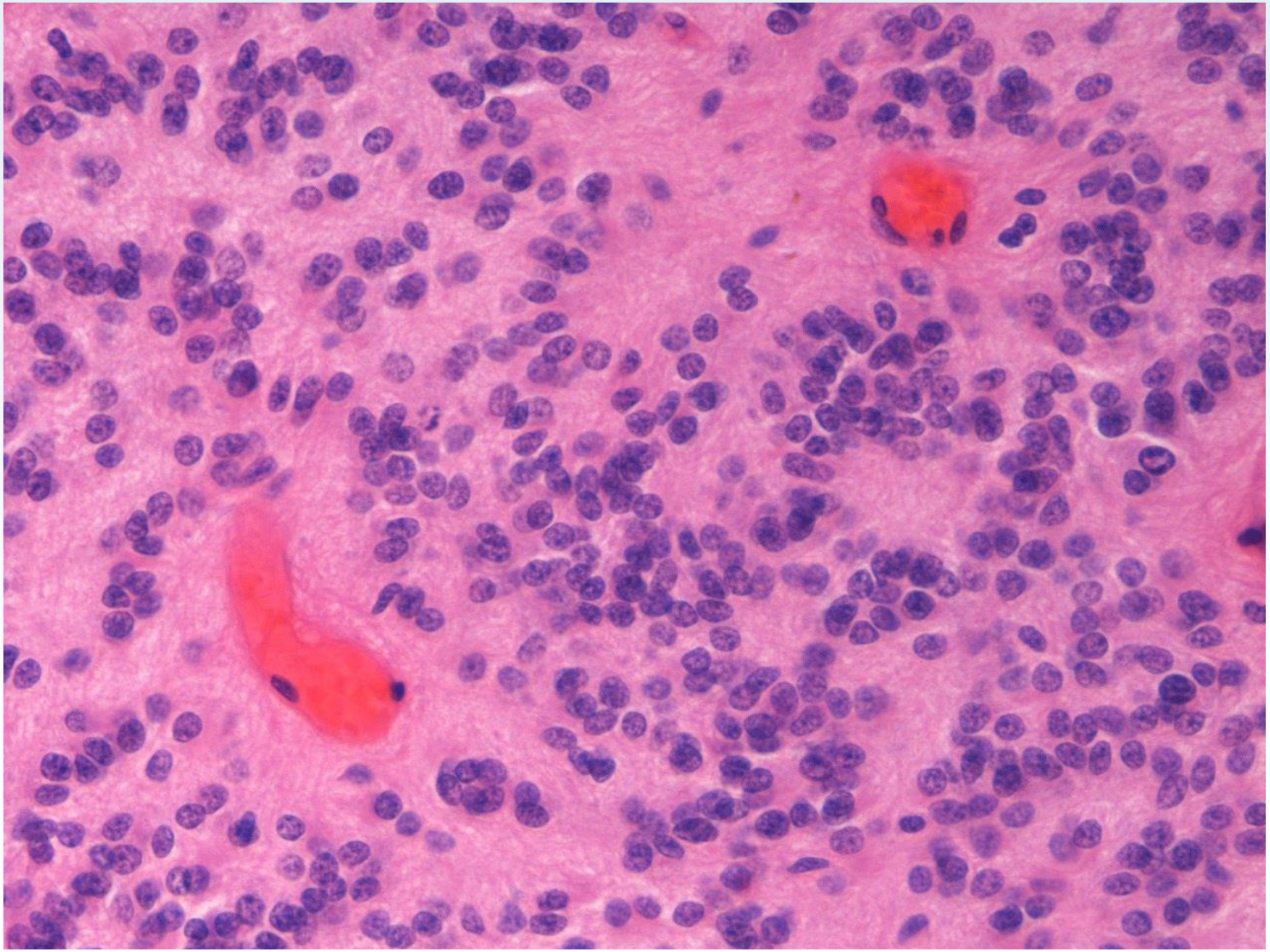


Ependymoma

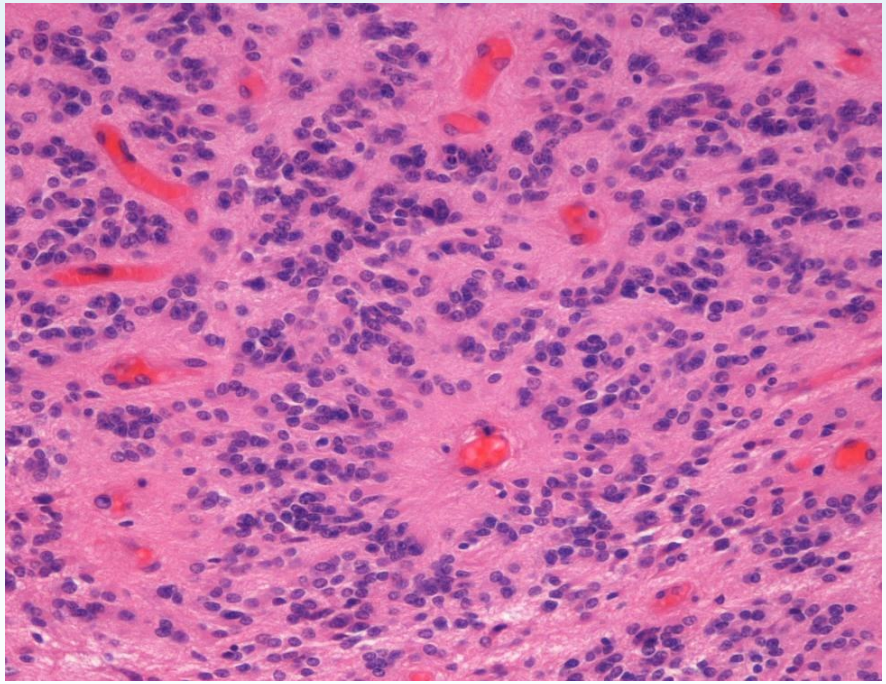
Ependymoma-Architecture

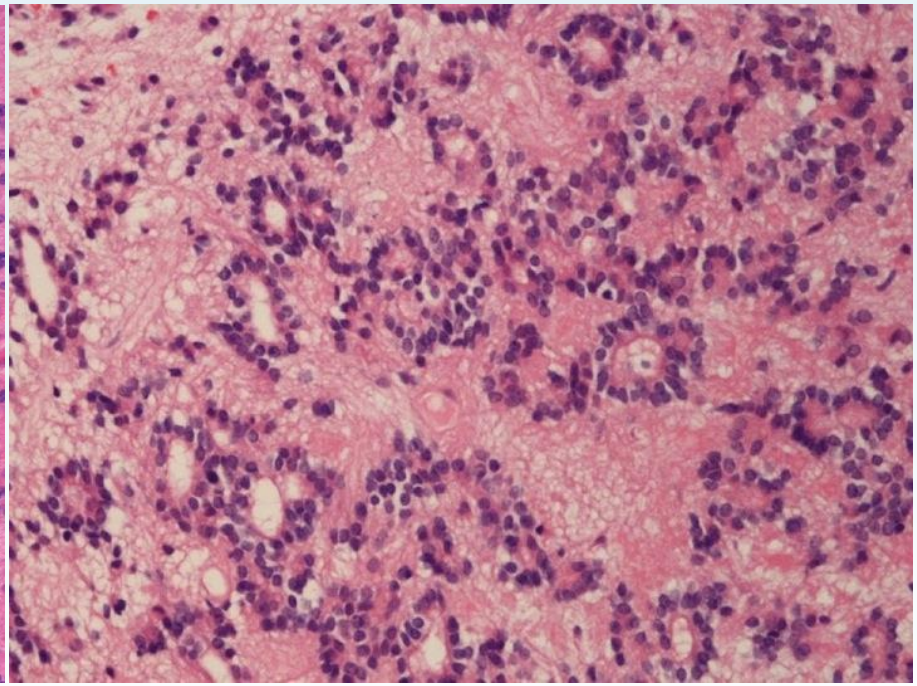


Ependymoma-Cytology



Ependymoma-Secondary structures





Challenges for ependymoma

- Prognosis in children is poor
- Criteria for anaplasia are poorly defined and subjective
- Large effect of surgical clearance on prognosis
- Variability in histology
- Conflicting studies

Approaches to grading in ependymoma

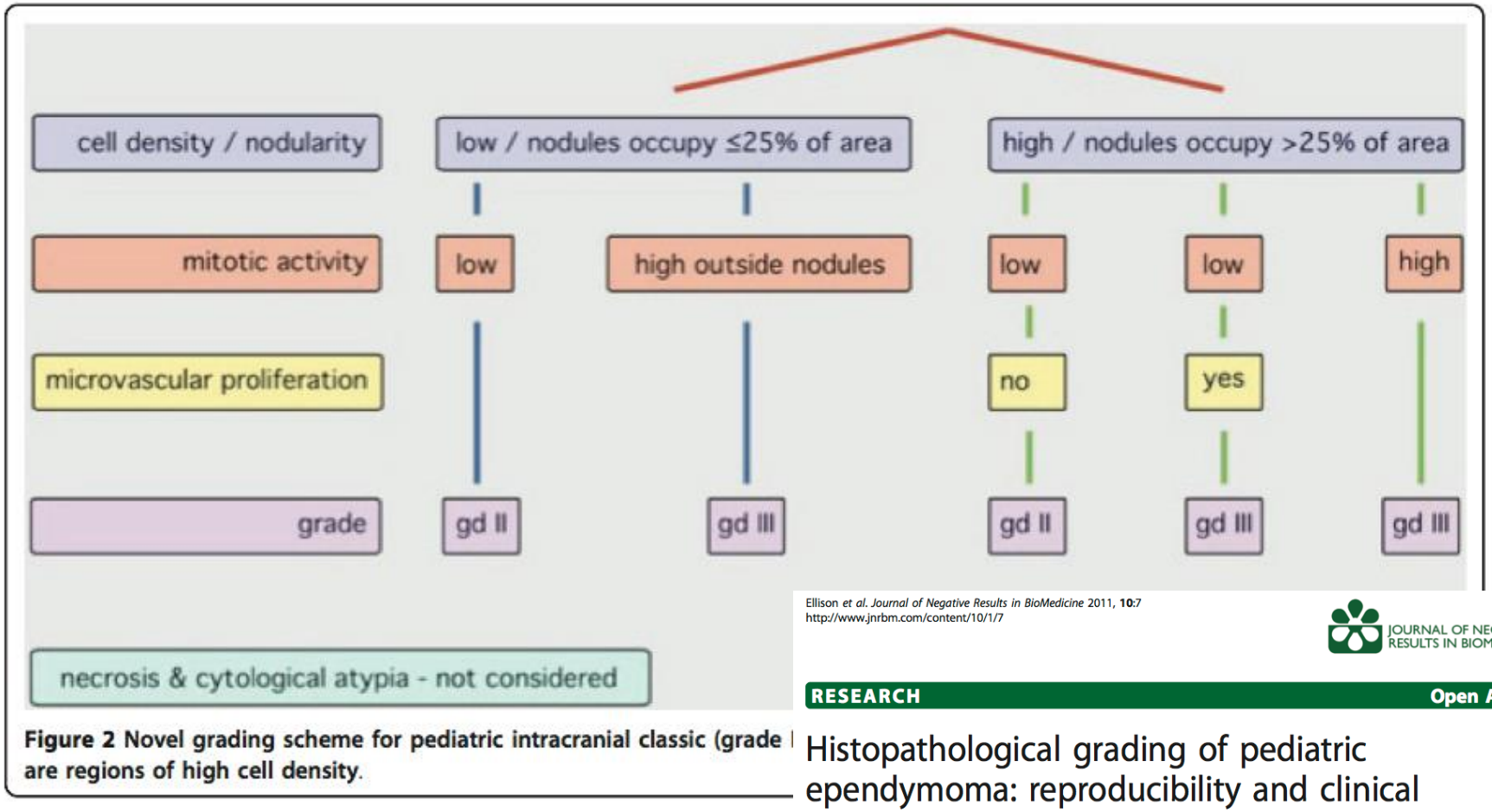


Figure 2 Novel grading scheme for pediatric intracranial classic (grade I are regions of high cell density.

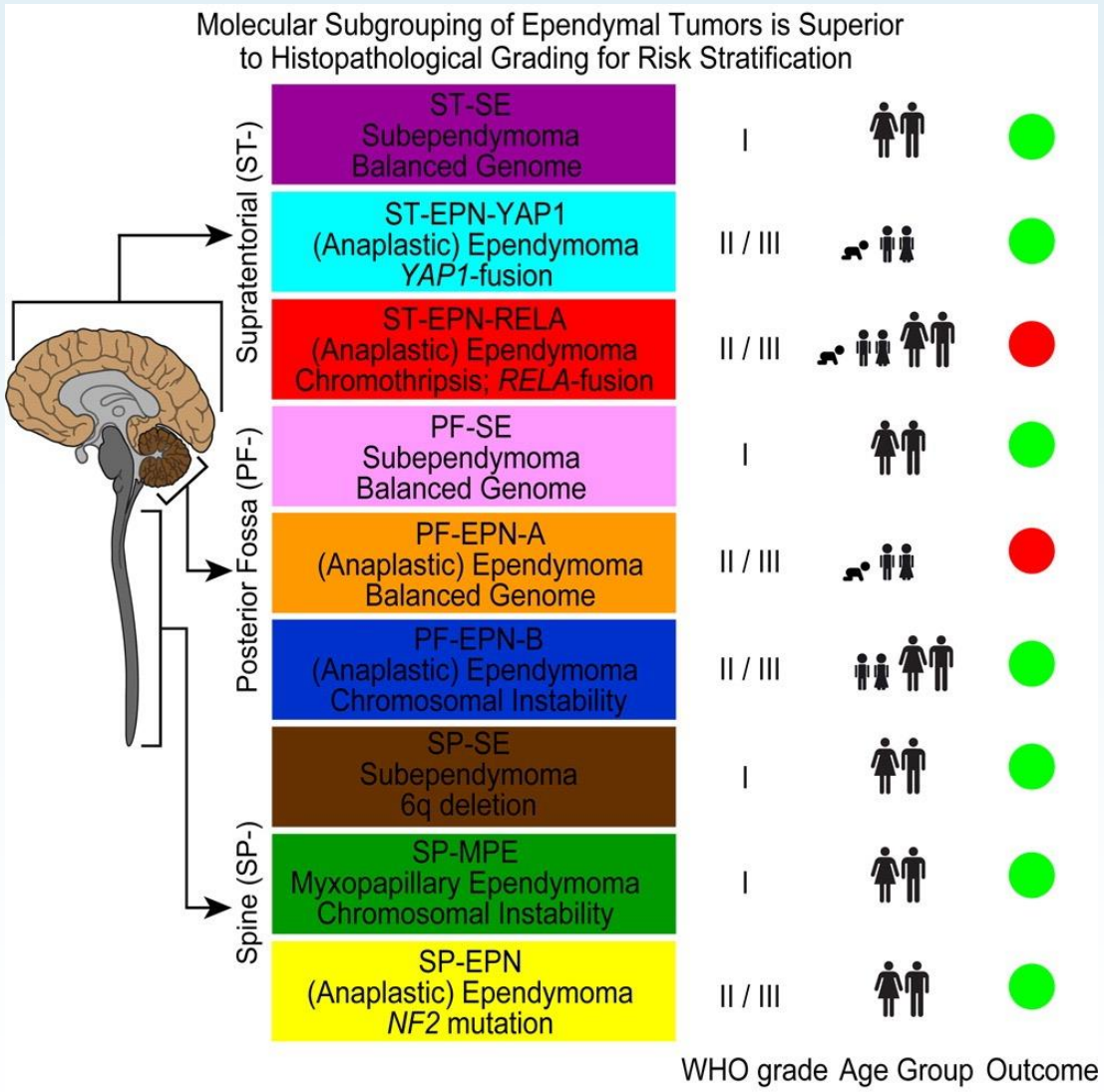
Ellison *et al. Journal of Negative Results in BioMedicine* 2011, **10**:7
http://www.jnrbm.com/content/10/1/7

JOURNAL OF NEGATIVE RESULTS IN BIOMEDICINE

RESEARCH Open Access

Histopathological grading of pediatric ependymoma: reproducibility and clinical relevance in European trial cohorts

David W Ellison[1*], Mehmet Kocak[2], Dominique Figarella-Branger[3], Giangaspero Felice[4], Godfraind Catherine[5], Torsten Pietsch[6], Didier Frappaz[7], Maura Massimino[8], Jacques Grill[9], James M Boyett[2] and Richard G Grundy[10]



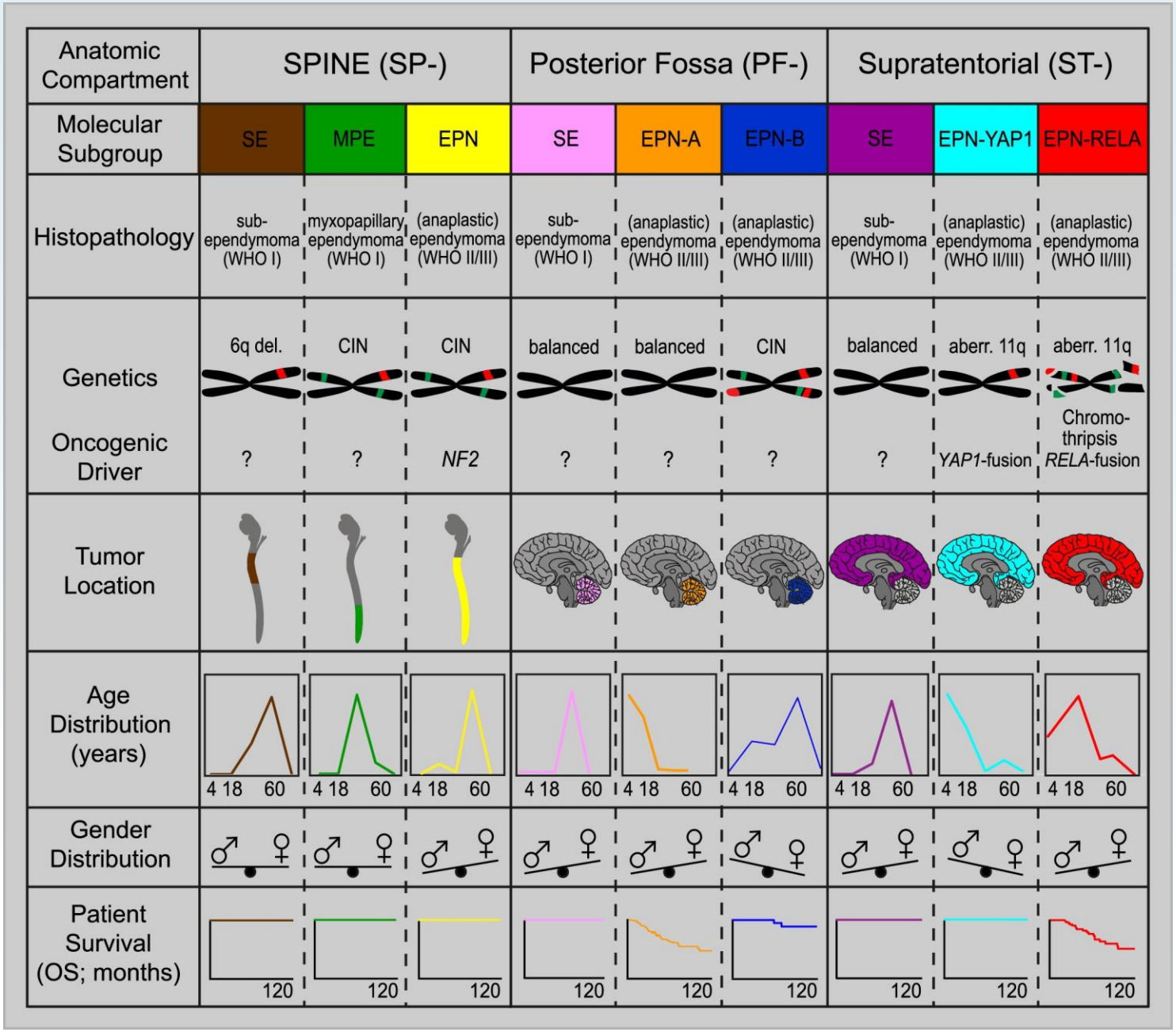
Article

Cancer Cell

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

Authors

Kristian W. Pajtler, Hendrik Witt, ..., Marcel Kool, Stefan M. Pfister


Anatomic Compartment
SPINE (SP-)
Posterior Fossa (PF-)
Supratentorial (ST-)
Molecular Subgroup
SE
MPE
EPN
SE
EPN-A
EPN-B
SE
EPN-YAP1
EPN-RELA
Histopathology
sub-ependymoma (WHO I)
myxopapillary ependymoma (WHO I)
(anaplastic) ependymoma (WHO II/III)
sub-ependymoma (WHO I)
(anaplastic) ependymoma (WHO II/III)
(anaplastic) ependymoma (WHO II/III)
sub-ependymoma (WHO I)
(anaplastic) ependymoma (WHO II/III)
(anaplastic) ependymoma (WHO II/III)
Genetics
6q del.
CIN
CIN
balanced
balanced
CIN
balanced
aberr. 11q
aberr. 11q
Oncogenic Driver
?
?
NF2
?
?
?
?
YAP1-fusion
Chromo-thripsis RELA-fusion
Tumor Location
Age Distribution (years)
4 18 60
Gender Distribution
Patient Survival (OS; months)
120

New entity: 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.

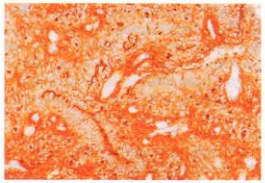


Fig. 3.15 *RELA* fusion–positive ependymoma. L1CAM protein expression correlates well with the presence of a *RELA* fusion gene.

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].

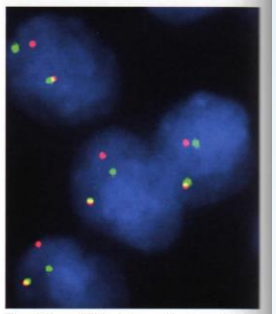


Fig. 3.16 *RELA* fusion–positive ependymoma. Interphase FISH with break-apart probes around the *RELA* gene. Overlapping probes (yellow) indicate an intact *RELA* gene, but probe separation (red/green) occurs with rearrangement of the *RELA* gene.

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].

Conclusions

- Childhood brain tumours can be cured but at the risk of long-term complications
- Real-time molecular diagnosis is required to stratify treatment

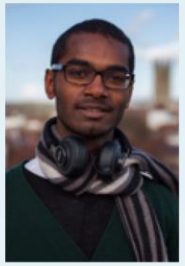
Jen Cotter

Jess Pickles

Tom Stone

Derek Li

Amy Fairchild



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Fatma Scerif

Sherry Yasin

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Simon Paine

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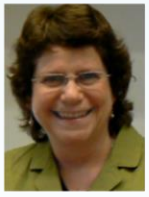

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Great Ormond Street Hospital Charity

NHS
National Institute for Health Research