Hospital Universitario 12 de Octubre

SaludMadrid

Comunidad de Madrid

EPIDEMIOLOGÍA Y CLASIFICACIÓN DE LOS TUMORES CEREBRALES WHO 2016 del SNC

i+12 Instituto de Investigación Hospital 12 de Octubre

Aurelio Hernández Laín

Sección Neuropatología

Hospital Universitario 12 de Octubre

Hospital Universitario 12 de Octubre

SaludMadrid

Comunidad de Madrid

EPIDEMIOLOGÍA Y CLASIFICACIÓN DE LOS ~~TUMORES CEREBRALES~~ GLIOMAS WHO 2016

i+12

Instituto de Investigación

Hospital 12 de Octubre

Aurelio Hernández Laín

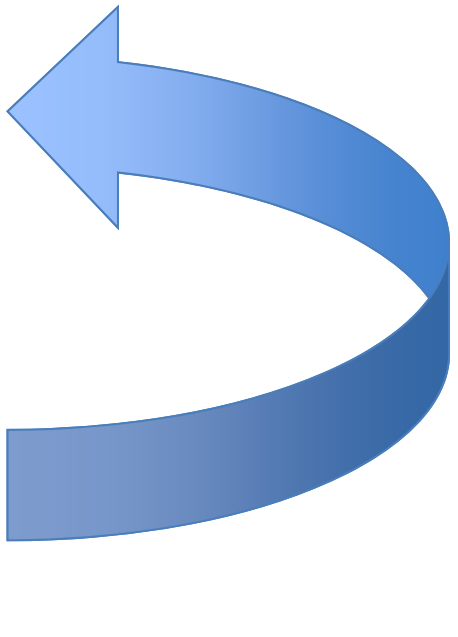
Sección Neuropatología

Hospital Universitario 12 de Octubre

Clasificación WHO 2016

Diagnóstico en “multi-estratos” o “multi- nivel”, integrando diagnóstico histológico + molecular.

- **DIAGNÓSTICO INTEGRADO (nivel 1)**



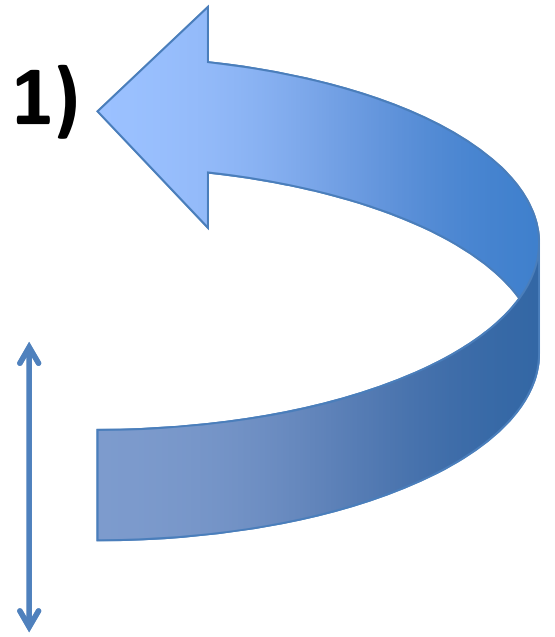
- Clasificación Histológica (nivel 2)
- Estadio WHO (nivel 3)
- Estudio molecular (nivel 4)

- David N. Louis. Brain Pathology 2014

Clasificación WHO 2016

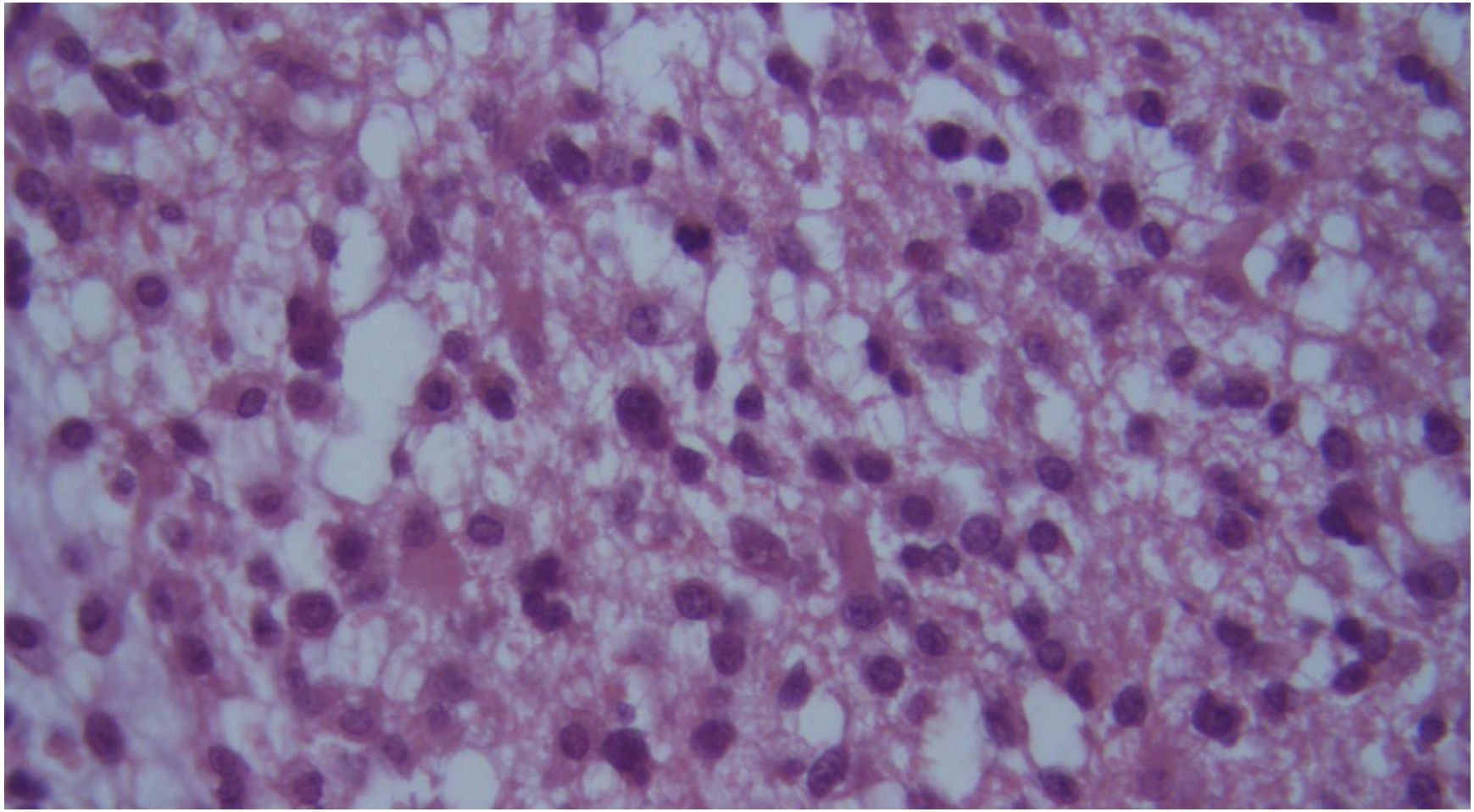
Diagnóstico en “multi-estratos” o “multi- nivel”, integrando diagnóstico histológico + molecular.

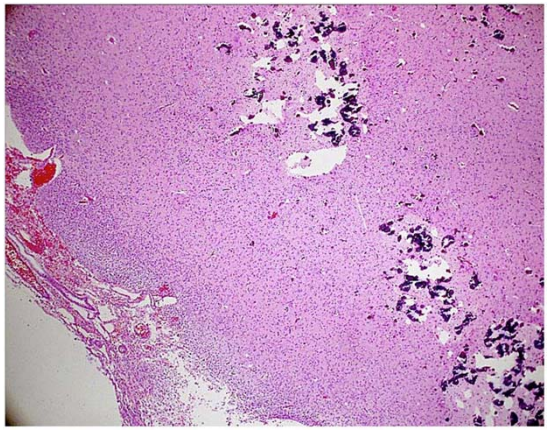
- **DIAGNÓSTICO INTEGRADO (nivel 1)**
- Clasificación Histológica (nivel 2)
- Estadio WHO (nivel 3)
- Estudio molecular (nivel 4)



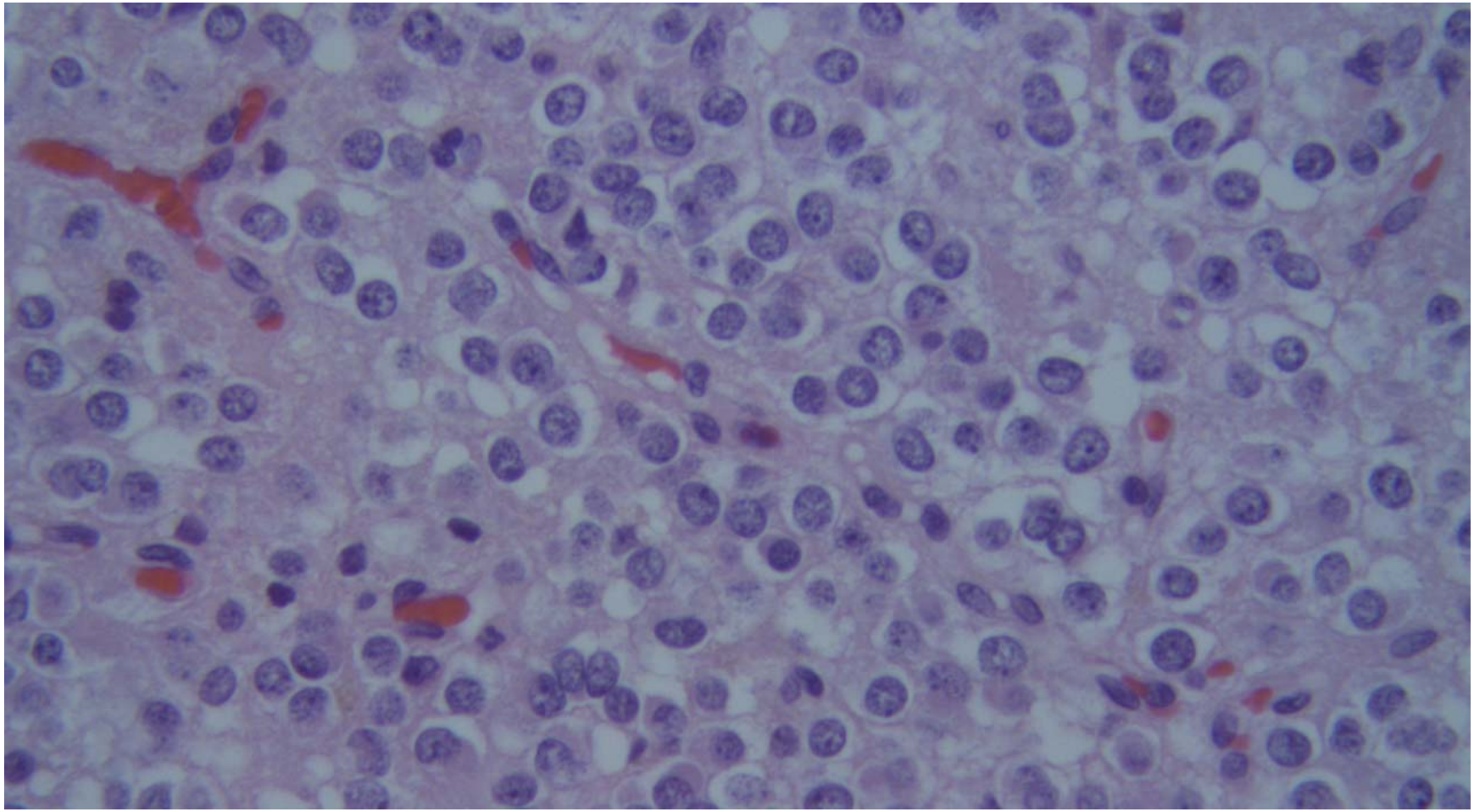
- David N. Louis. Brain Pathology 2014

Astrocitoma

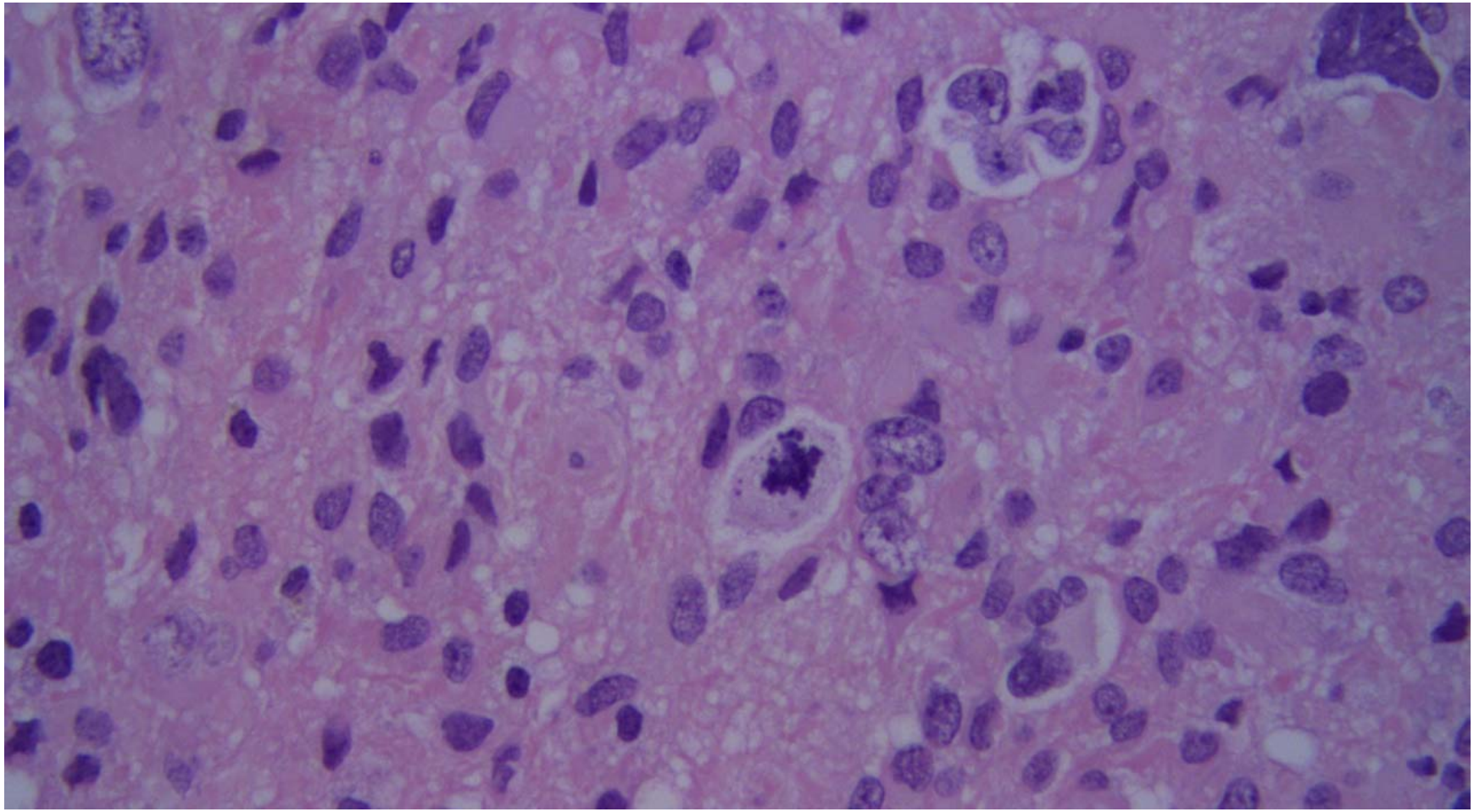




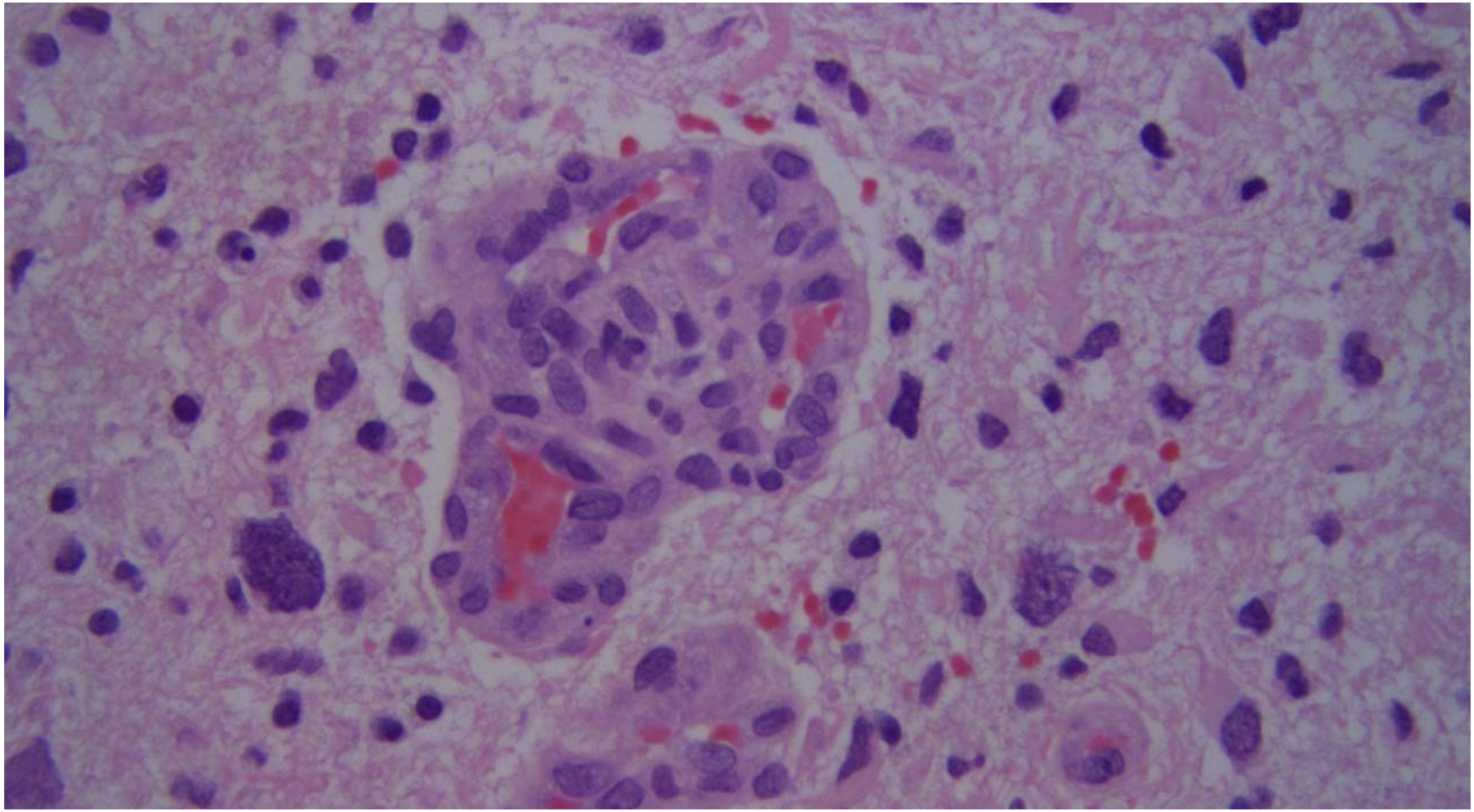
Oligodendroglioma



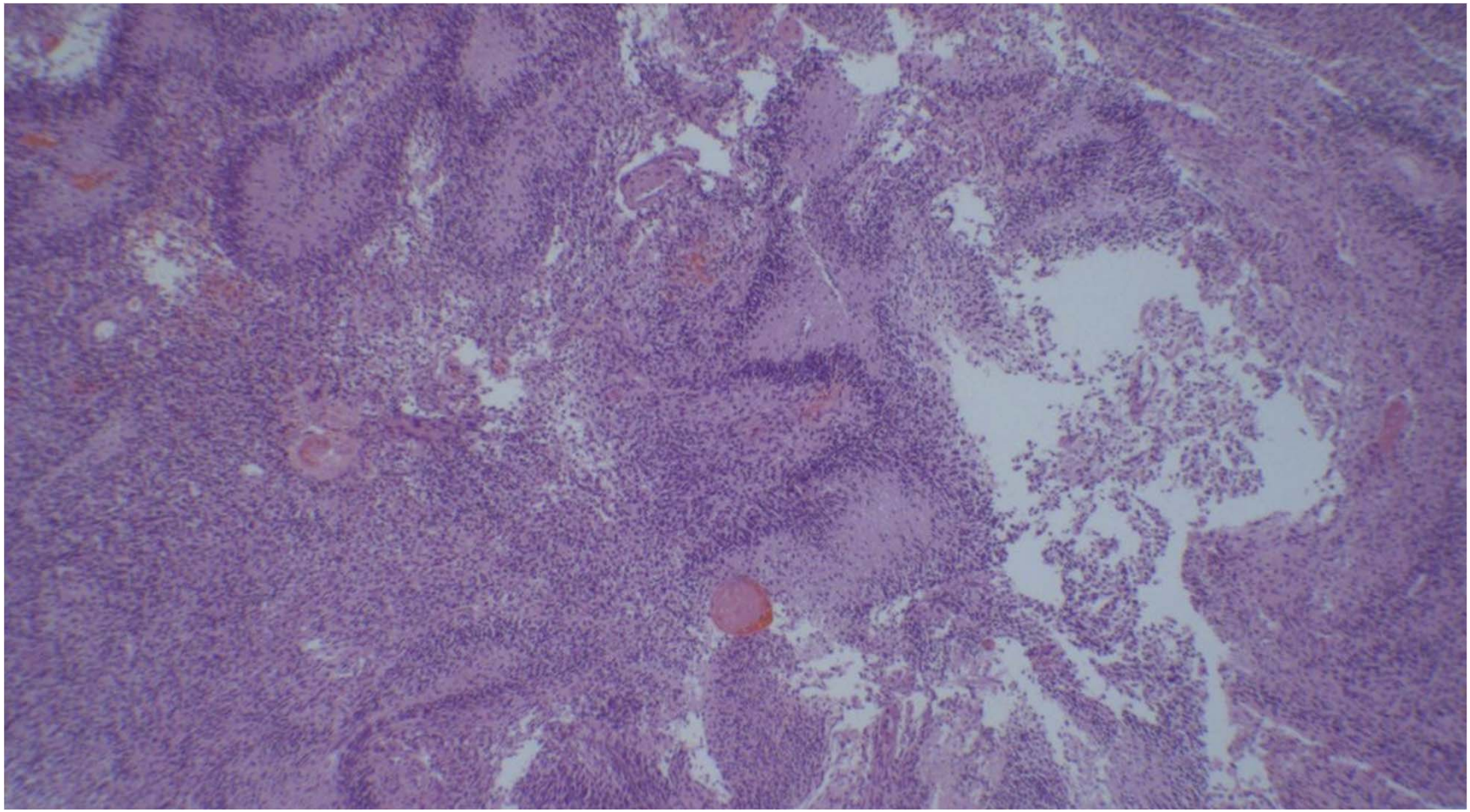
Mitosis



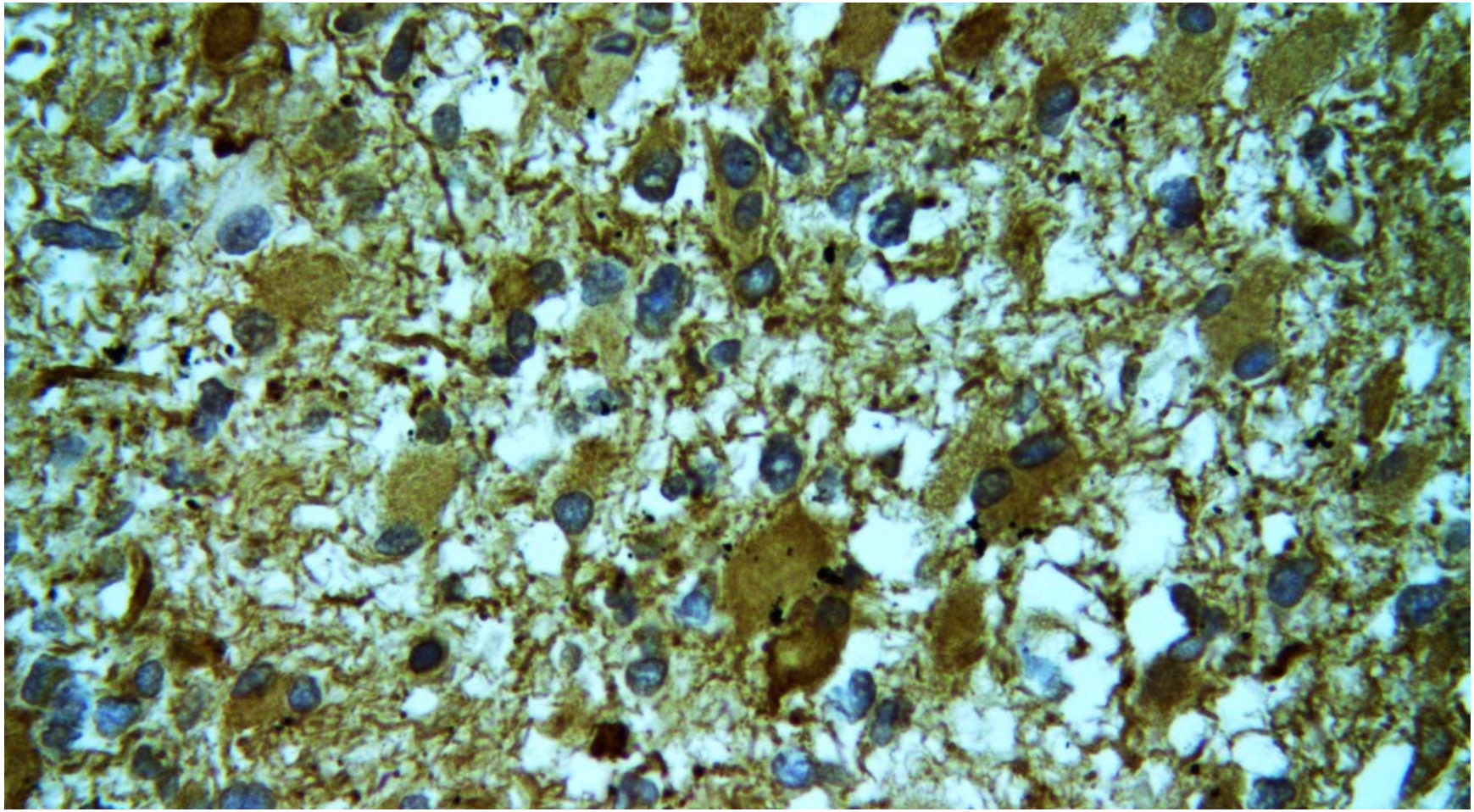
Proliferación vascular



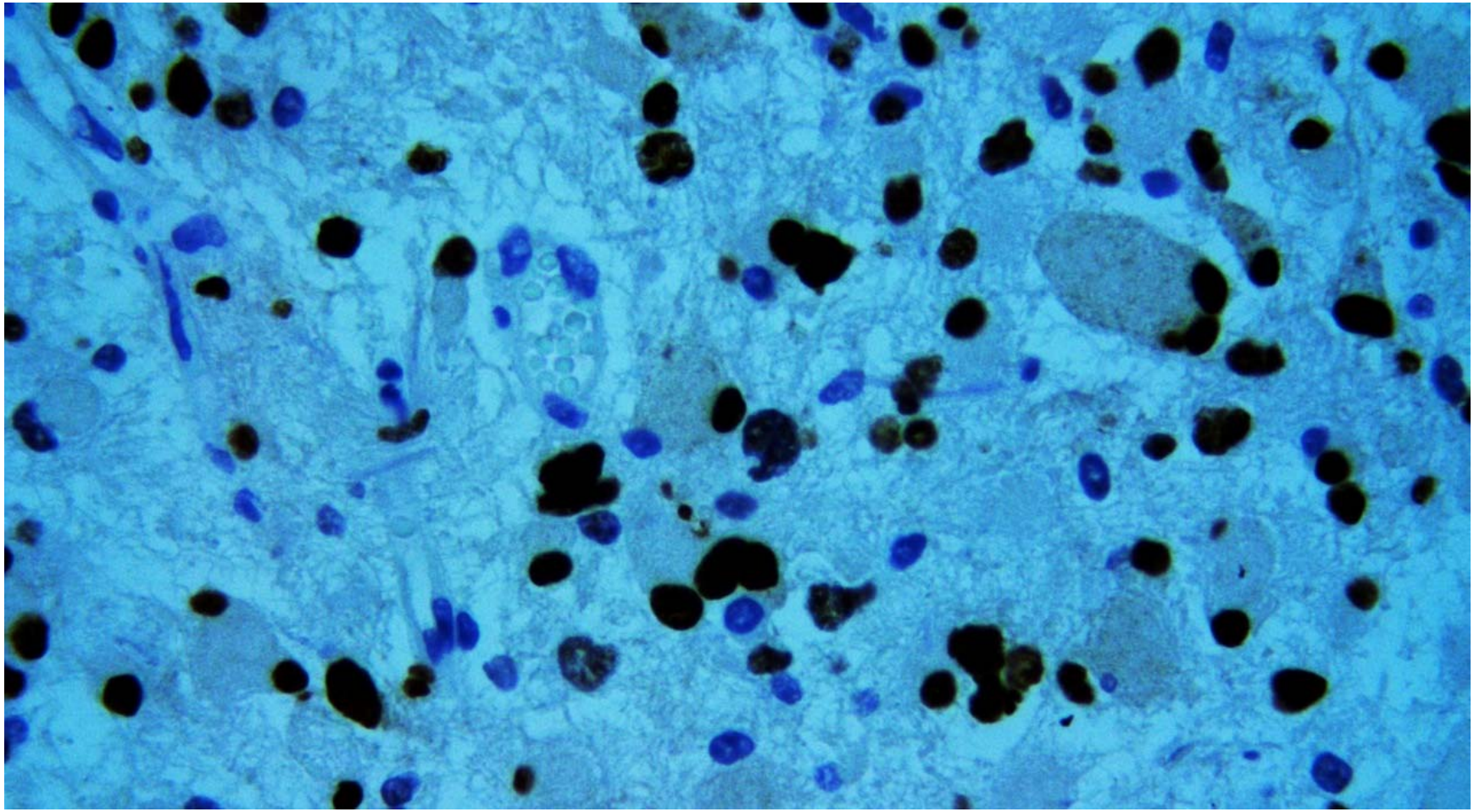
Necrosis



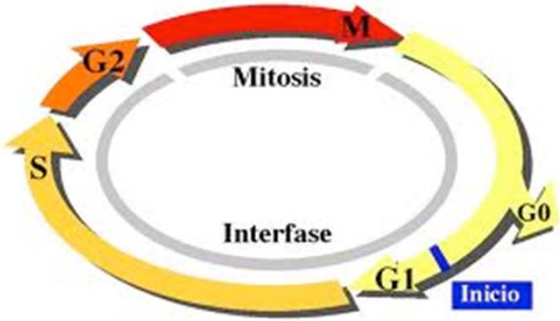
GFAP

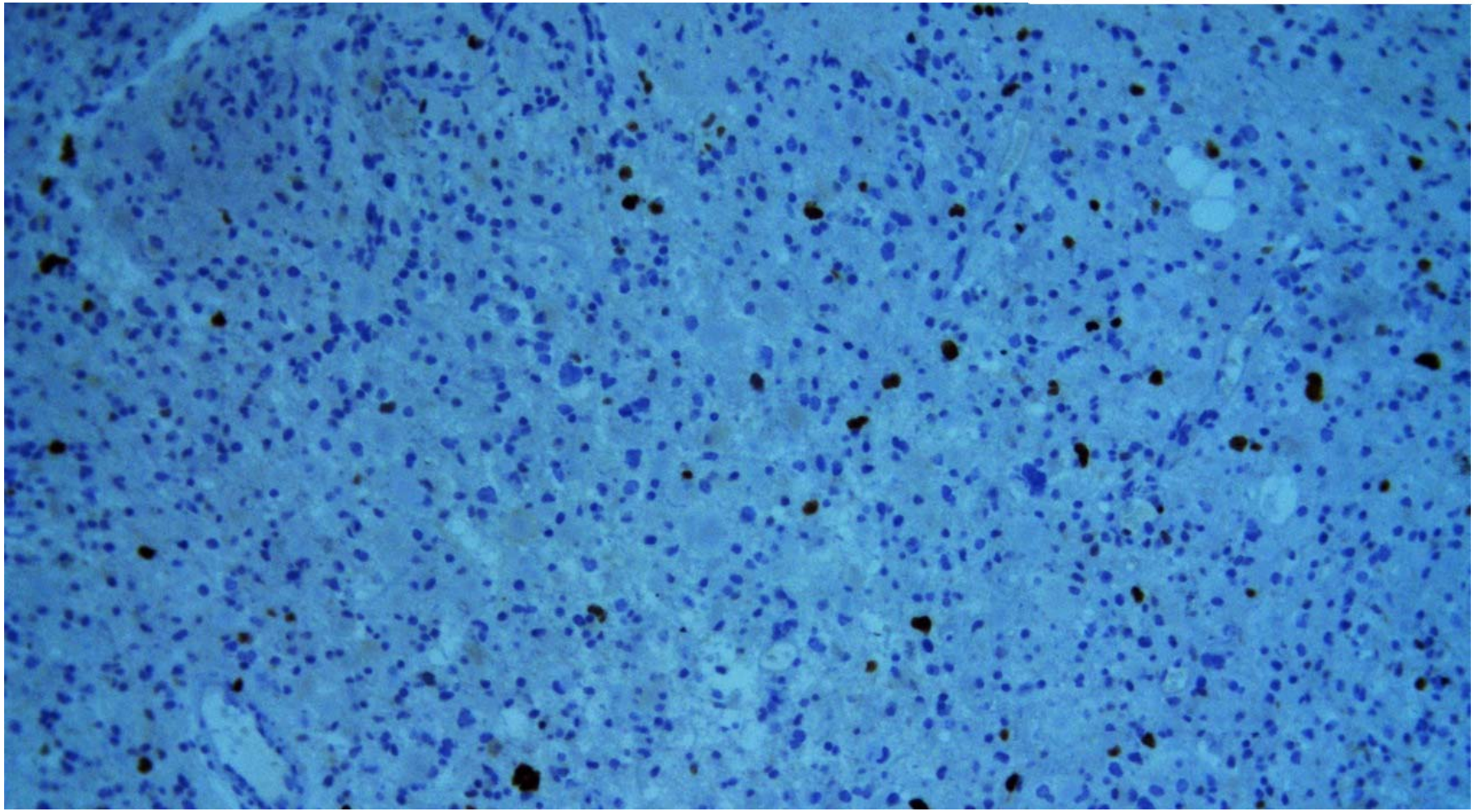


p53



MIB-1



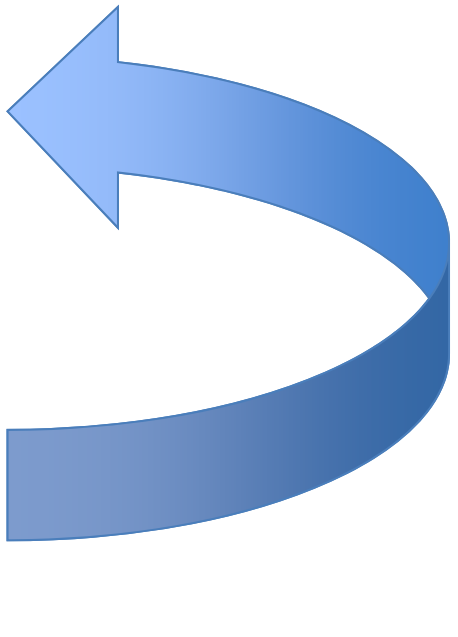


WHO 2016	GRADO I	GRADO II	GRADO III	GRADO IV
ASTROCITOMA	Muchos de ellos: Gliomas Circunscritos	ASTROCITOMA DIFUSO II ⇧Celularidad, Atipia	ASTROCITOMA ANAPLASICO III Mitosis	GBM Necrosis y/o prolif vascular
OLIGO-DENDROGLIOMA		OLIGODENDRO-GLIOMA II ⇧Celularidad, Atipia	OLIGO-DENDROGLIOMA ANAPLASICO III Mitosis signific (6/10HPF), prolif.vascular prominente	

Clasificación WHO 2016

Diagnóstico en “multi-estratos” o “multi- nivel”, integrando diagnóstico histológico + molecular.

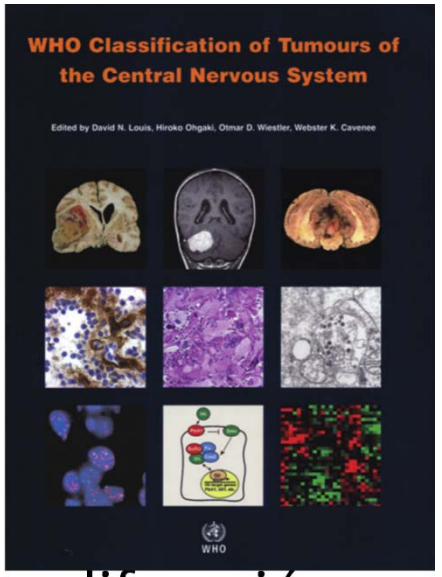
- **DIAGNÓSTICO INTEGRADO (nivel 1)**



- Clasificación Histológica (nivel 2)
- Estadio WHO (nivel 3)
- Estudio molecular (nivel 4)

- David N. Louis. Brain Pathology 2014

Grados de la OMS



Predicen el comportamiento biológico del tumor

Otros: edad, estado funcional, extensión resección

•Grado I: Bien circunscritos, crecimiento lento, baja proliferación, posibilidad de curación con resección solamente

•Grado II: En general infiltrantes y suelen recurrir a pesar de baja proliferación

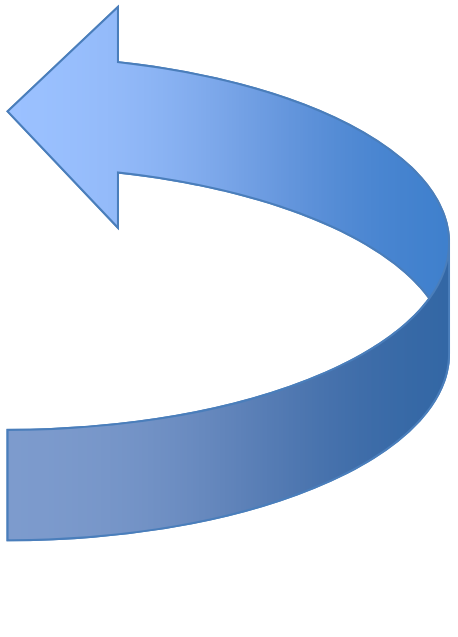
•Grado III: Signos histológicos de malignidad, como atipia y mitosis abundantes. Suelen requerir tratamiento adyuvante.

•Grado IV: Muy malignos histológicamente. Suelen tener evolución muy rápida y mal pronóstico

Clasificación WHO 2016

Diagnóstico en “multi-estratos” o “multi- nivel”, integrando diagnóstico histológico + molecular.

- **DIAGNÓSTICO INTEGRADO (nivel 1)**

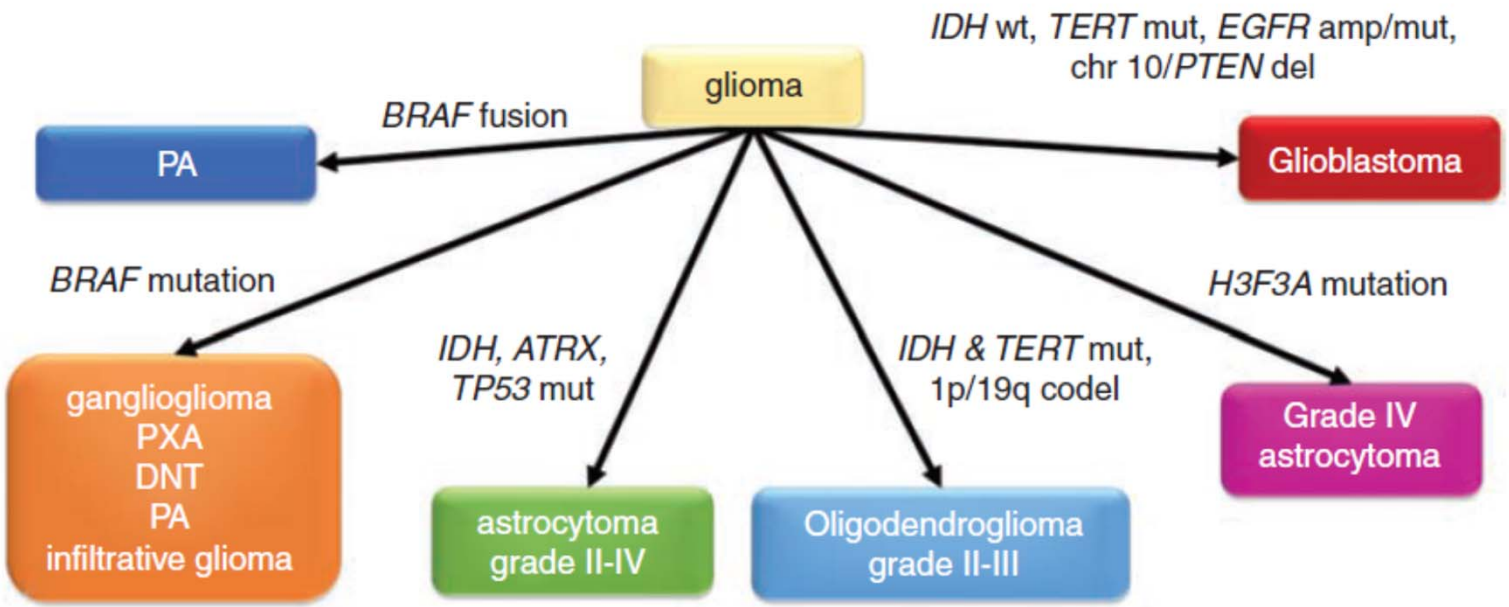


- Clasificación Histológica (nivel 2)
- Estadio WHO (nivel 3)
- Estudio molecular (nivel 4)

- David N. Louis. Brain Pathology 2014

1498 Neuro-Oncology
21(12), 1498–1508, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

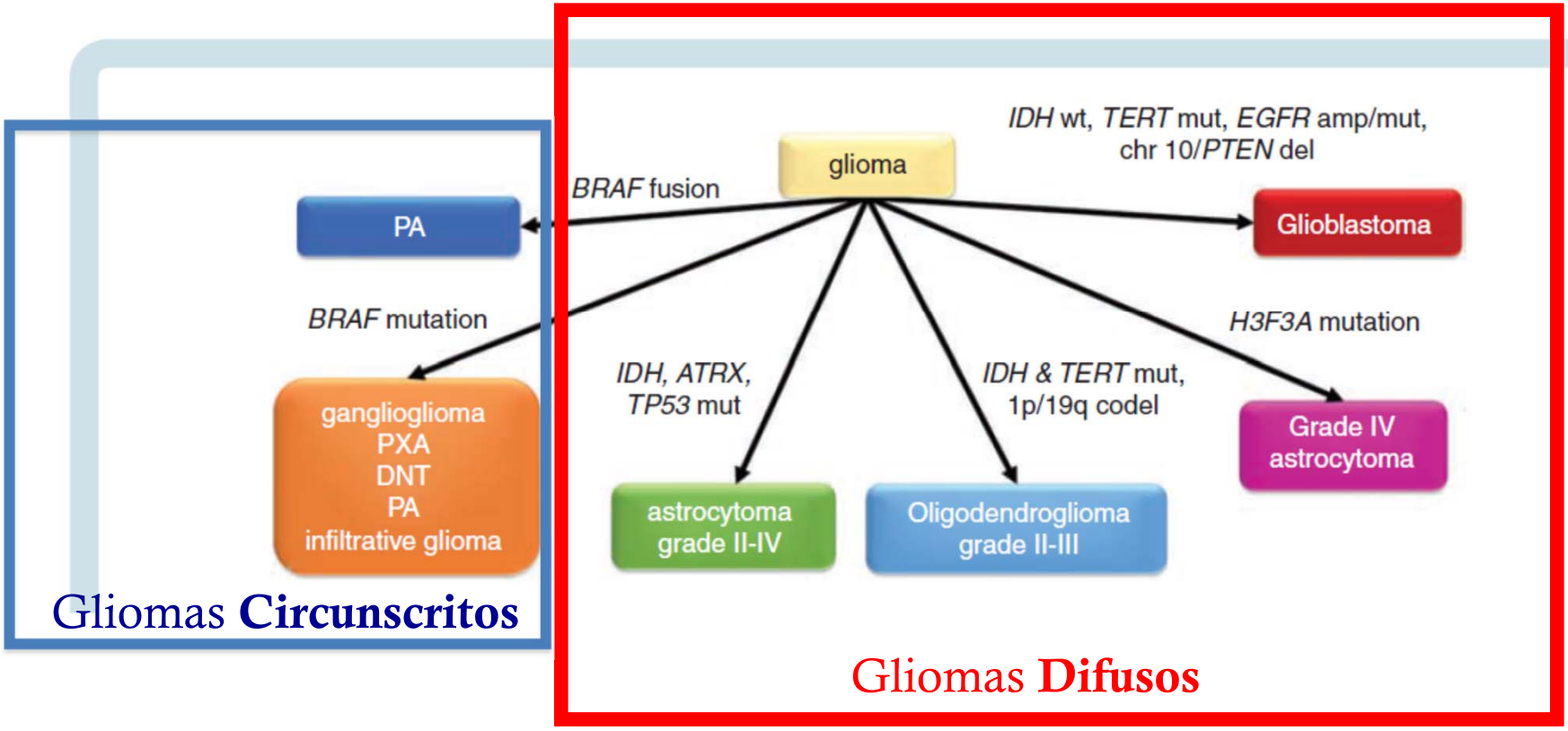
The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients



- Horbinski C, *et al*. Neuro Oncol. 2019

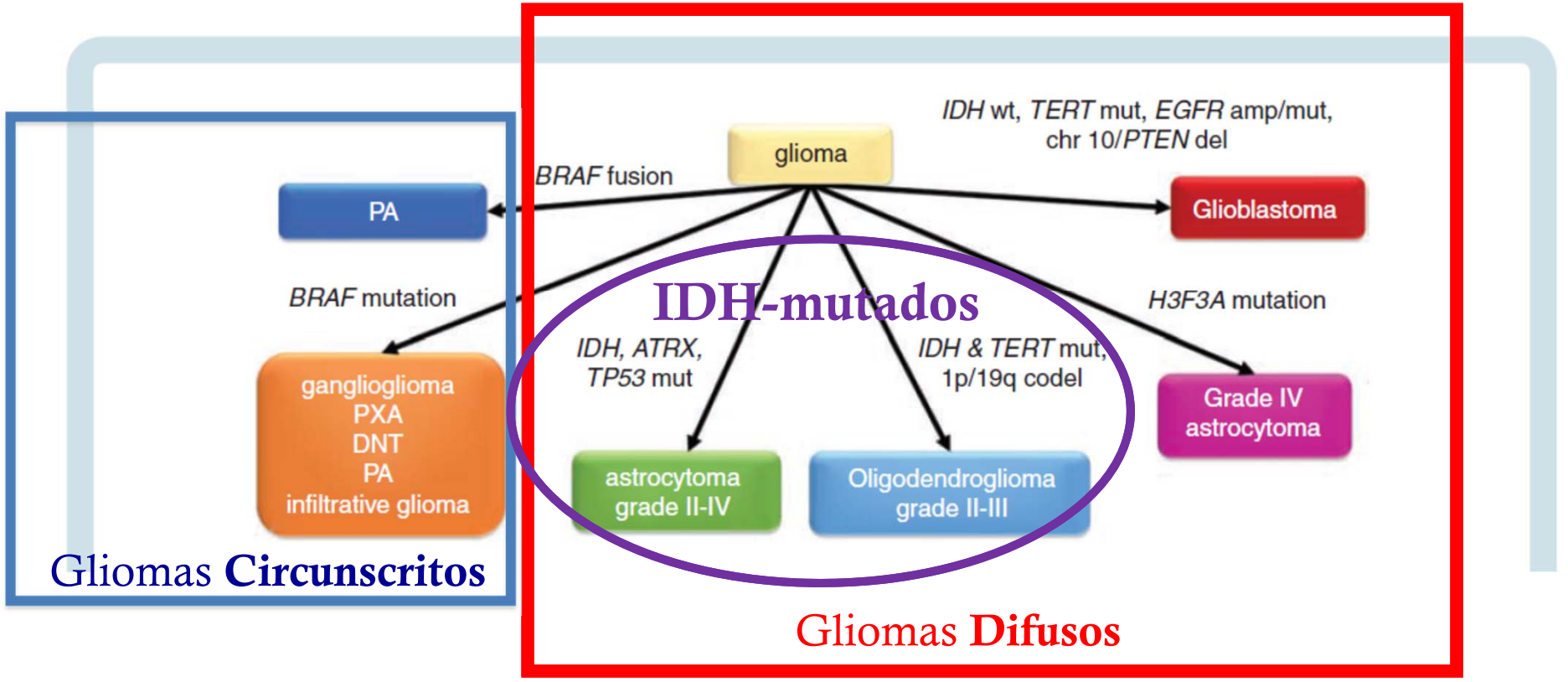
1498 Neuro-Oncology
21(12), 1498–1508, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients



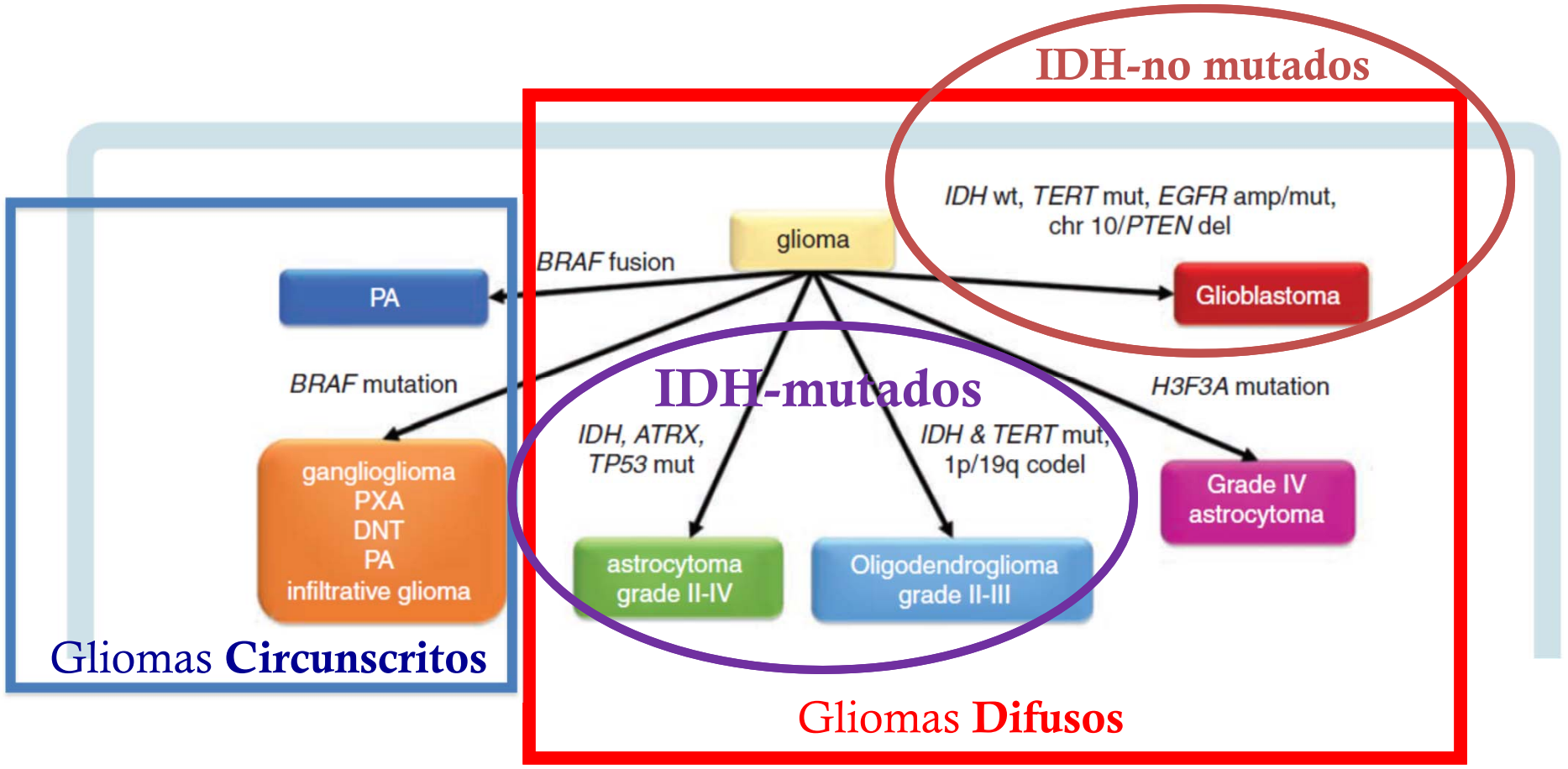
1498 Neuro-Oncology
21(12), 1498–1508, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients



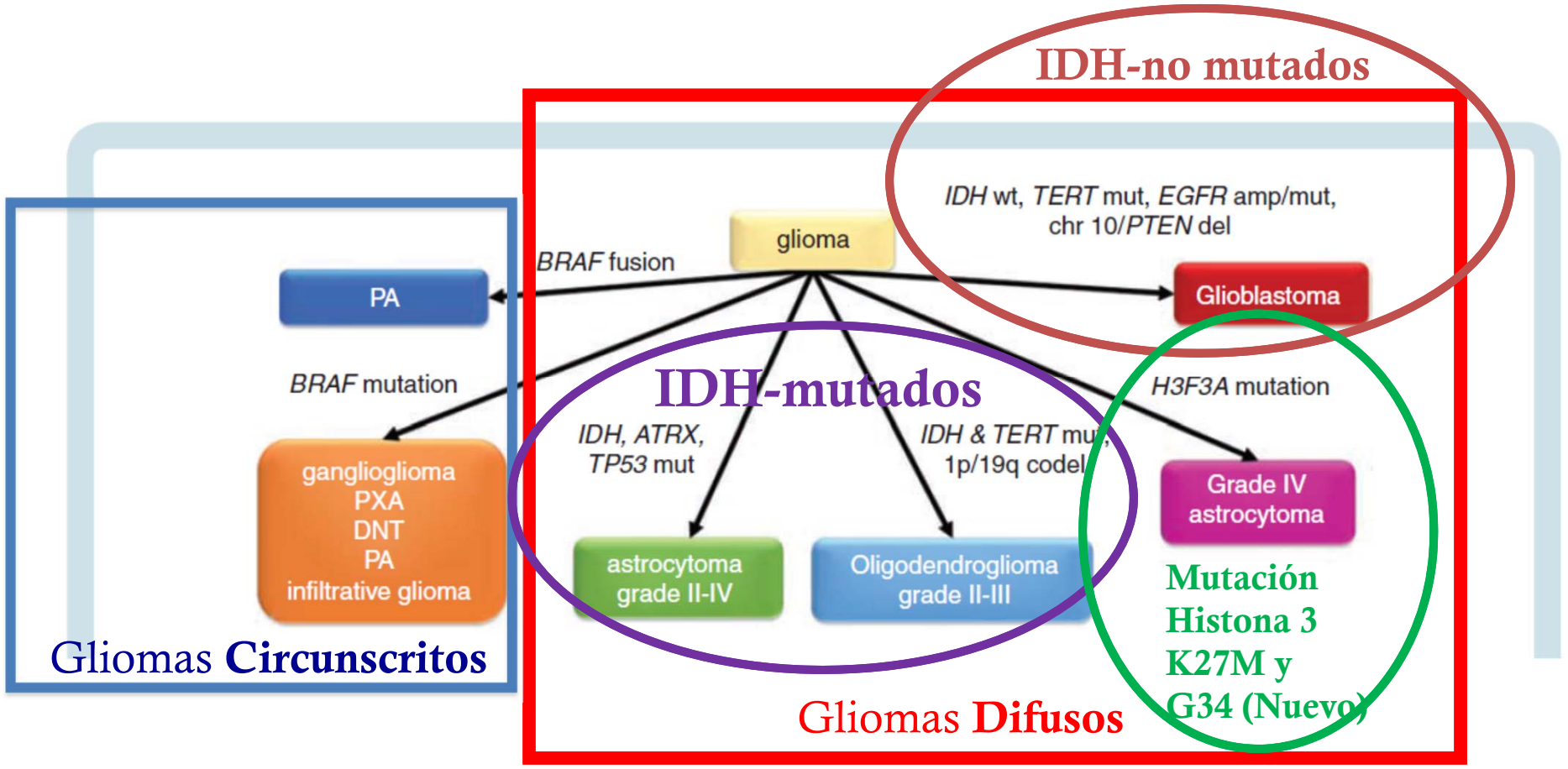
1498 Neuro-Oncology
21(12), 1498–1508, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

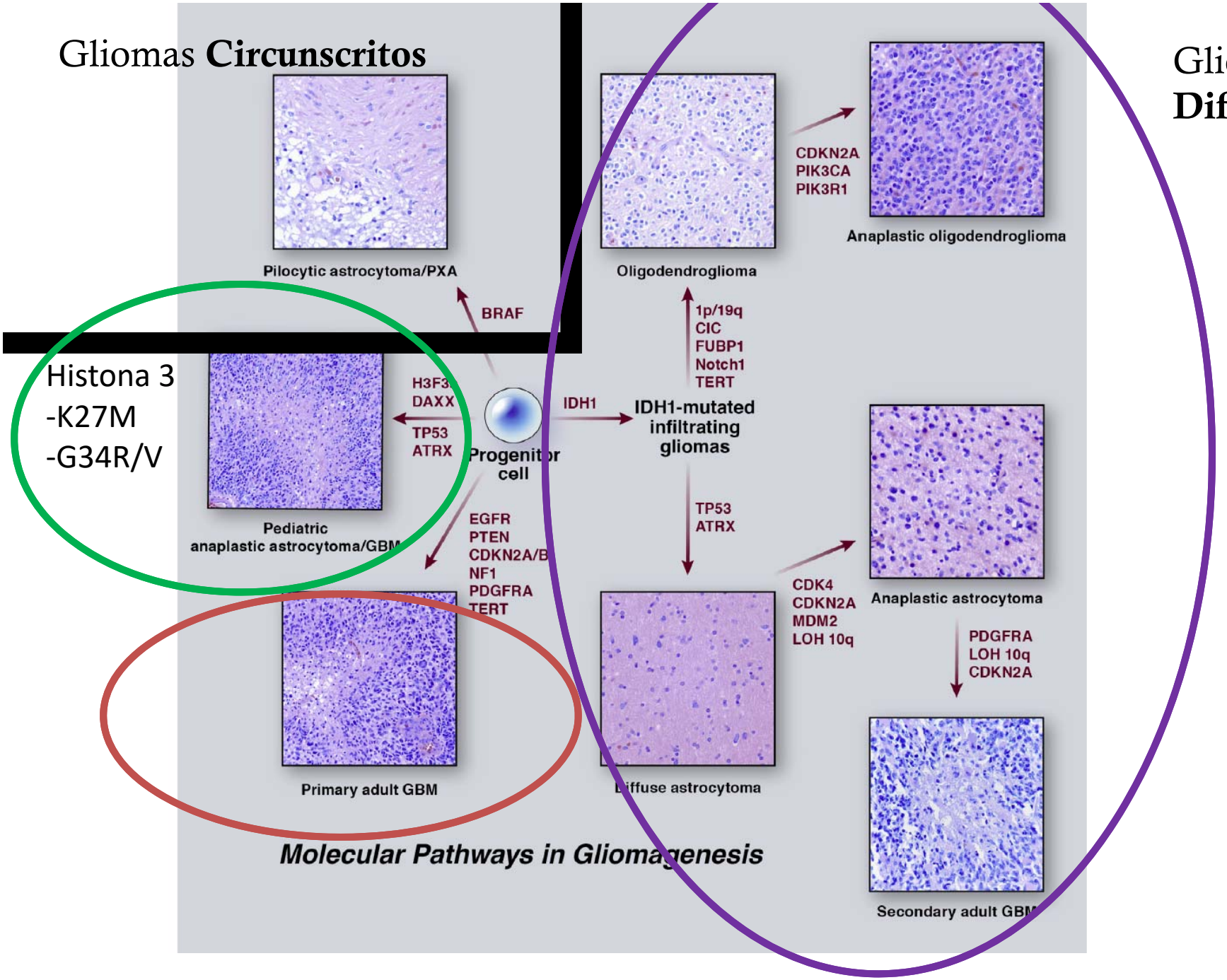
The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients



1498 Neuro-Oncology
21(12), 1498–1508, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients





- Appin CL, Brat DJ. Mol Aspects Med. 2015

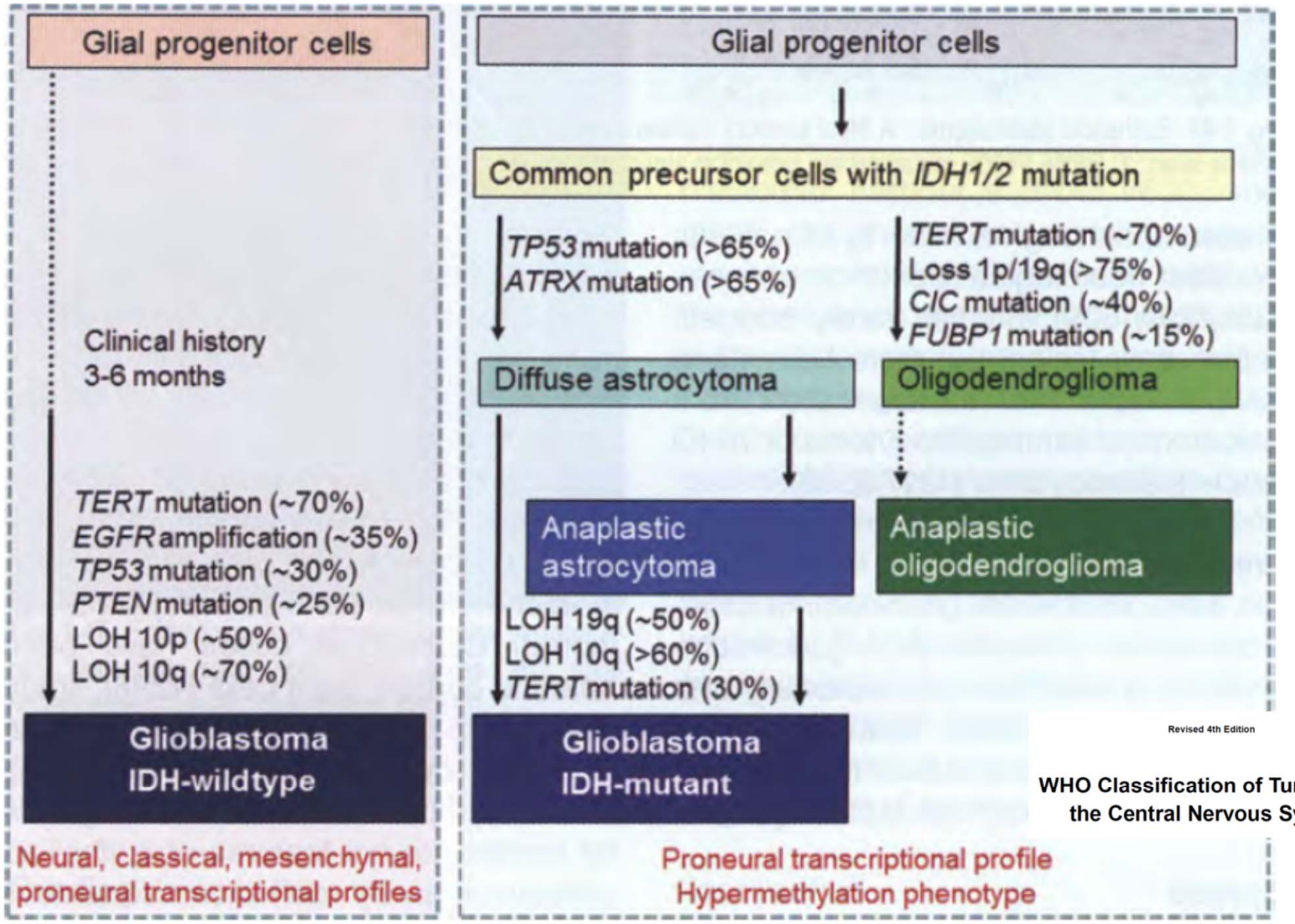


Fig. 1.50 Genetic pathways to IDH-wildtype and IDH-mutant glioblastoma. This chart is based on the hypothesis that IDH-mutant glioblastomas share common glial progenitor cells not only with diffuse and anaplastic astrocytomas, but also with oligodendrogliomas and anaplastic oligodendrogliomas. Adapted from Ohgaki H and Kleihues P {1830}.

Brain Pathology ISSN 1015-6305

REVIEW

cIMPACT-NOW: a practical summary of diagnostic points from Round 1 updates

David N. Louis[1]; David W. Ellison[2]; Daniel J. Brat[3]; Kenneth Aldape[4]; David Capper[5,6,7,8]; Cynthia Hawkins[9]; Werner Paulus[10]; Arie Perry[11]; Guido Reifenberger[12,13]; Dominique Figarella-Branger[14]; Andreas von Deimling[15,16,17]; Pieter Wesseling[18,19]

Brain Pathology **29** (2019) 469–472

CIMPACT UPDATE 3

cIMPACT Update 3 (1) was from Working Committee 1. It determined molecular criteria that could be used in the setting of an *IDH-wildtype* diffuse or anaplastic *astrocytic* glioma without histological features of glioblastoma (i.e., microvascular proliferation and/or necrosis) to infer that the tumor would follow a clinical course more similar to a WHO grade IV glioblastoma.

- For diffuse and anaplastic astrocytic gliomas without IDH mutation, the finding of any or all of the following molecular criteria corresponds to WHO grade IV behavior and tumors can be referred to as *Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV*:

  - *EGFR* amplification

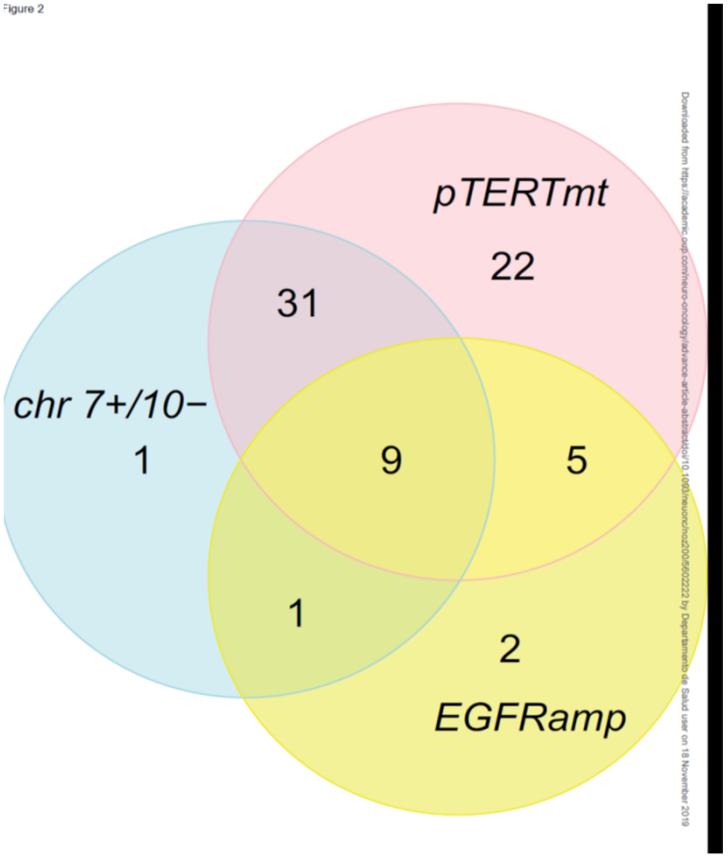
and/or

  - *Whole chromosome 7 gain and whole chromosome 10 loss (+7/-10)*

and/or

  - *TERT promoter mutation*

Figure 2



Brain Pathology **29** (2019) 469–472

Neuro Oncol. 2019 Oct 22. pii: noz200. doi: 10.1093/neuonc/noz200. [Epub ahead of print]

Survival of diffuse astrocytic glioma, IDH1/2-wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria.

Acta Neuropathologica
https://doi.org/10.1007/s00401-020-02127-9

CORRESPONDENCE

cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas

Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Dominique Figrarella-Branger[4] · Gregory N. Fuller[5] · Caterina Giannini[6] · Eric C. Holland[7] · Robert B. Jenkins[6] · Bette Kleinschmidt-DeMasters[8] · Takashi Komori[9] · Johan M. Kros[10] · David N. Louis[11] · Catriona McLean[12] · Arie Perry[13] · Guido Reifenberger[14,15] · Chitra Sarkar[16] · Roger Stupp[17] · Martin J. van den Bent[18] · Andreas von Deimling[19,20] · Michael Weller[21]

Table 1 IDH-mutant astrocytomas

Astrocytoma, IDH-mutant, grade 2
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or low[a]. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent
Astrocytoma, IDH-mutant, grade 3
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity[a]. Microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions are absent
Astrocytoma, IDH-mutant, grade 4
A diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation that exhibits microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion or any combination of these features

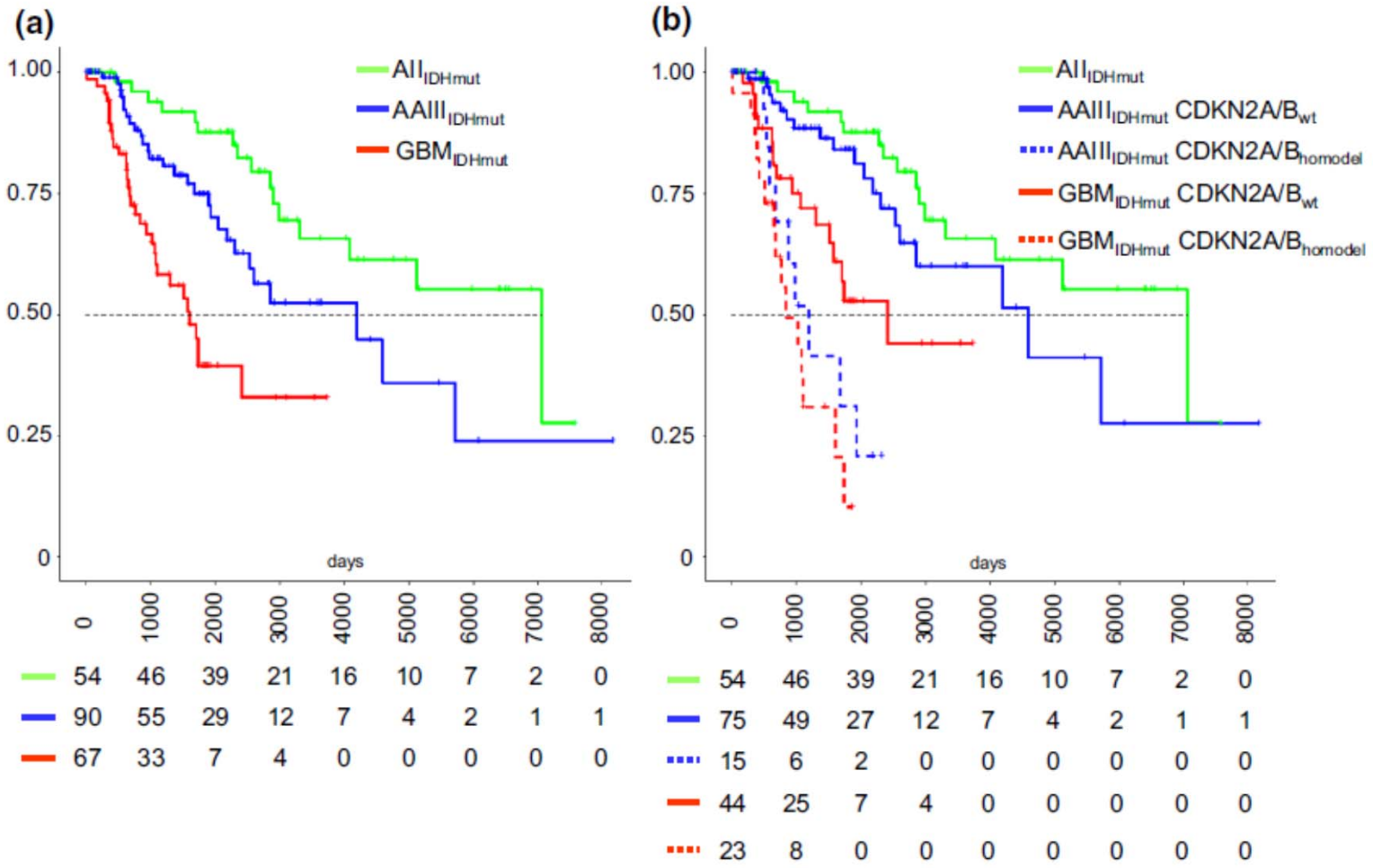


Fig. 1 Kaplan–Meier plot stratifying according to WHO in the discovery set (**a**). **b** The same patients with additional stratification for homozygous deletion of *CDKN2A/B*

Acta Neuropathologica (2018) 136:153–166
https://doi.org/10.1007/s00401-018-1849-4

ORIGINAL PAPER

Novel, improved grading system(s) for IDH-mutant astrocytic gliomas

Mitsuaki Shirahata[1,2] · Takahiro Ono[1,3] · Damian Stichel[4] · Daniel Schrimpf[1,4] · David E. Reuss[1,4] · Felix Sahm[1,4] · Christian Koelsche[1,4] · Annika Wefers[1,4] · Annekathrin Reinhardt[1,4] · Kristin Huang[1,4] · Philipp Sievers[1,4] · Hiroaki Shimizu[3] · Hiroshi Nanjo[5,6] · Yusuke Kobayashi[2] · Yohei Miyake[2] · Tomonari Suzuki[2] · Jun-ichi Adachi[2] · Kazuhiko Mishima[2] · Atsushi Sasaki[7] · Ryo Nishikawa[2] · Melanie Bewerunge-Hudler[8] · Marina Ryzhova[9] · Oksana Absalyamova[9] · Andrey Golanov[9] · Peter Sinn[10] · Michael Platten[11] · Christine Jungk[12] · Frank Winkler[13,14] · Antje Wick[13,14] · Daniel Hänggi[15] · Andreas Unterberg[12] · Stefan M. Pfister[16,17,18] · David T. W. Jones[16,17] · Martin van den Bent[19] · Monika Hegi[20,21] · Pim French[19] · Brigitta G. Baumert[22] · Roger Stupp[23] · Thierry Gorlia[24] · Michael Weller[25] · David Capper[1,26,27,28] · Andrey Korshunov[1,4] · Christel Herold-Mende[12] · Wolfgang Wick[13,14] · David N. Louis[29] · Andreas von Deimling[1,4,30]

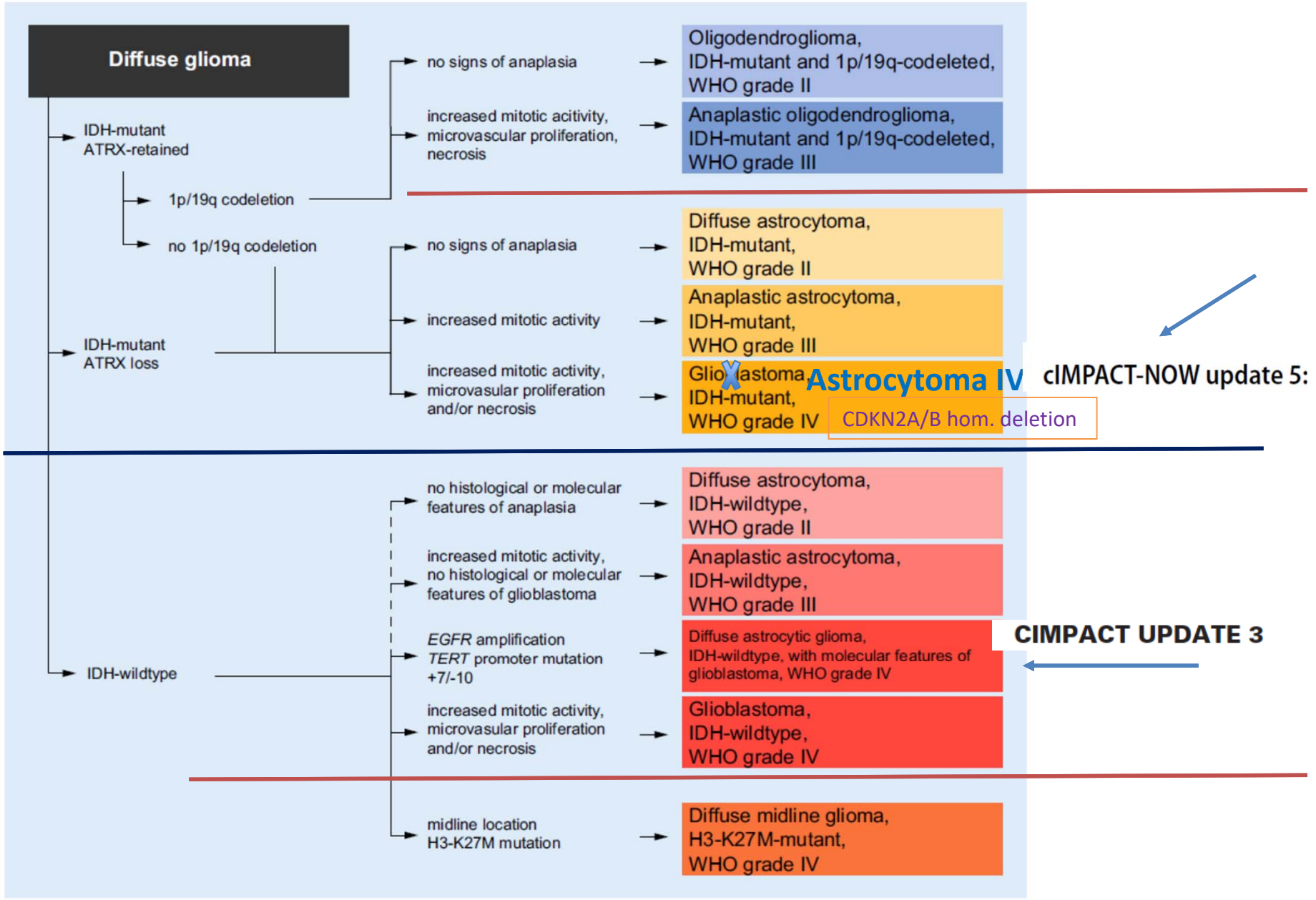


Fig. 1 ▲ Overview of the essential histological and molecular criteria for differential diagnosis of diffuse gliomas according to the 2016 WHO classification [14] and the recommendations of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Officially WHO (cIMPACT-NOW consortium) [2]. *IDH* isocitrate dehydrogenase

- Malzkorn B,et al. Pathologe. 2019

Clasificación WHO 2016

GLIOMAS

(difusos e infiltrantes)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

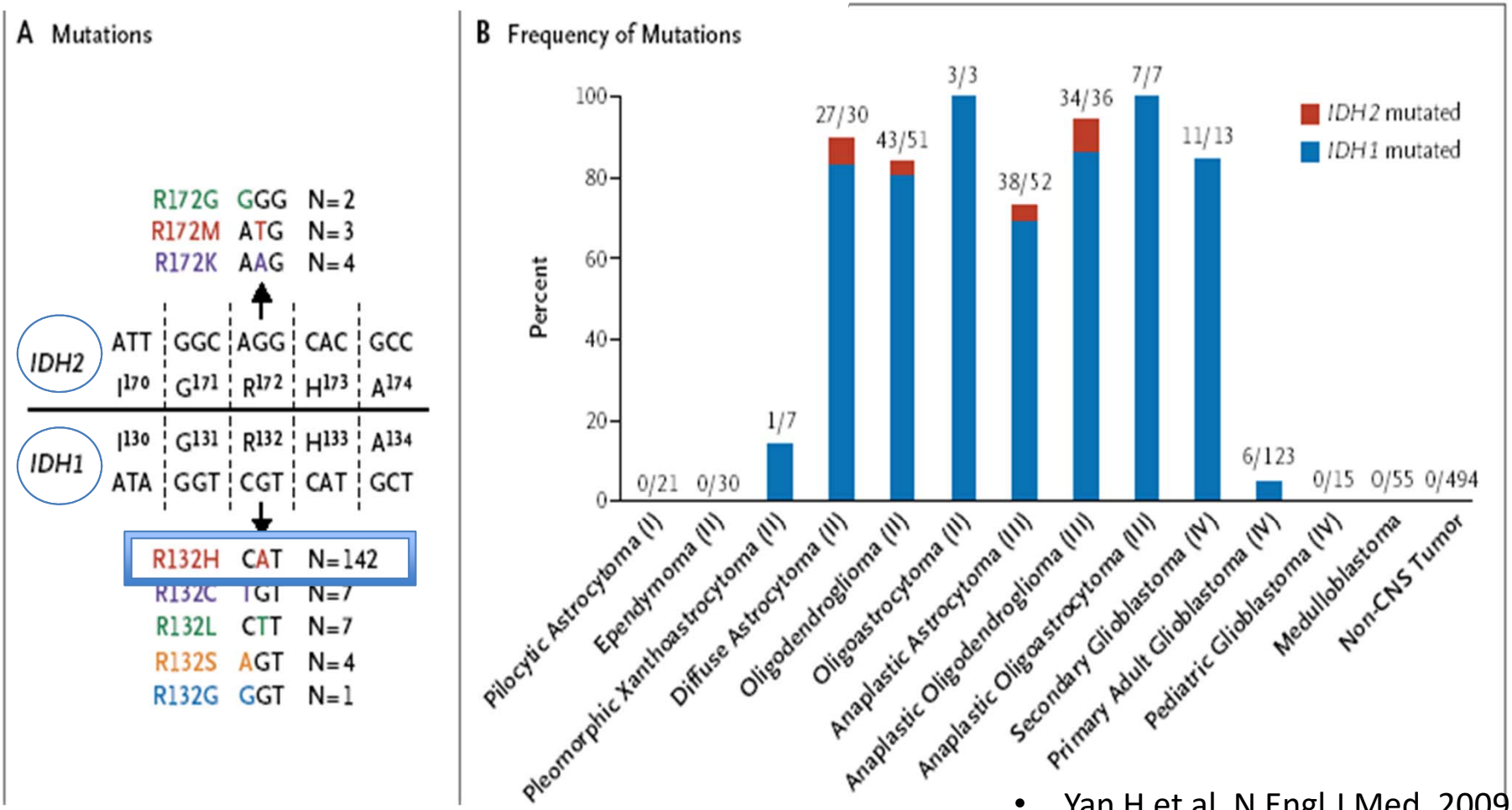
IDH1 and *IDH2* Mutations in Gliomas

Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

IDH

Secuencian 445 tumores SNC y 494 no-SNC

Mutaciones en 85% grado II, III y 2ºGBM



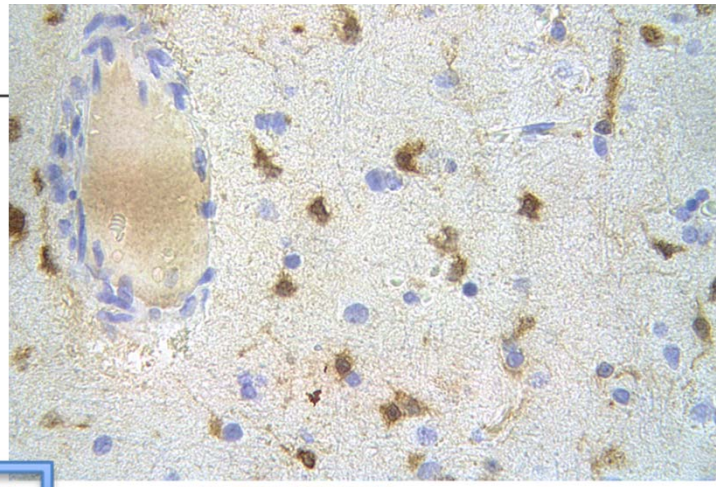
- Yan H et al. N Engl J Med. 2009

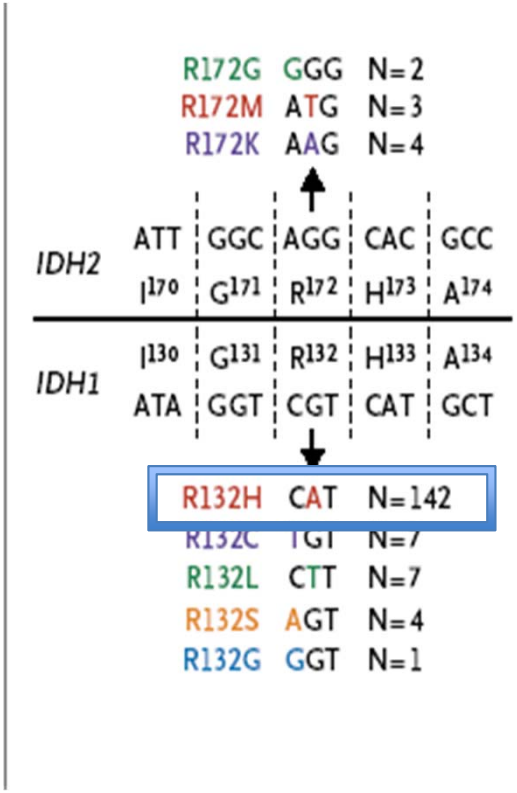
Acta Neuropathol (2009) 118:599–601
DOI 10.1007/s00401-009-0595-z

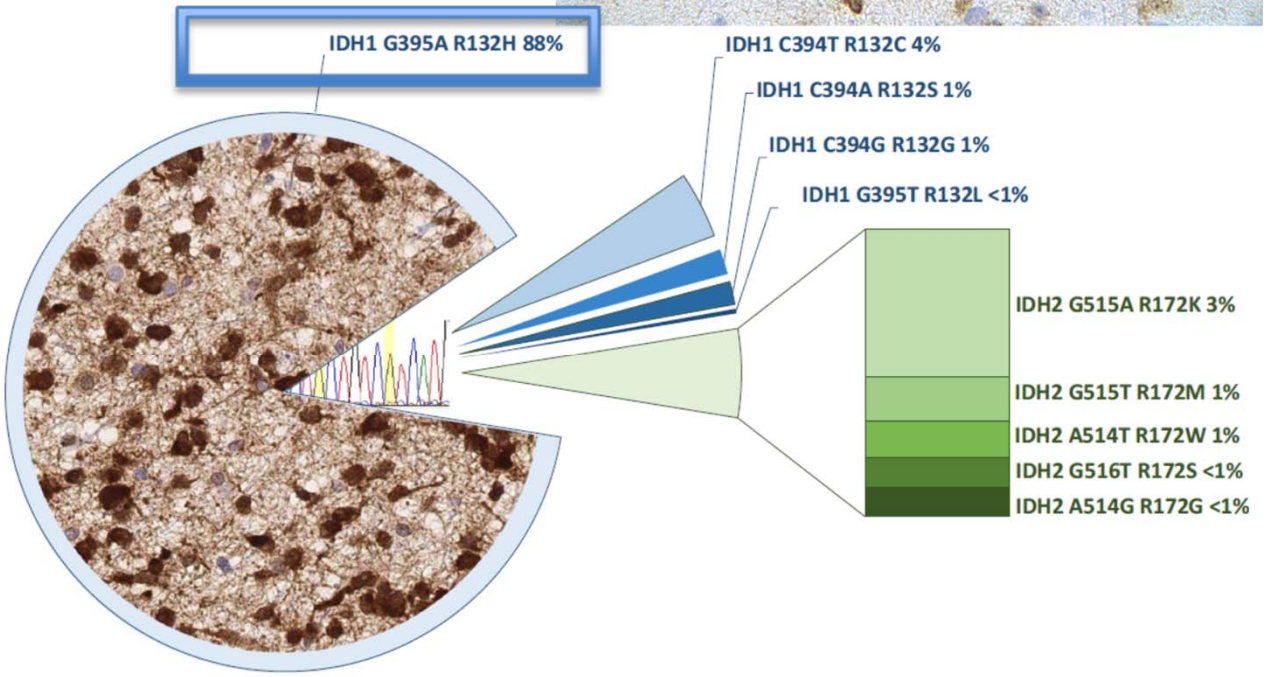
SHORT REPORT

Monoclonal antibody specific for *IDH1* R132H mutation

David Capper · Hanswalter Zentgraf · Jörg Balss · Christian Hartmann · Andreas von Deimling







Si IDH-1 negativo por IHQ: secuenciar?
GBM en menores de <55 años (mayores de 55, probabilidad <1%)

- Capper D et al. Acta Neuropathol. 2009
- Bradner et al. J Neurol 2018

IDH

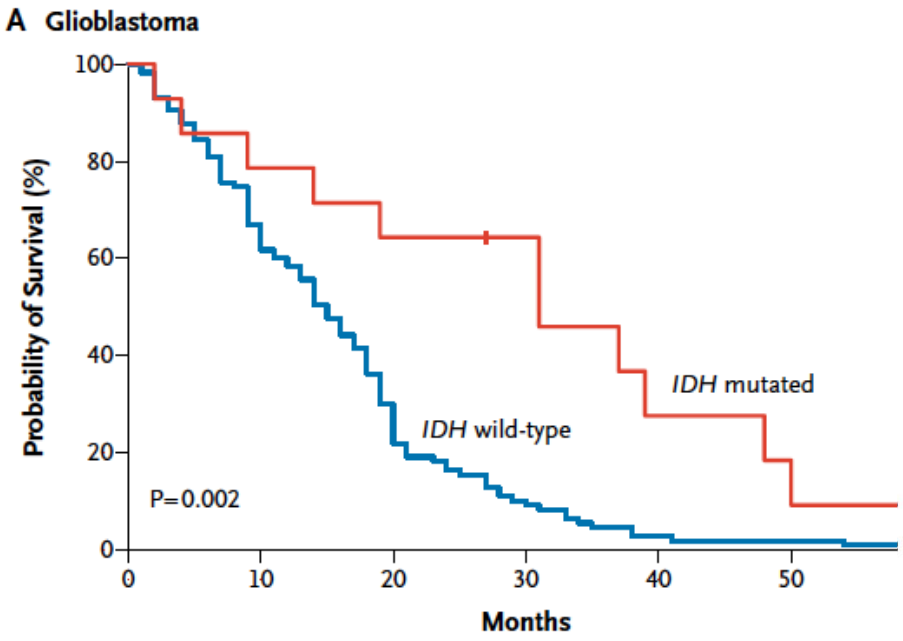
Table 2. Frequently asked questions in the molecular neuro-oncology of gliomas in adulthood

***IDH1/2* mutations**	
Can I use the *IDH1/2* status for diagnostic purposes?	Yes. *IDH1/2* mutations are common in WHO grades II and III gliomas and can aid in the differential diagnosis vs reactive gliosis and other glioma entities, eg, pilocytic astrocytomas, gangliogliomas, and ependymomas, which typically lack *IDH1/2* mutations.
Is the *IDH1/2* status homogeneous within gliomas?	Yes. This is confirmed at least in WHO grades II and III tumors, whereas no data exist for glioblastoma.
Can I use the *IDH1/2* status for prognostic purposes?	Yes. *IDH1/2* mutations are prognostically favorable, in particular in WHO grades III and IV gliomas.
Can I use the *IDH1/2* status as a predictive marker for clinical decision making?	No.

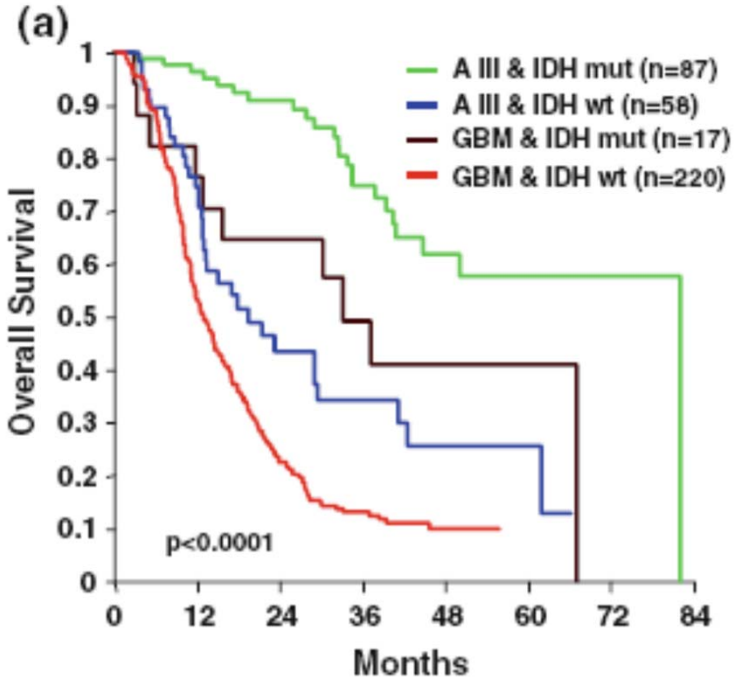
Agios Pharmaceuticals has developed potent and orally available selective inhibitors of both *IDH1* and *IDH2* mutant enzymes. Preliminary studies of in vivo tumor models have shown they are capable of lowering 2HG levels by greater than 90% and reversed the altered methylation profiles of the *IDH* mutant cells.

- Weller M et al. NeuroOncol 2012

IDH
Marcador pronóstico



- Yan H et al. N Engl J Med. 2009



- Hartmann C et al. Acta Neuropathol. 2010

Acta Neuropathol (2015) 129:867–873
DOI 10.1007/s00401-015-1438-8

ORIGINAL PAPER

IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO

David E. Reuss[1,2] · Yasin Mamatjan[3] · Daniel Schrimpf[1,2] · David Capper[1,2] · Volker Hovestadt[4] · Annekathrin Kratz[1,2] · Felix Sahm[1,2] · Christian Koelsche[1,2] · Andrey Korshunov[1,2] · Adriana Olar[5] · Christian Hartmann[6] · Jaap C. Reijneveld[7] · Pieter Wesseling[8,9] · Andreas Unterberg[10] · Michael Platten[11,12] · Wolfgang Wick[12,13] · Christel Herold-Mende[10] · Kenneth Aldape[3] · Andreas von Deimling[1,2]

Received: 17 April 2015 / Revised: 30 April 2015 / Accepted: 30 April 2015 / Published online: 12 May 2015

Abstract The WHO 2007 classification of tumors of the CNS distinguishes between diffuse astrocytoma WHO grade II (A II $_{WHO2007}$) and anaplastic astrocytoma WHO grade III (AA III $_{WHO2007}$). Patients with A II $_{WHO2007}$ are significantly younger and survive significantly longer than those with AA III $_{WHO2007}$. So far, classification and grading relies on morphological grounds only and does not yet take into account *IDH* status, a molecular marker of prognostic relevance. We here demonstrate that WHO 2007 grading performs poorly in predicting prognosis when applied to astrocytoma carrying *IDH* mutations. Three independent series including a total of 1360 adult diffuse astrocytic gliomas with *IDH* mutation containing 683 A II $_{IDHmut}$, 562 AA III $_{IDHmut}$, and 115 GBM $_{IDHmut}$, have been examined for with A II $_{IDHmut}$ and AA III $_{IDHmut}$ were of identical age at presentation of disease (36–37 years) and the difference in survival between grades was much less (10.9 years for A II $_{IDHmut}$, 9.3 years for AA III $_{IDHmut}$) than that reported for A II $_{WHO2007}$ versus AA III $_{WHO2007}$. Our analyses imply that the differences in age and survival between A II and AA III $_{WHO2007}$ predominantly depend on the fraction of *IDH*-non-mutant astrocytomas in the cohort. This data poses a substantial challenge for the current practice of astrocytoma grading and risk stratification and is likely

Acta Neuropathol (2015) 129:585–596
DOI 10.1007/s00401-015-1398-z

ORIGINAL PAPER

IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II–III diffuse gliomas

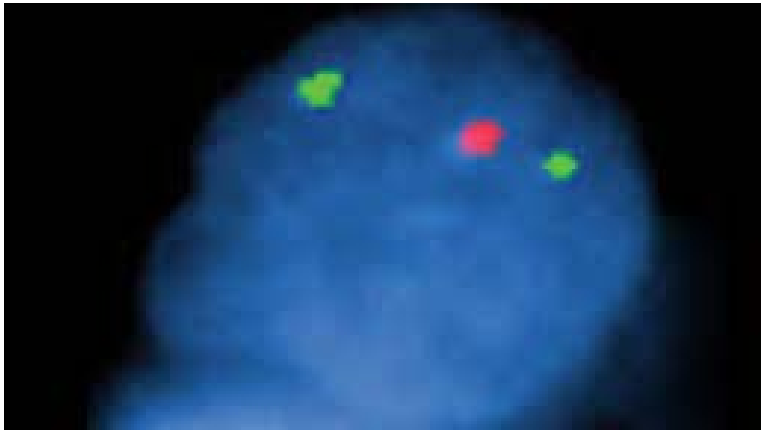
Adriana Olar · Khalida M. Wani · Kristin D. Alfaro-Munoz · Lindsey E. Heathcock · Hinke F. van Thuijl · Mark R. Gilbert · Terri S. Armstrong · Erik P. Sulman · Daniel P. Cahill · Elizabeth Vera-Bolanos · Ying Yuan · Jaap C. Reijneveld · Bauke Ylstra · Pieter Wesseling · Kenneth D. Aldape

GBM

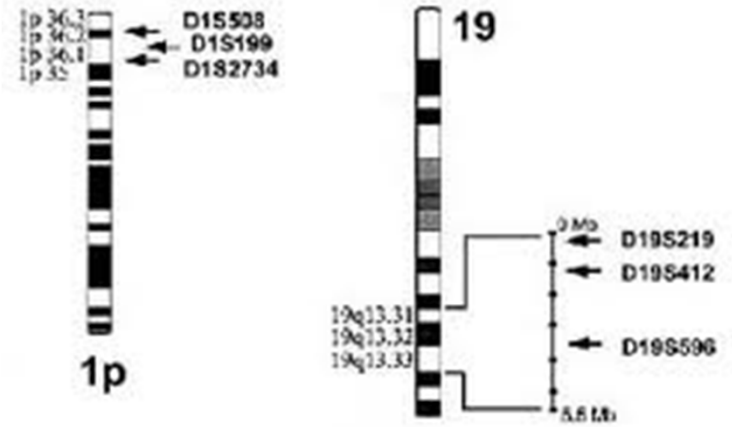
	IDH-wildtype glioblastoma	IDH-mutant glioblast
Synonym	Primary glioblastoma, IDH-wildtype	Secondary glioblastom IDH-mutant
Precursor lesion	Not identifiable; develops de novo	Diffuse astrocytoma Anaplastic astrocytoma
Proportion of glioblastomas	~90%	~10%
Median age at diagnosis	~62 years	~44 years
Male-to-female ratio	1.42:1	1.05:1
Mean length of clinical history	4 months	15 months
Median overall survival		
Surgery + radiotherapy	9.9 months	24 months
Surgery + radiotherapy + chemotherapy	15 months	31 months
Location	Supratentorial	Preferentially frontal
Necrosis	Extensive	Limited
TERT promoter mutations	72%	26%
TP53 mutations	27%	81%
ATRX mutations	Exceptional	71%
EGFR amplification	35%	Exceptional
PTEN mutations	24%	Exceptional

•Louis DN et al. Acta Neuropathol 2016

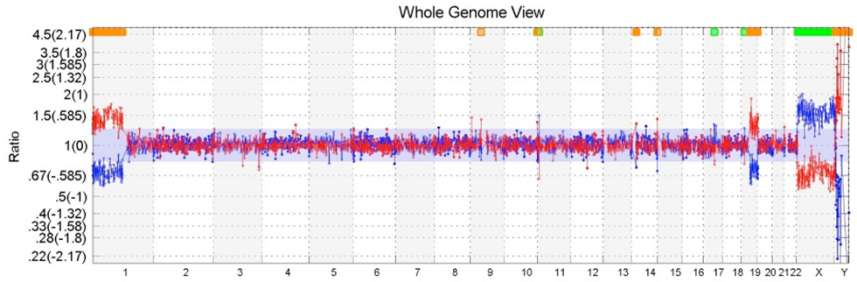
1p19q



FISH



PCR



Arrays CGH

- Bello MJ, Rey JA et al. Int J Cancer. 1994
- Nikiforova MN, Hamilton RL. Arch Pathol Lab Med. 2011
- Snuderl M et al Clin Cancer Res. 2009
- Wiens AL et al. J Neuropathol Exp Neurol. 2012

Clinical Neuropathology, Vol. 33 – No. 2/2014 (108-111)

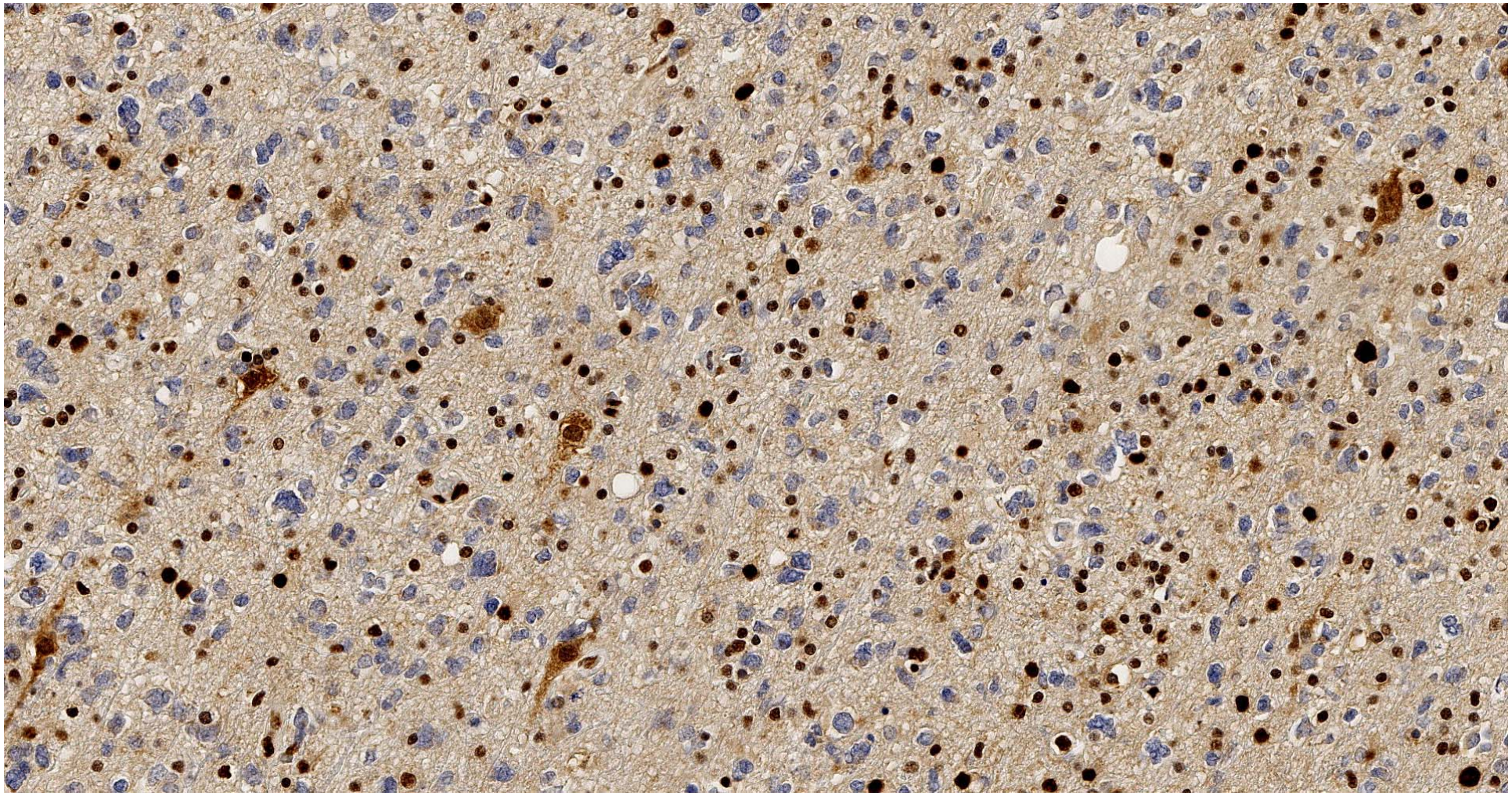
Clinical Neuropathology practice news 2-2014: *ATRX*, a new candidate biomarker in gliomas

Christine Haberler and Adelheid Wöhrer

Institute of Neurology, Medical University of Vienna, Austria

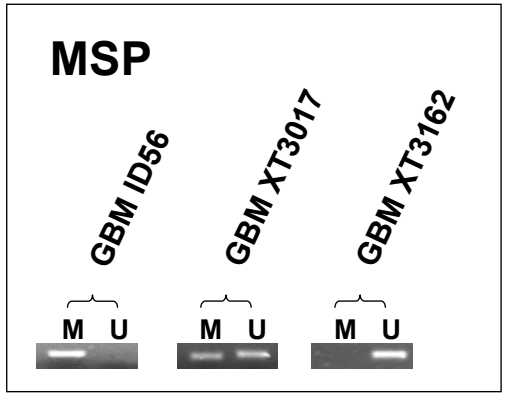
ISSN 0722-5091

ATRX



- Haberler C et al. Clin Neuropathol. 2014

MGMT



40-90% O, A y OA: II y III
40-60% GBM 2º
40% GBM 1º

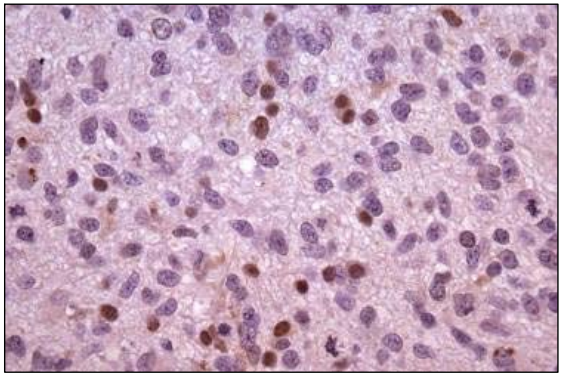
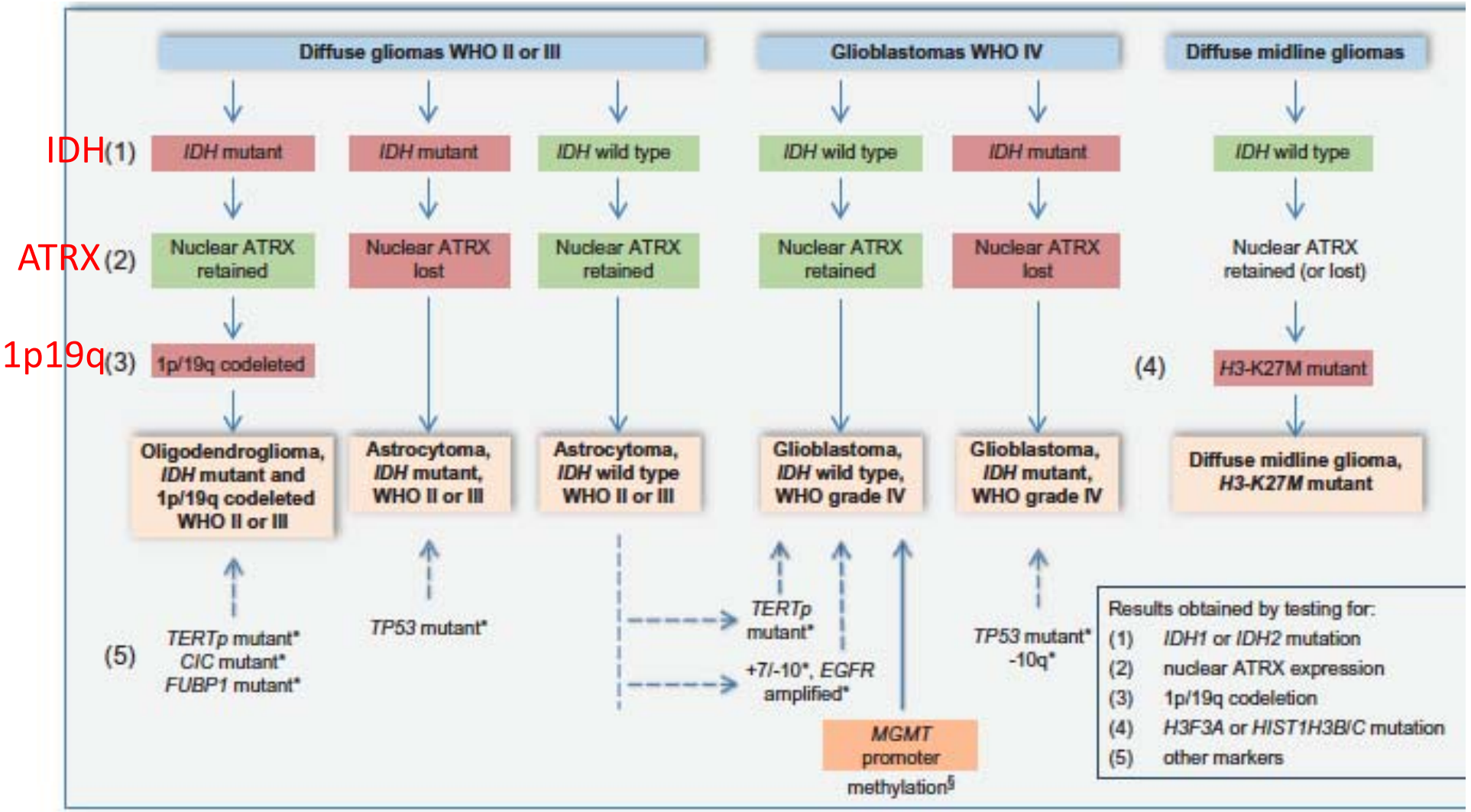


Table 2. Frequently asked questions in the molecular neuro-oncology of gliomas in adulthood

***MGMT* promoter methylation**	
Can I use the *MGMT* status for diagnostic purposes?	No.
Is the *MGMT* status homogeneous within gliomas?	Yes.
Does the *MGMT* status change in the course of disease?	No. Most gliomas show the same *MGMT* status at recurrence.
Can I use the *MGMT* status for prognostic purposes?	Yes. *MGMT* promoter methylation is positively prognostic in anaplastic glioma patients receiving RT or chemotherapy or both (NOA-04, EORTC 26951).
Can I use the *MGMT* status as a predictive marker for clinical decision making?	Yes. *MGMT* promoter methylation predicts benefit from alkylating agent chemotherapy in glioblastoma (EORTC 26981) and is particularly useful in elderly glioblastoma patients (NOA-08, Nordic trial).

- Weller M et al. NeuroOncol 2012
- Esteller M et al. N Engl J Med. 2000
- Hegi ME et al. N Engl J Med. 2005
- Preusser M et al. Brain Pathology 2008



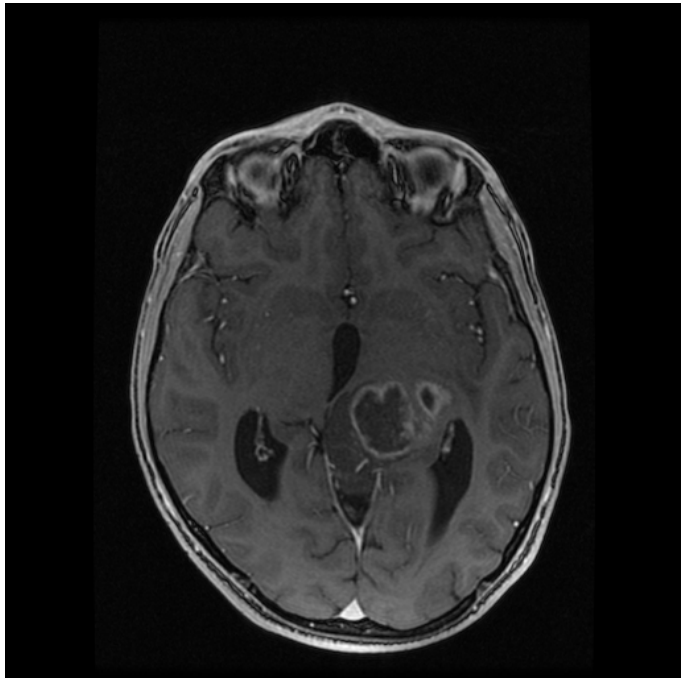
- Masui K, Mischel PS, Reifenberger G. Handb Clin Neurol. 2016

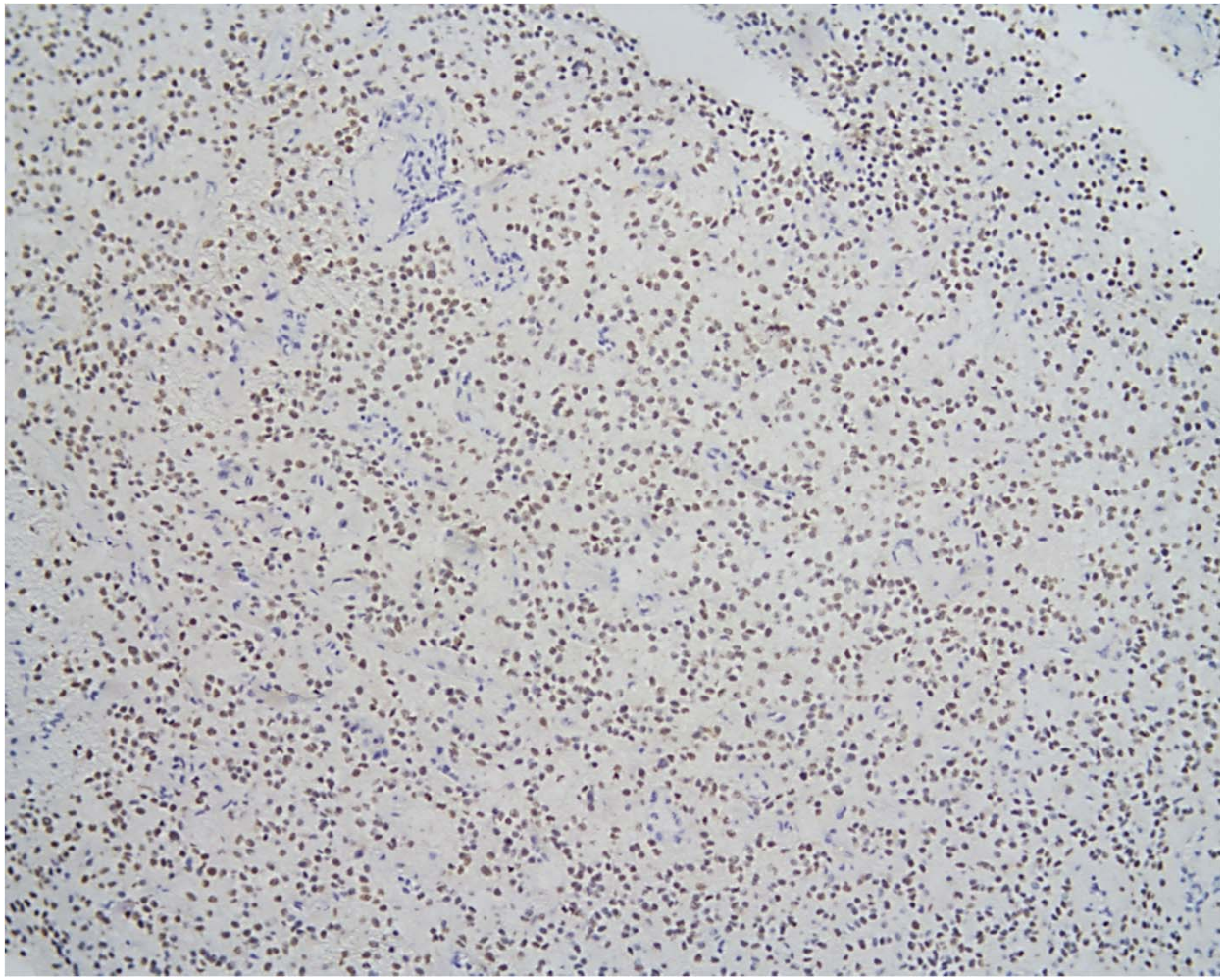
Glioma Difuso de Línea Media Histona 3. K27M

- Predominantemente histología astrocitaria pero variada.
- No depende el grado, el pronóstico lo da la mutación (grado IV).
- Diencéfalo, tronco, médula espinal. Incluye glioma difuso del puente (DIPG)
- Sobre todo jóvenes (pero amplio rango edad).
- Inmunohistoquímica

- Masui K, Mischel PS, Reifenberger G. Handb Clin Neurol. 2016

Glioma Difuso de Línea Media
Histona 3. K27M





Anticuerpo anti-Histona 3. K27M

- Masui K, Mischel PS, Reifenberger G. Handb Clin Neurol. 2016

Clasificación WHO 2016
Otros cambios en Gliomas

- Variante Histona 3. G34 R/V mas como GBM hemisférico, pero no se ha incluido como variante (jóvenes, supratentorial, pronóstico intermedio) .

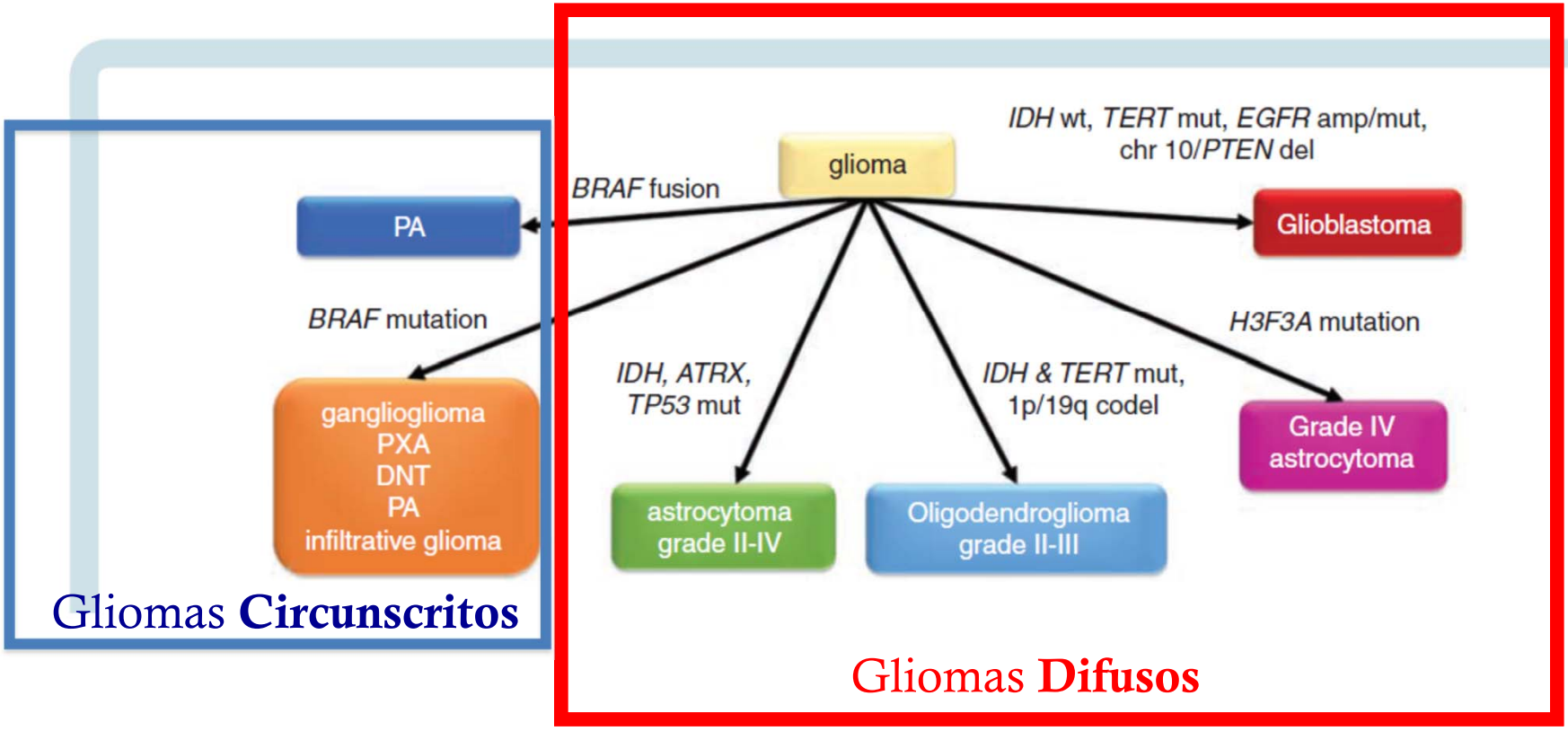
Clasificación WHO 2016

GLIOMAS

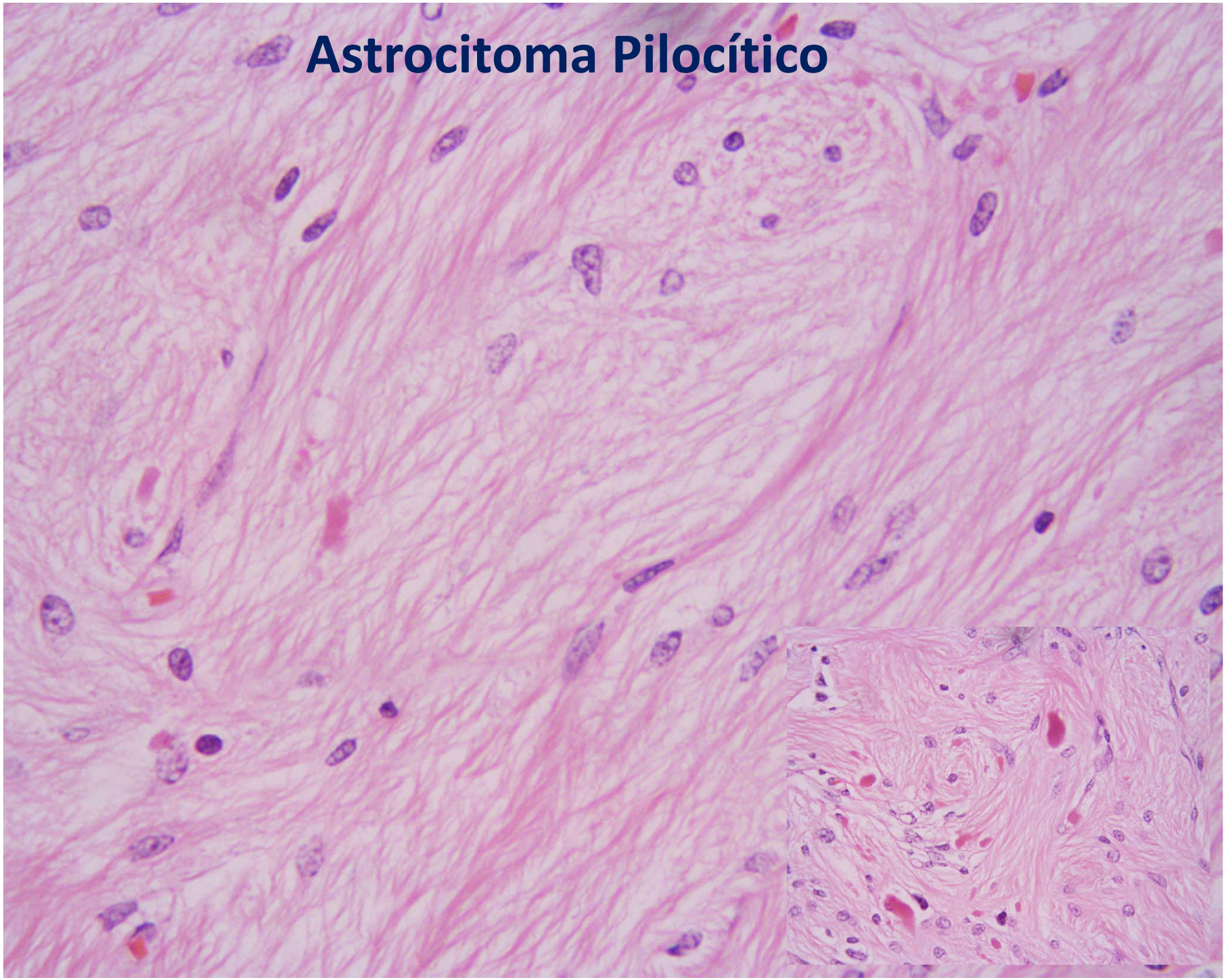
(Circunscritos)

1498 Neuro-Oncology
21(12), 1498–1508, 2019 | doi:10.1093/neuonc/noz119 | Advance Access date 4 July 2019

The medical necessity of advanced molecular testing in the diagnosis and treatment of brain tumor patients



Astrocitoma Pilocítico



Fusión BRAF

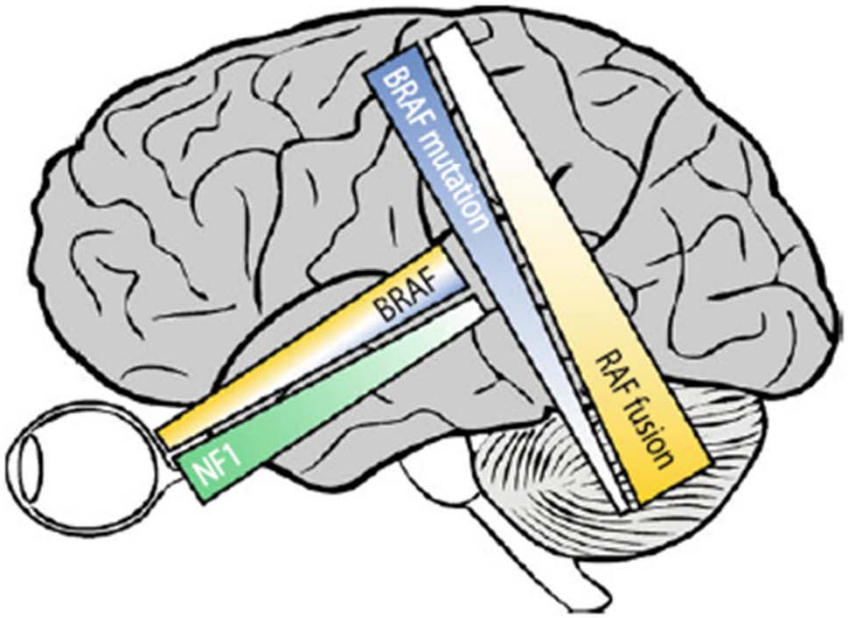
60-80% A. Pilocíticos

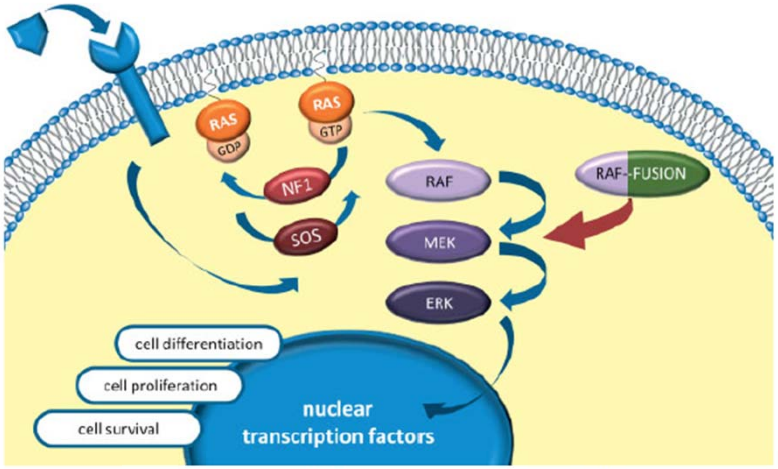
Priority

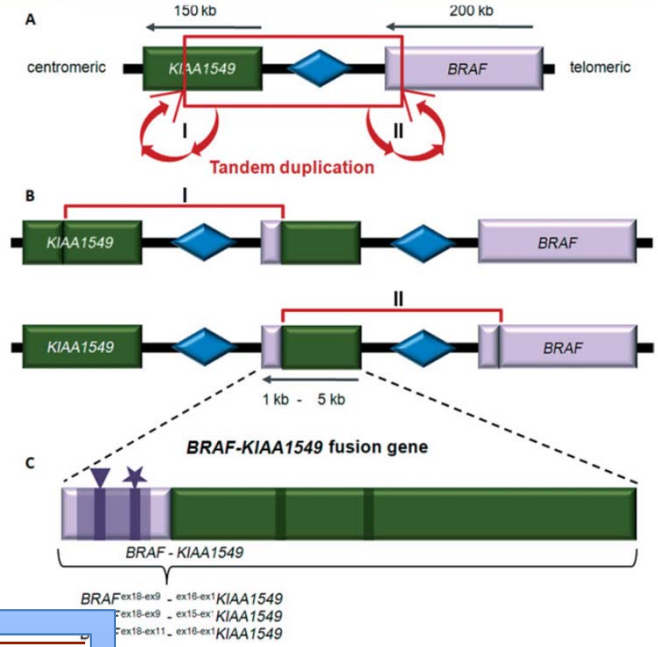
Tandem Duplication Producing a Novel Oncogenic *BRAF* Fusion Gene Defines the Majority of Pilocytic Astrocytomas

David T.W. Jones,[1] Sylvia Kocialkowski,[1] Lu Liu,[1] Danita M. Pearson,[1] L. Magnus Bäcklund,[2] Koichi Ichimura,[1] and V. Peter Collins[1]

[1]Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom and [2]Department of Oncology-Pathology, Karolinska Hospital, Stockholm, Sweden







Genetic Alteration	Tumor	Diagnostic Value	Prognostic Value	Predictive Value	Most Common Methods
BRAF fusion	>75% of PAs (mostly fusions), ~50% PMA	Fusion suggests a PA or PMA	Fusion may be a favorable marker	No specific therapy to date; anti-MEK clinical trials ongoing	PCR breakpoint analysis, FISH

- Jones DT et al. Cancer Res. 2008
- Jeuken J et al., J Pathol. 2010

BRAF –Mutación V600E

BRAF

Genetic Alteration	Tumor	Diagnostic Value	Prognostic Value	Predictive Value	Most Common Methods
BRAF V600E mutation	80% PXA; 25% GG	Mutation suggests PXA or GG (although not a perfect discriminator from PAs or diffusely infiltrative gliomas)	*V600E* may be unfavorable	No specific therapy to date; anti-*BRAF V600E* clinical trials ongoing	PCR and sequencing, IHC

Acta Neuropathol (2011) 121:397–405
DOI 10.1007/s00401-011-0802-6

ORIGINAL PAPER

Analysis of *BRAF* V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma

Genevieve Schindler · David Capper · Jochen Meyer · Wibke Janzarik · Heymut Omran · Christel Herold-Mende · Kirsten Schmieder · Pieter Wesseling · Christian Mawrin · Martin Hasselblatt · David N. Louis · Andrey Korshunov · Stefan Pfister · Christian Hartmann · Werner Paulus · Guido Reifenberger · Andreas von Deimling

Received: 11 January 2011 / Revised: 18 January 2011 / Accepted: 18 January 2011 / Published online: 29 January 2011

Table 2 *BRAF*^{V600E} mutation according to tumor location

Tumor entity (*N*)	Location	*N* (*BRAF*^{V600E}; %)
PA I (94)	Cerebral hemisphere	16 (2; 13%)[a]
	Non-temporal	2 (0)
	Temporal	2 (0)
	Cerebellar	53 (1; 2%)[a]
	Brain stem	10 (1; 10%)
	Diencephalic	12 (4; 33%)
	Optic tract	2 (0)
	Spinal	1 (1)
GG (69)	Cerebral hemisphere	59 (14; 24%)
	Non-temporal	18 (3; 17%)
	Temporal	39 (11; 28%)
	Cerebellar	5 (2)
	Brain stem	3 (0)
	Spinal	2 (0)
PXA (29)	Cerebral hemisphere	27 (16; 59%)
	Non-temporal	6 (4)
	Temporal	17 (11; 65%)
	Cerebellar	1 (0)[a]
	Diencephalic	1 (0)

Diencephalic tumors include chiasmic/hypothalamic, thalamic and pineal region lesions

PA I pilocytic astrocytoma, *GG* ganglioglioma WHO grade I and III, *PXA* pleomorphic xanthoastrocytoma and pleomorphic xanthoastrocytoma with anaplasia

[a] One additional case had a three bp insertion resulting in BRAF p.T599_V600insT

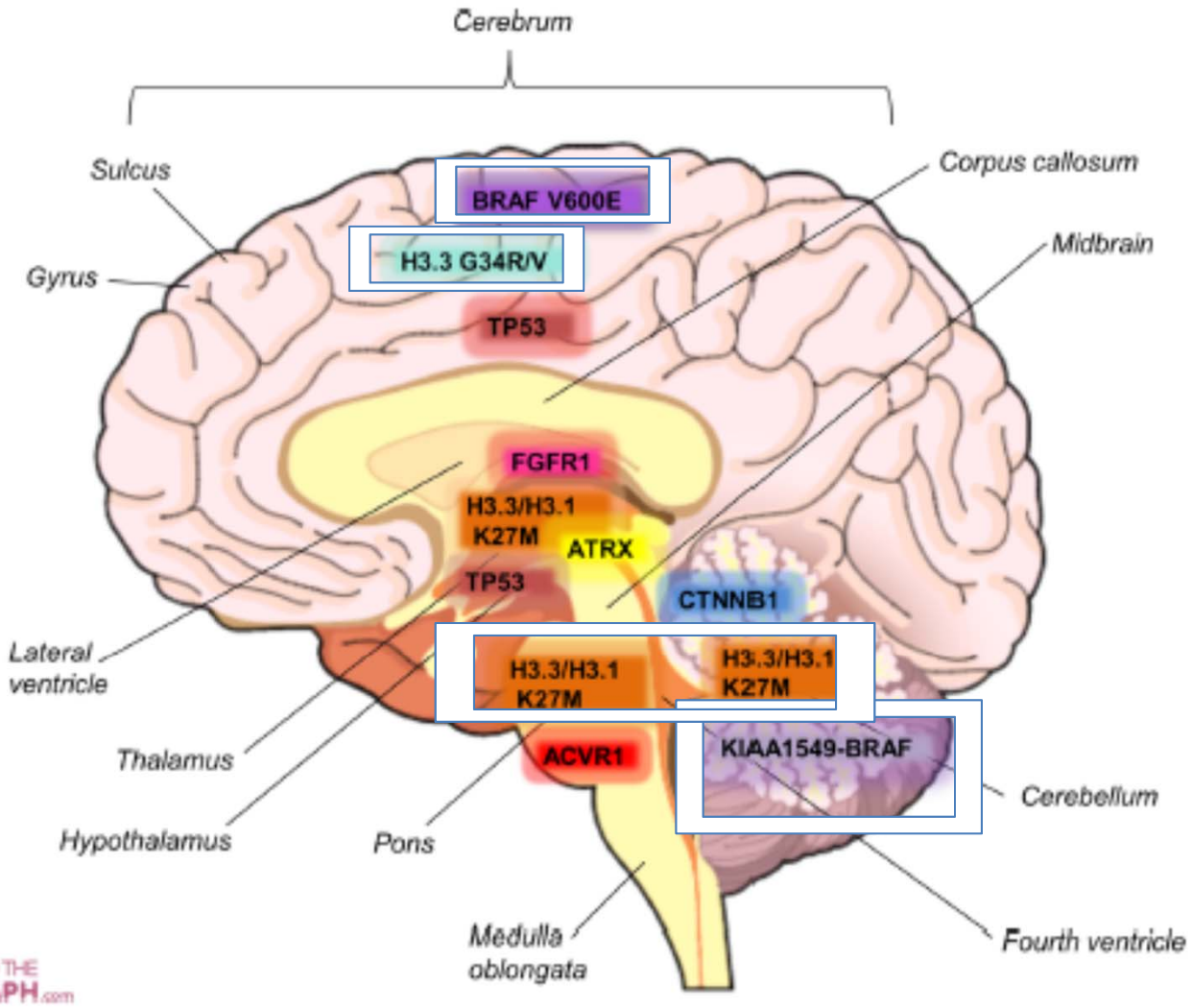


Fig. 1 Mutations associated with different neuroanatomical sites in pediatric brain tumors. Pediatric high-grade gliomas are distinguished into subgroups based on specific mutations that appear in different neuroanatomical sites. HGGs are frequently arising as DIPG in the pons and thalamus areas. *BRAF* mutations (*BRAF V600E*) and *H3* mutations (*G34R/V*) mainly characterize cerebral cortical tumors. *ACVR1* mutations are associated with *H3.1 K27M* and they are predominantly found in midline locations such as DIPG. In thalamic HGGs, *FGFR1* mutations are present, whereas *ATRX* mutations are seen in G34V/R tumors. Furthermore, *TP53* mutations are associated with *G34R/V* and *K27M* tumors while *CTNNB1* mutations are found in the area of cerebellum

Klonou A, et al. Neuromolecular Med. 2017

Published in final edited form as:
Nature. 2018 March 22; 555(7697): 469–474. doi:10.1038/nature26000.

DNA methylation-based classification of central nervous system tumours

A full list of authors and affiliations appears at the end of the article.
[#] These authors contributed equally to this work.

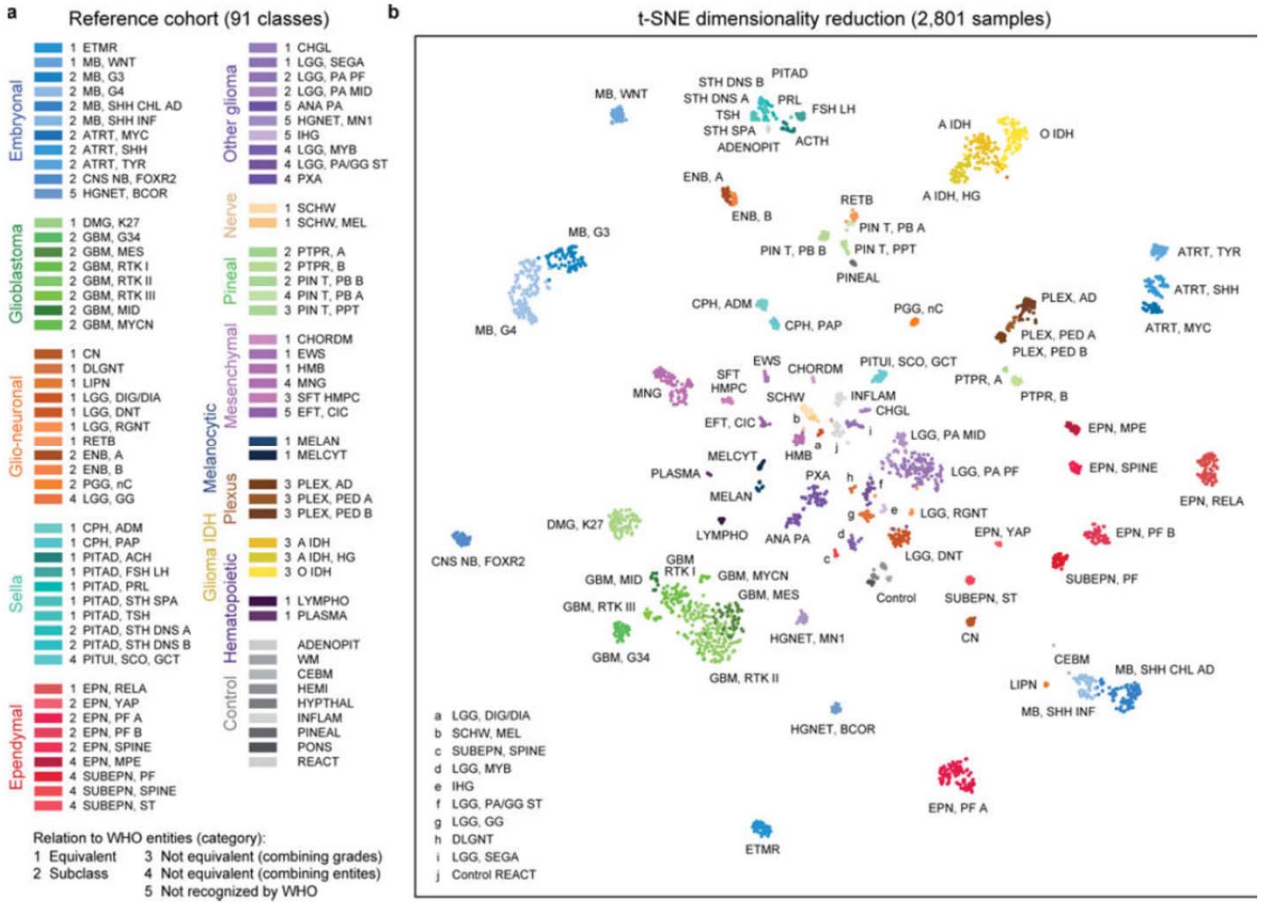


Figure 1 |. Establishing of the DNA methylation-based CNS tumour reference cohort.

Neuro-Oncology
20(5), 579–581, 2018 | doi:10.1093/neuonc/noy023 | Advance Access date 23 March 2018

Toward methylation-based classification of central nervous system tumors

Monika E. Hegi, Paul Kleihues, Patrick Y. Wen, and Mario L. Suvà

Department of Clinical Neurosciences, Lausanne University Hospital, Lausanne, Switzerland (M.E.H.); Medical Faculty, University of Zürich, Zürich, Switzerland (P.K.); Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA (P.Y.W.); Department of Pathology and Center for Cancer Research, Massachusetts General Hospital, Broad Institute of Harvard and MIT, Boston, Massachusetts, USA (M.L.S.)

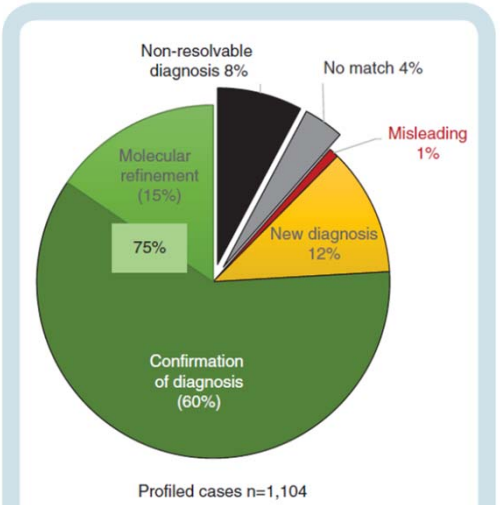
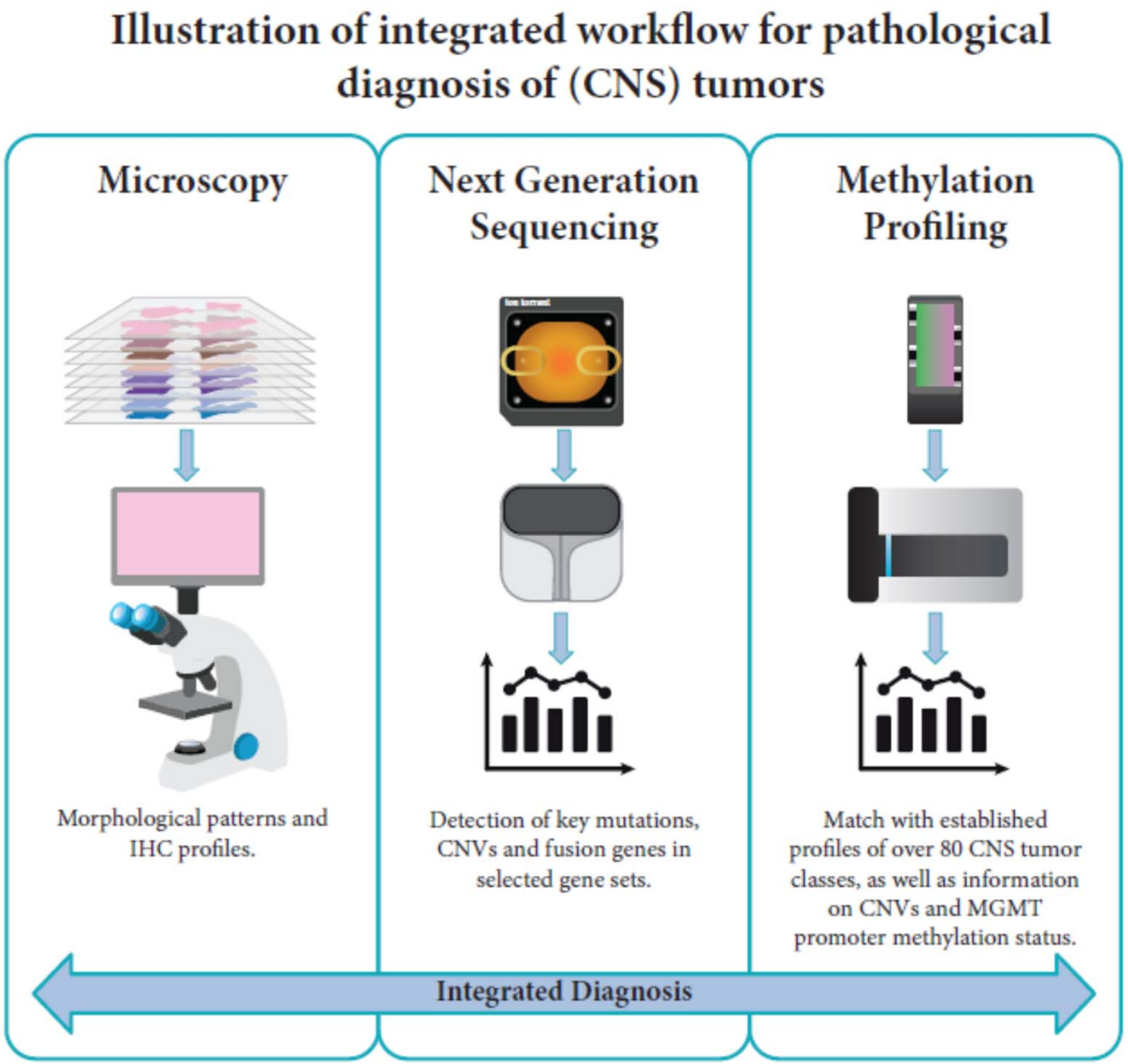


Fig. 1 Methylation-based classifier in prospective cohort of diagnostic samples. Adapted from Capper et al.[2]

- Capper et al. Nature. 2018
- Hegi et al. Neuro-Oncology 2018



- Kristensen BW. Ann Oncol. 2019

Muchas gracias

i+12
Instituto de Investigación
Hospital 12 de Octubre

Hospital Universitario
12 de Octubre

Madrid