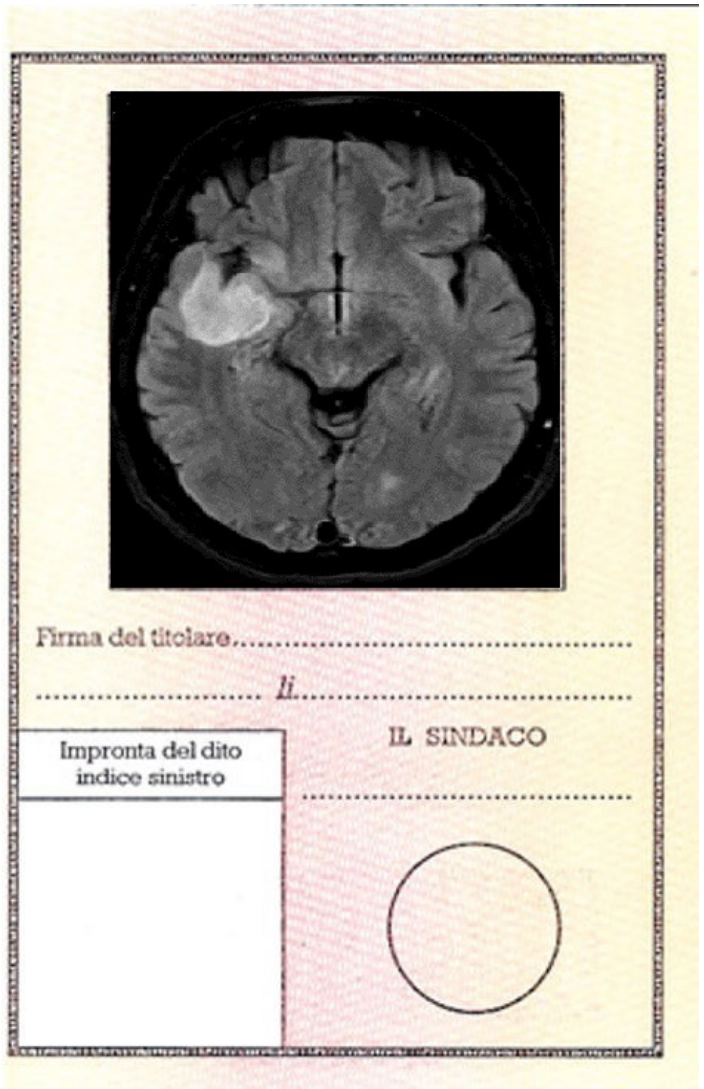
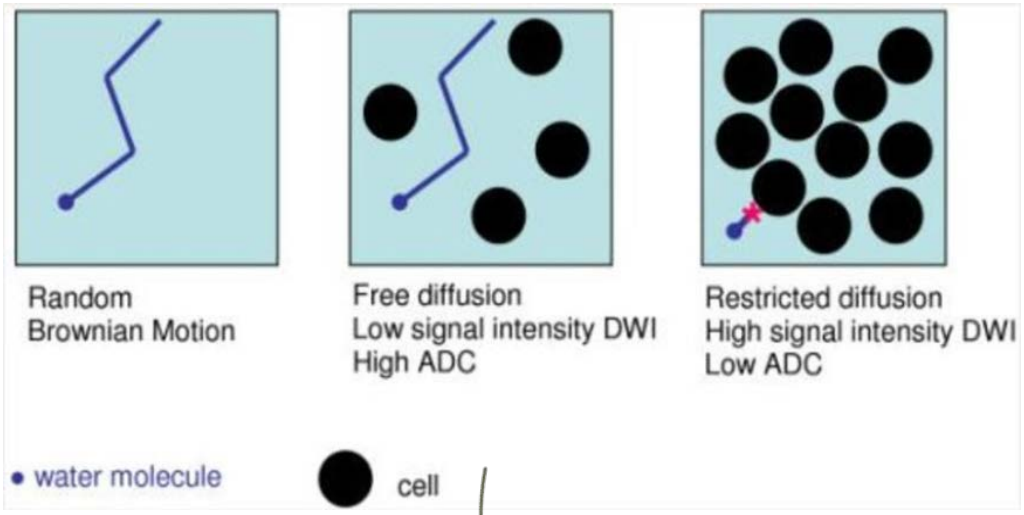
L'IMAGING MOLECOLARE NELLA DIAGNOSI E NELLA VALUTAZIONE DELLA RISPOSTA TERAPEUTICA: LOW GRADE

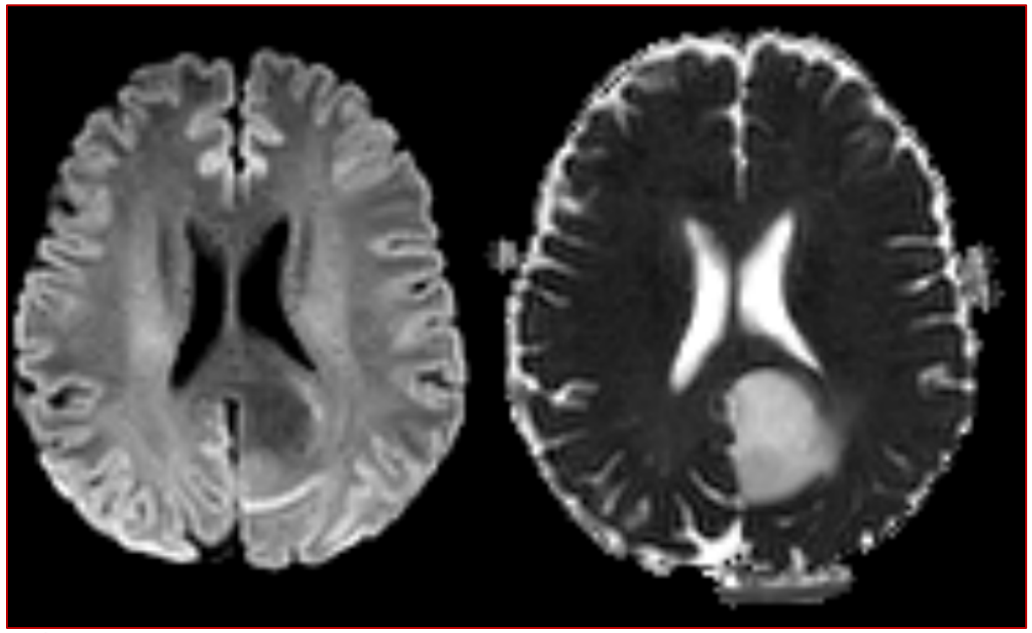
Dott.ssa Giulia Moltoni

GLIOMI DI BASSO GRADO: ID

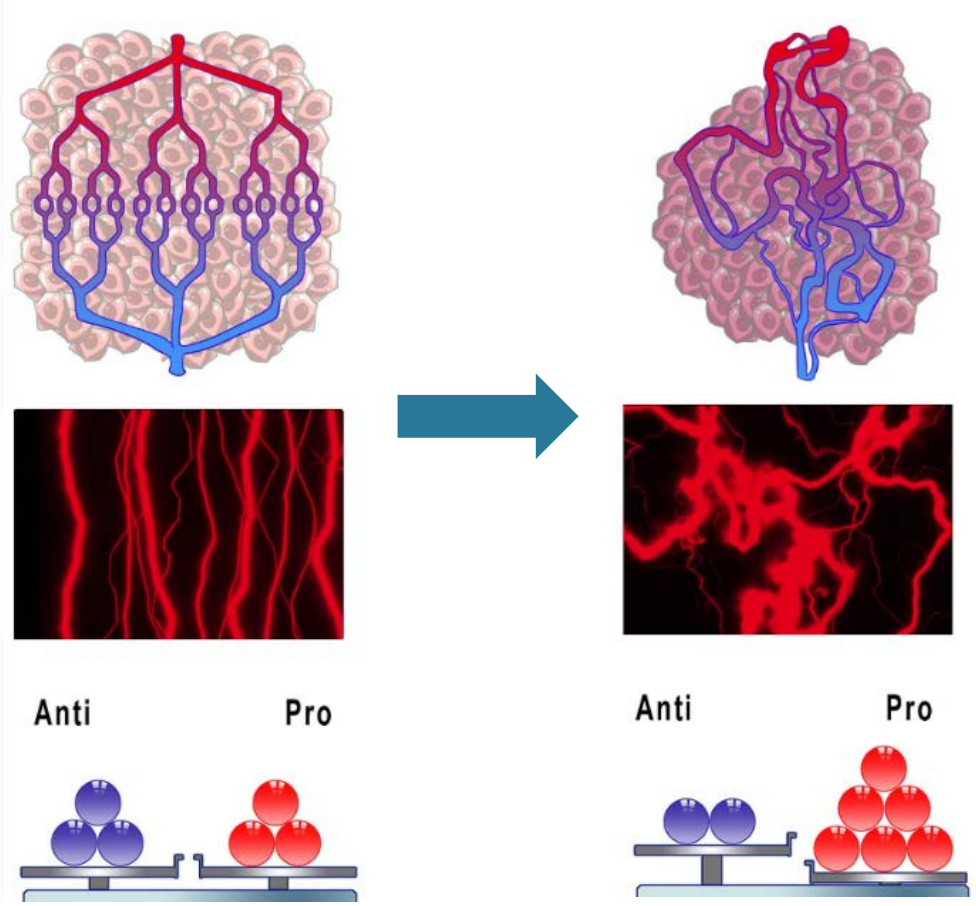


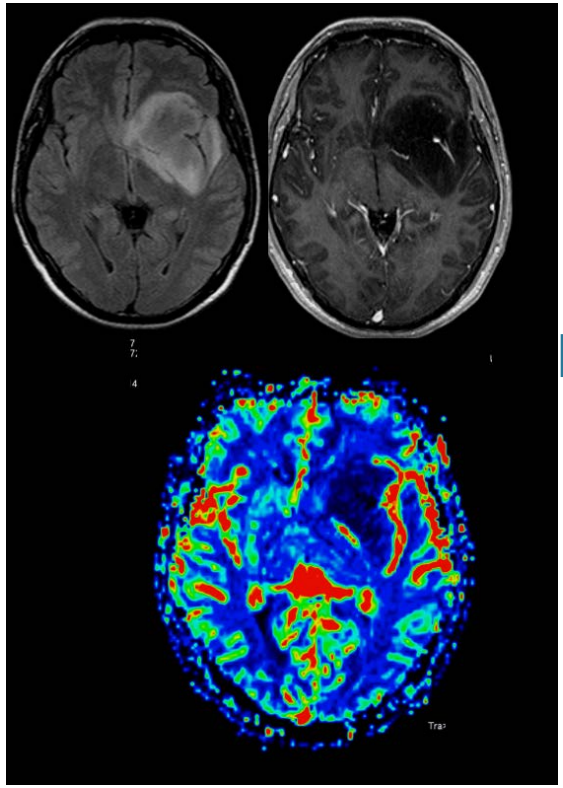
GLIOMI DI BASSO GRADO: BASSA CELLULARITÀ

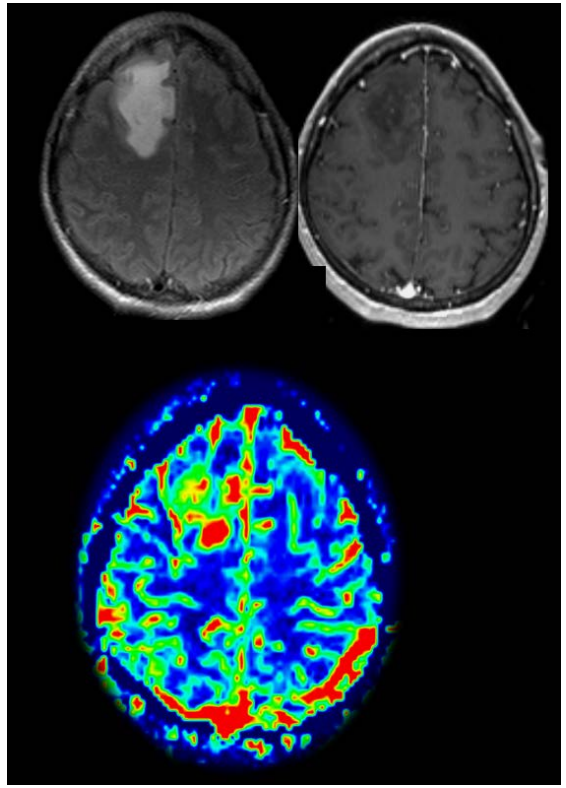




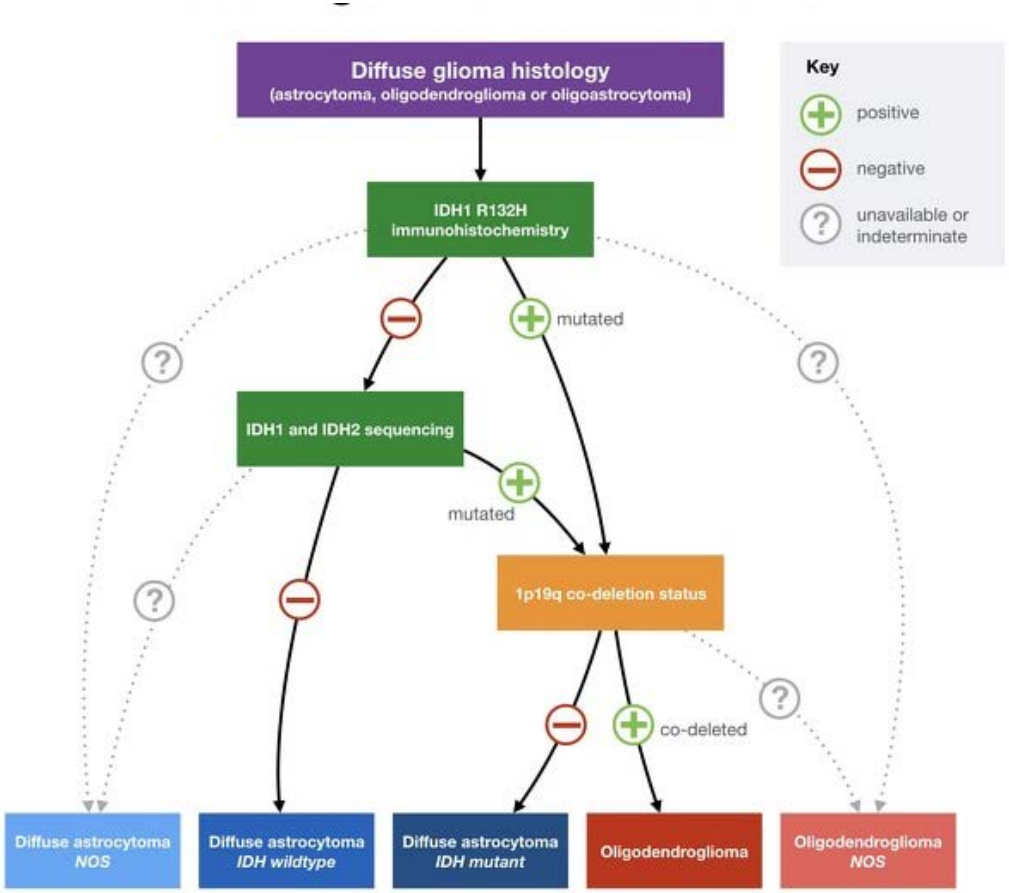
GLIOMI DI BASSO GRADO: ASSENZA DI NEOANGIOGENESI







GLIOMI DI BASSO GRADO: WHO 2016



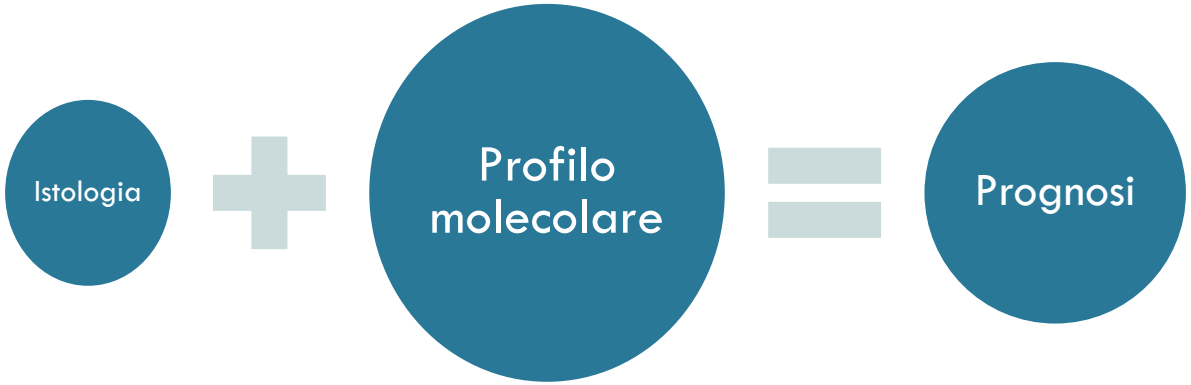
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3

Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

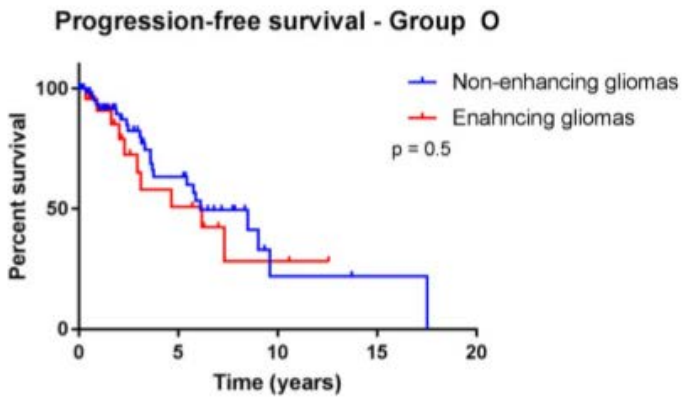
GLIOMI DI BASSO GRADO: PROFILO MOLECOLARE

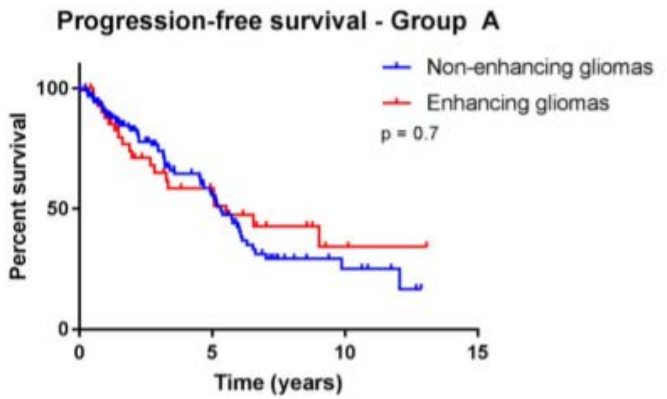
- **IDH mutato e 1p/19q codeleto ⇨ OLIGODENDROGLIOMA Sopravvivenza media: 12-14 anni**
- **IDH mutato, NO 1p/19q codelezione ⇨ ASTROCITOMA DIFFUSO Sopravvivenza media: 3-8 anni**
- **IDH wild type ⇨ LGG glioblastoma like Sopravvivenza media: 14 mesi**

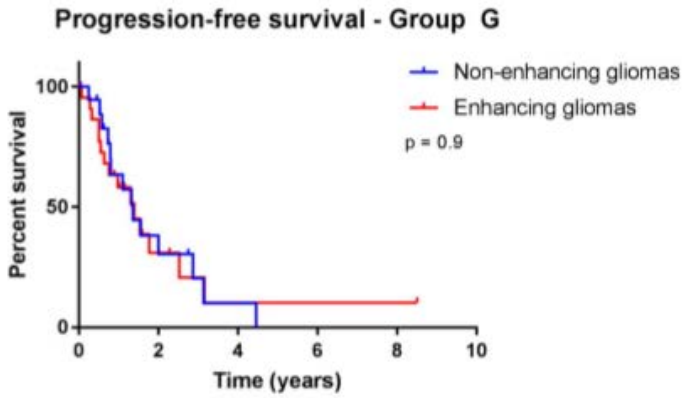
The Cancer Genome Atlas Research Network. N Engl J Med 372, 2481-2498 (2015)

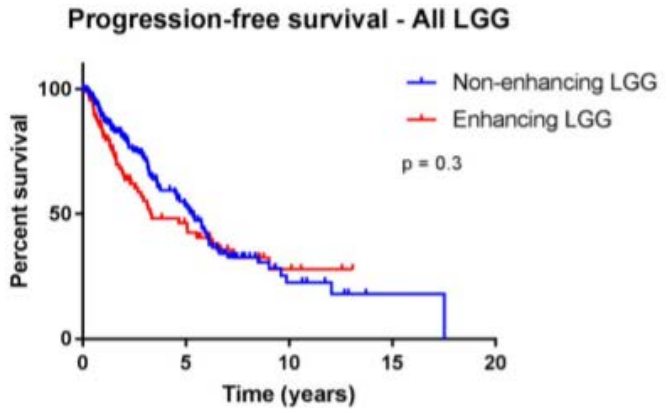


GLIOMI DI BASSI GRADI: MDC



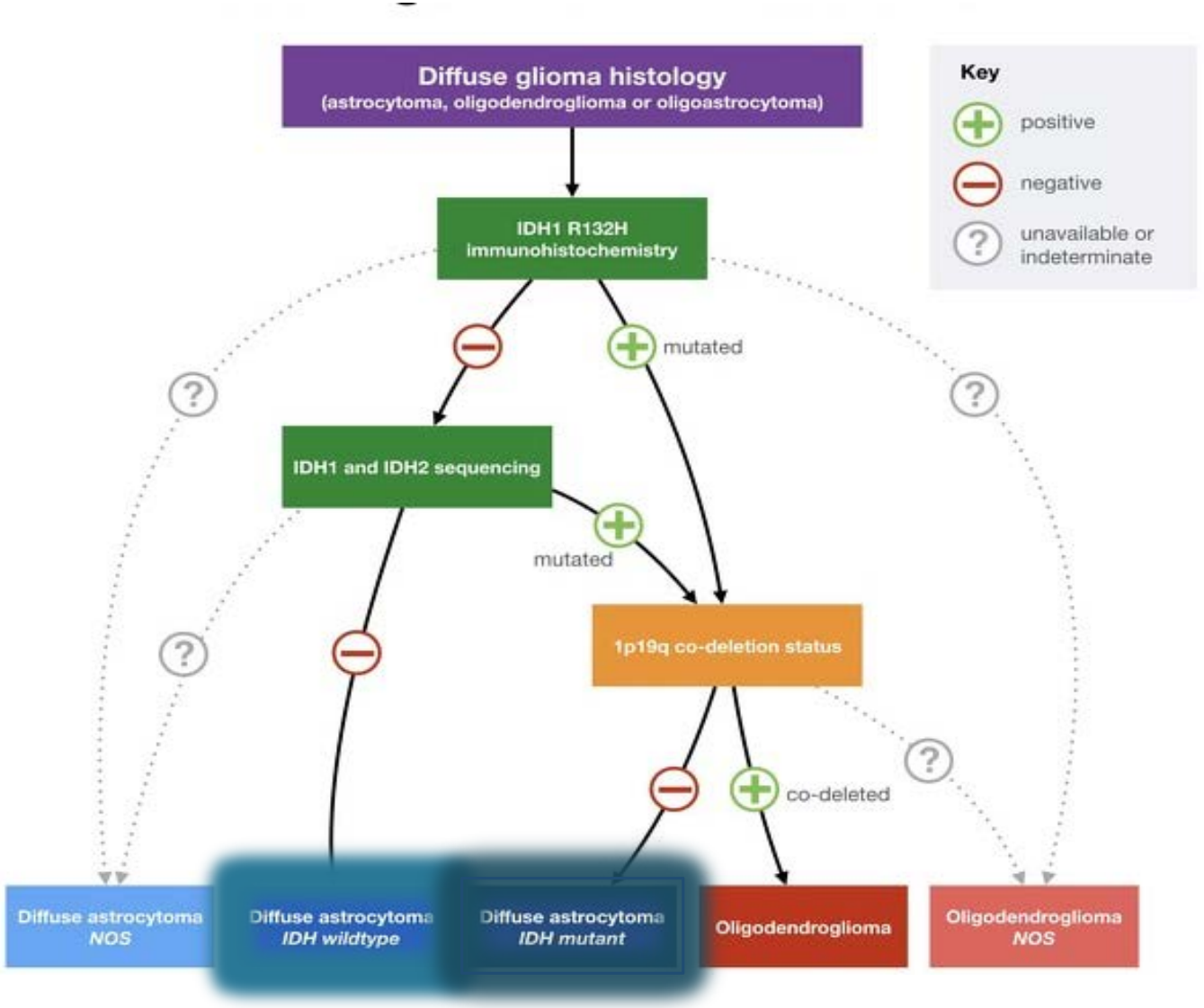






Juratli, Tummala et al, 2018, Journal of Neuro-Oncology

IMAGING MOLECOLARE: IDH MUTATO O IDH WT?



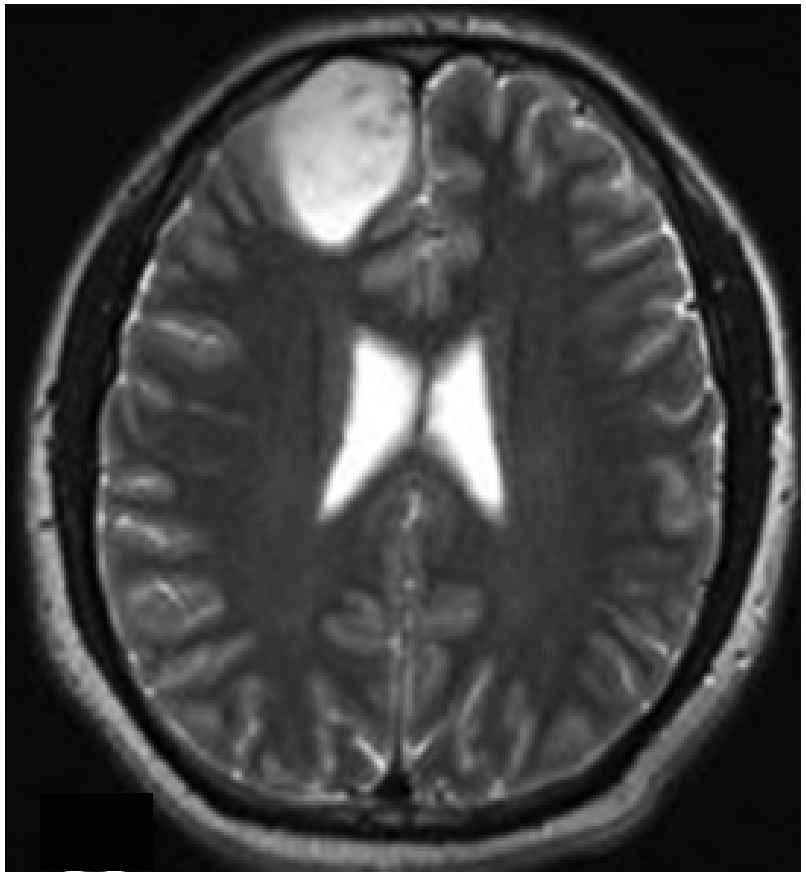
IMAGING MOLECOLARE: LOCALIZZAZIONE

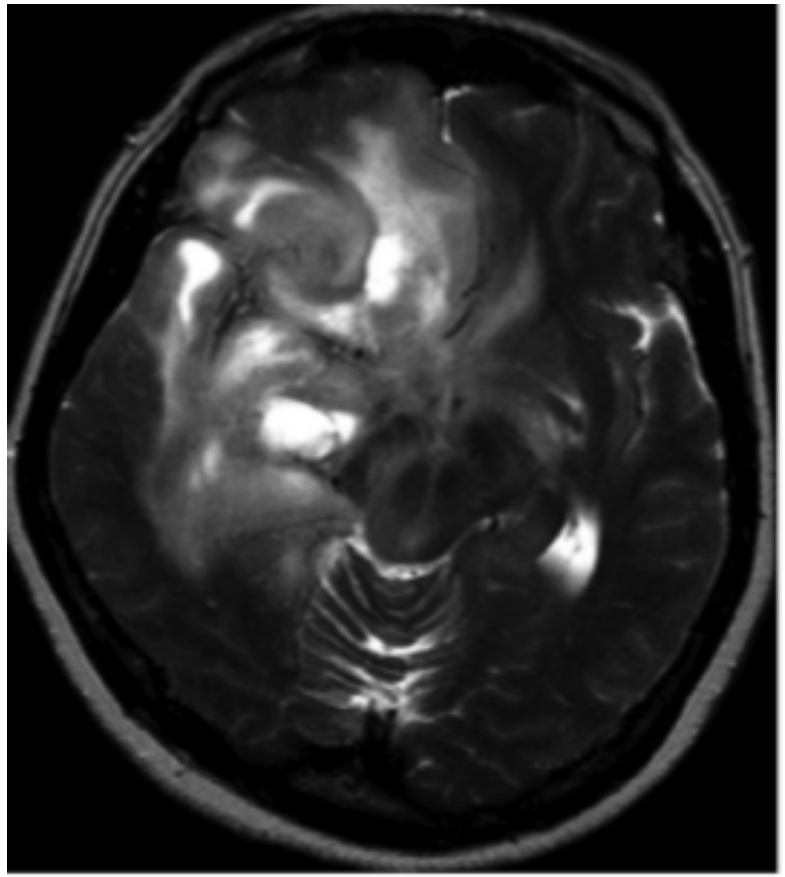
Imaging Correlates of Adult Glioma Genotypes[1]

Radiology

IDH - MUT

Frontale, singolo lobo





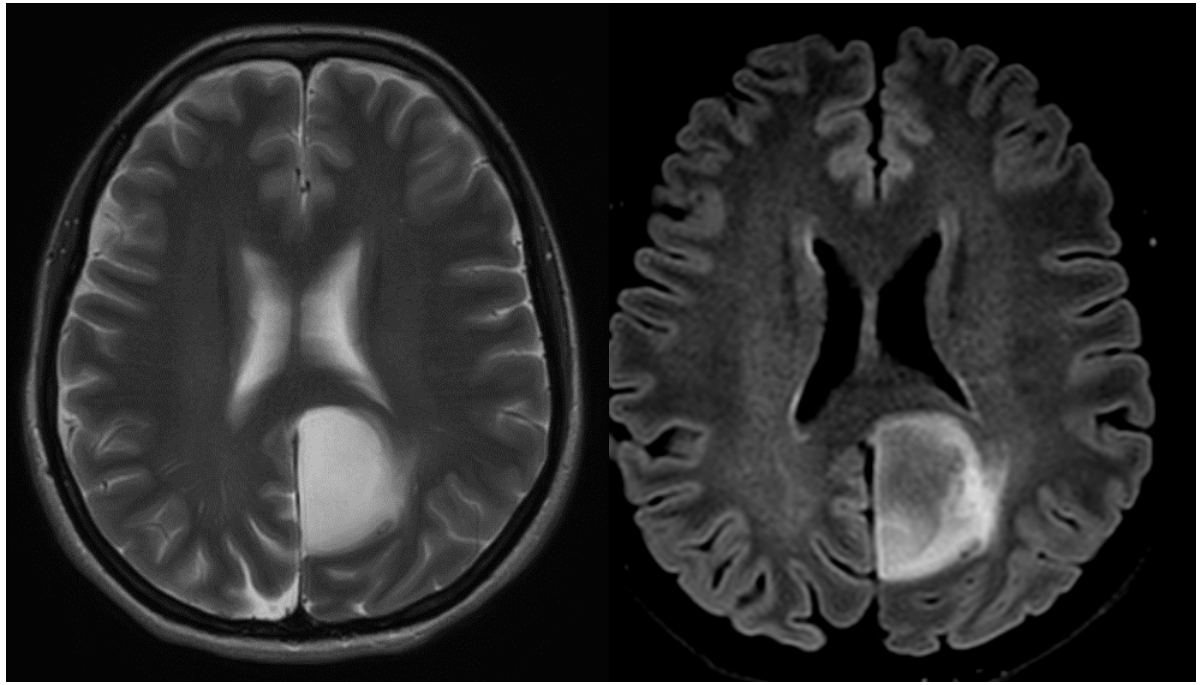
IDH - WT

Fronto-temporo-insulare, maggiormente infiltrativo

IMAGING MOLECOLARE: T2/ FLAIR MISMATCH

- T2: omogenea iperintensità
- FLAIR: ipointensità con rim iperintenso periferico

VPP: 100% per glioma di basso grado IDH-mut non codeleto



Cancer Therapy: Clinical

T2–FLAIR Mismatch, an Imaging Biomarker for IDH and 1p/19q Status in Lower-grade Gliomas: A TCGA/TCIA Project

Sohil H. Patel, Laila M. Poisson, Daniel J. Brat, Yueren Zhou, Lee Cooper, Matija Snuderl, Cheddhi Thomas, Ana M. Franceschi, Brent Griffith, Adam E. Flanders, John G. Golfinos, Andrew S. Chi, and Rajan Jain

DOI: 10.1158/1078-0432.CCR-17-0560 Published October 2017

IMAGING MOLECOLARE: T2/FLAIR MISMATCH

Neuro Oncol. 2018 Sep 3;20(10):1393-1399. doi: 10.1093/neuonc/noy048.

The T2-FLAIR mismatch sign as an imaging marker for non-enhancing IDH-mutant, 1p/19q-intact lower-grade glioma: a validation study.

Broen MPG[1,2], Smits M[3], Wijnenga MMJ[2], Dubbink HJ[4], Anten MHME[1], Schijns OEMG[5], Beckervordersandforth J[6], Postma AA[7], van den Bent MJ[2].

Table 1 Characteristics of the LGG cohort

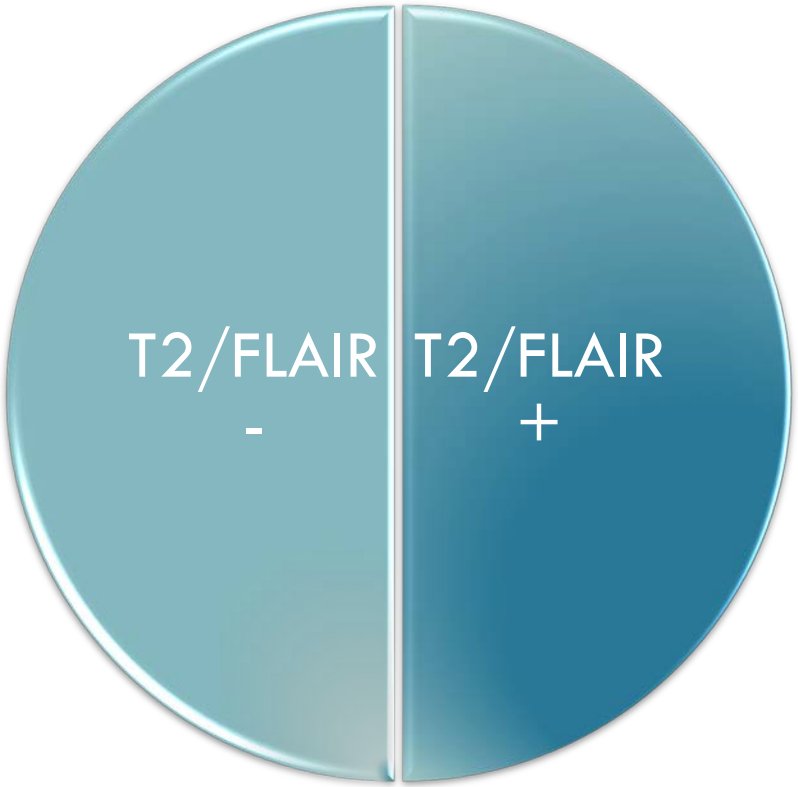
	EMC1 *N* = 121	EMC2 *N* = 26	MUMC+ *N* = 7	Total *N* = 154	T2-FLAIR mismatch sign (*N*)
Male (*N*)	65	18	3	86 (55.8%)	
Mean age at diagnosis, y (range)	43 (20–82)	46 (27–74)	41 (24–52)	43 (20–82)	
Diffuse astrocytoma, *IDH*-mutant (WHO grade II)	59	5	6	70 (45.5%)	34
Diffuse oligodendroglioma, *IDH*-mutant, 1p/19q codeleted (WHO grade II)	50	12	1	63 (40.9%)	0
Anaplastic astrocytoma, *IDH*-mutant (WHO grade III)	0	5	0	5 (3.2%)	4
Anaplastic oligodendroglioma, *IDH*-mutant, 1p/19q codeleted (WHO grade III)	0	4	0	4 (2.6%)	0
IDH-wildtype, GBM-like	12	0	0	12 (7.8%)	0

- 100% VPP per identificare astrocitoma IDH-mutato
- VPN del 68%
- sensibilità del 51%
- specificità del 100%
- In nessuno dei glioma di basso grado IDH-wildtype, era presente il mismatch.

IMAGING MOLECOLARE: T2/ FLAIR MISMATCH

IDH-mutato, no-codeleto:

- specificità del 100%
- sensibilità del 51% ?



IPOTESI:
Sottogruppo molecolare con aumento delle proteine del pathway di mTOR

Patel et al, 2017, Clinical Cancer Research

IMAGING MOLECOLARE: CRITERI CLINICO-RADIOLOGICI

IDH MUTATO:

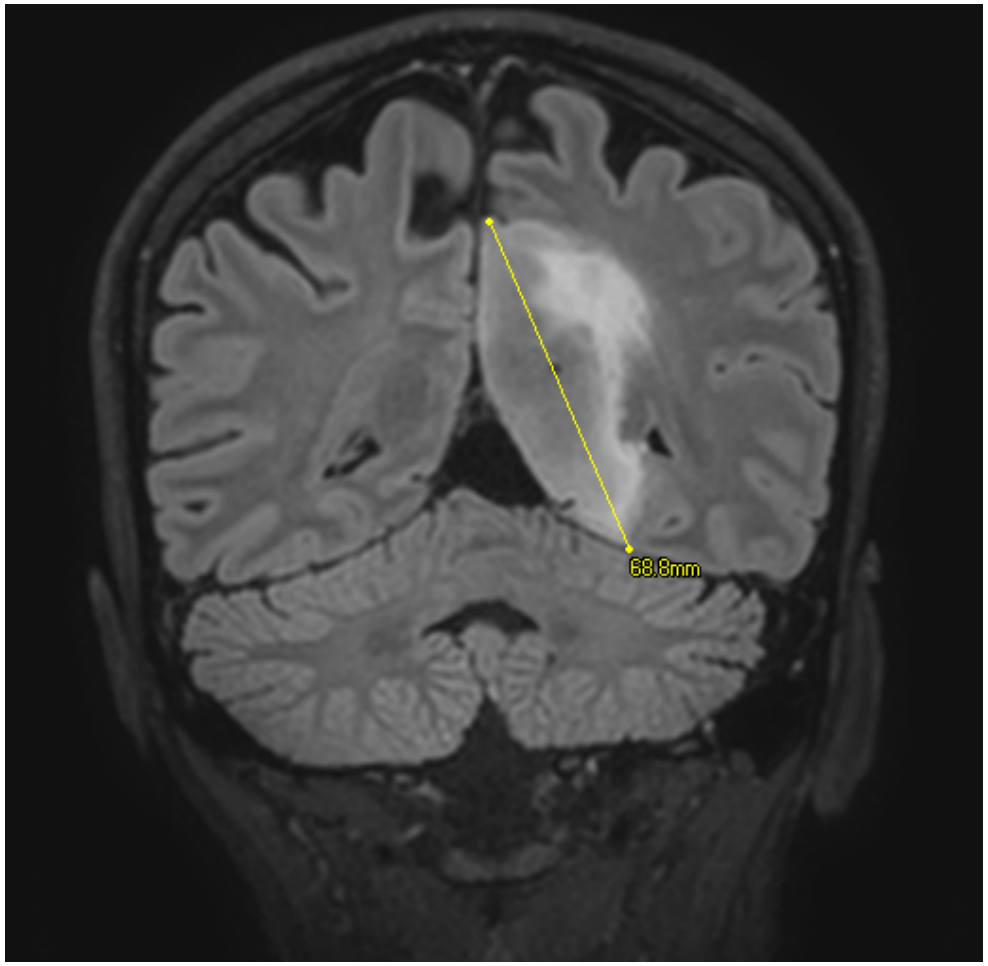
1. Presenza del mismatch T2-FLAIR
2. Lesioni di grandi dimensioni, diametro massimo > 6 cm
3. Età del paziente < 40 anni.

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-018-03034-6

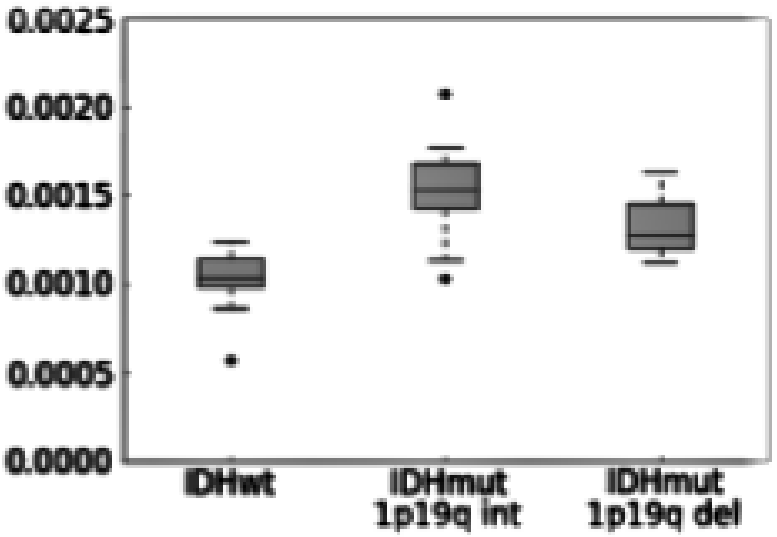
CLINICAL STUDY

Radiographic assessment of contrast enhancement and T2/FLAIR mismatch sign in lower grade gliomas: correlation with molecular groups

Tareq A. Juratli[1,2] · Shilpa S. Tummala[1] · Angelika Riedl[2] · Dirk Daubner[3] · Silke Hennig[2] · Tristan Penson[1] · Amir Zolal[2] · Christian Thiede[4] · Gabriele Schackert[2] · Dietmar Krex[2] · Julie J. Miller[1,5] · Daniel P. Cahill[1,6]



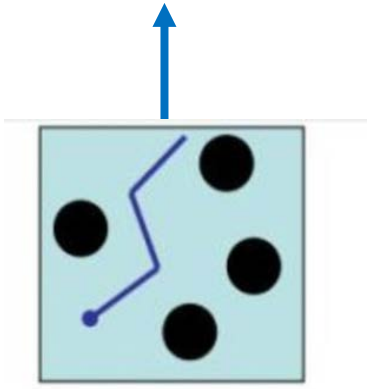
IMAGING MOLECOLARE: DWI/ADC



Apparent diffusion coefficient for molecular subtyping of non-gadolinium-enhancing WHO grade II/III glioma: volumetric segmentation versus two-dimensional region of interest analysis

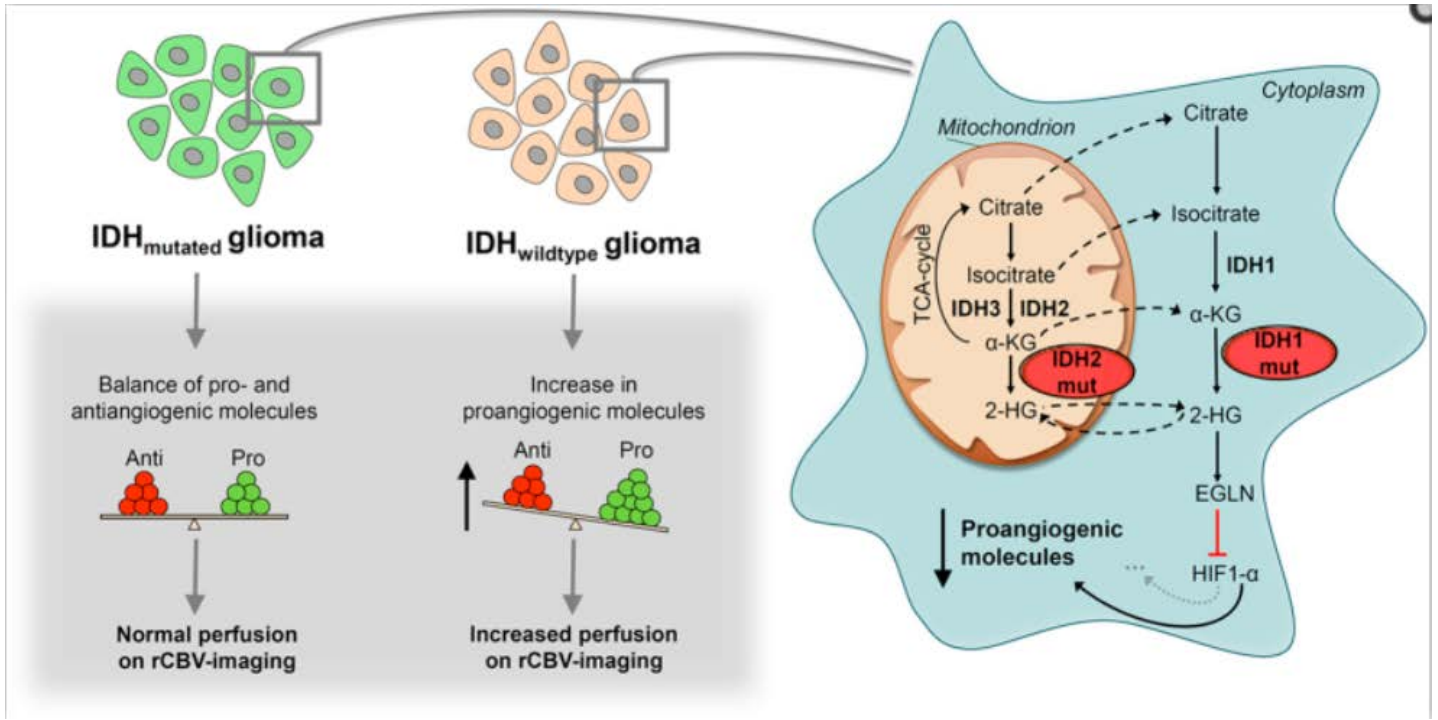
S. C. Thust[1,2,3] · S. Hassanein[1,3] · S. Bisdas[1,3] · J. H. Rees[4] · H. Hyare[1,2] · J. A. Maynard[2] · S. Brandner[5] · C. Tur[6] · H. R. Jäger[1,2,3] · T. A. Yousry[1,3] · L. Mancini[1,3]

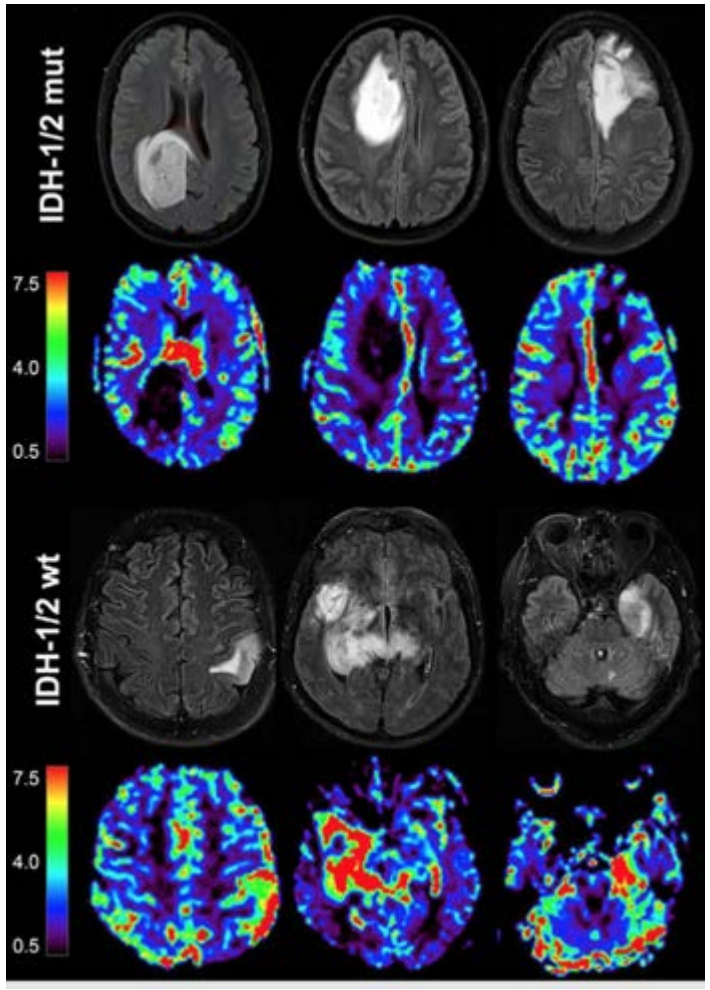
Received: 17 October 2017 / Revised: 26 December 2017 / Accepted: 23 January 2018 / Published online: 23 March 2018



BASSA CELLULARITÀ : BASSA AGGRESSIVITÀ

IMAGING MOLECOLARE: PWI





Sci Rep. 2015 Nov 5;5:16238. doi: 10.1038/srep16238.

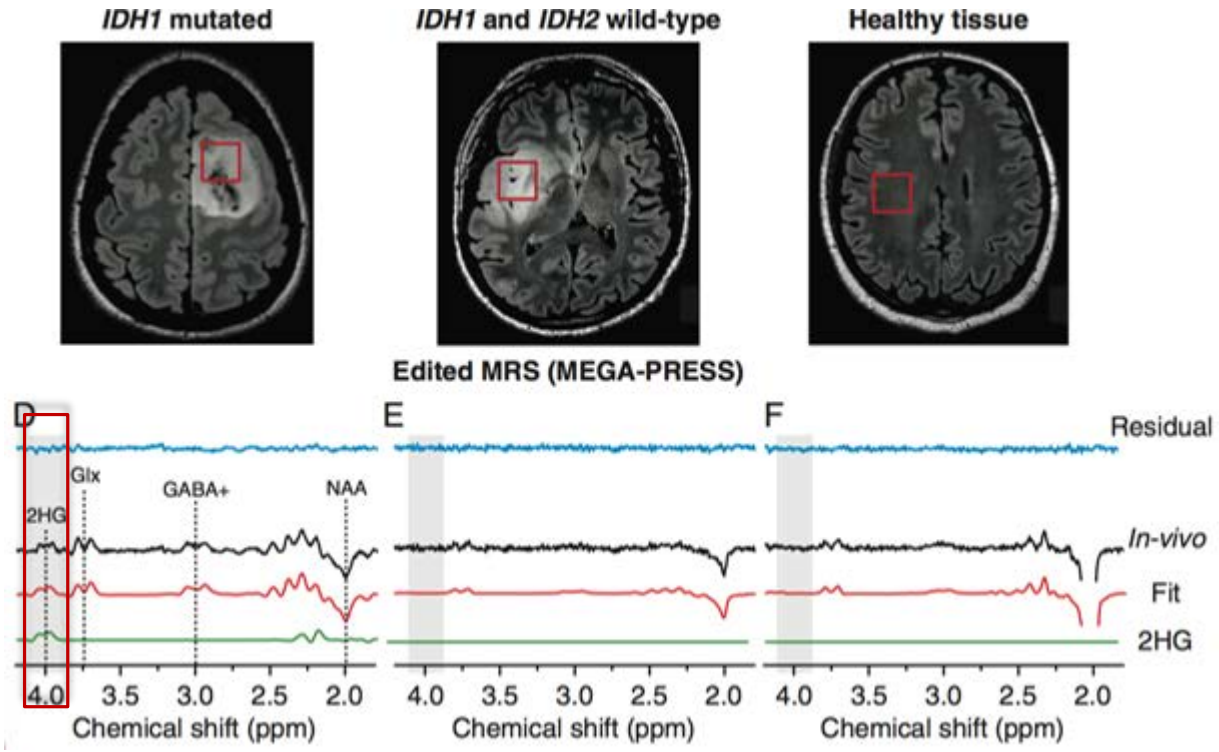
IDH mutation status is associated with a distinct hypoxia/angiogenesis transcriptome signature which is non-invasively predictable with rCBV imaging in human glioma.

Kickingereder P[1], Sahm F[2,3], Radbruch A[1,4], Wick W[5,6], Heiland S[1], Deimling Av[2,3], Bendszus M[1], Wiestler B[1,5,6].

IMAGING MOLECOLARE: MRS

La mutazione dell'IDH si associa all'accumulo di 2-idrossiglutarato (2HG)

Oncometabolita potenzialmente riconoscibile in MRS a 3T



Nat Med. 2012 Jan 26;18(4):624-9. doi: 10.1038/nm.2682.

2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas.

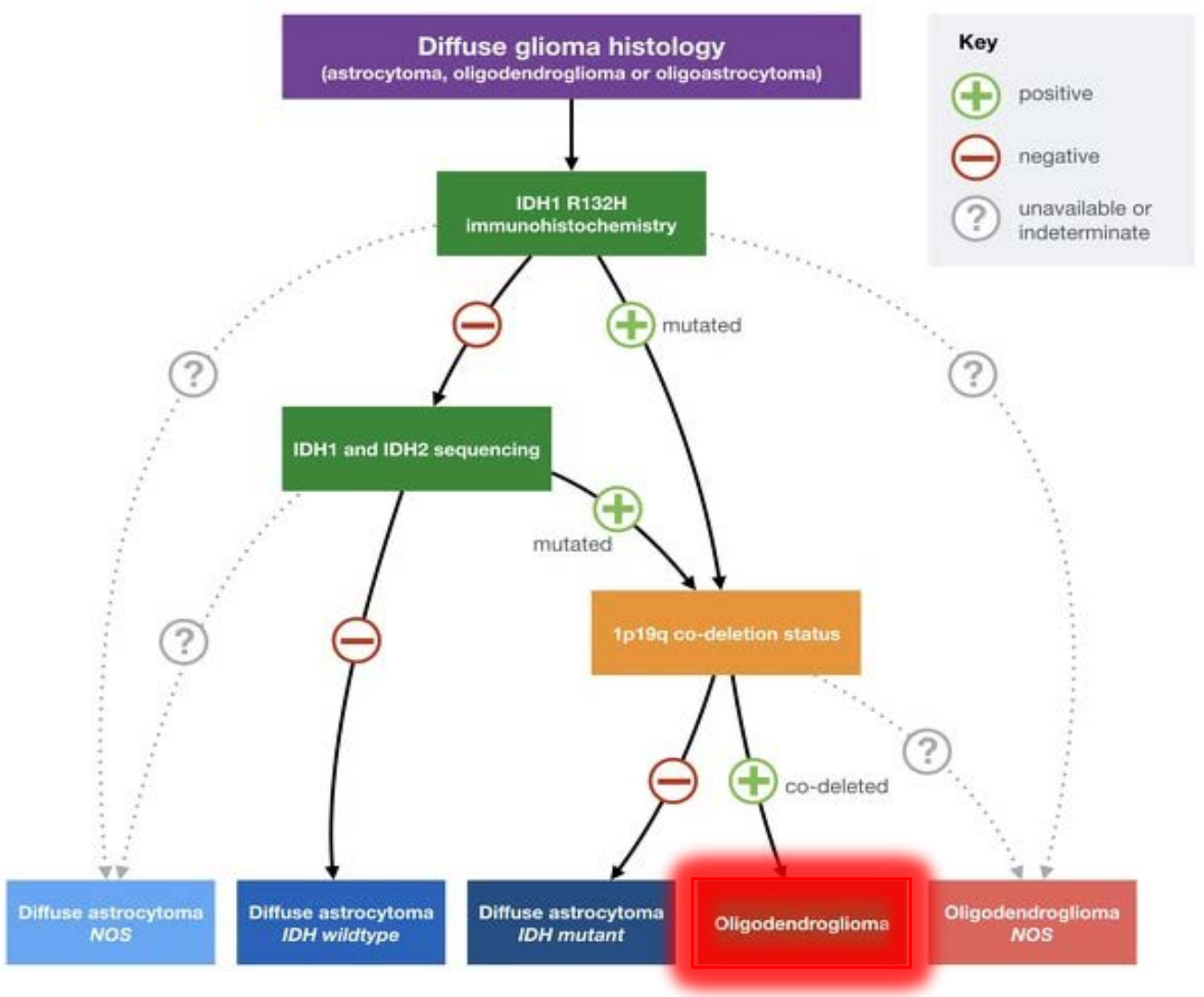
Choi C[1], Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, Yang XL, Mashimo T, Raisanen JM, Marin-Valencia I, Pascual JM, Madden CJ, Mickey BE, Malloy CR, Bachoo RM, Maher EA.

Neuro-Oncology
20(7), 907–916, 2018 | doi:10.1093/neuonc/nox214 | Advance Access date 6 November 2017

Highly specific determination of *IDH* status using edited in vivo magnetic resonance spectroscopy

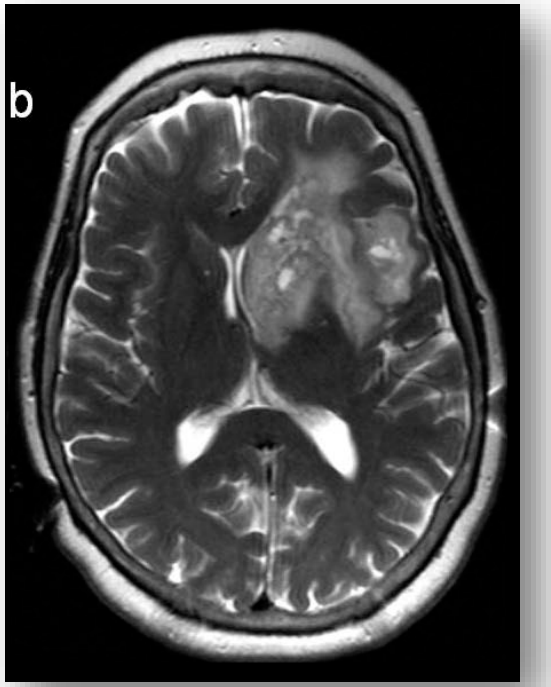
Francesca Branzoli,* Anna Luisa Di Stefano,* Laurent Capelle, Chris Ottolenghi, Romain Valabrègue, Dinesh K. Deelchand, Franck Bielle, Chiara Villa, Bertrand Baussart, Stéphane Lehéricy, Marc Sanson,§ and Małgorzata Marjańska§

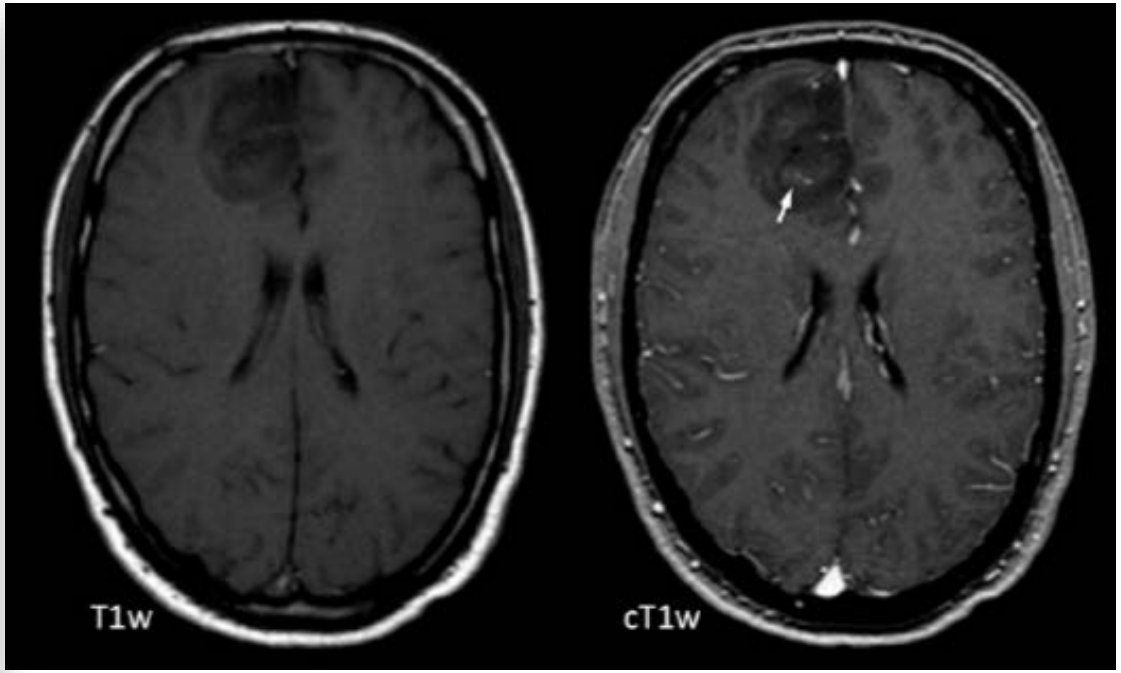
OLIGODENDROGLIOMA: FATTORE CONFONDENTE

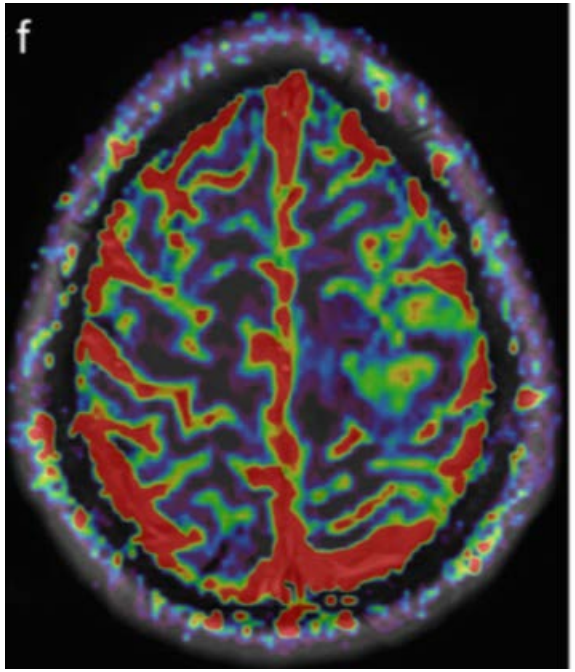


OLIGODENDROGLIOMA: FATTORE CONFONDENTE

- **IDH mutato e 1p/19q codeleto : OLIGODENDROGLIOMA -> Sopravvivenza media: 12-14 anni**





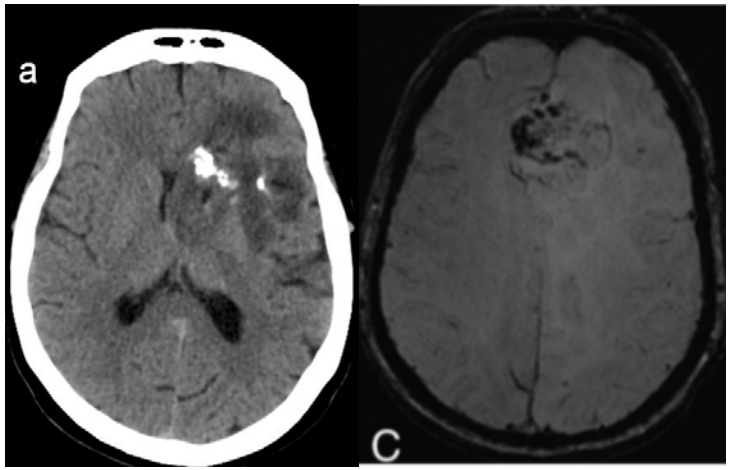


- Segnale disomogeneo
- Margini non definiti

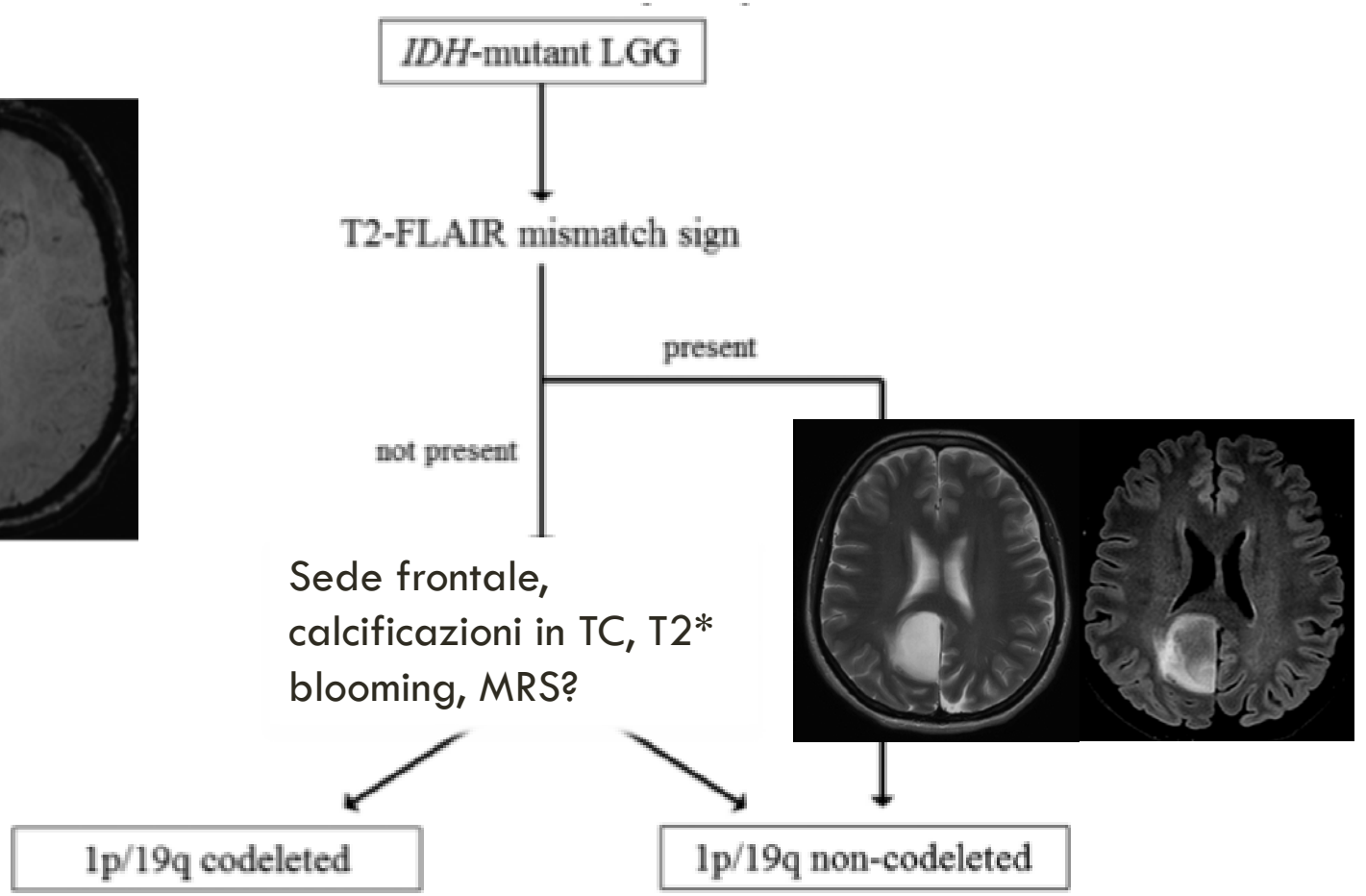
- Possibili potenziamenti nodulari

- Aumento della perfusione

OLIGODENDROGLIOMA: COME RICONOSCERLO?

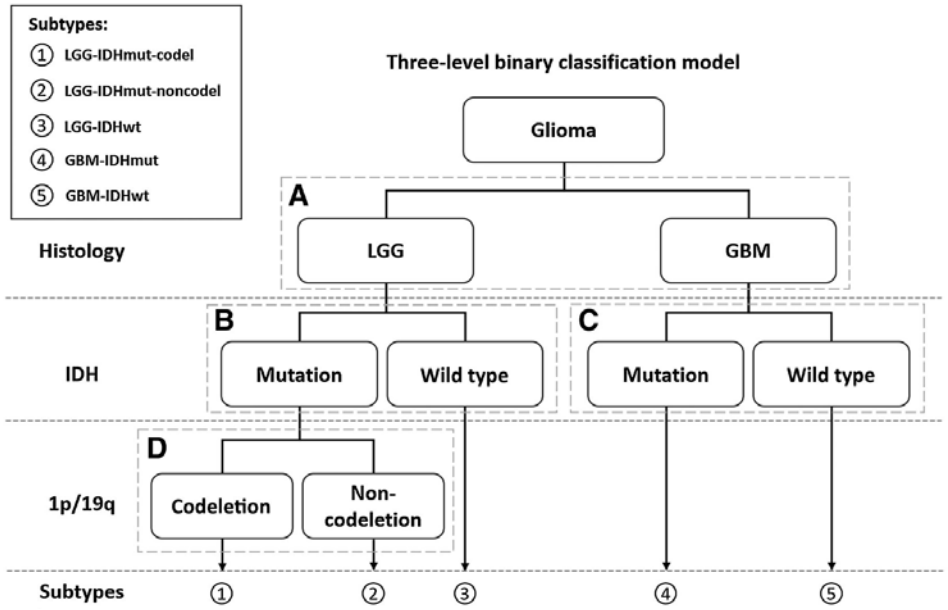


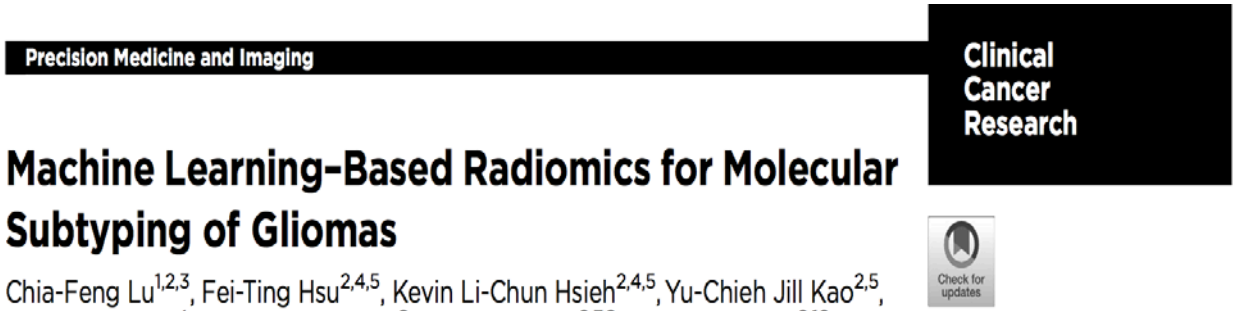
Perdita di due enzimi localizzati nel cromosoma 1p (PHGDG e CTH) -> Accumulo di cistationina, potenzialmente riconoscibile in MRS



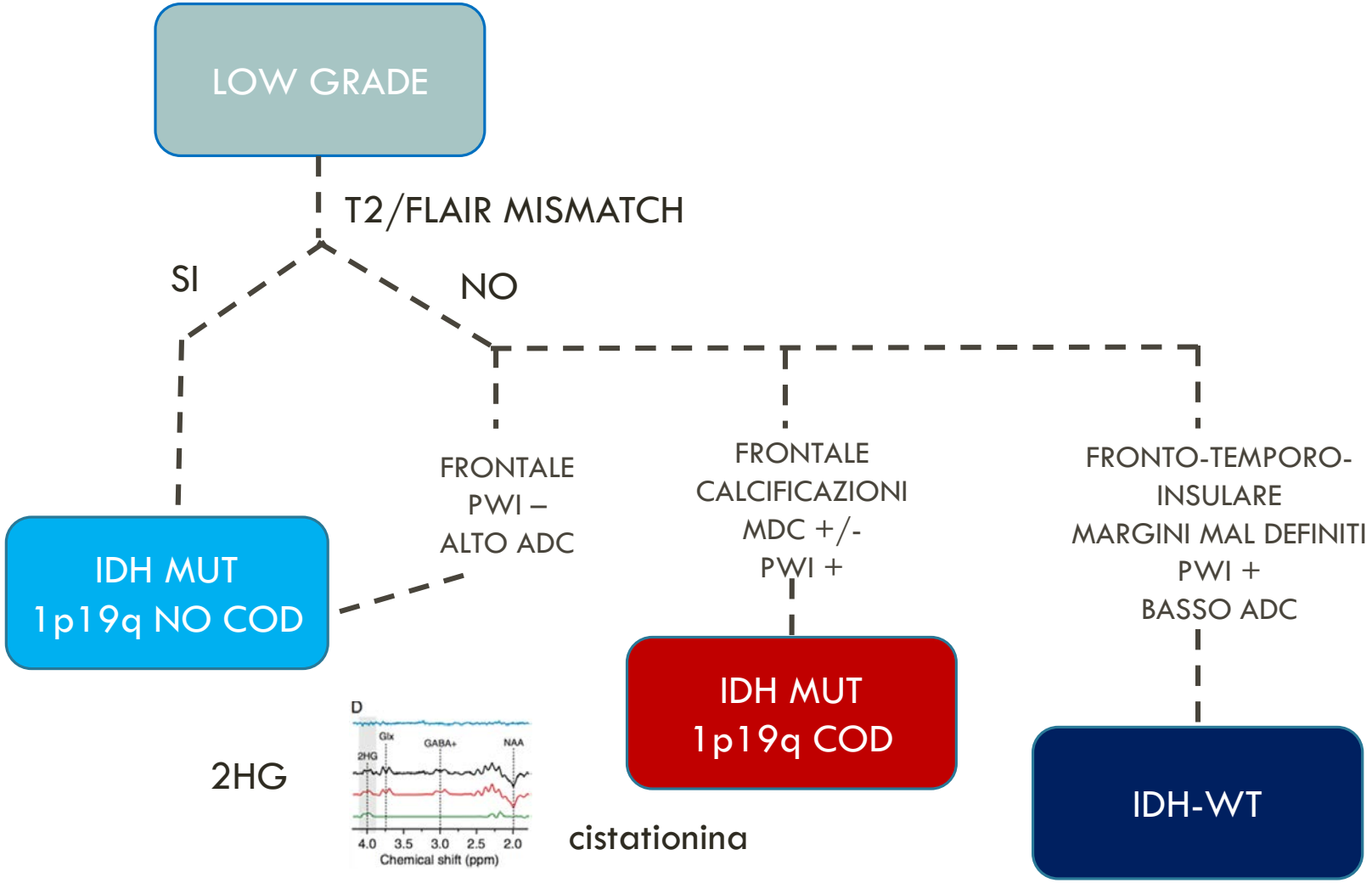
AI: MACHINE LEARNING-BASED RADIOMICA

Classification (subject numbers)	Model/required image contrasts	AUC	Accuracy	Sensitivity	Specificity
GBM vs. LGG (214 subjects)	Linear SVM/T1+C, T2 FLAIR	0.944	90.7%	94.3% (true rate for GBM)	87.0% (true rate for LGG)
IDH wt vs. mut in GBMs (77 subjects)	Cubic SVM/T1+C, T2 FLAIR, T2W	0.975	96.1%	95.7% (true rate for wt)	100.0% (true rate for mut)
IDH wt vs. mut in LGGs (71 subjects)	Linear SVM/T1+C, T2 FLAIR, T2W, DWI	0.936	91.6%	85.7% (true rate for wt)	93.0% (true rate for mut)
1p/19q noncodel vs. codel in IDH mut LGGs (81 subjects)	Quadratic SVM/T1+C, T2 FLAIR, T2W	0.922	87.7%	88.5% (true rate for noncodel)	86.2% (true rate for codel)





TAKE HOME: FLOW CHART



GRAZIE