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Molecularly targeted therapy and radiogenomic imaging in glioblastoma

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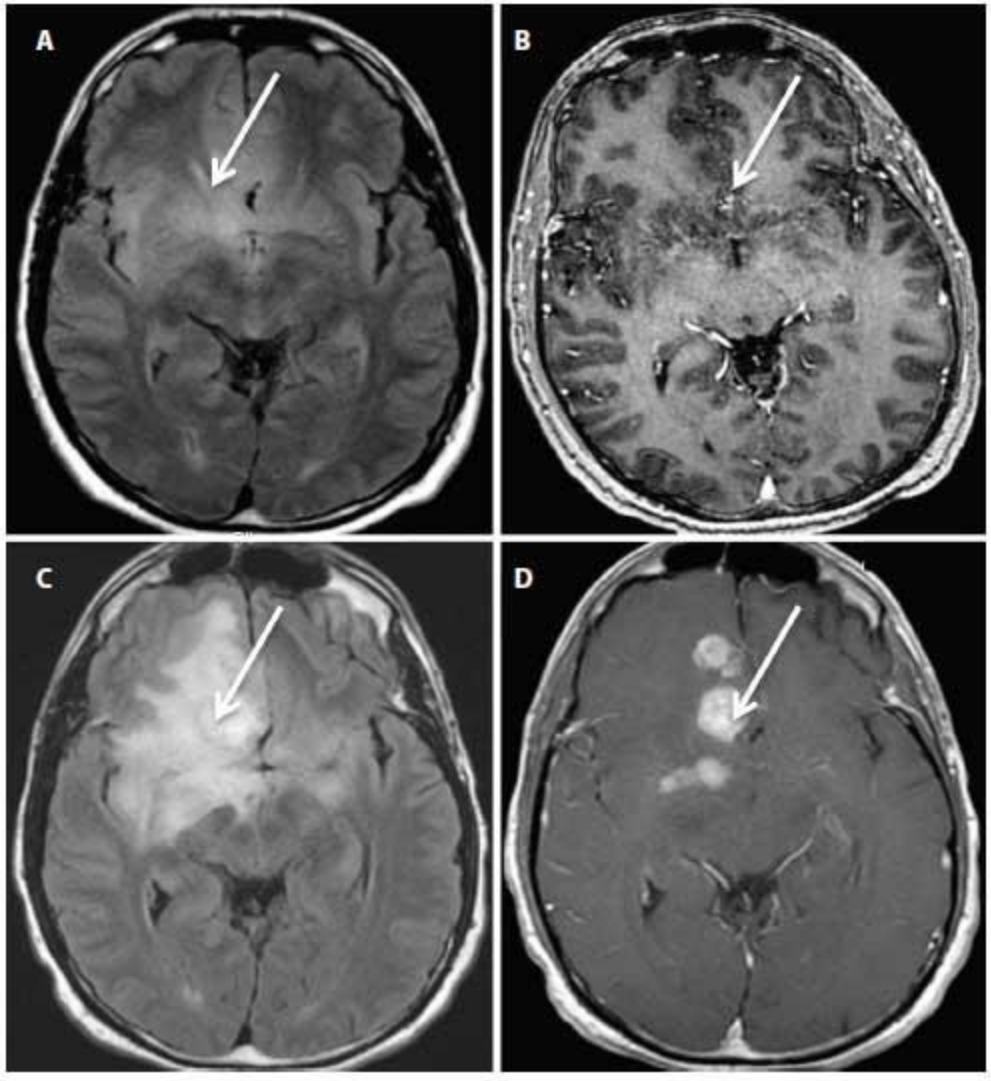
Glioblastoma (WHO grade IV)

- The most common malignant primary brain tumor
- Dismal prognosis; median OS ~ 14 months (Stupp et al., NEJM, 2005), despite intense radio-/chemotherapy
- Single predictive biomarker: *MGMT* methylation (Hegi et al., NEJM, 2005)
- Variable clinical course (though mostly dismal prognosis)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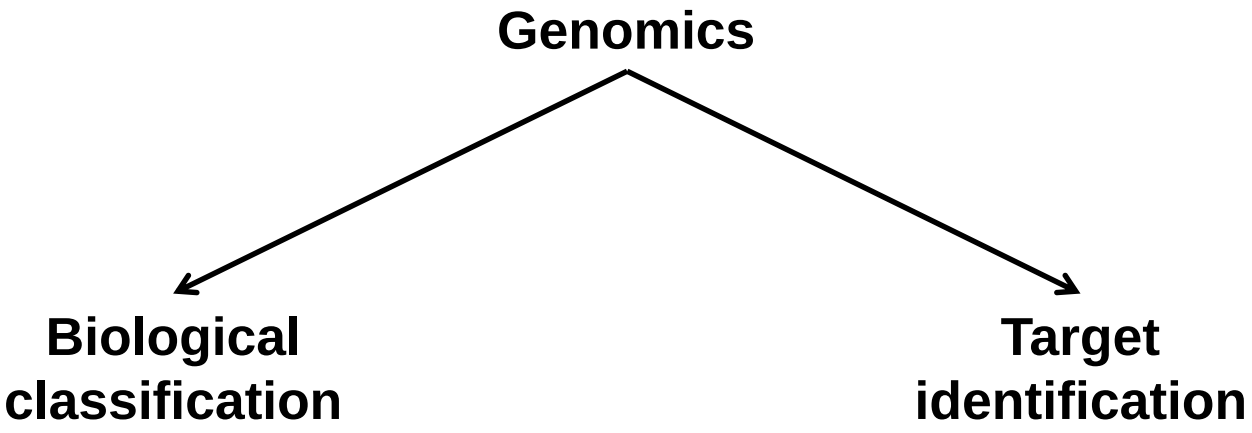
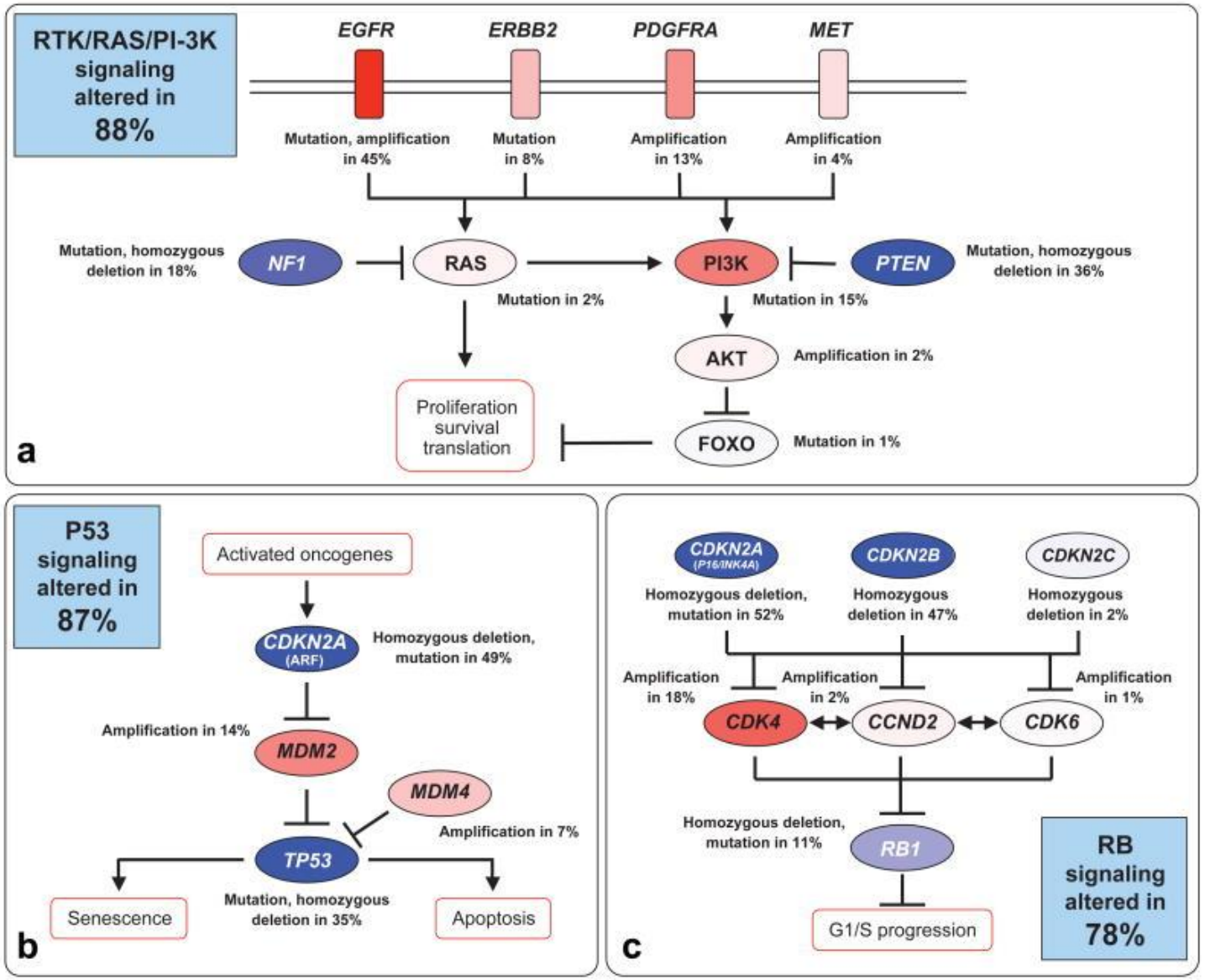

Genomics
Biological classification
Target identification



TCGA, Nature, 2008

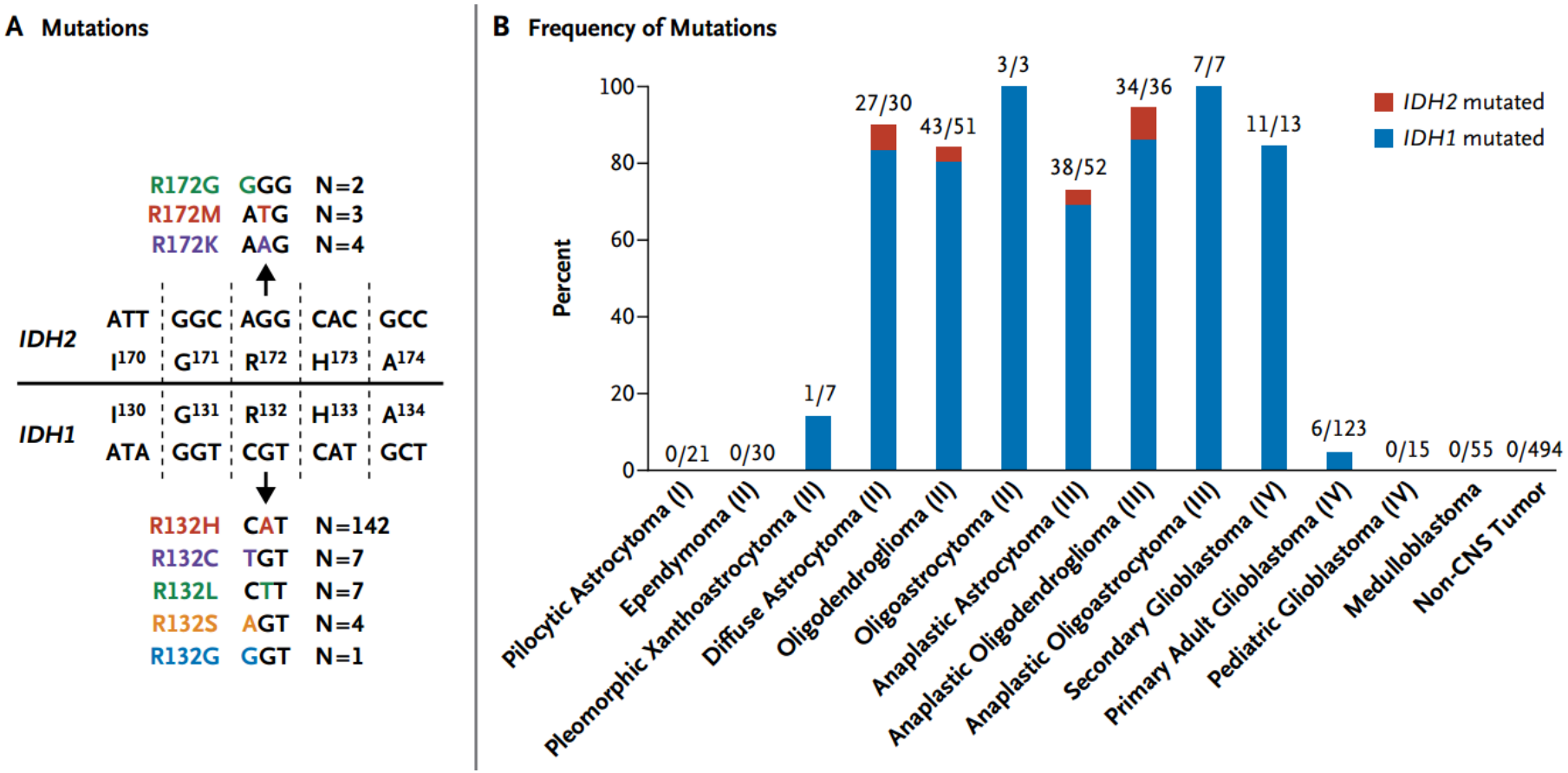
Gene	No. of tumors	Fraction of tumors (%)	No. of tumors	Fraction of tumors (%)	No. of tumors	Fraction of tumors (%)	Fraction of tumors with any alteration (%)	Passenger probability ‡
CDKN2A	0/22	0	0/22	0	11/22	50	50	<0.01
TP53	37/105	35	0/22	0	1/22	5	40	<0.01
EGFR	15/105	14	5/22	23	0/22	0	37	<0.01
PTEN	27/105	26	0/22	0	1/22	5	30	<0.01
NF1	16/105	15	0/22	0	0/22	0	15	0.04
CDK4	0/22	0	3/22	14	0/22	0	14	<0.01
RB1	8/105	8	0/22	0	1/22	5	12	0.02
IDH1	12/105	11	0/22	0	0/22	0	11	<0.01
PIK3CA	10/105	10	0/22	0	0/22	0	10	0.10
PIK3R1	8/105	8	0/22	0	0/22	0	8	0.10

↵* Fraction of tumors with point mutations indicates the fraction of mutated GBMs out of the 105 samples in the Discovery and Prevalence Screens. CDKN2A and CDK4 were not analyzed for point mutations in the Prevalence Screen because no sequence alterations were detected in these genes in the Discovery Screen.

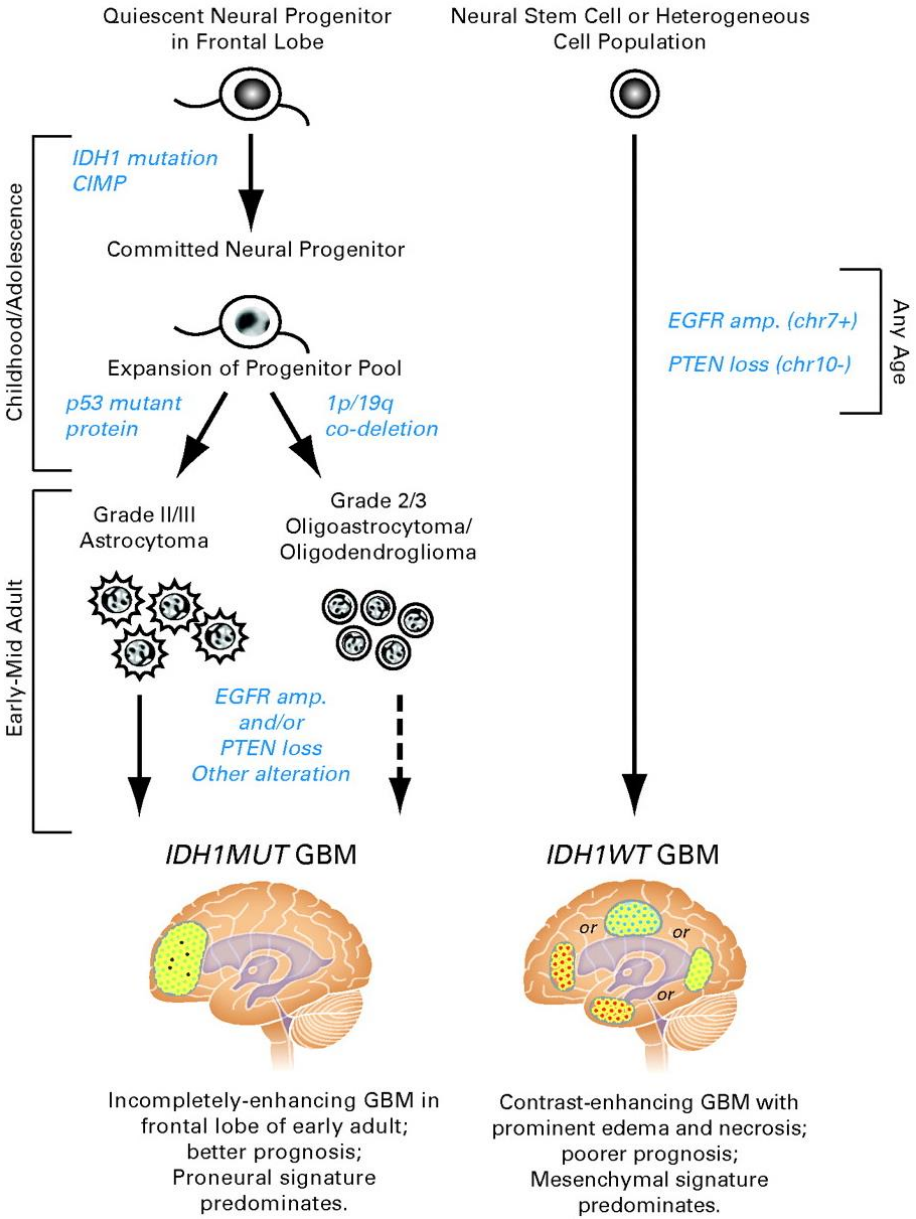
↵† Fraction of tumors with amplifications and deletions indicates the number of tumors with these types of alterations in the 22 Discovery Screen samples.

↵‡ Passenger probability indicates the probability obtained using the average of the lower and upper bound background mutation rates (*12*).

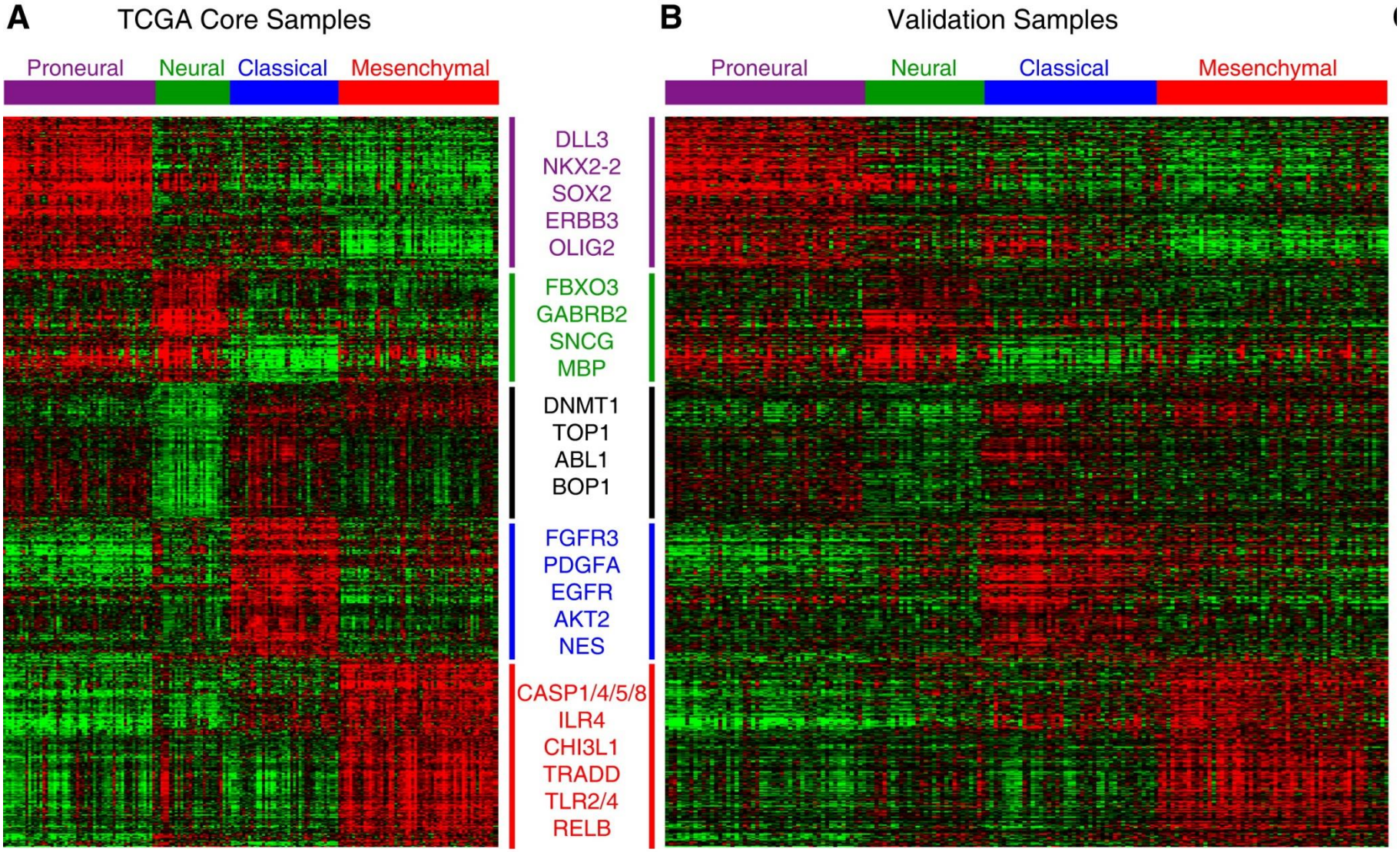
Parsons et al., Science, 2008



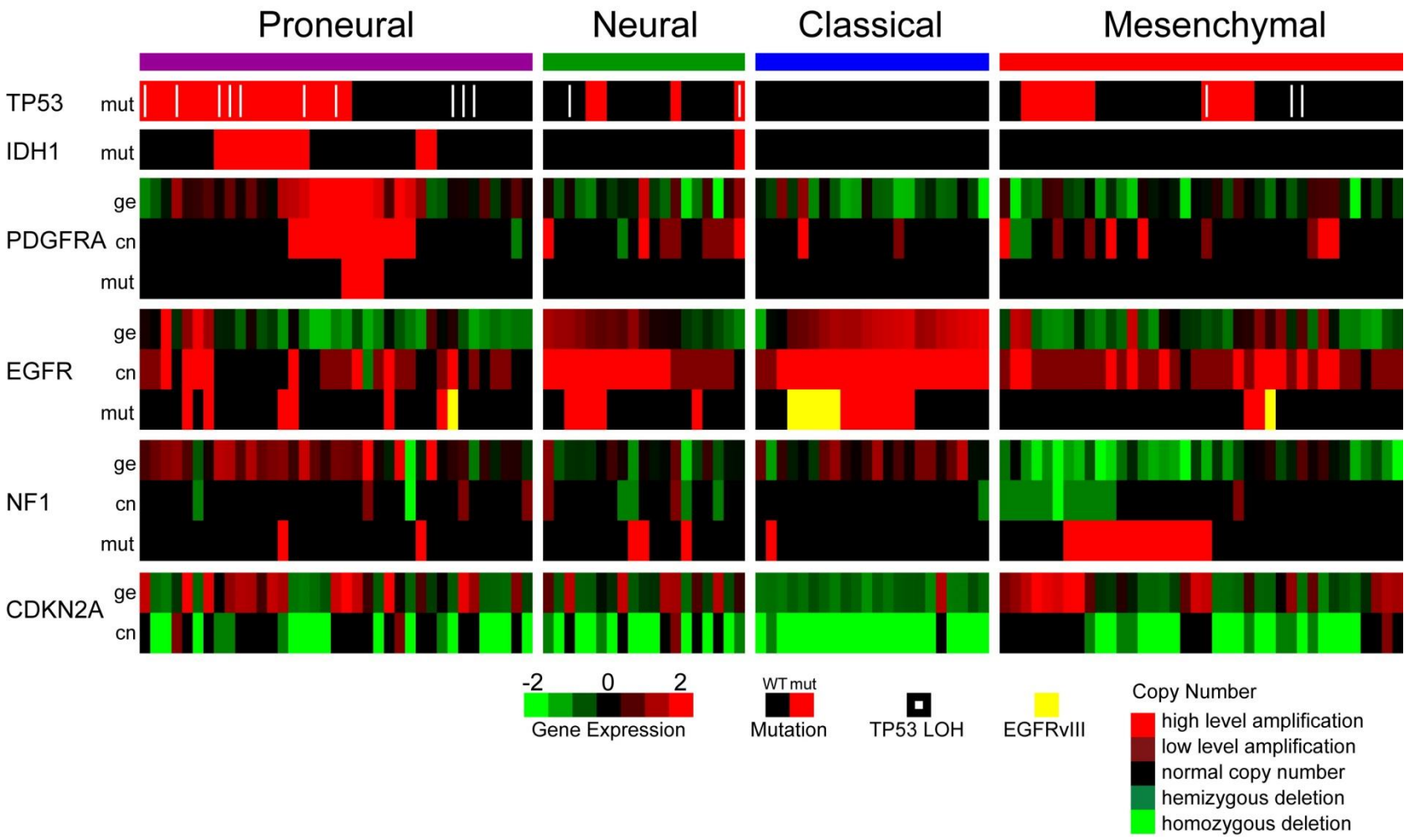
Yan et al., NEJM, 2009



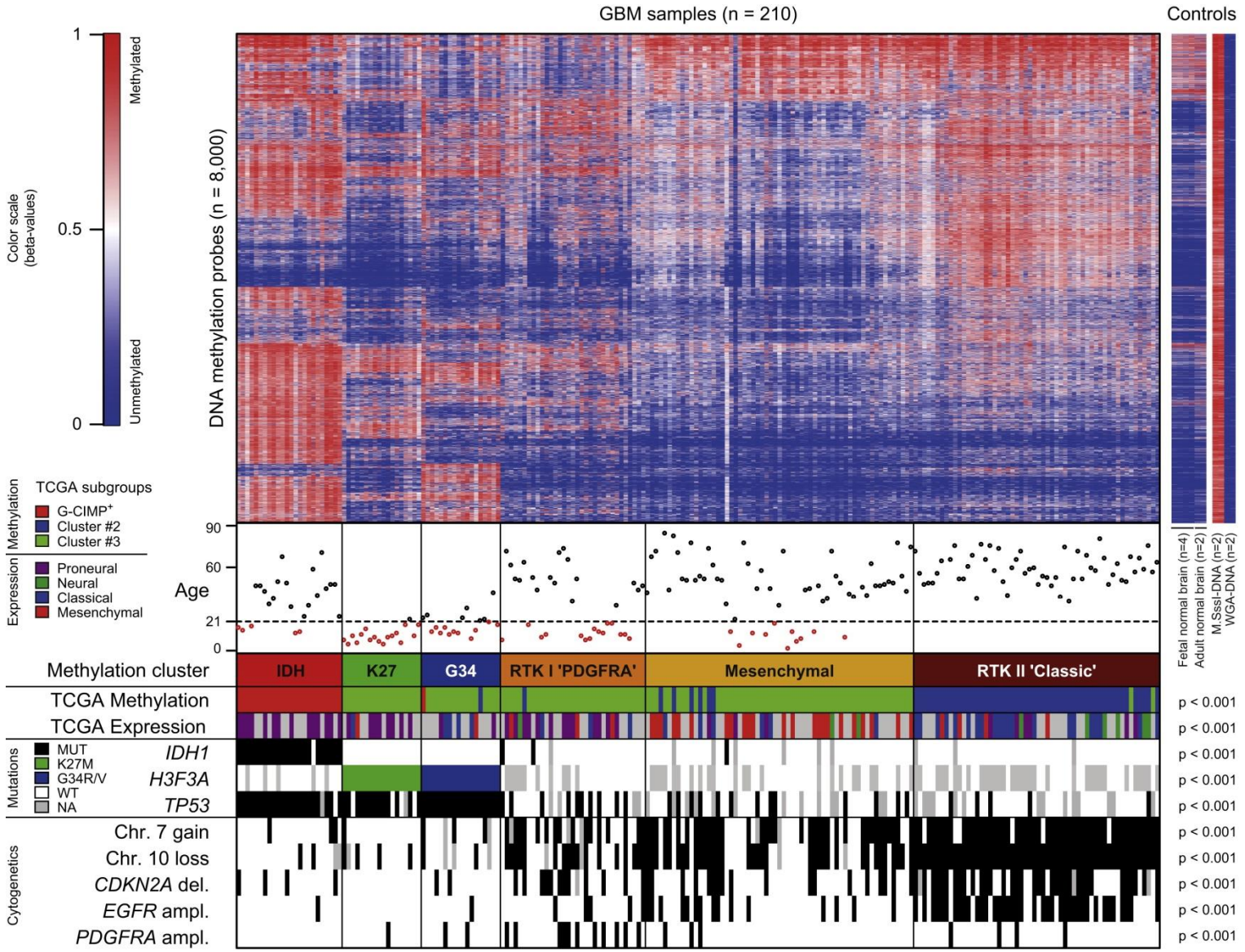
Lai et al., JCO, 2011



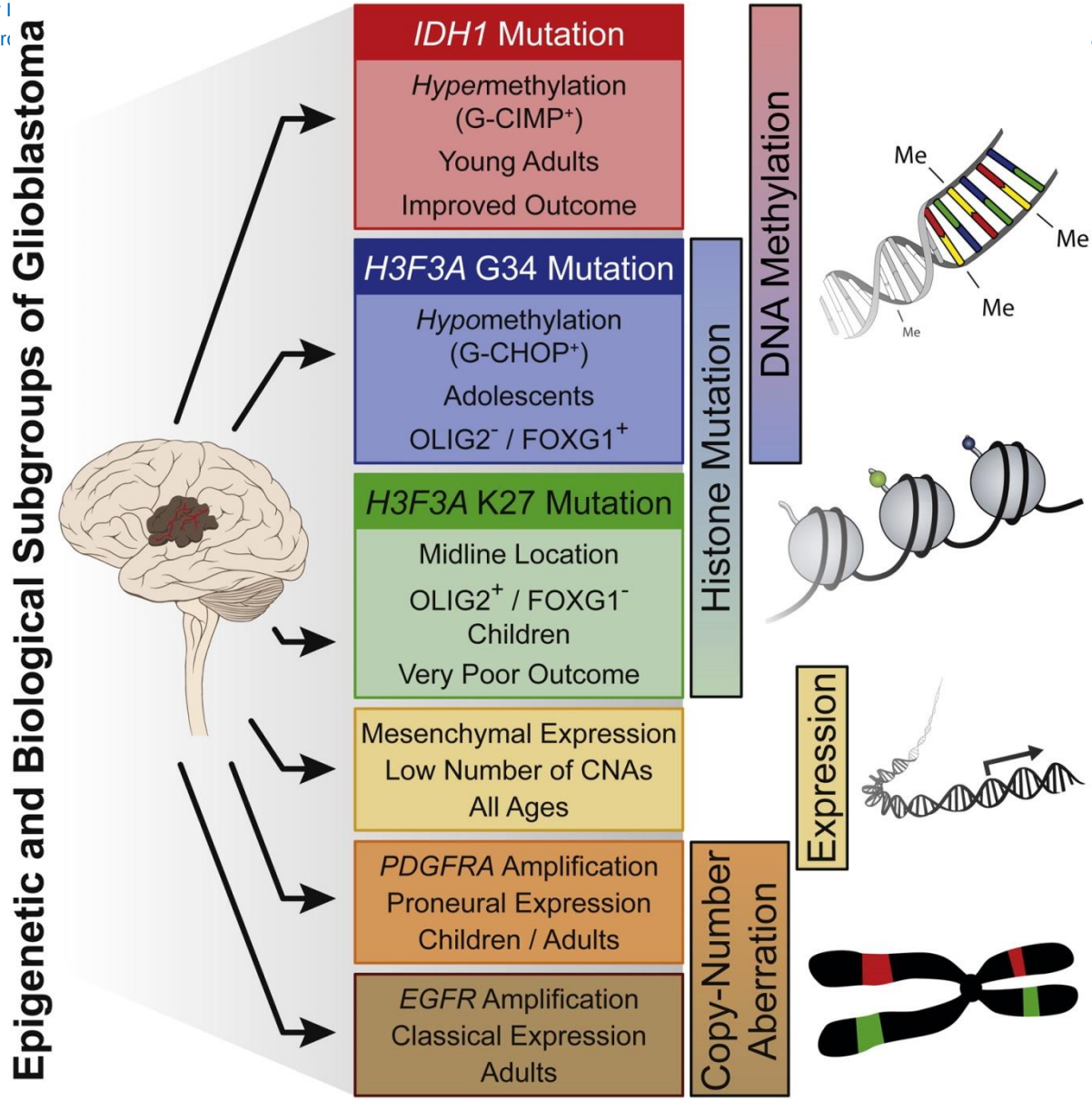
Verhaak et al., Cancer Cell, 2010



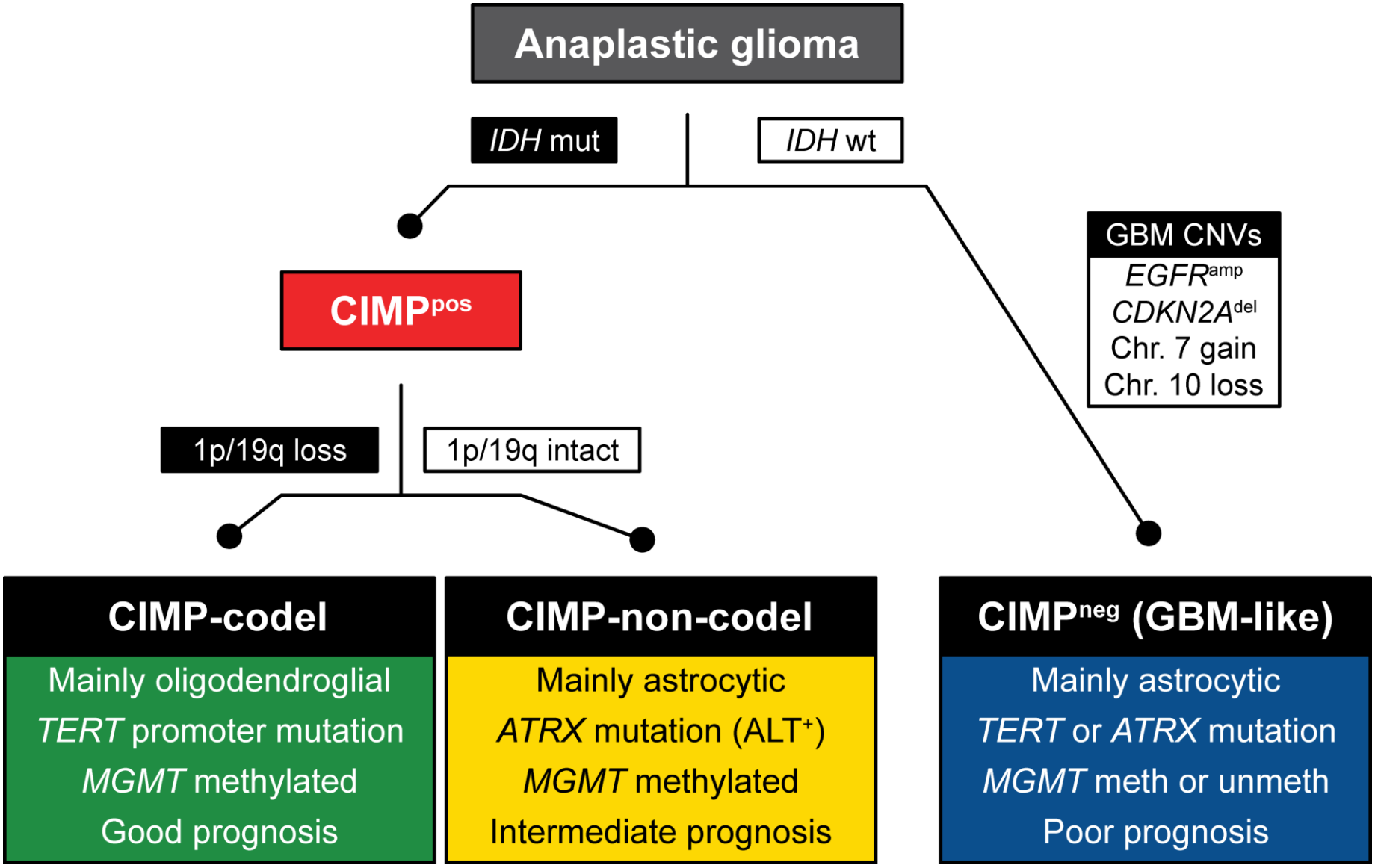
Verhaak et al., Cancer Cell, 2010



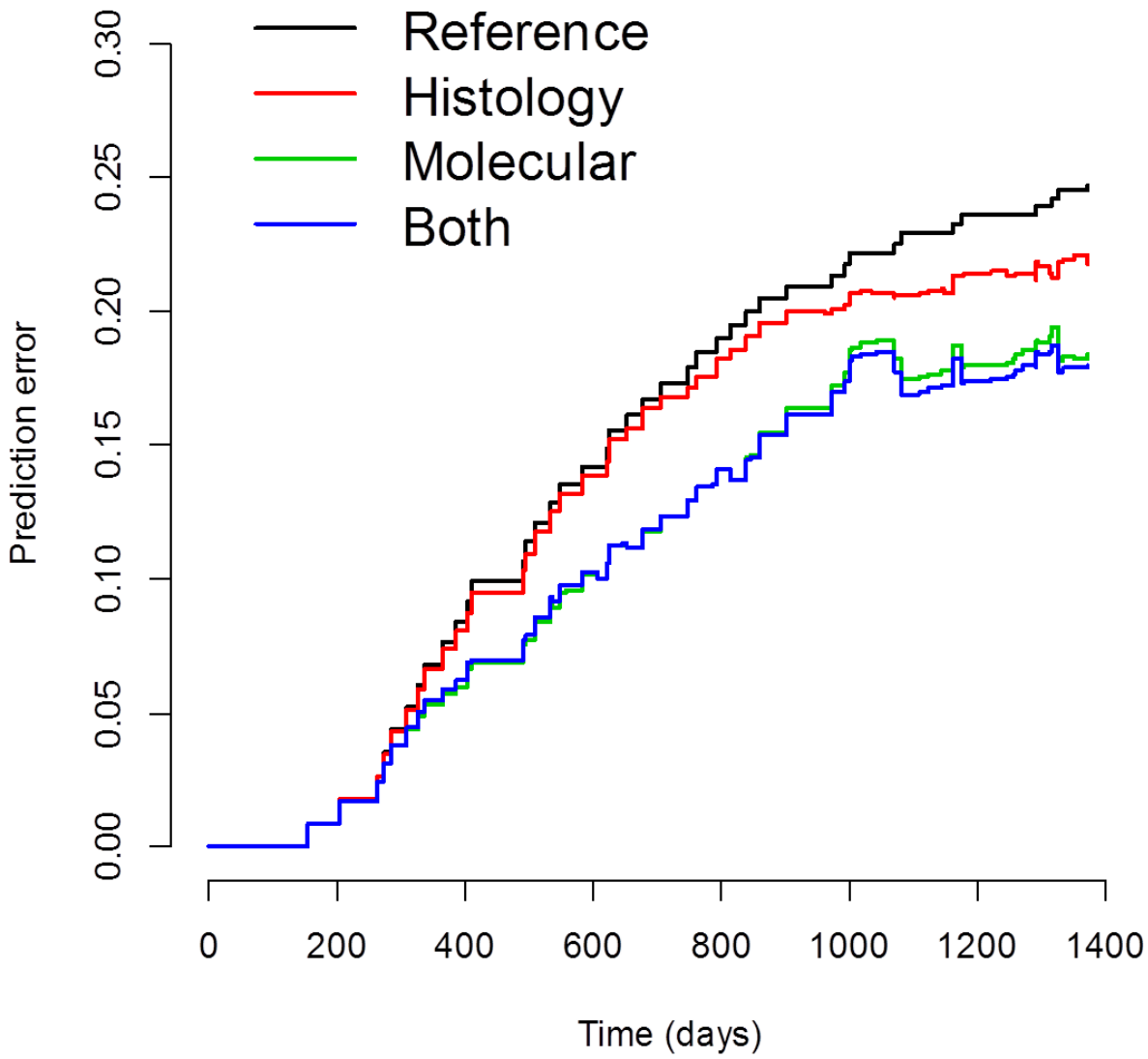
Sturm, …, Wiestler, et al., Cancer Cell, 2012



Sturm, …, Wiestler, et al., Cancer Cell, 2012



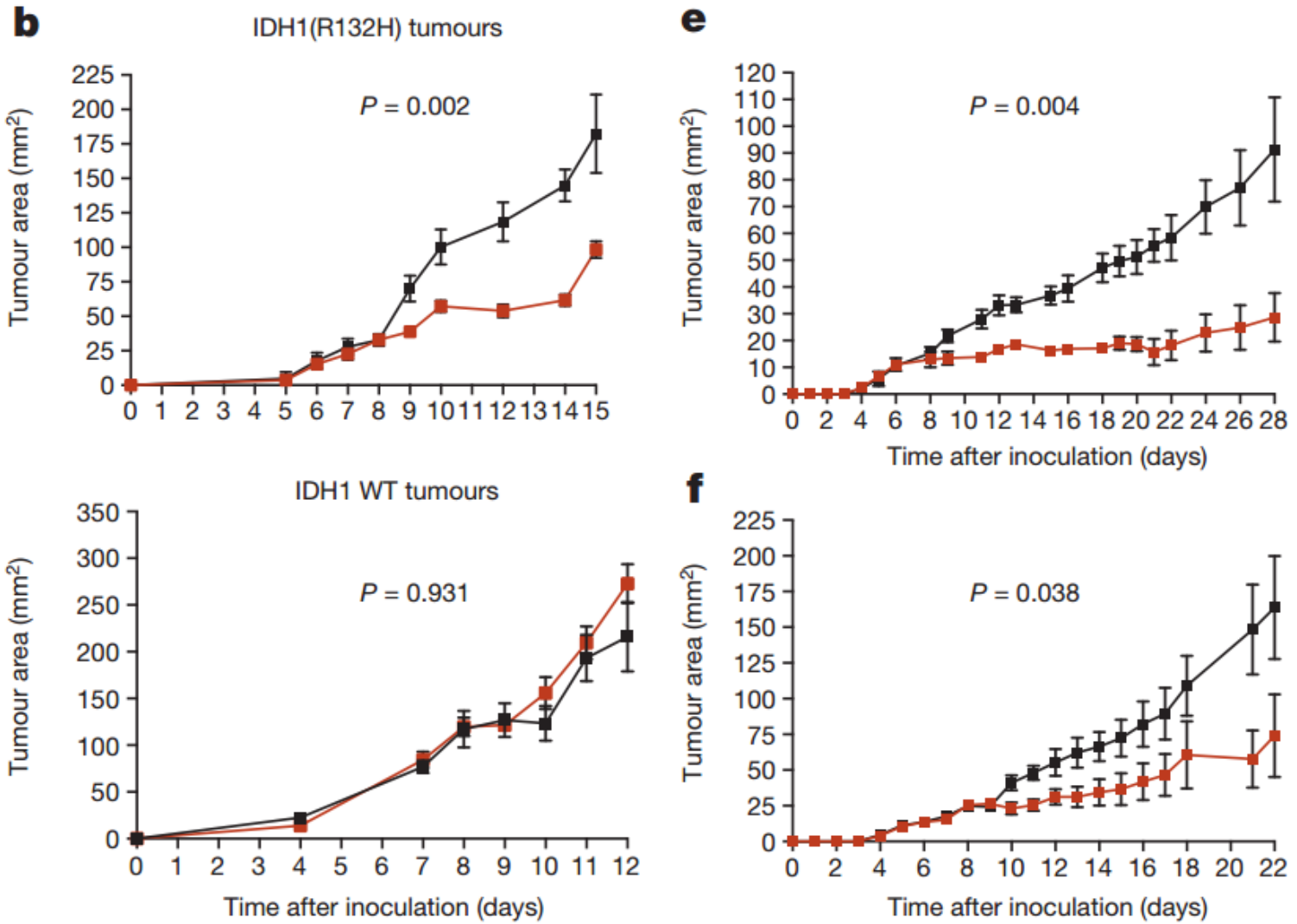
Wiestler et al., Acta Neuropathologica, 2014



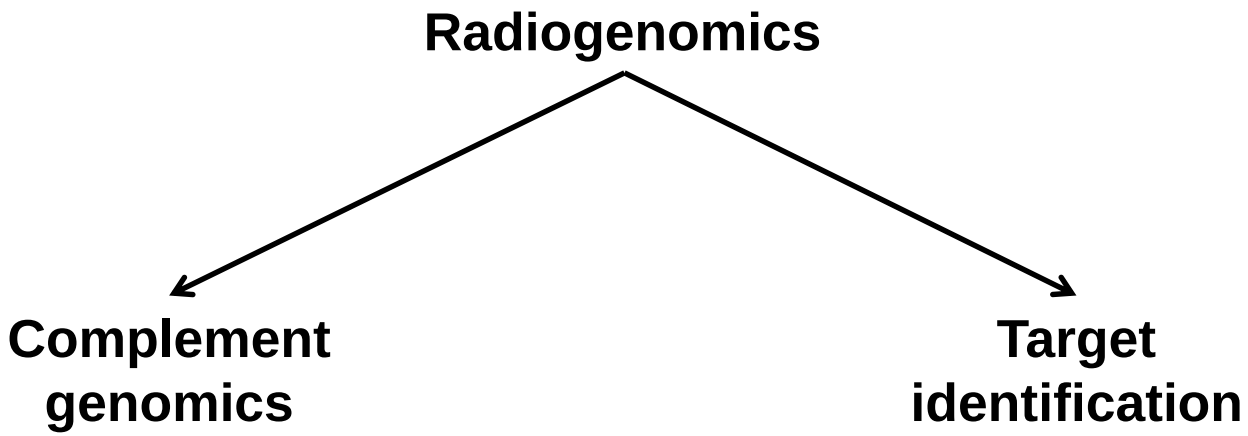
Wiestler et al., Acta Neuropathologica, 2014

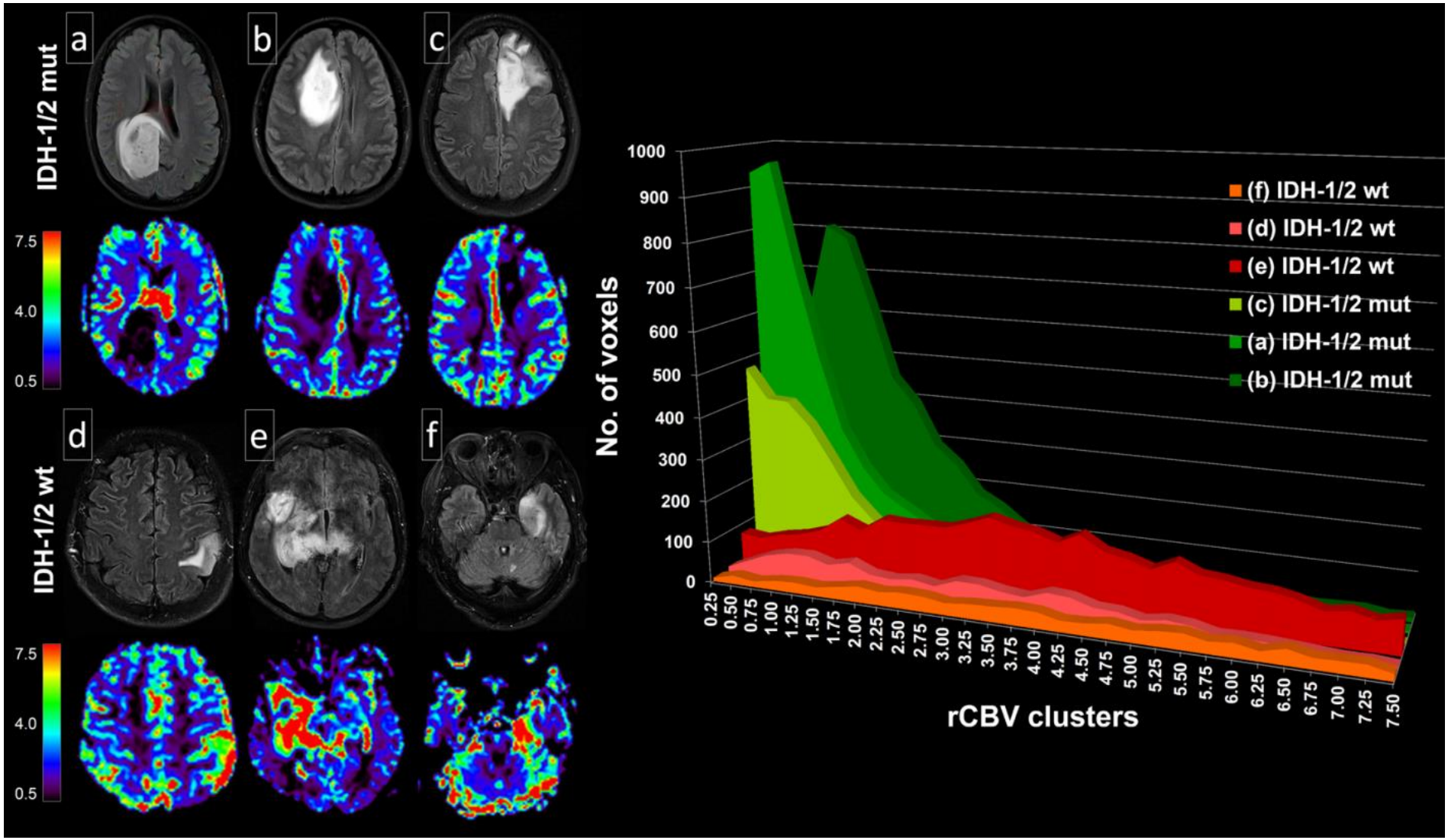
A plethora of actionable targets has been identified

- IDH
- FGFR/TACC fusions
- EGFRvIII
- Angiogenesis pathways
- Integrins



Schumacher, …, Wiestler et al., Nature, 2014


Radiogenomics
Complement genomics
Target identification



Kickingereder, … & Wiestler, Scientific Reports, 2015

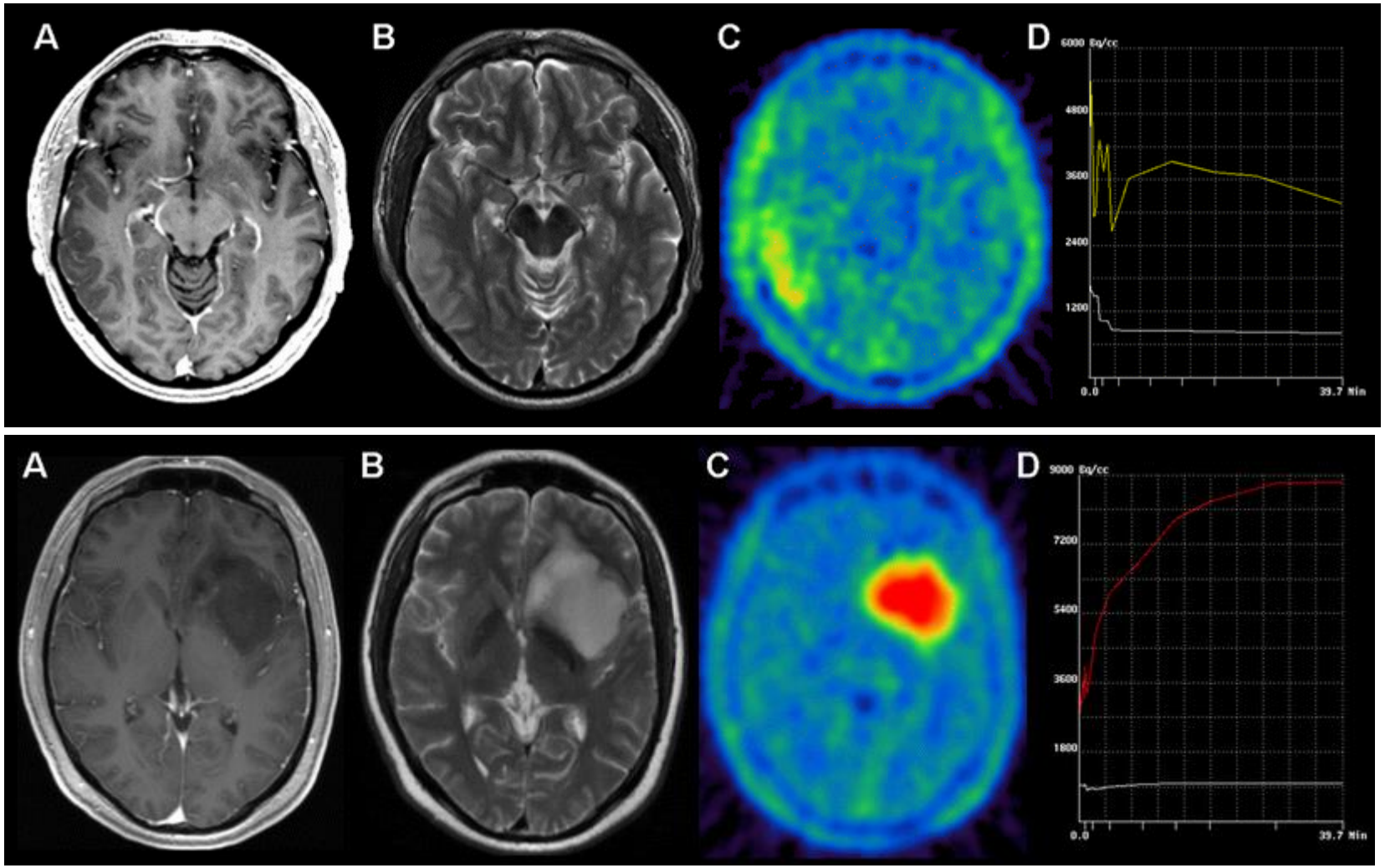
A) Upstream regulators in *IDH-1/2* mutant tumors.

Upstream regulator	Molecule type	p value of overlap	Activation z score	Predicted activation state
Vegf	Group	4.11E-30	-7.287	Inhibited
PDGF BB	Complex	3.94E-36	-5.17	Inhibited
HIF1A	Transcription regulator	6.54E-10	-4.65	Inhibited
VEGFA	Growth factor	1.27E-10	-4.306	Inhibited
Pdgf	Complex	2.94E-10	-3.646	Inhibited
ANGPT2	Growth factor	6.79E-09	-3.361	Inhibited

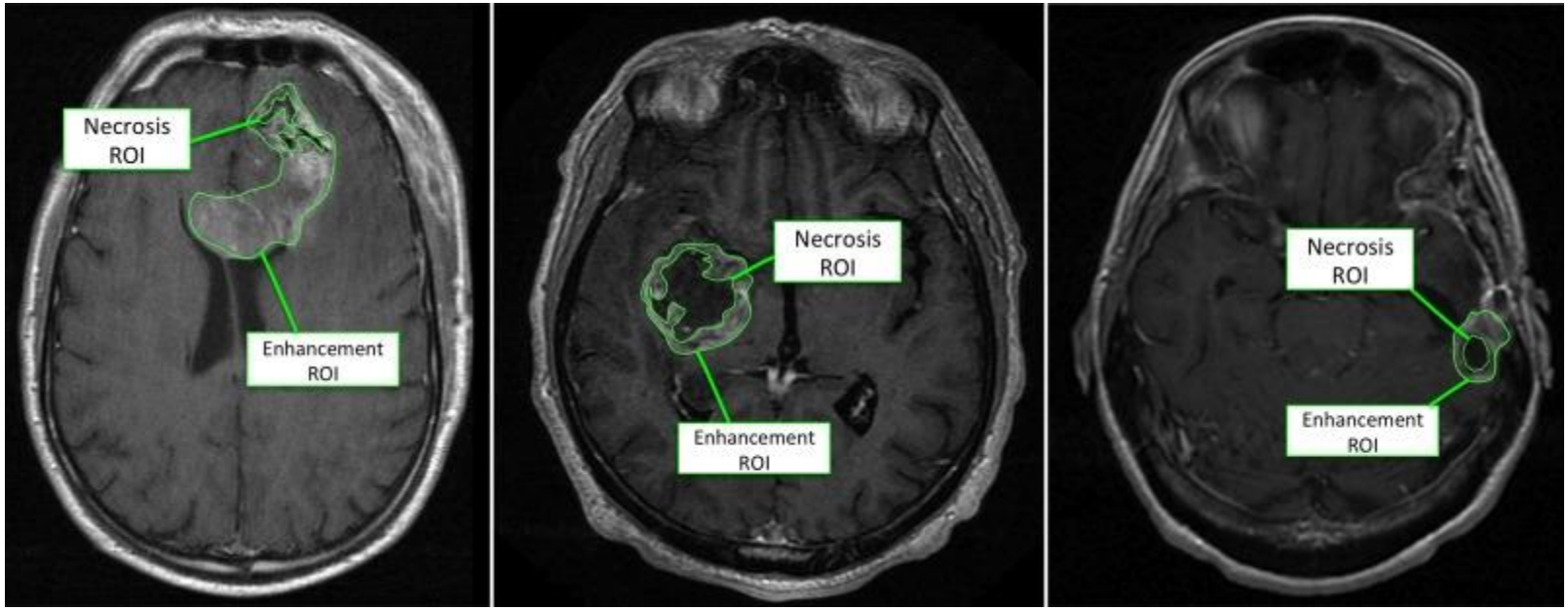
B) Downstream biological functions in *IDH-1/2* mutant tumors.

Biological function	p value of overlap	Activation z score	Predicted activation state
Development of blood vessel	7.87E-30	-4.185	Decreased
Migration of endothelial cells	3.26E-15	-3.799	Decreased
Vasculogenesis	8.89E-28	-3.717	Decreased
Movement of endothelial cells	2.66E-16	-3.540	Decreased
Angiogenesis	9.39E-28	-3.556	Decreased
Neovascularization	1.53E-10	-2.451	Decreased
Vascularization	6.85E-12	-2.319	Decreased
Development of endothelial cells	6.58E-12	-2.020	Decreased

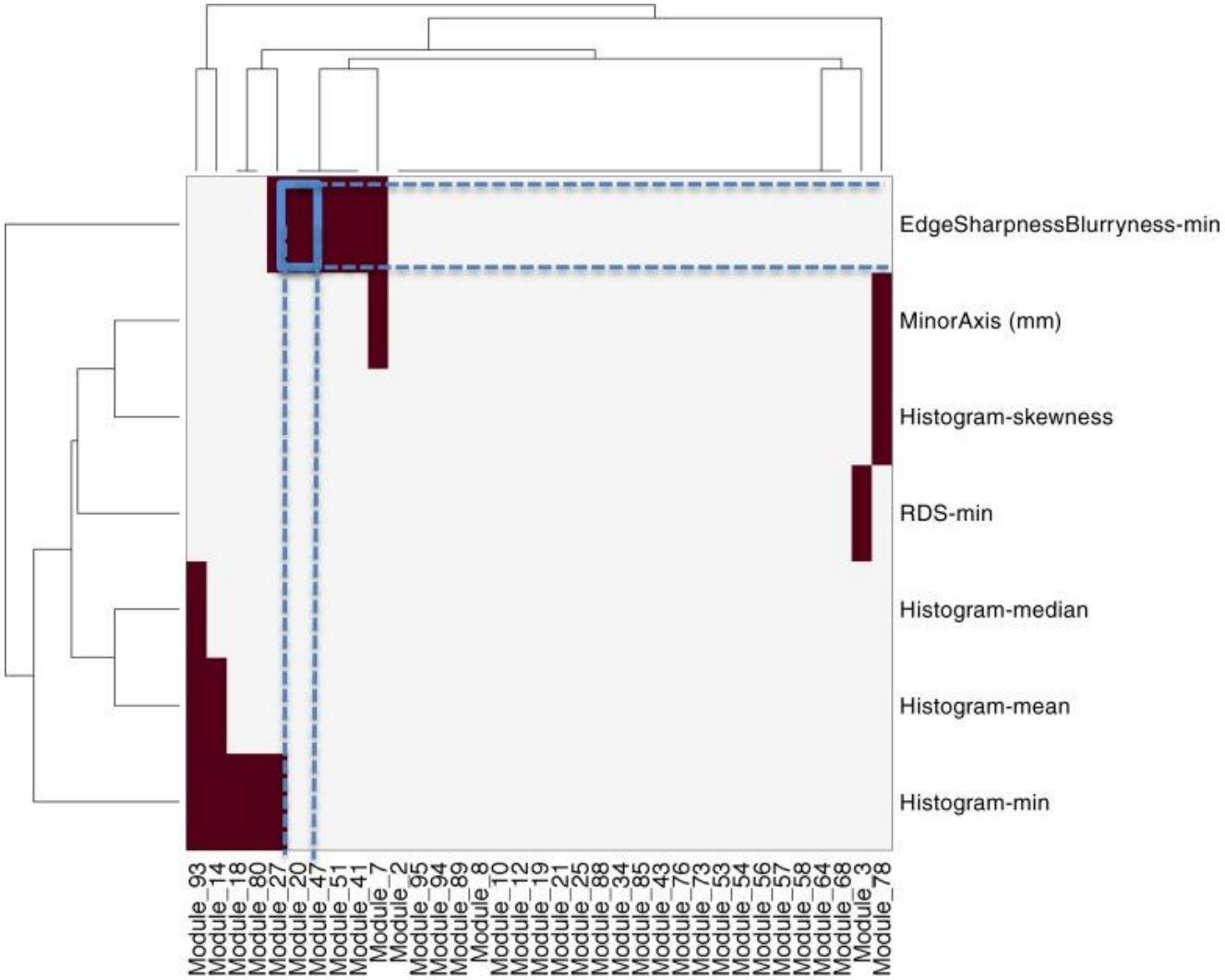
Kickingereder, … & Wiestler, Scientific Reports, 2015



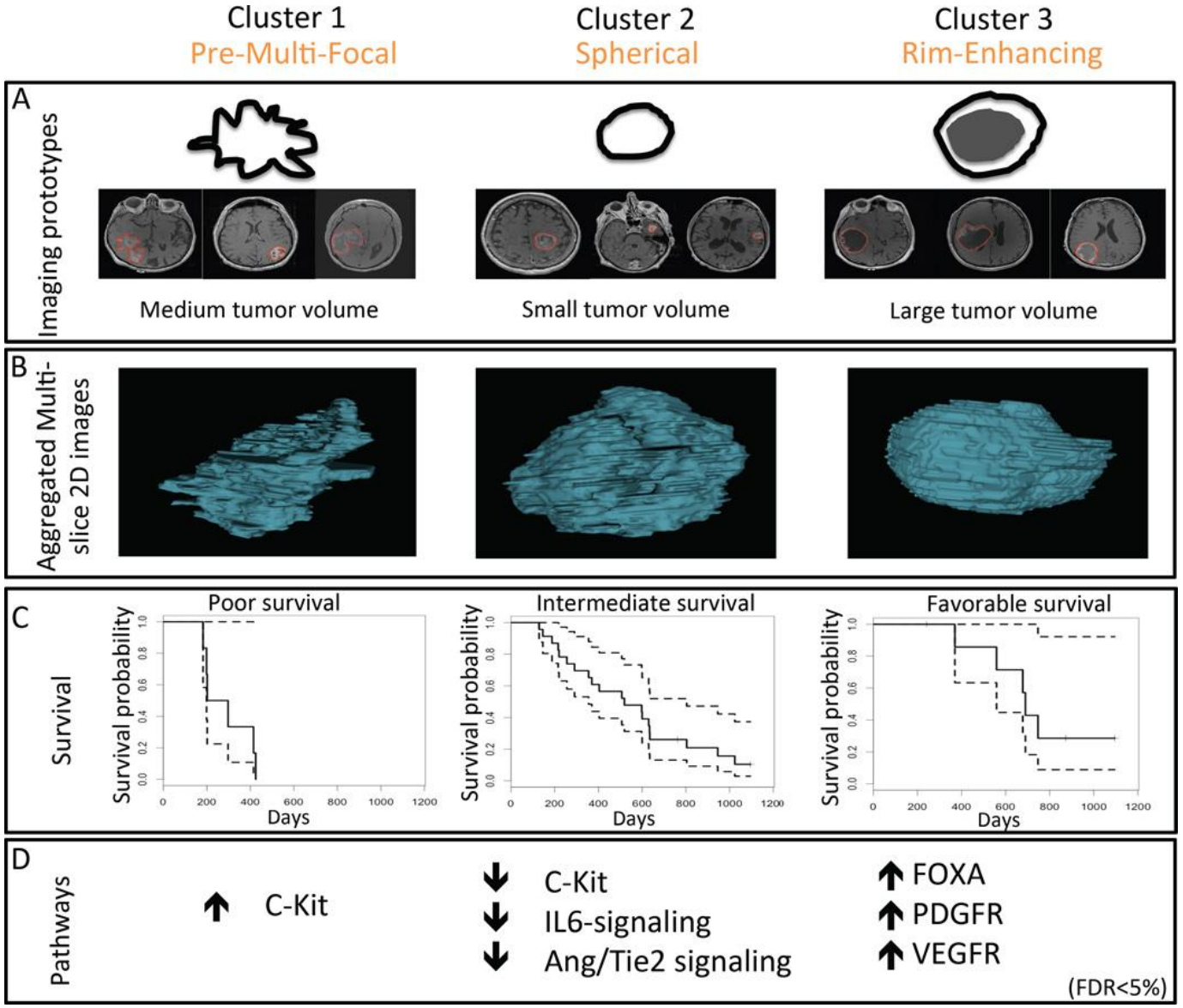
Jansen et al., Europ. J. of Nuc. Medicine & Mol. Imaging, 2012



Gevaert et al., Radiology, 2014



Gevaert et al., Radiology, 2014



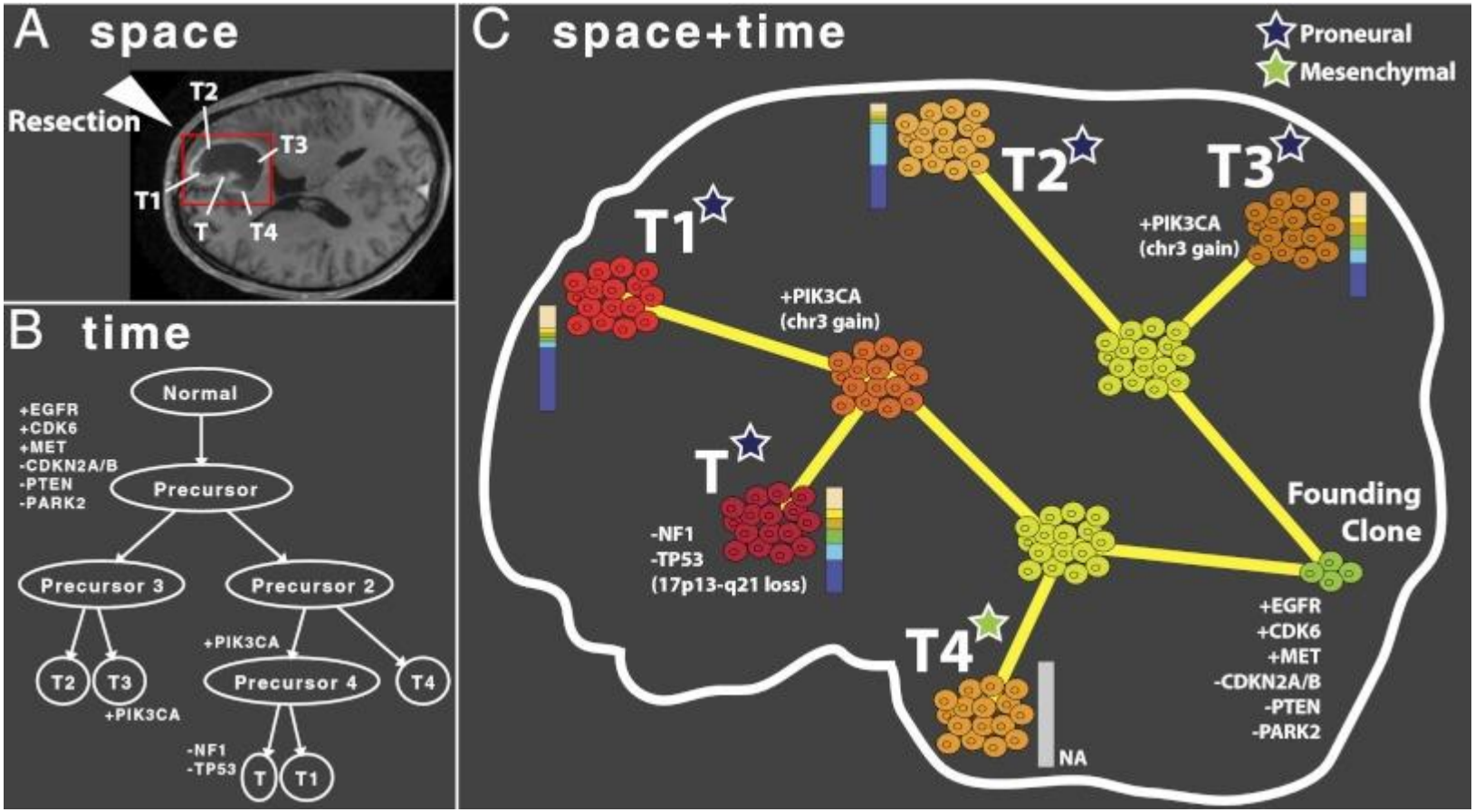
Itakura et al., Science Translational Medicine, 2015

Table 2. Selected Agents Tested in Recurrent GBM.

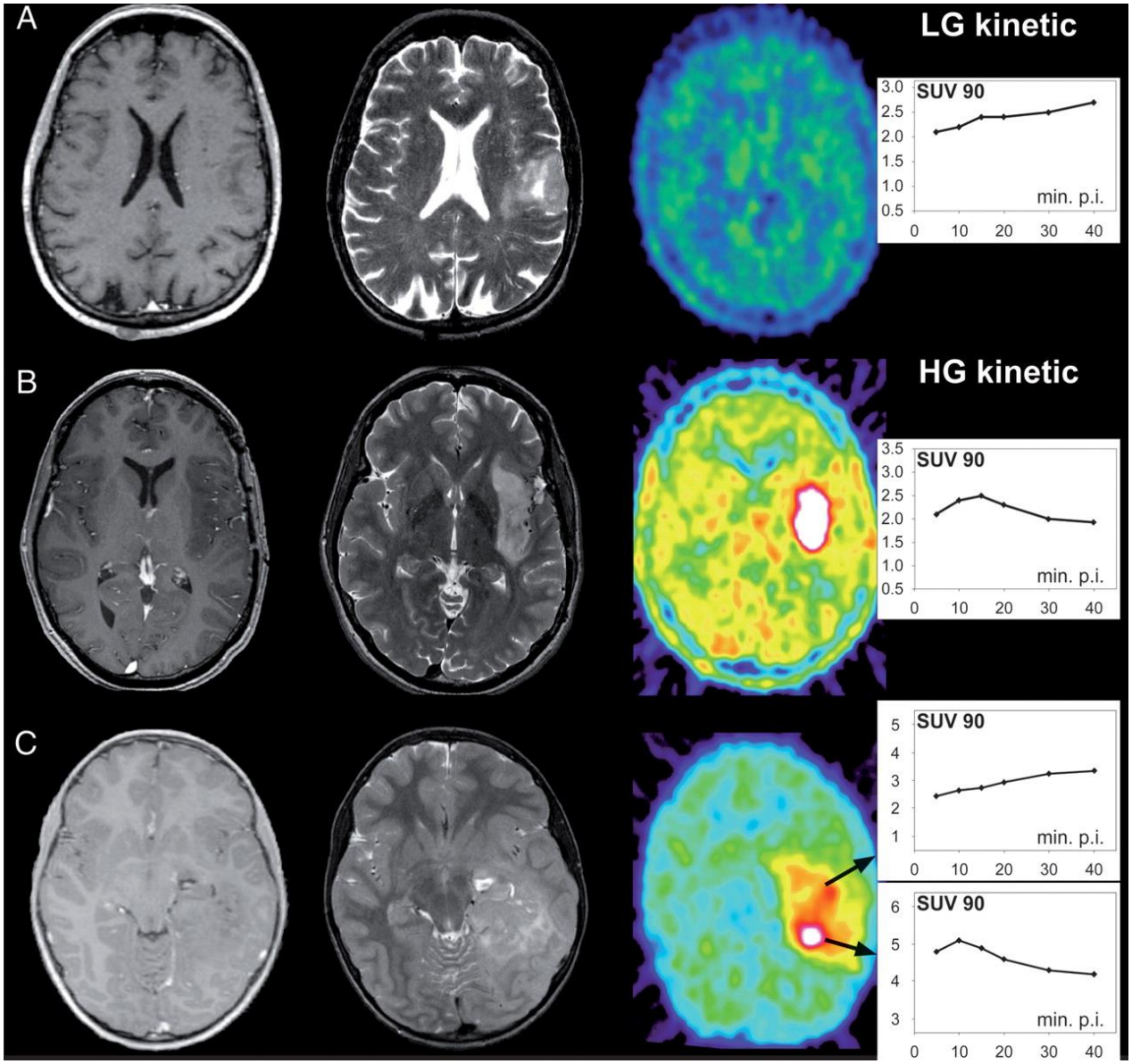
Agents	Target	Reference
Cediranib	pan-VEGFR	Batchelor *et al.*, 2010
Erlotinib	EGFR	van den Bendt *et al.*, 2009
Gefitinib	EGFR	Franceschi *et al.*, 2007 Rich *et al.*, 2004
Bevacizumab	VEGF-A	Zhang *et al.*, 2012
Cilengitide	A and β integrins	Reardon *et al.*, 2008 Gilbert *et al.*, 2012
Rindopepimut	EGFRvIII	Sampson *et al.*, 2009
Vorinostat	HDAC	Galanis *et al.*, 2009
XL-184	EGFR, C-MET	Wen *et al.*, 2010
Tipifarnib	Farnesyltransferase	Cloughsey *et al.*, 2006
Enzasturin	PKC	Wick *et al.*, 2010 Kreisl *et al.*, 2010
Temsirolimus	mTOR	Galanis *et al.*, 2005 Chang *et al.*, 2005

Abbreviations: VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; C-MET, met proto-oncogene; PKC, protein kinase.

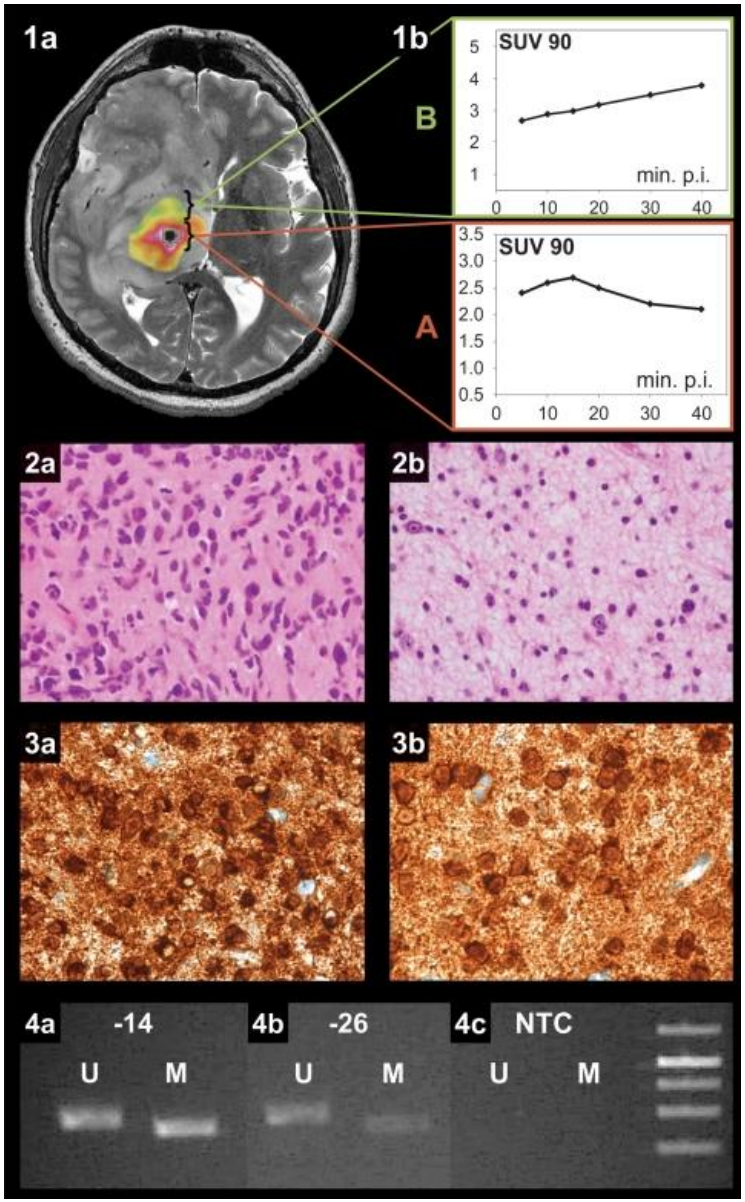
Mrugala, Discovery Medicine, 2013



Sottoriva et al., PNAS, 2013



Kunz et al., Neuro-Oncology, 2010



Kunz et al., Neuro-Oncology, 2010

Future challenges

- Identify key oncogenic drivers
- Better understand intratumoral heterogeneity (How does it change over time / during therapy?)
- Learn, how genomics and heterogeneity are reflected in imaging (Non-invasively assessable)

Thank you for your attention