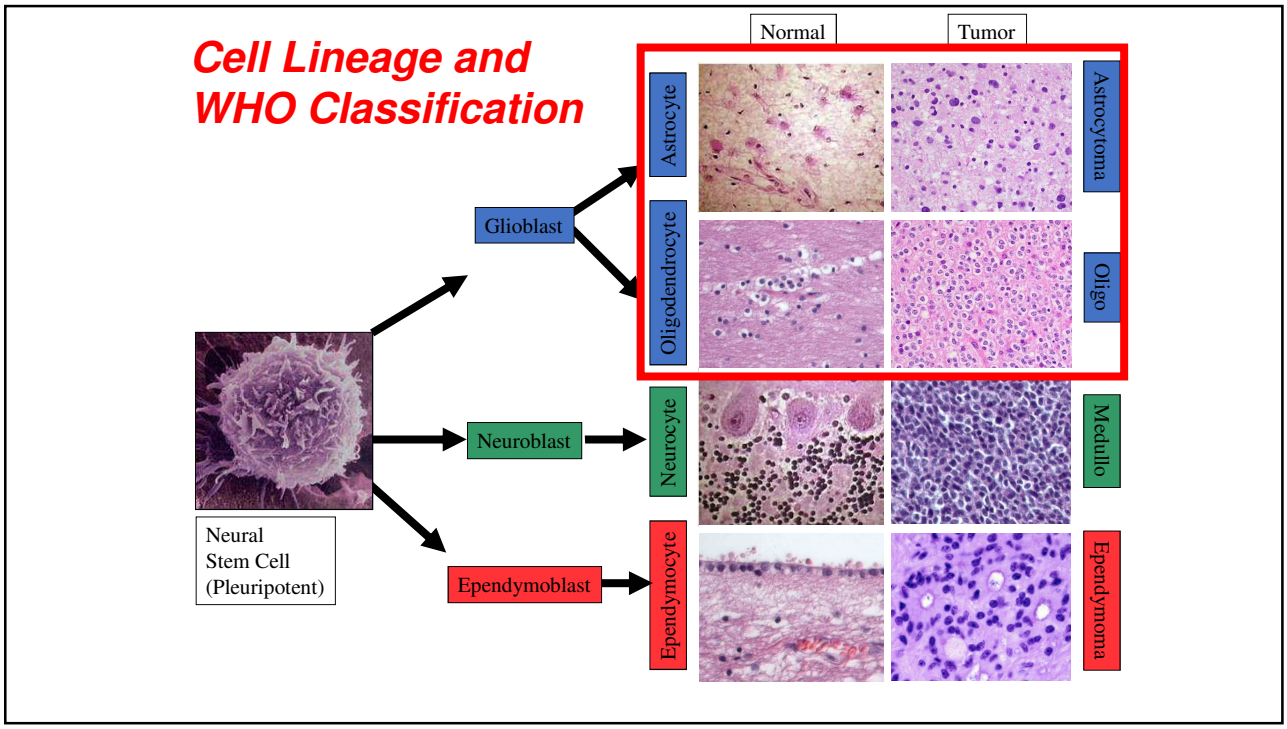
NOTICE OF DISCLOSURE

I have no relevant financial relationships with any commercial interest related to the content of this presentation.



Diagnostic approach in Neuropathology (old)

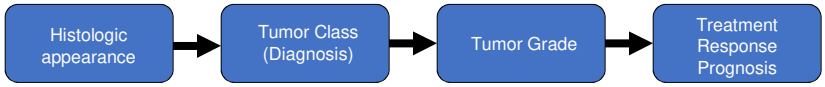
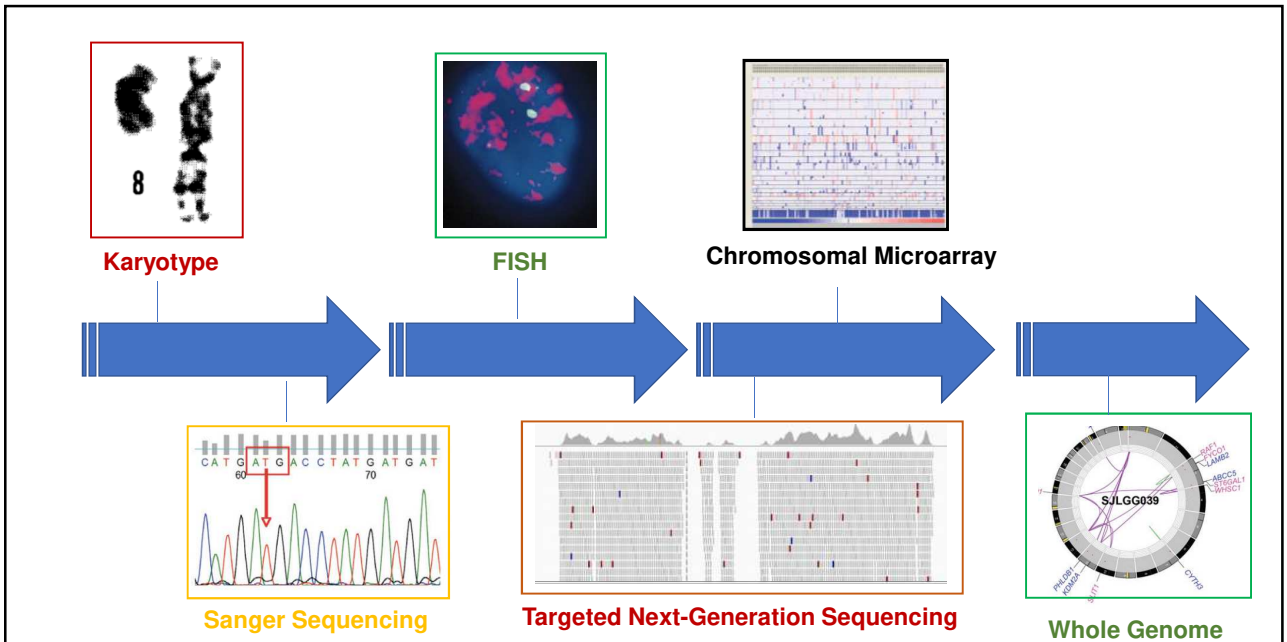


Table 1 WHO 2007 classification for diffuse gliomas

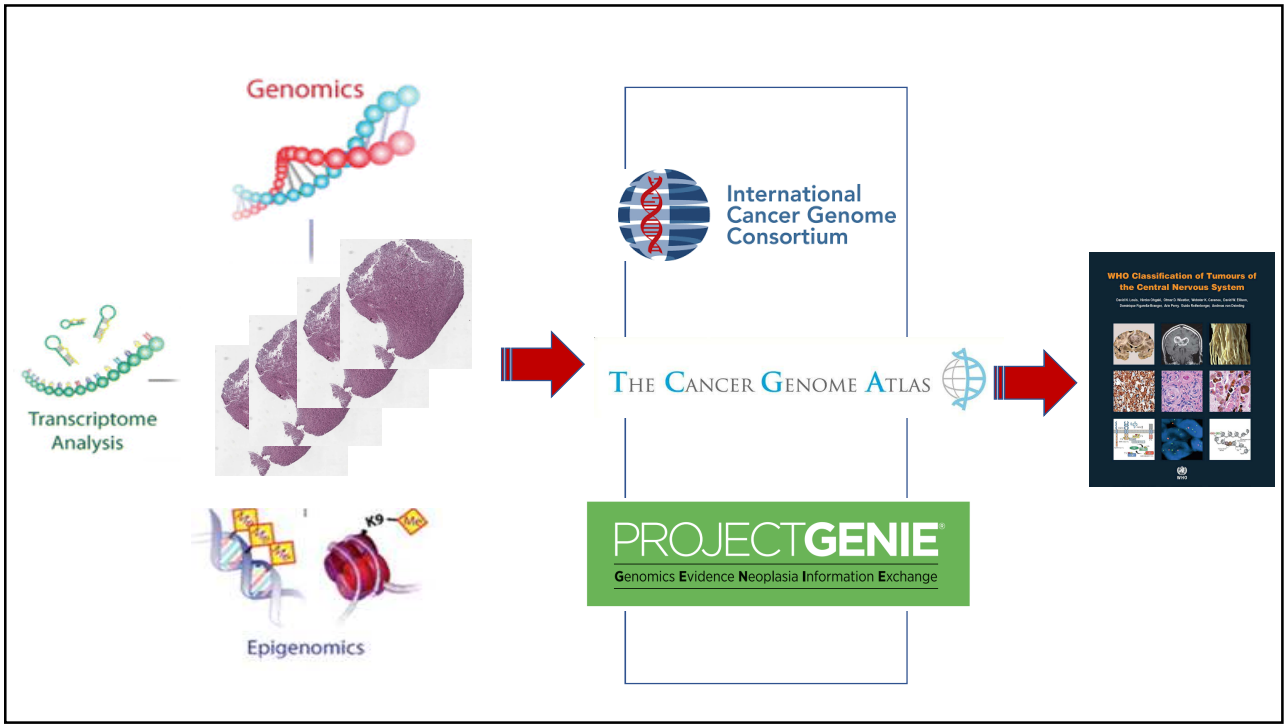
Type	Grade	Description	Median survival (years)
Astrocytoma	II	Found diffusely infiltrating into surrounding neural tissue; increased hypercellularity, no mitosis	6-8
Oligodendroglioma	II	Occur in the white matter and cortex of the cerebral hemispheres, low mitotic activity, no necrosis	12
Oligoastrocytoma	II	Diffuse mixed tumor with mixed glial background	3 to >10
Anaplastic-astrocytoma/ oligodendroglioma	III	Highly infiltrating tumors with increased mitotic activity; no necrosis or vascular proliferation	3
Glioblastoma	IV	Infiltrating glial neoplasm with necrosis and micro-vascular proliferation; high rate of mitosis	1 to 2

WHO, World Health Organization.

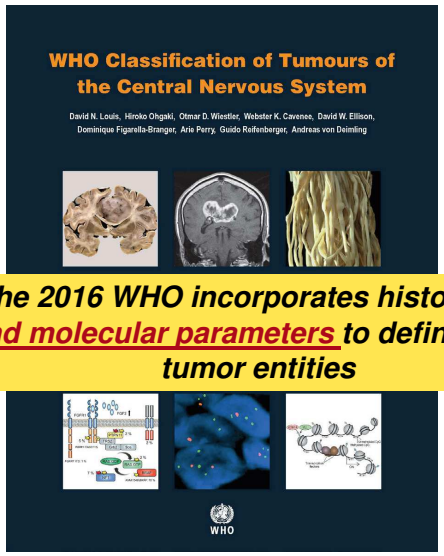
Vigneswaran et al., Ann Transl Med. 2015 May;3(7):95. PMID:26015937



Setty et al., J Mol Diagn. 2010 Nov; 12(6): 750–756. PMID:20847279
Bigner, SH et al. *Cancer Genet Cytogenet.* 1990 Jul 15;47(2):141-54. PMID: 2192793
Aldosari, N et al., *Arch Pathol Lab Med.* 2002 May;126(5):540-4. PMID: 11958658



Classification of CNS Tumors in 2016



The 2016 WHO incorporates histological and molecular parameters to define many tumor entities

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours		**Neuronal and mixed neuronal-glial tumours**	
Diffuse astrocytoma, IDH-mutant	9400/3	Dysembryoplastic neuroepithelial tumour	9413/0
Gemistocytic astrocytoma, IDH-mutant	9411/3	Gangliocytoma	9492/0
Diffuse astrocytoma, IDH-wildtype	9400/3	Ganglioglioma	9505/1
Diffuse astrocytoma, NOS	9400/3	Anaplastic ganglioglioma	9505/3
		Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Anaplastic astrocytoma, IDH-mutant	9401/3	Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Anaplastic astrocytoma, IDH-wildtype	9401/3	Papillary glioneuronal tumour	9509/1
Anaplastic astrocytoma, NOS	9401/3	Rosette-forming glioneuronal tumour	9509/1
		Diffuse leptomeningeal glioneuronal tumour	
Glioblastoma, IDH-wildtype	9440/3	Central neurocytoma	9506/1
Giant cell glioblastoma	9441/3	Extraventricular neurocytoma	9506/1
Gliosarcoma	9442/3	Cerebellar liponeurocytoma	9506/1
Epithelioid glioblastoma	9440/3	Paraganglioma	8693/1
Glioblastoma, IDH-mutant	9445/3		
Glioblastoma, NOS	9440/3		
		Tumours of the pineal region	
Diffuse midline glioma, H3 K27M-mutant	9385/3	Pineocytoma	9361/1
		Pinealparenchymal tumour of intermediate differentiation	9362/3
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3	Pineoblastoma	9362/3
Oligodendroglioma, NOS	9450/3	Papillary tumour of the pineal region	9395/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3	**Embryonal tumours**	
Anaplastic oligodendroglioma, NOS	9451/3	Medulloblastomas, genetically defined	
		Medulloblastoma, WNT-activated	9475/3
Oligoastrocytoma, NOS	9382/3	Medulloblastoma, SHH-activated and *TP53*-mutant	9474/3
Anaplastic oligoastrocytoma, NOS	9382/3	Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
		Medulloblastoma, non-WNT/non-SHH	9477/3
Other astrocytic tumours		*Medulloblastoma, group 3*	
Pilocytic astrocytoma	9421/1	*Medulloblastoma, group 4*	
Pilomyxoid astrocytoma	9425/3	Medulloblastomas, histologically defined	
Subependymal giant cell astrocytoma	9384/1	Medulloblastoma, classic	9470/3
Pleomorphic xanthoastrocytoma	9424/3	Medulloblastoma, desmoplastic/nodular	9471/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3	Medulloblastoma with extensive nodularity	9471/3
		Medulloblastoma, large cell / anaplastic	9474/3
Ependymal tumours		Medulloblastoma, NOS	9470/3
Subependymoma	9383/1		
Myxopapillary ependymoma	9394/1	Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3
Ependymoma	9391/3	*Embryonal tumour with multilayered rosettes, NOS*	9478/3
Papillary ependymoma	9393/3	Medulloepithelioma	9501/3
Clear cell ependymoma	9391/3	CNS neuroblastoma	9500/3
Tanycytic ependymoma	9391/3	CNS ganglioneuroblastoma	9490/3
Ependymoma, RELA fusion-positive	9396/3*	CNS embryonal tumour, NOS	9473/3
Anaplastic ependymoma	9392/3	Atypical teratoid/rhabdoid tumour	9508/3
		CNS embryonal tumour with rhabdoid features	9508/3
Other gliomas			
Chordoid glioma of the third ventricle	9444/1	**Tumours of the cranial and paraspinal nerves**	
Angiocentric glioma	9431/1	Schwannoma	9560/0
Astroblastoma	9430/3	Cellular schwannoma	9560/0
		Plexiform schwannoma	9560/0
Choroid plexus tumours			
Choroid plexus papilloma	9390/0		
Atypical choroid plexus papilloma	9390/1		
Choroid plexus carcinoma	9390/3		

Molecular component to diagnosis ←

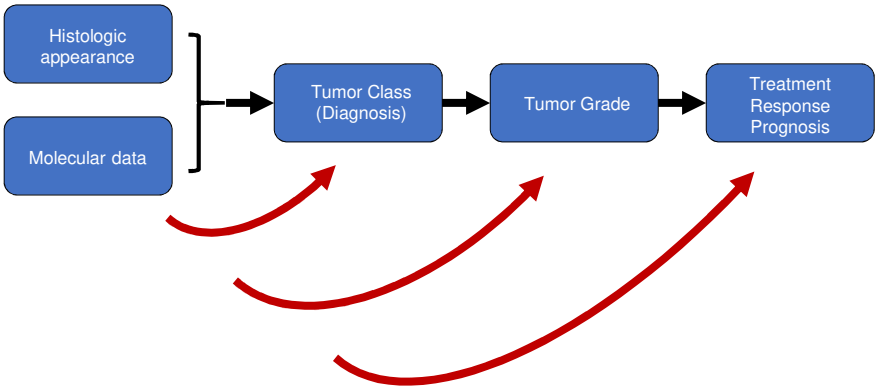
Classification of CNS tumors in 2021

Tumor Type	Genes/Molecular Profiles Characteristically Altered[a]
Astrocytoma, IDH-mutant	*IDH1, IDH2, ATRX, TP53, CDKN2A/B*
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1, IDH2,* 1p/19q, *TERT* promoter, *CIC, FUBP1, NOTCH1*
Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, chromosomes 7/10, *EGFR*
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	*MYB, MYBL1*
Angiocentric glioma	*MYB*
Polymorphous low-grade neuroepithelial tumor of the young	*BRAF*, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	*FGFR1, BRAF*
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53, ACVR1, PDGFRA, EGFR, EZHIP*
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53, ATRX*
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, *PDGFRA, MYCN, EGFR* (methylome)
Infant-type hemispheric glioma	NTRK family, *ALK, ROS, MET*
Pilocytic astrocytoma	*KIAA1549-BRAF, BRAF, NF1*
High-grade astrocytoma with piloid features	*BRAF, NF1, ATRX, CDKN2A/B* (methylome)
Pleomorphic xanthoastrocytoma	*BRAF, CDKN2A/B*
Subependymal giant cell astrocytoma	*TSC1, TSC2*
Chordoid glioma	*PRKCA*
Astroblastoma, *MN1*-altered	*MN1*
Ganglion cell tumors	*BRAF*
Dysembryoplastic neuroepithelial tumor	*FGFR1*
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chromosome 14, (methylome)
Papillary glioneuronal tumor	*PRKCA*
Rosette-forming glioneuronal tumor	*FGFR1, PIK3CA, NF1*
Myxoid glioneuronal tumor	*PDFGRA*

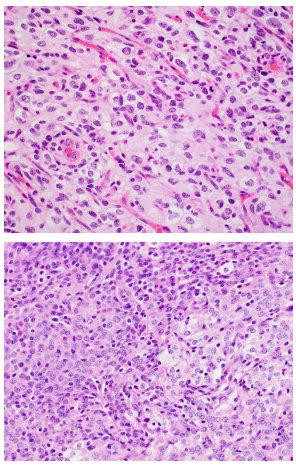
Tumor Type	Genes/Molecular Profiles Characteristically Altered[a]
Diffuse leptomeningeal glioneuronal tumor	*KIAA1549-BRAF* fusion, 1p (methylome)
Multinodular and vacuolating neuronal tumor	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	*PTEN*
Extraventricular neurocytoma	FGFR (*FGFR1-TACC1* fusion), IDH-wildtype
Supratentorial ependymomas	*ZFTA, RELA, YAP1, MAML2*
Posterior fossa ependymomas	H3 K27me3, *EZHIP* (methylome)
Spinal ependymomas	*NF2, MYCN*
Medulloblastoma, WNT-activated	*CTNNB1, APC*
Medulloblastoma, SHH-activated	*TP53, PTCH1, SUFU, SMO, MYCN, GLI2* (methylome)
Medulloblastoma, non-WNT/non-SHH	*MYC, MYCN, PRDM6, KDM6A* (methylome)
Atypical teratoid/rhabdoid tumor	*SMARCB1, SMARCA4*
Embryonal tumor with multilayered rosettes	C19MC, *DICER1*
CNS neuroblastoma, *FOXR2*-activated	*FOXR2*
CNS tumor with *BCOR* internal tandem duplication	*BCOR*
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant	*SMARCB1*
Meningiomas	*NF2, AKT1, TRAF7, SMO, PIK3CA*; *KLF4, SMARCE1, BAP1* in subtypes; H3K27me3; *TERT* promoter, *CDKN2A/B* in CNS WHO grade 3
Solitary fibrous tumor	*NAB2-STAT6*
Meningeal melanocytic tumors	*NRAS* (diffuse); *GNAQ, GNA11, PLCB4, CYSLTR2* (circumscribed)
Adamantinomatous craniopharyngioma	*CTNNB1*
Papillary craniopharyngioma	*BRAF*

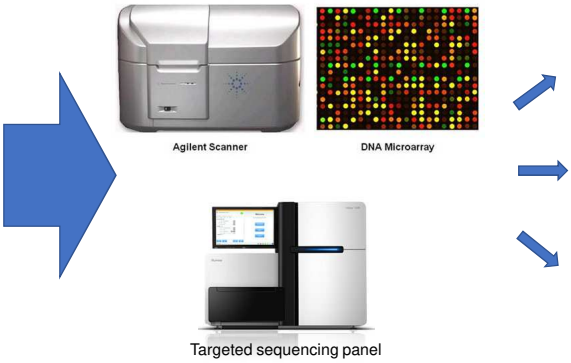
Louis, DN et al. *Neuro Oncol*. 2021 Jun 29. PMID: 34185076

Diagnostic approach in Neuropathology (new)



Molecular testing workflow at BWH



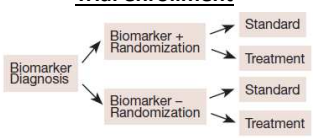


Integrated Diagnosis

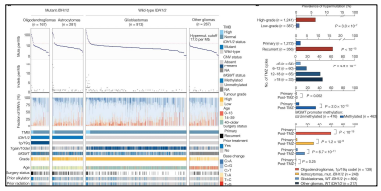
```
DIFFUSE ASTROCYTOMA, IDH-MUTANT
WHO GRADE 2

IDH1 R132H
TP53 R273H
ATRX K1054*
1p/19q RETAINED
```

Trial enrollment



Investigation



Touat, M et al Nature. 580, 517–523(2020). PMID: 32322066

Consensus guidelines for integrated diagnoses

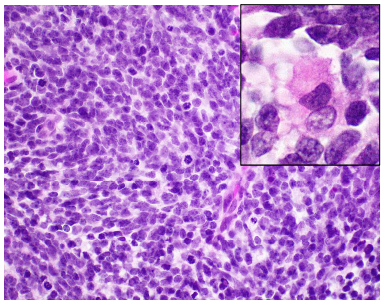
ISN-Haarlem meeting at 2014 issued recommended format for integrating molecular diagnostic data with histopathology:

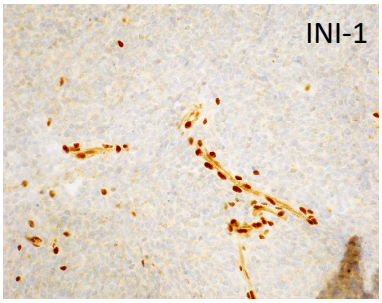
Layer 1: Integrated diagnosis (incorporating all tissue-based information)
Layer 2: Histological classification
Layer 3: WHO grade (reflecting natural history)
Layer 4: Molecular information

Louis, DN et al. *Brain Pathol*. 2014 Sep;24(5):429-35.

Consensus guidelines for integrated diagnoses

Example:

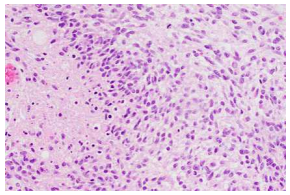


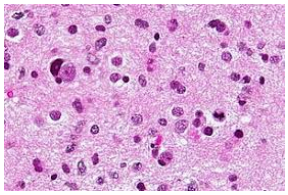


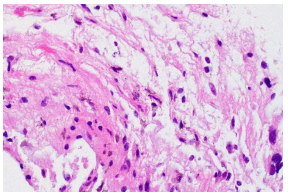
	A	B
Integrated diagnosis	Atypical teratoid/rhabdoid tumor, WHO grade IV	Embryonal tumor with rhabdoid features, WHO grade IV
Histological classification	Embryonal tumor with rhabdoid features	Embryonal tumor with rhabdoid features
WHO grade	IV	IV
Molecular information	INI1 loss of protein expression/mutation or BRG1 loss of protein expression/mutation	INI1 and BRG1 protein expression retained/not mutated or molecular/immunohistochemical testing not performed

Louis, DN et al. *Brain Pathol*. 2014 Sep;24(5):429-35.

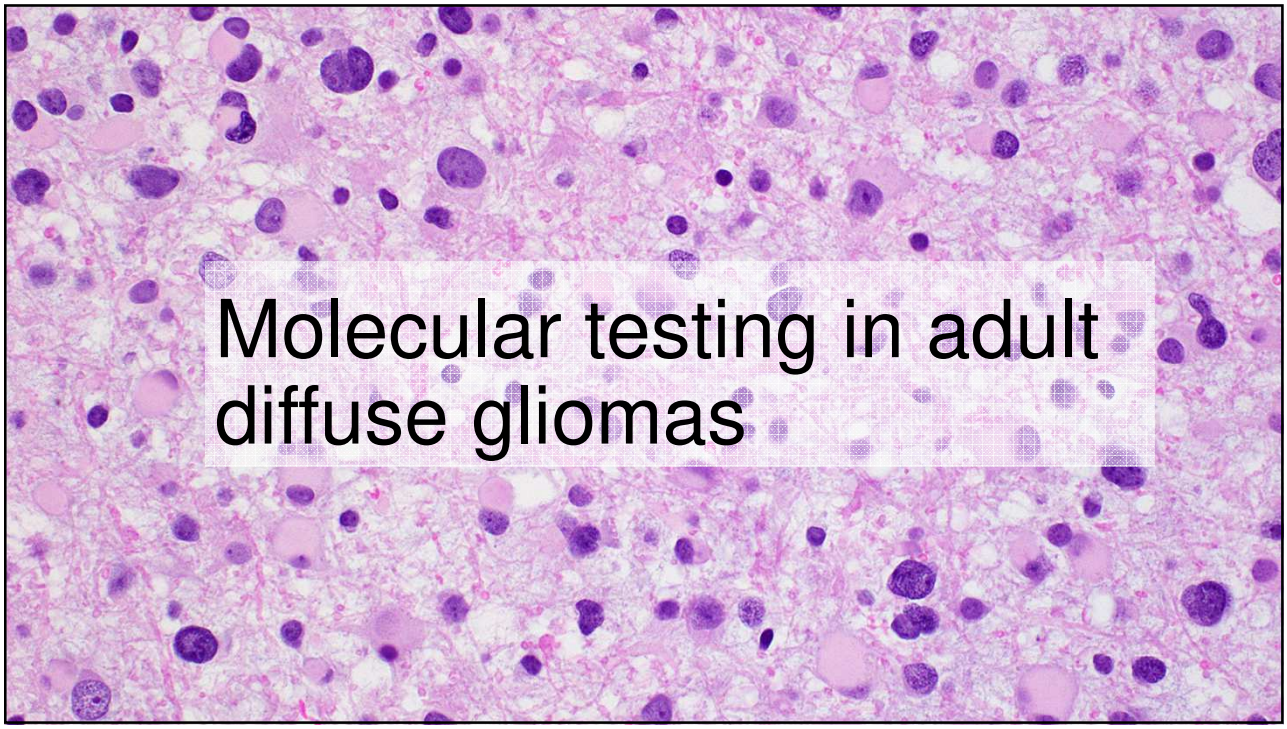
Integrated diagnoses in practice



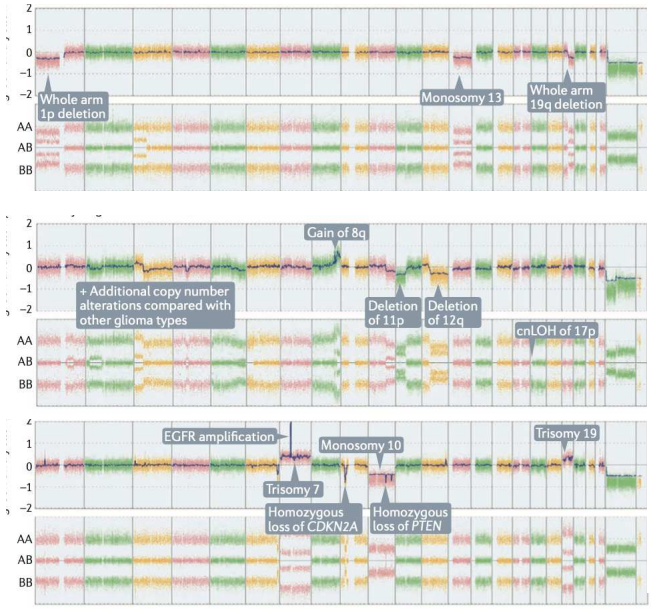




Histologic classification:	Glioblastoma, WHO grade 4	Diffuse glioma, grading deferred	Low grade glioma with piloid features
Molecular data:	TERT C228T Negative for IDH1/2 mutations +7/-10 EGFR amp	IDH1 R132H ATRX R781* TP53 R248W 1p/19q intact Negative for CDKN2A/B deletion	KIAA1549-BRAF fusion
Integrated diagnosis:	Glioblastoma, IDH-wildtype WHO grade 4	Diffuse Astrocytoma, IDH-mutant WHO grade 2	Pilocytic Astrocytoma, *BRAF*-rearranged WHO grade 1



Value in genome-wide CN assessment in adult gliomas



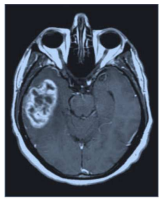
Oligodendroglioma, IDH-mutant, 1p/19q co-deleted

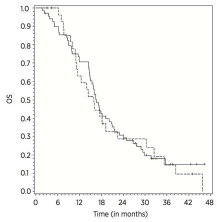
Astrocytoma, IDH-mutant

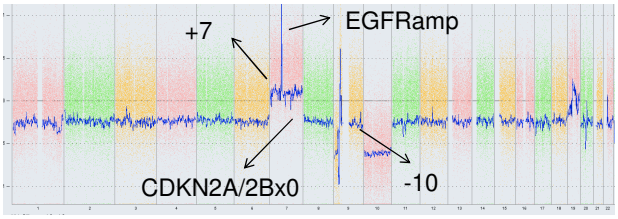
Glioblastoma, IDH-wildtype

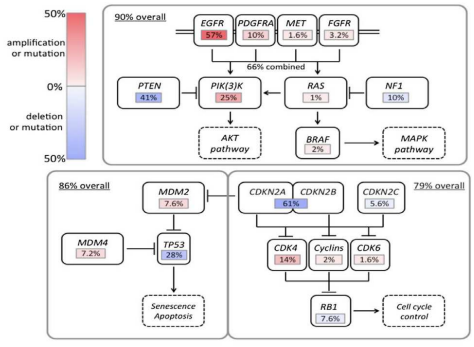
Buckner et al., Nat Rev Neurol. 2017 Jun;13(6):340-351. PMID: 28497806

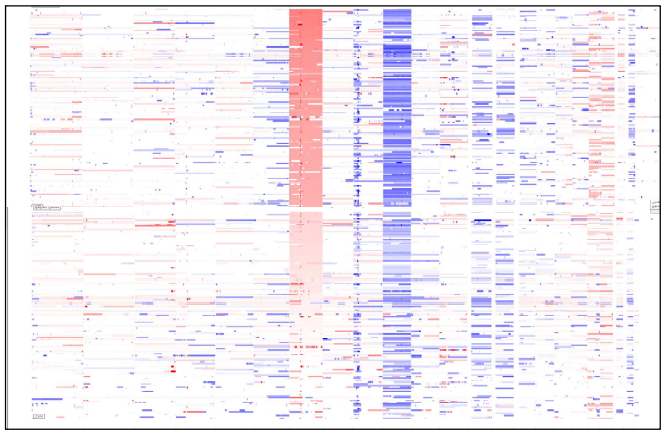
Glioblastoma, IDHwt





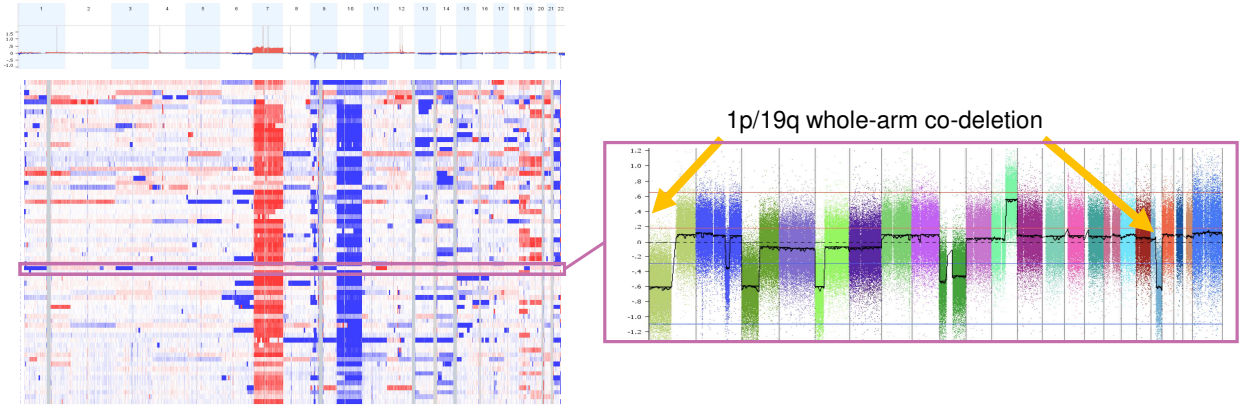






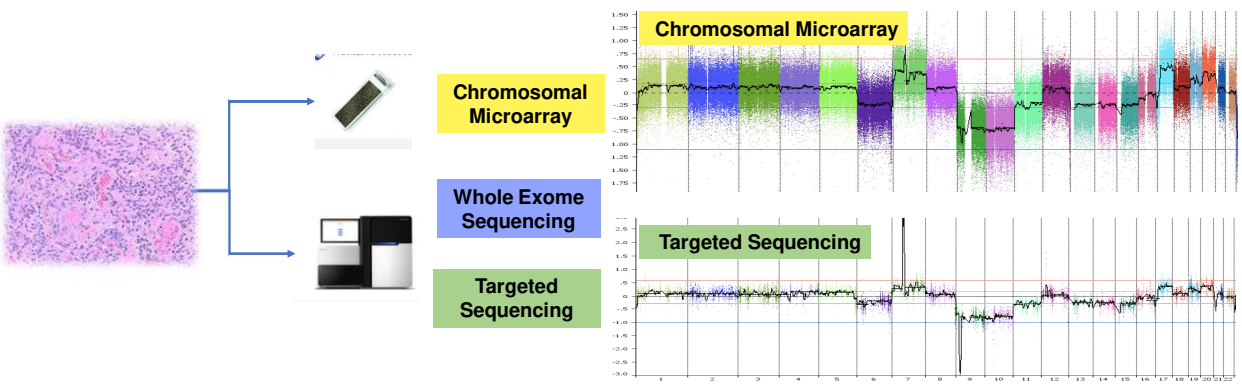
Alexander et al., Clin Cancer Res. 2018 Feb 15;24(4):737-743. PMID: 28814435
Brennan et al., Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
Omuro & DeAngelis. JAMA. 2013 Nov 6;310(17):1842-50. PMID: 24193082
Lee et al., Clin Cancer Res. 2015 Aug 15;21(16):3610-8. PMID:25910950

CN assessment of Glioblastoma



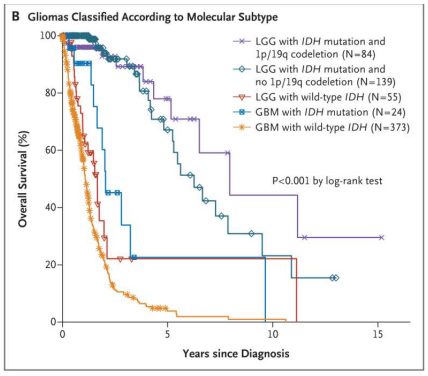
While there exists heterogeneity in the CN landscape of GBMs, this approach may lead to the identification of unanticipated outliers…

Methods to Obtain a Copy Number Signature



Copy number profile can be effectively evaluated by multiple assays

“Low-grade” IDH-wildtype gliomas



Acta Neuropathologica (2018) 136:805–810
https://doi.org/10.1007/s00401-018-1913-0

CORRESPONDENCE

cIMPACT-NOW update 3: recommended diagnostic criteria for “Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV”

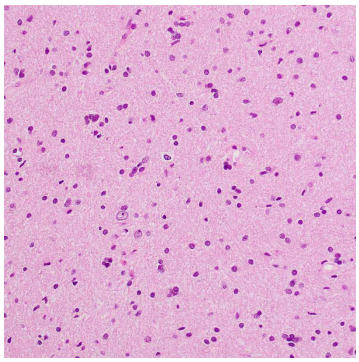
Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Robert B. Jenkins[6] · B. K. Kleinschmidt-DeMasters[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Roger Stupp[11] · Andreas von Deimling[12,13] · Michael Weller[14]

“Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV”
- Introduced to better capture biologic potential of LG IDH-wt astros

Histologically grade 2 or 3 astrocytoma with:
- EGFR amplification or
- Poly 7 and mono 10 or
- *TERT* promoter mutation

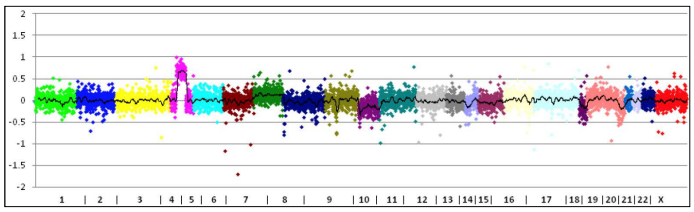
Brat et al., N Engl J Med. 2015 June 25; 372(26): 2481–2498. PMID: 26061751

For example:



Initial Diagnosis:

INFILTRATING GLIOMA, final classification and grading to be performed upon integration of molecular testing.



Integrated Diagnosis:

DIFFUSE ASTROCYTIC GLIOMA, IDH-wildtype, with molecular features of GLIOBLASTOMA.

WHO GRADE 4

Negative for IDH1/2 mutations

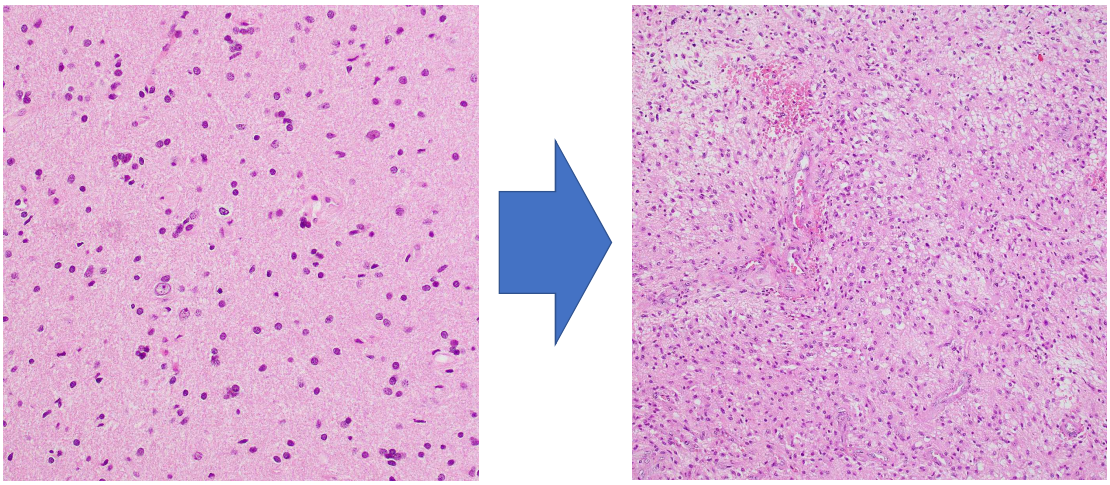
1p/19q RETAINED

MGMT promoter: UNMETHYLATED

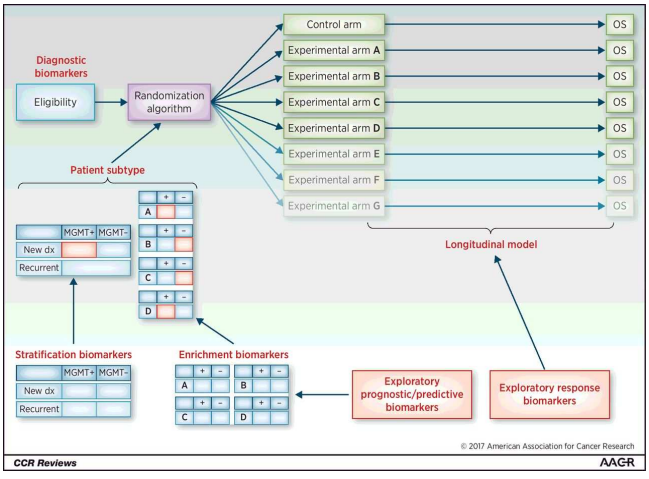
Polysomy 7, monosomy 10

PTEN p.K254Rfs*42

Four weeks later…



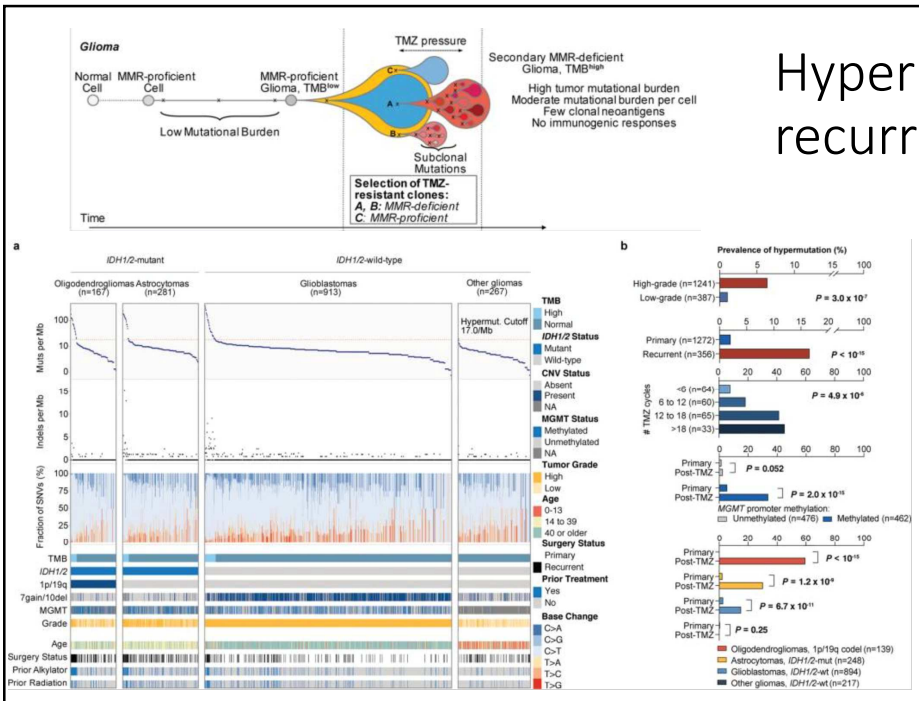
There remains an imminent need to improve outcomes for GBMs



Patients with potentially actionable alteration/example molecule (trial)	30 (50%)
EGFR amplification / depatuxizumab mafodotin (NCT02573324)	23 (38%)
BRAFV600E mutation / dabrafenib + trametinib (NCT02034110)	2 (3.3%)
IDH1/2 mutation / AG881 (NCT02481154)	2 (3.3%)
FGFR1-3 fusion or mutation / TAS-120 (NCT02052778)	2 (3.3%)
PTPRZ1-MET fusion / crizotinib (NCT02465060)	1 (1.7%)
Patients with incidental pathogenic germline variant (*CHEK2* and *PTPN11* mutations[1])	2 (3.3%)
Patients with tumor diagnosis refined	4 (6.7%)

Alexander et al., Clin Cancer Res. 2018 Feb 15;24(4):737-743. PMID: 28814435

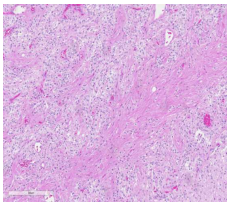
Hypermutation in recurrent gliomas



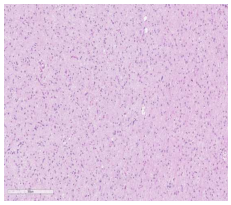
Touat et al., Nature. 2020 Apr;580(7804):517-523. PMID: 32322066

NCT04145115: A Study Testing the Effect of Immunotherapy (Ipilimumab and Nivolumab) in Patients With Recurrent Glioblastoma With Elevated Mutational Burden

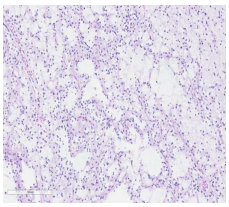
Workflow considerations for pediatric gliomas



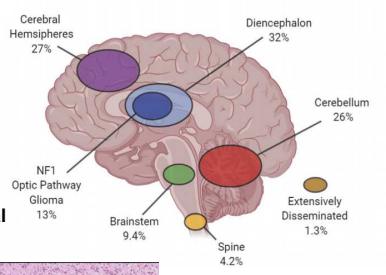
Pilocytic Astrocytoma (PA)

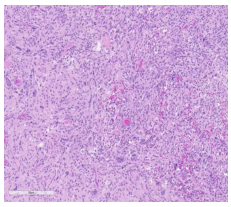


Diffuse Astrocytoma (DA)

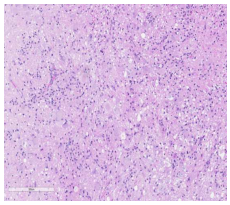


Dysembryoplastic Neuroepithelial Tumor (DNET)

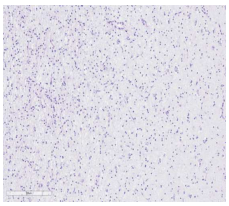




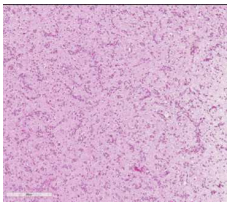
Pleomorphic Xanthoastrocytoma (PXA)



Ganglioglioma (GA)



Oligodendroglioma

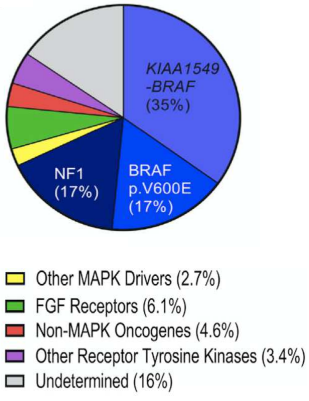


Angiocentric glioma

Pediatric low-grade gliomas (pLGG) – the most common childhood CNS tumor - include a spectrum of histological WHO Grade I and II entities

Ryall et al., Cancer Cell. 2020 Apr 13;37(4):569-583.e5. PMID: 32289278
Ryall et al., Acta Neuropathol Commun. 2020 Mar 12;8(1):30.PMID:32164789

Pilocytic Astrocytoma	*KIAA1549-BRAF* (70-80%) *FGFR1-TACC1* (3-5%) *FGFR1* SNV (3-5%) BRAF p.V600E (3-5%) Other *BRAF* Fusions (2-5%) *CRAF* Fusions (2-5%) *PTPN11* SNV (2-5%) *KRAS/HRAS* SNV (2-5%)
Subependymal Giant Cell Astrocytoma	*TSC1/2* SNV (85-95%)
Diffuse Astrocytoma	BRAF p.V600E (20-40%) *MYBL1* alteration (5-10%) *KIAA1549-BRAF* (5-10%) *FGFR1* SNV (2-5%) H3.3 p.K27M (2-5%) IDH1 p.R132H (2-5%) Other RTK SNV/Fusions (2-3%)
Pleomorphic Xanthoastrocytoma	BRAF p.V600E (80-90%)
Oligodendroglioma	*FGFR1*-TKD duplication (10-20%) *FGFR1* SNV (10-20%) BRAF p.V600E (5-10%) *FGFR1-TACC1* (3-5%) IDH1 p.R132H (3-5%) 1p/19q co-deletion (3-5%)
Ganglioglioma	BRAF p.V600E (40-50%) *KIAA1549-BRAF* (10-15%)
Desmoplastic Infantile Astrocytoma and Ganglioglioma	BRAF pV600E/D (40-60%) *FGFR1* SNV (5-10%) *KIAA1549-BRAF* (2-5%)
Dysembryoplastic Neuroepithelial Tumor	*FGFR1*-TKD duplication (20-30%) *FGFR1* SNV (20-30%) *FGFR1-TACC1* (10-15%) Other RTK SNV/Fusions (5-10%) BRAF p.V600E (5-10)
Papillary Glioneuronal Tumor	*SLC44A1-PRKCA* (80-90%)
Rosette-forming Glioneuronal Tumor	*PIK3CA* SNV (20-30%) *KIAA1549-BRAF* (20-30%) *FGFR1* SNV (20-30%)
Angiocentric Glioma	*MYB* (80-90%)
Chordoid Glioma of Third Ventricle	*PRKCA* SNV (80-90%)
Polymorphous Low-Grade Neuroepithelial tumor of the Young (PLNTY)	BRAF p.V600E (30-40%) *FGFR2/3* Fusions (30-40%)
Multinodular and vacuolating neuronal tumor (MVNT)	*MAP2K1* SNV/Indel (50-60%) BRAF p.V600E (5-10%) Other *BRAF* SNV (5-10%) *FGFR2* Fusions (3-5%)

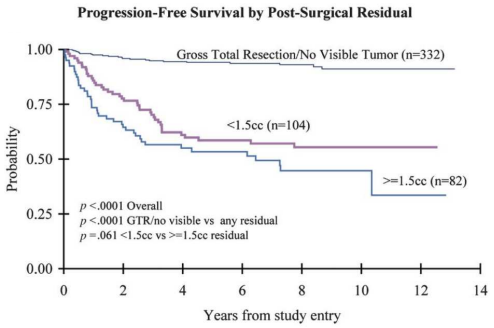


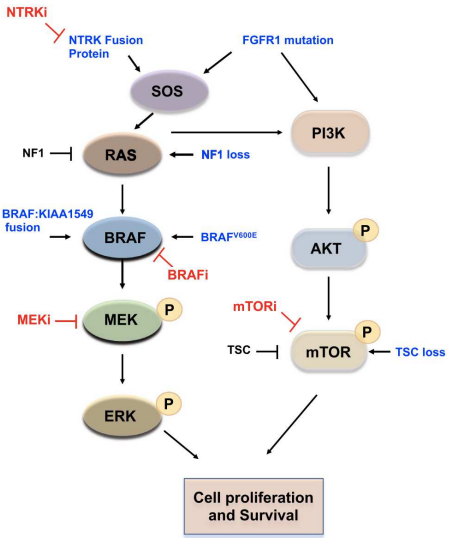
Recurrent/promiscuous genomic alterations can be found across histological subtypes of pLGG

Ryall et al., Cancer Cell. 2020 Apr 13;37(4):569583.e5.PMID: 32289278

Unlike adult gliomas, pLGG rarely transform.

- **Extent of resection** plays critical role in determining outcomes





Genomic characterization has revealed **near-universal defects in MAPK pathway**

Wisoff et al., Neurosurgery 2011 Jun;68(6):1548-54; discussion 1554-5. PMID:21368693
Tateishi et al., Brain Tumor Pathol. 2019 Apr;36(2):74-83. PMID: 30929113

Acta Neuropathologica (2019) 137:683–687
https://doi.org/10.1007/s00401-019-01987-0

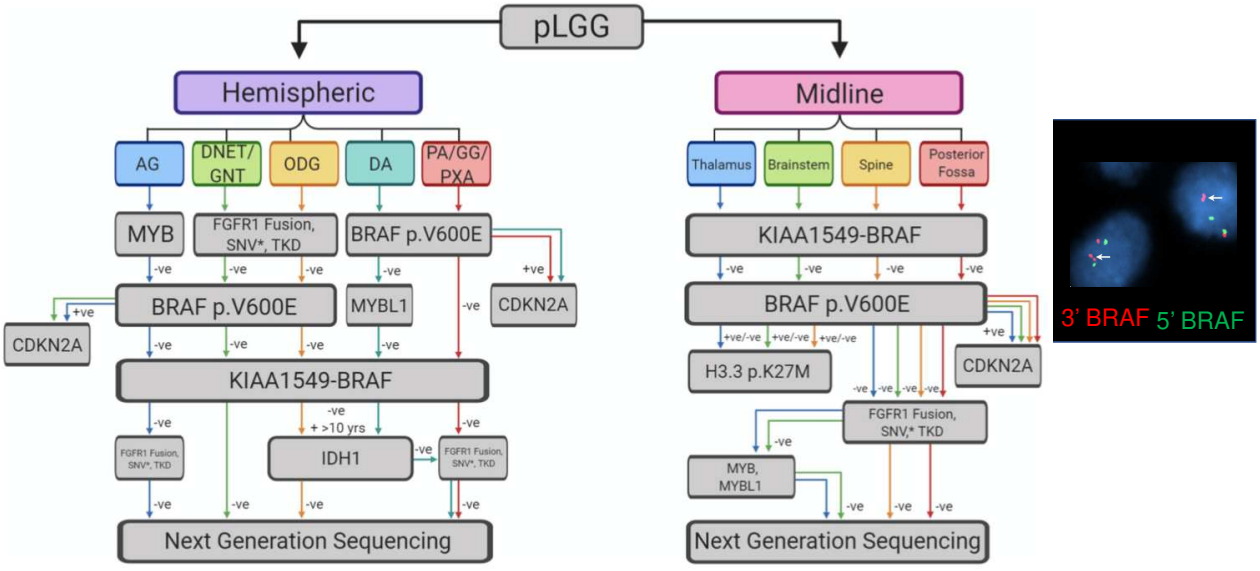
CORRESPONDENCE

cIMPACT-NOW update 4: diffuse gliomas characterized by *MYB*, *MYBL1*, or *FGFR1* alterations or *BRAF*^{V600E} mutation

David W. Ellison[1] · Cynthia Hawkins[2] · David T. W. Jones[3,4] · Arzu Onar-Thomas[5] · Stefan M. Pfister[3,6] · Guido Reifenberger[7] · David N. Louis[8]

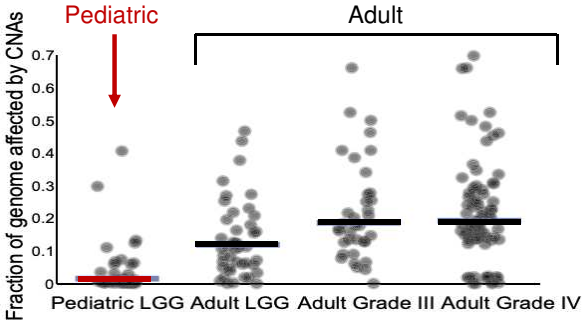
- The majority (~84%) of LG diffuse gliomas in children have one of the above alterations as sole driver event
- Tumors usually show grade 2 histology (i.e. no vascular proliferation, necrosis, or high mitotic rate)
- Survival rate far superior to adult IDH/H3 wild-type tumors
- Recommend vague classification with named alteration in top line

Report format for diffuse glioma	
Integrated diagnosis	Diffuse glioma, *MYB*-altered
Histologic classification	Diffuse astrocytoma
WHO grade	TBD[a]
Molecular data	IDH-wildtype, H3-wildtype, *MYB–PCDHGA1* fusion gene

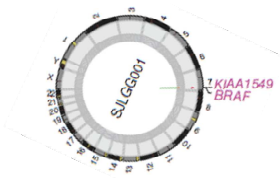


Targeted or genome-wide NGS testing provides highest yield for dx of pLGG

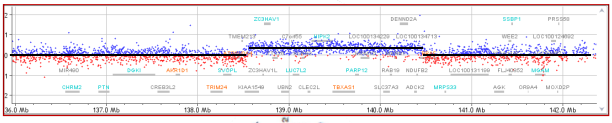
Gupta et al., Acta Neuropathol Commu 2014 Feb 14;2:18. PMID:24529209
Ryall et al., Acta Neuropathol Commun. 2020 Mar 12;8(1):30.PMID:32164789

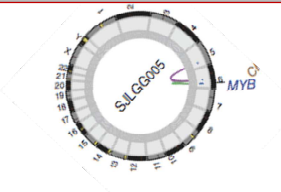


pLGG display relatively **simple genomes** predominantly **driven by structural variants** often associated with copy number imbalance

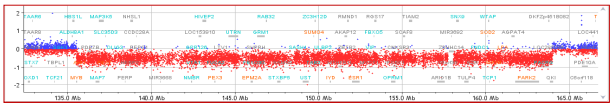


1.9 Mb single copy gain, characteristic of KIAA1549-BRAF fusion



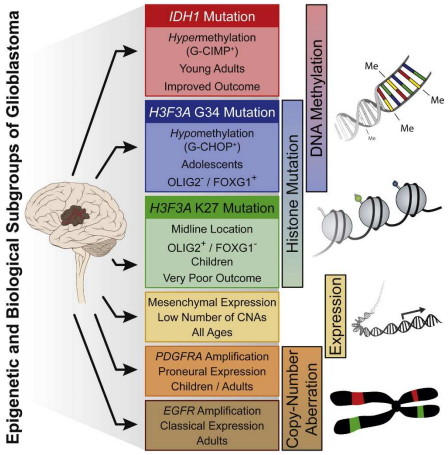


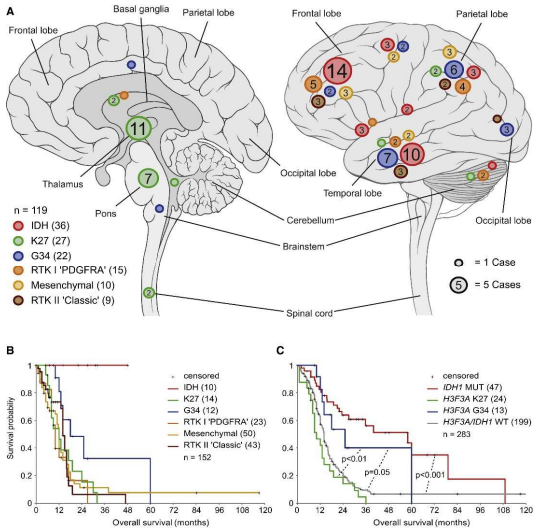
28.5 Mb deletion resulting in QKI-MYB fusion



Zhang et al., Nat Genet. 2013 Jun;45(6):602-12. PMID:23583981
Ramkisoon *et al.*, Proc Natl Acad Sci U S A 2013 May 14;110(20):8188-93. PMID: 23633565

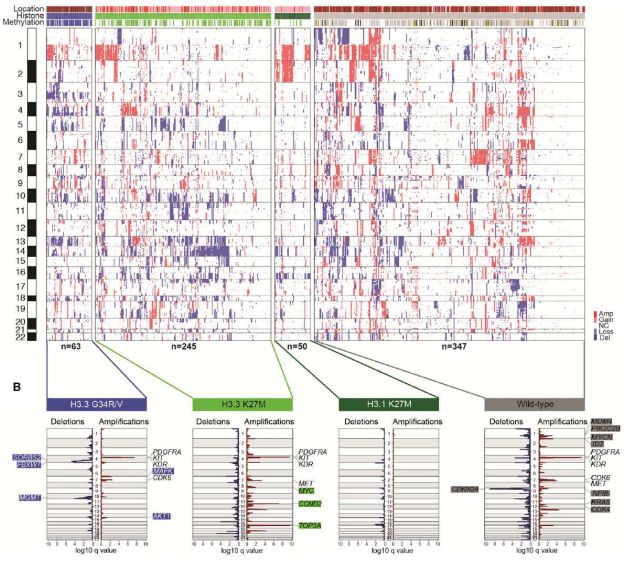
pHGG are frequently driven by chromatin modifying SNVs





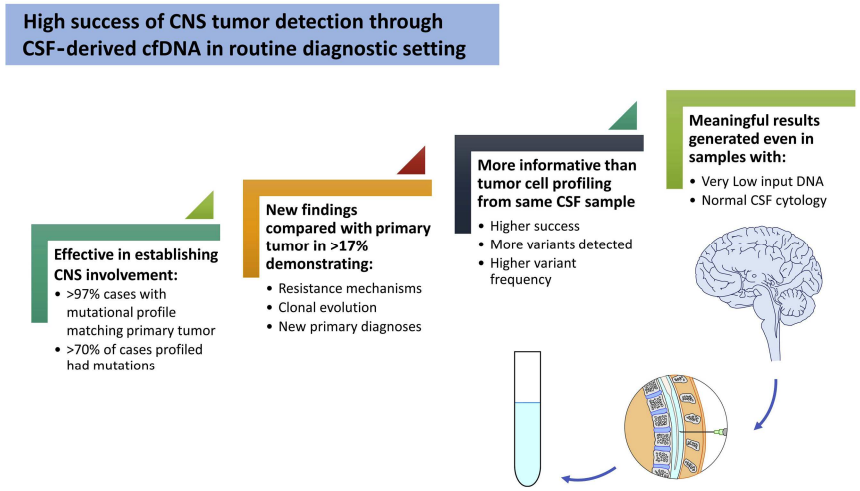
Sturm, et al. Cancer Cell. 2012 Oct 16;22(4):425-37. PMID: 2307965

CN profile pHGG



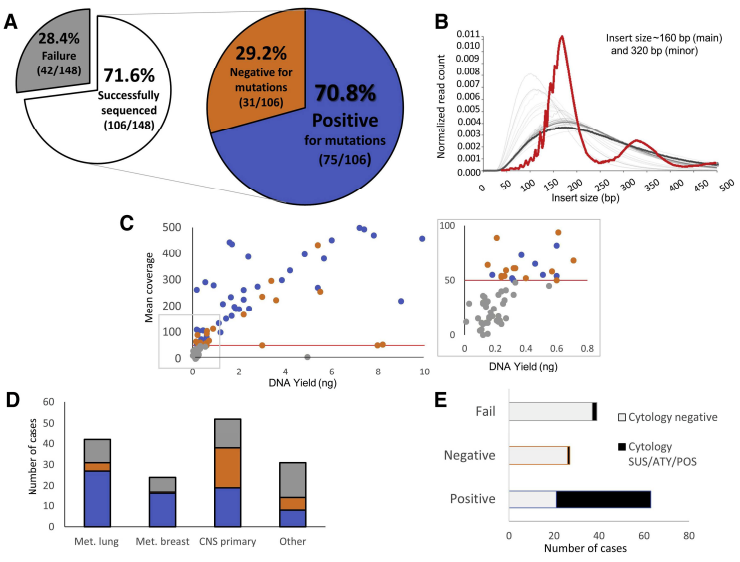
Mackay et al., 2017, Cancer Cell 32, 520–537.

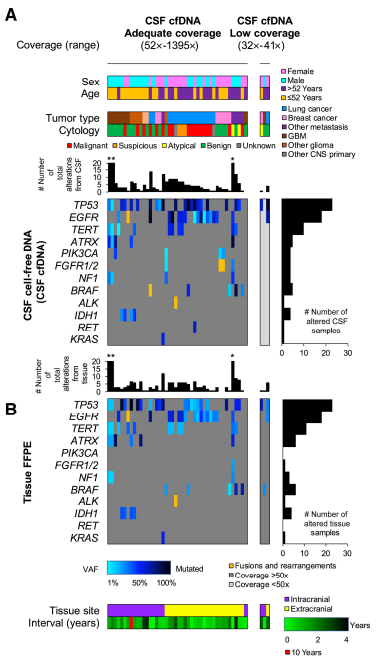
Prospect of liquid biopsy samples in CNS tumors



Bale et al., J Mol Diagn. 2021 Jun;23(6):742-752. PMID: 33781965

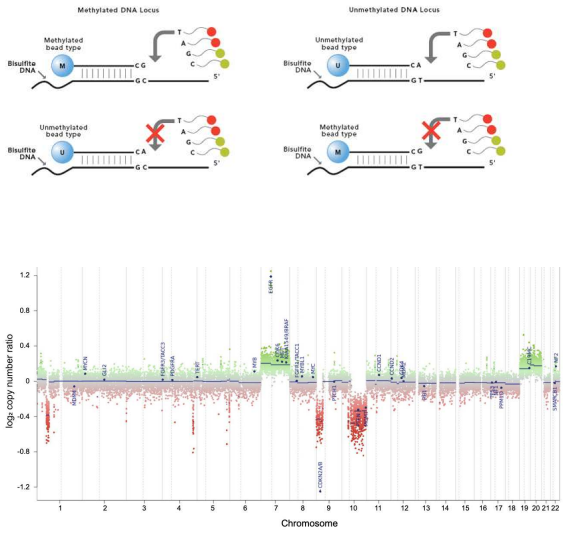
Robustness of CSF cfDNA testing

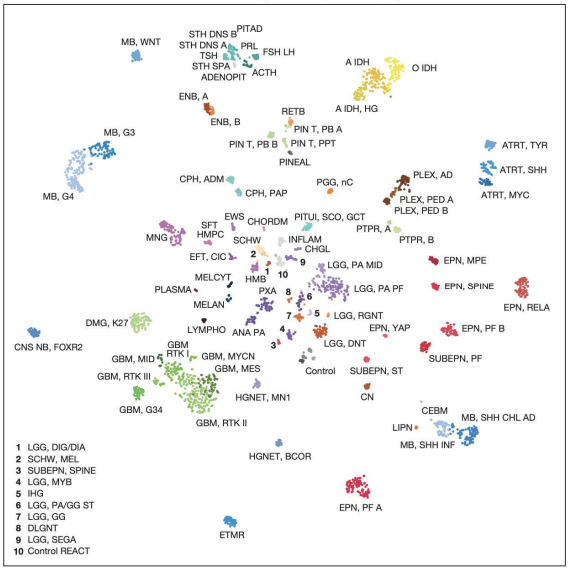




Bale et al., J Mol Diagn. 2021 Jun;23(6):742-752. PMID: 33781965

DNA Methylome as a Diagnostic Tool

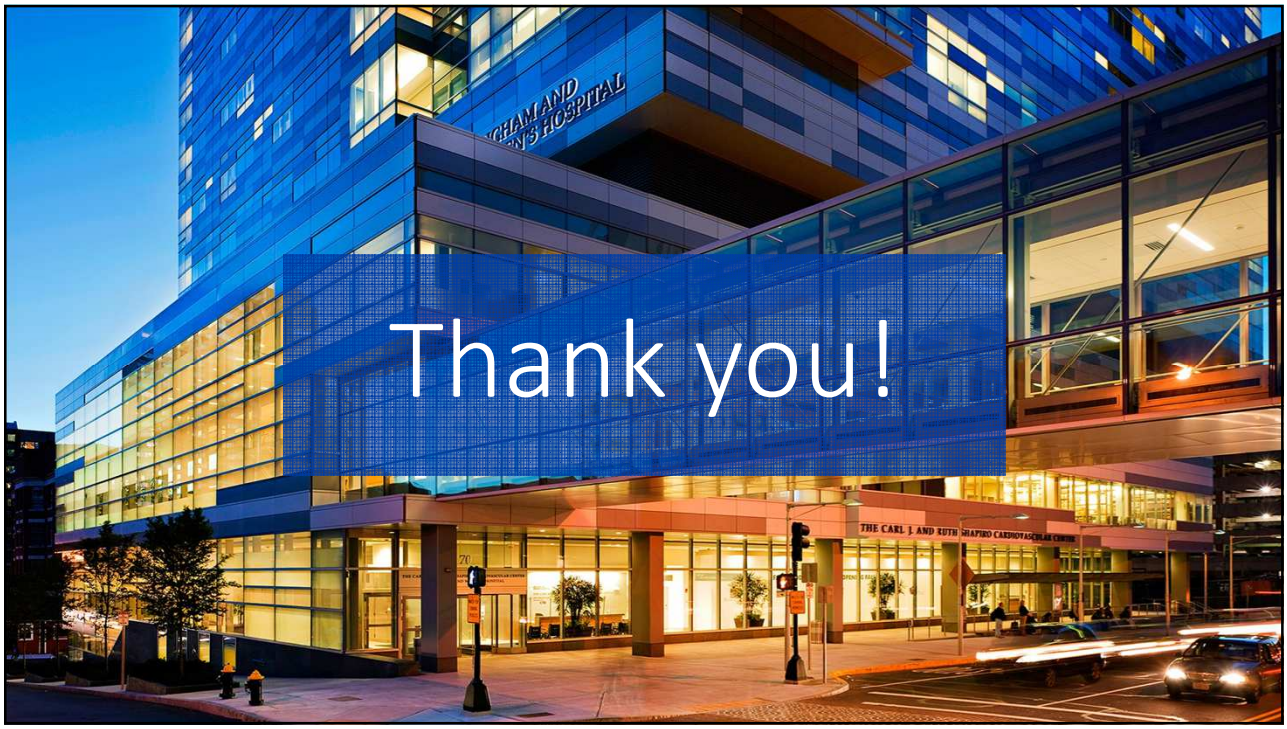




Capper et al., Nature. 2018 Mar 22;555(7697):469-474.

Summary

- Widespread adoption of genomic criteria in CNS WHO classification necessitates routine molecular profiling of CNS tumors for diagnosis.
- Biomarker based clinical trials are commonplace, especially as newer targeted agents are developed.
- No single testing strategy is best; decision regarding the incorporation of genomics into the diagnostic workup of specific CNS entities must be considered in the context of institutional policies and practices.
- Interpretation of genomic events must be carefully considered within the context of standard clinicopathologic features.


Thank you!