PEDIATRIC GLIOMAS– A CASE-BASED, PRACTICAL APPROACH TO USING THE WHO 2021 CLASSIFICATION

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DISCLOSURE

- I have nothing to declare

OBJECTIVES - AT THE END OF THIS TALK YOU SHOULD BE ABLE TO:

1

Approach the workup of a pediatric glioma

2

Apply the changes in the new WHO classification of CNS tumors as it applies to gliomas

3

Integrate molecular and morphologic data to generate a layered neuropathologic diagnosis

WHO 2016

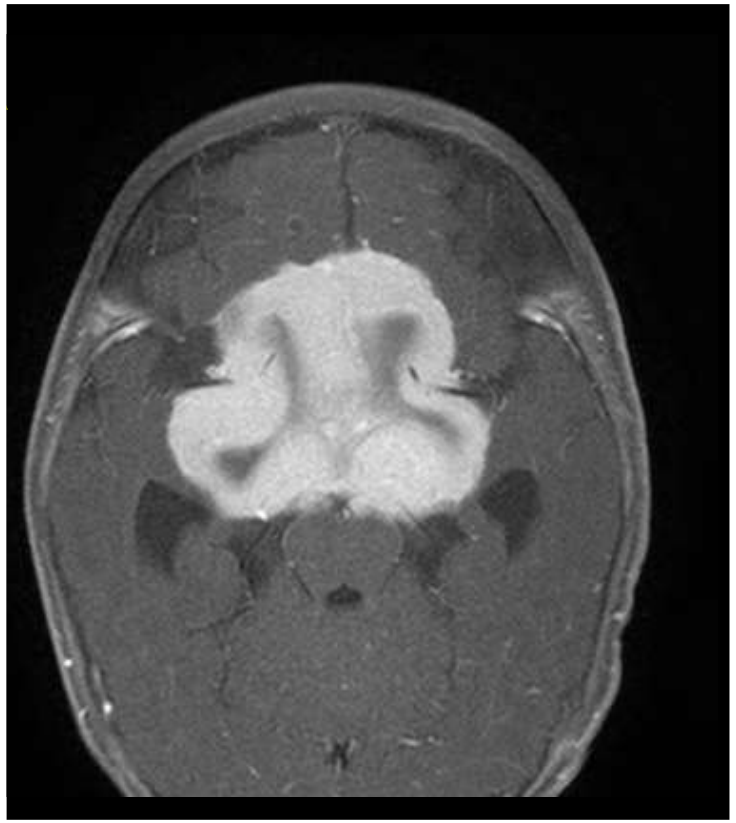
- Major goal of 2016 WHO was formulating concept of how CNS tumour diagnoses could be structured in the molecular era
- Integrated Diagnosis – incorporating molecular and morphologic data
- Incorporation of molecularly defined entities

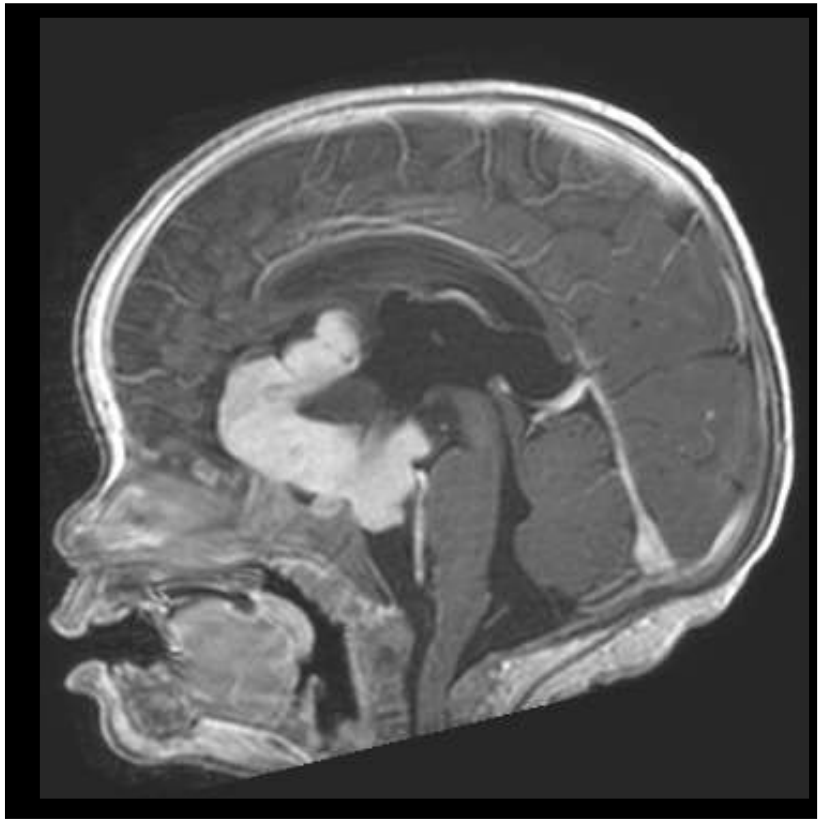
WHO 2021 – WHAT'S NEW FOR PEDIATRICS

- Major restructuring of **diffuse gliomas**:
  - Incorporation of distinct pediatric-type vs adult-type entities
  - Additional molecularly-defined entities
- Restructuring of **ependymomas** to recognize distinct location-based and molecular entities
- Additional molecularly-defined **embryonal tumors**
- Move away from assigned grades based on entity name to grading within an entity

CASE 1

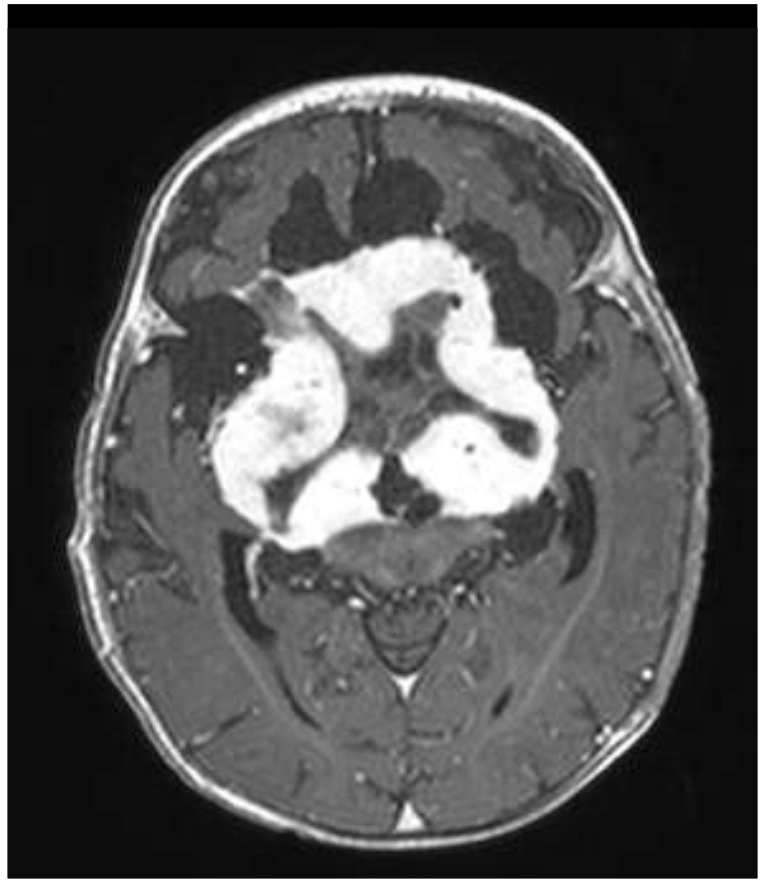
- 3-month-old girl presented with diencephalic syndrome and nystagmus

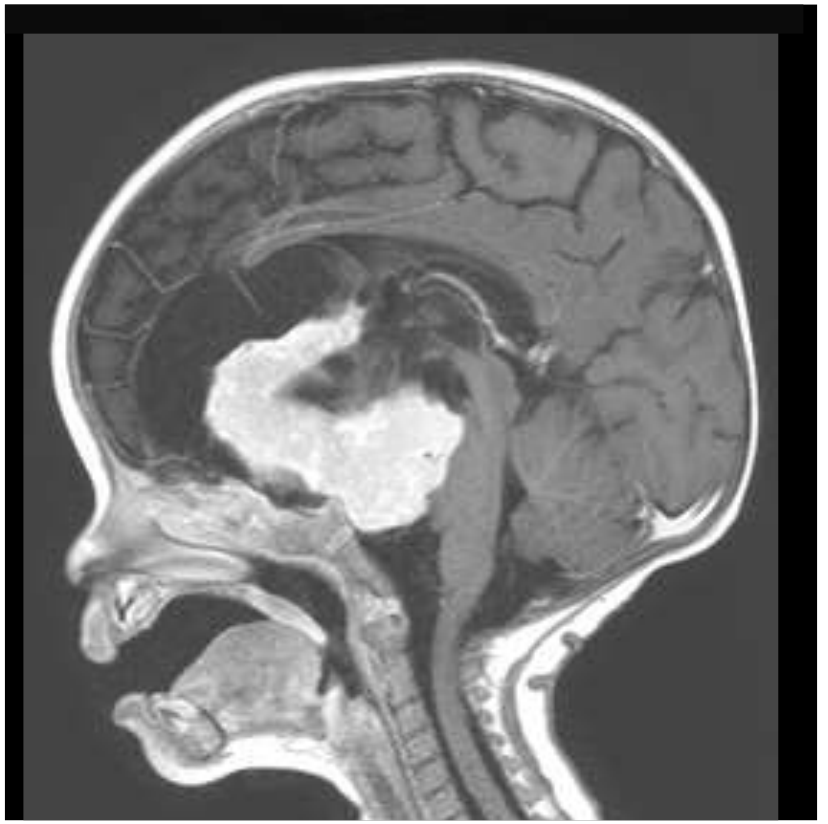


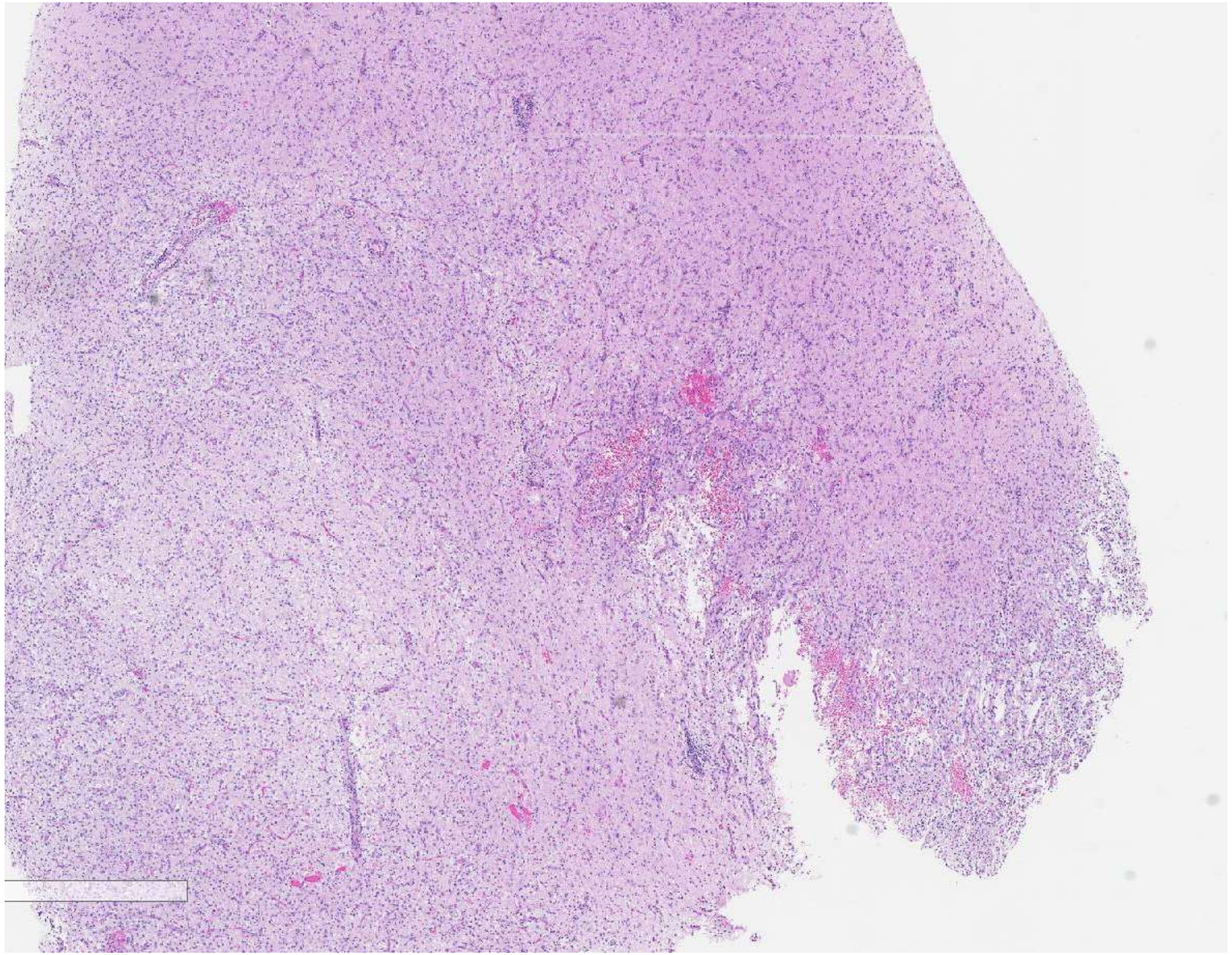


CASE 1

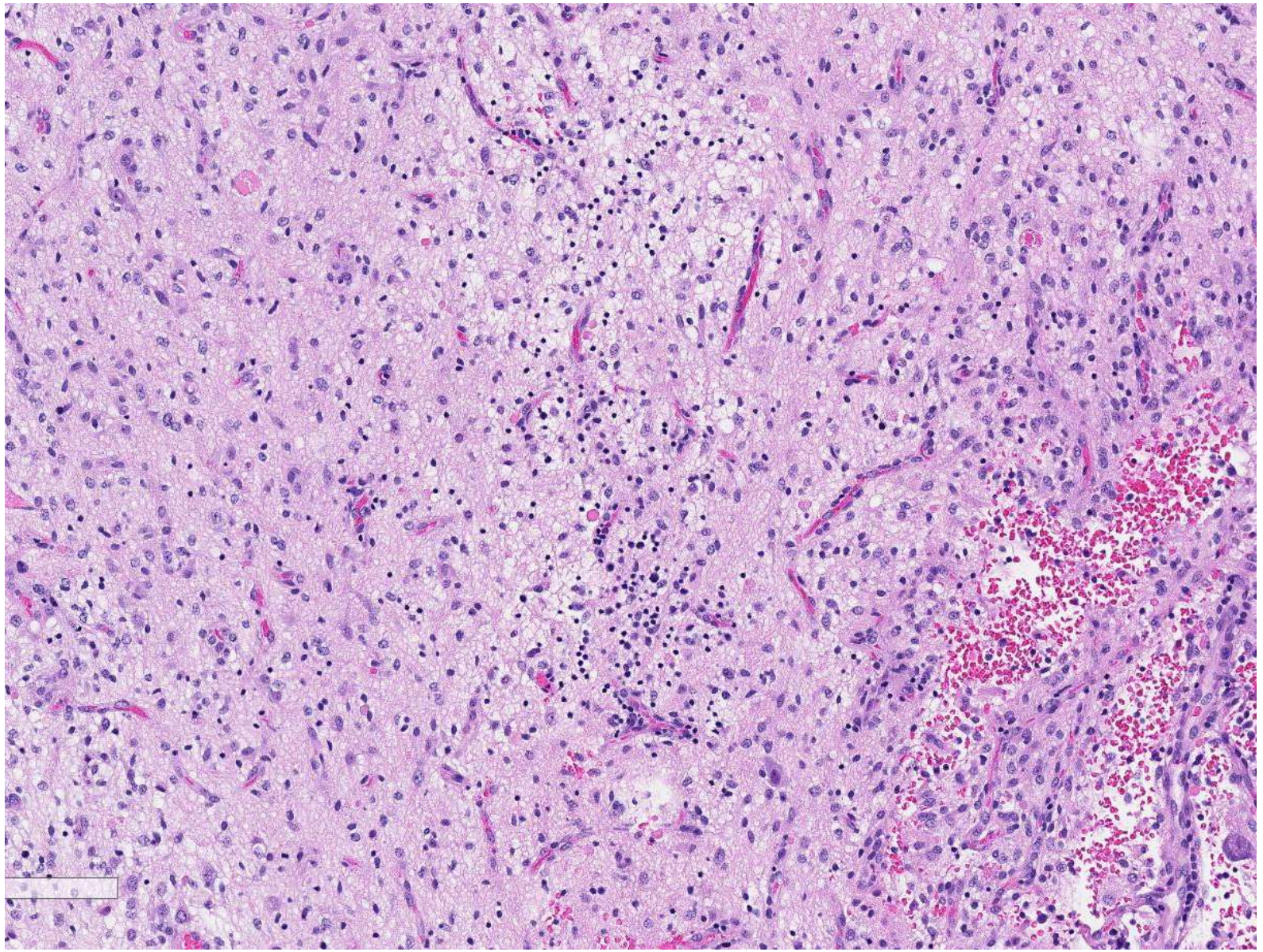
- Rapid clinical deterioration despite chemotherapy (Vinblastine)
- Biopsy







CASE 1 - BIOPSY



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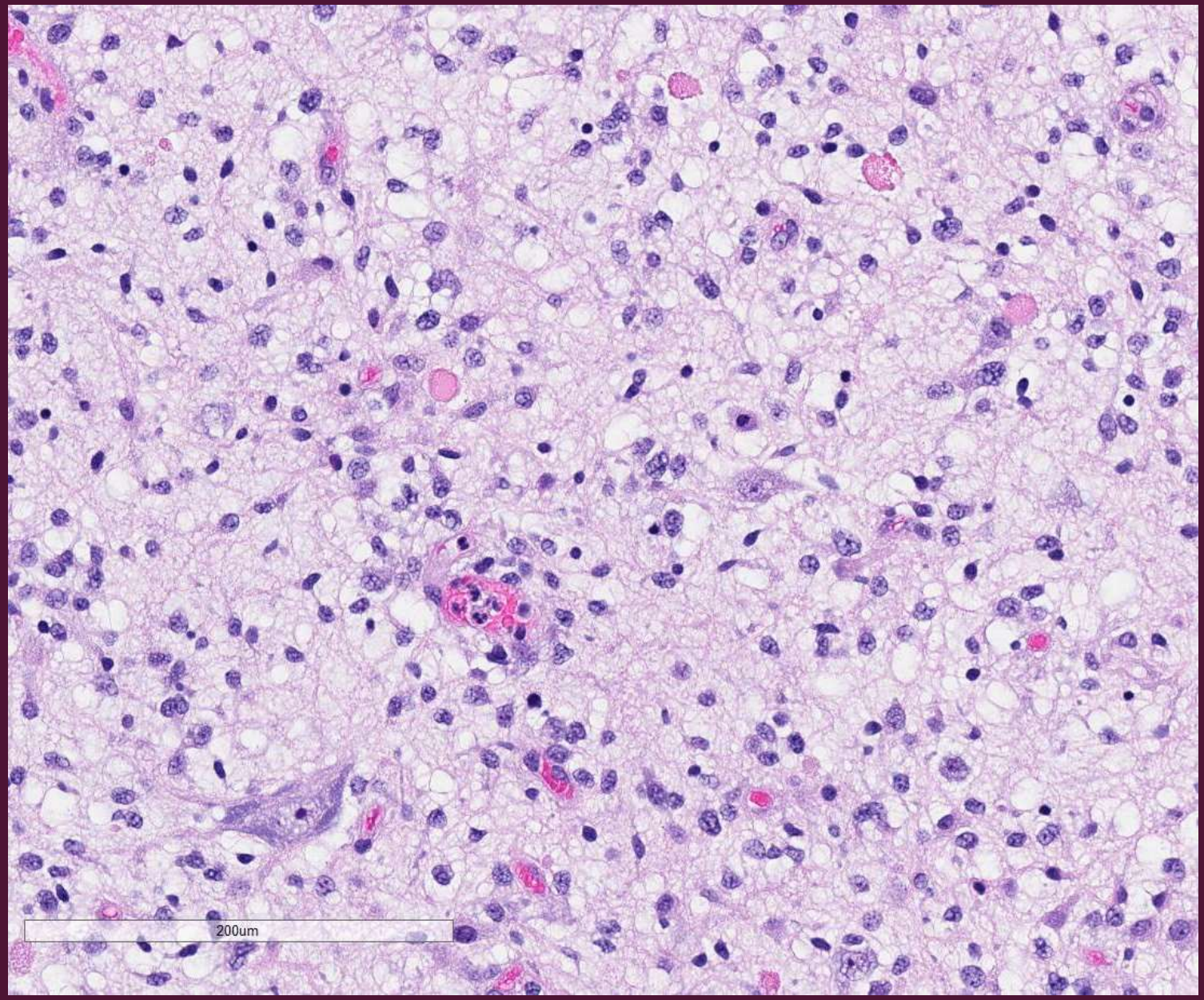

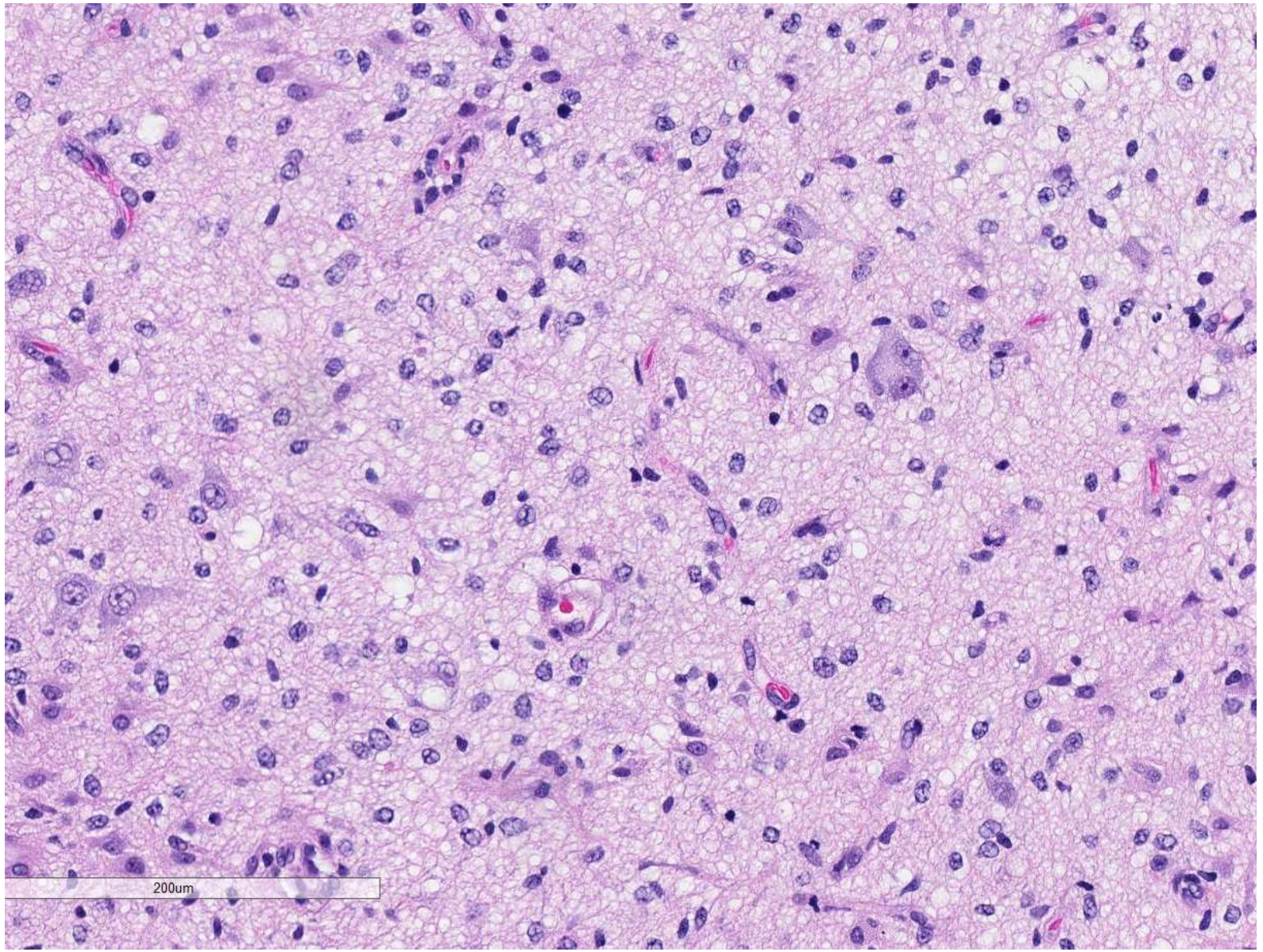

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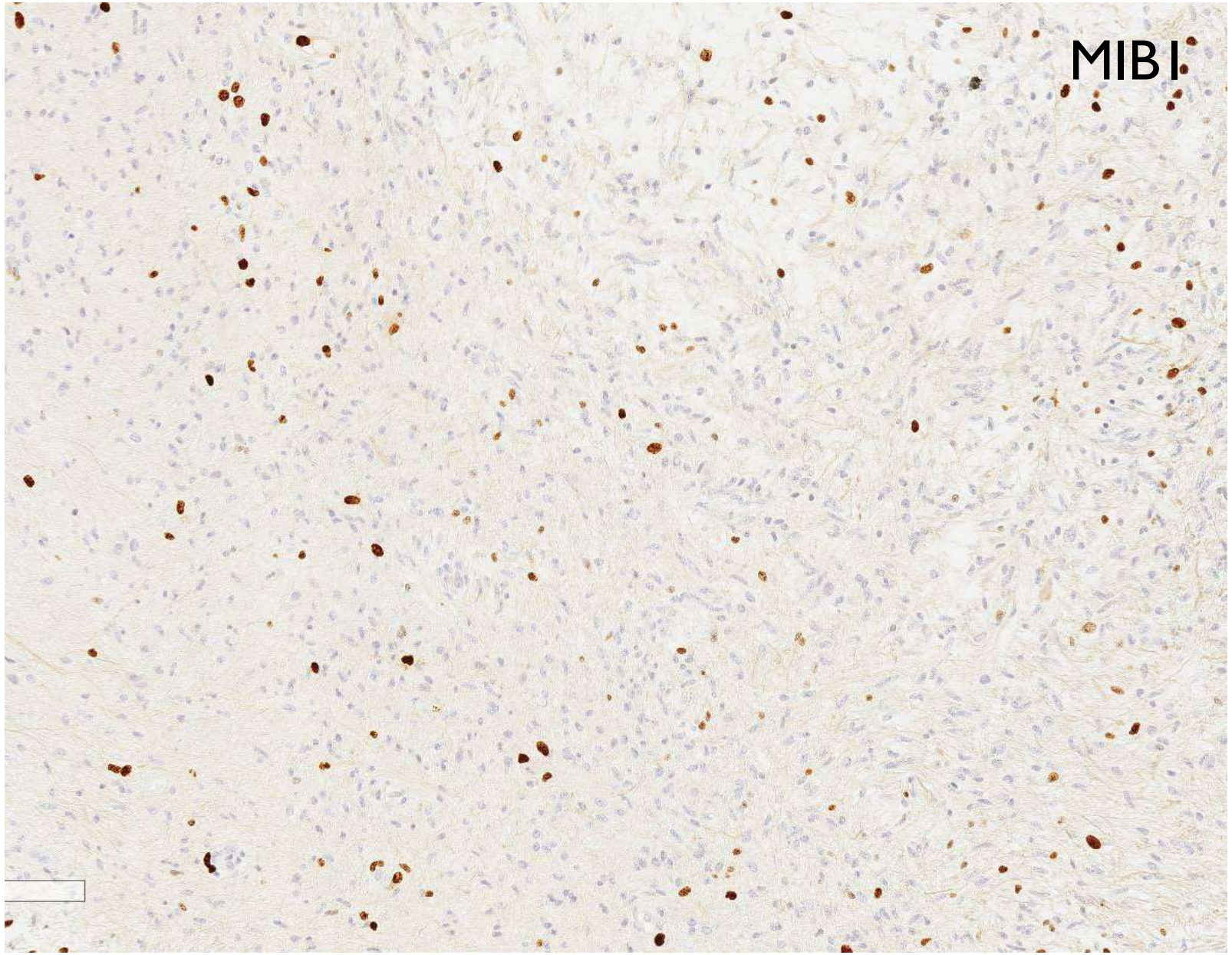
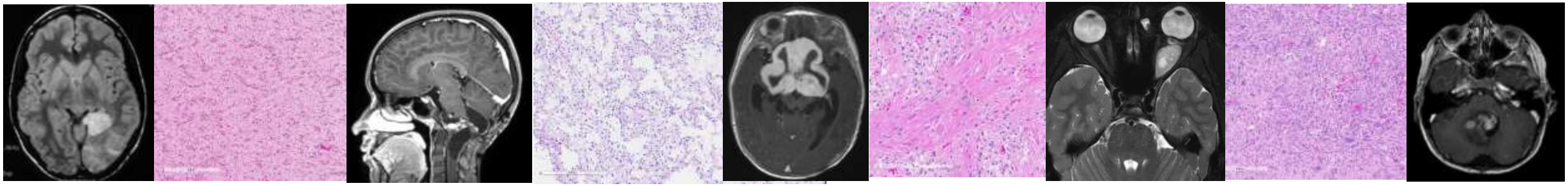


CASE 1- BIOPSY

PEDIATRIC LOW GRADE GLIOMA – GENERAL CONCEPTS

- Most common CNS neoplasm in children
- Distinct from adult "lower grade glioma"
- Histologically diverse group of tumors arising throughout CNS
- Now categorised under one of Paediatric-type diffuse low-grade gliomas, Circumscribed astrocytic gliomas or Glioneuronal and neuronal tumours

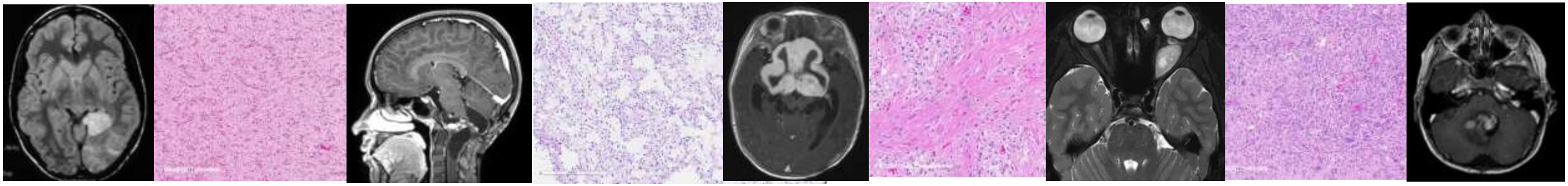


CLASSIFICATION OF GLIOMAS

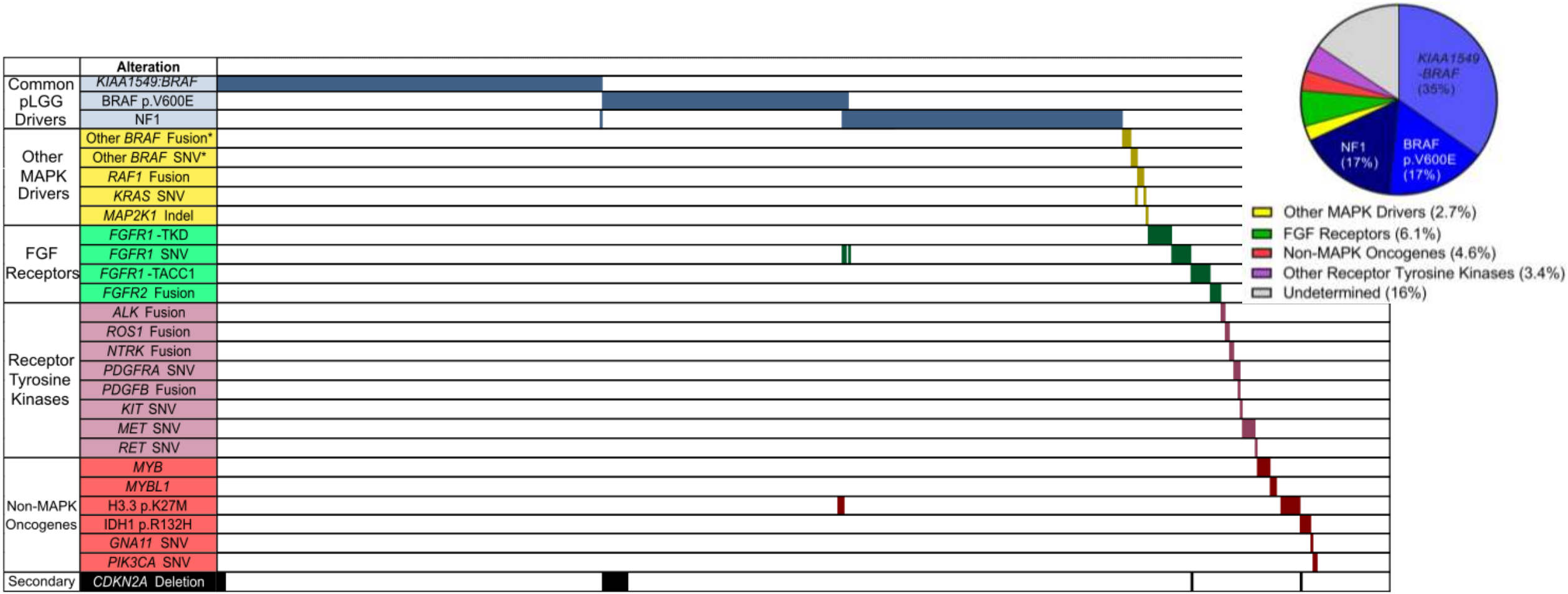
- **Adult-type diffuse gliomas**
  - Astrocytoma, IDH-mutant
  - Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  - Glioblastoma, IDH-wildtype
- **Paediatric-type diffuse high-grade gliomas**
  - Diffuse midline glioma, H3 K27-altered
  - Diffuse hemispheric glioma, H3 G34-mutant
  - Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
  - Infant-type hemispheric glioma
- **Paediatric-type diffuse low-grade gliomas**
  - Diffuse astrocytoma, MYB- or MYBL1-altered
  - Angiocentric glioma
  - Polymorphous low-grade neuroepithelial tumour of the young
  - Diffuse low-grade glioma, MAPK-altered
- **Circumscribed astrocytic gliomas**
  - Pilocytic astrocytoma
  - High-grade astrocytoma with piloid features
  - Pleomorphic xanthoastrocytoma
  - Subependymal giant cell astrocytoma
  - Chordoid glioma
  - Astroblastoma
- **Glioneuronal and neuronal tumours**
  - Ganglioglioma
  - DIG/DIA
  - *DGONC*
  - DNT
  - Papillary glioneuronal tumour
  - RGNT
  - MGNT
  - DLGNT
  - Central neurocytoma
  - Extraventricular neurocytoma

PEDIATRIC LOW GRADE GLIOMA – GENERAL CONCEPTS

- Molecular vs Histology
- Do I really need molecular?
- What does the molecular mean?



THE MOLECULAR LANDSCAPE OF PLGG

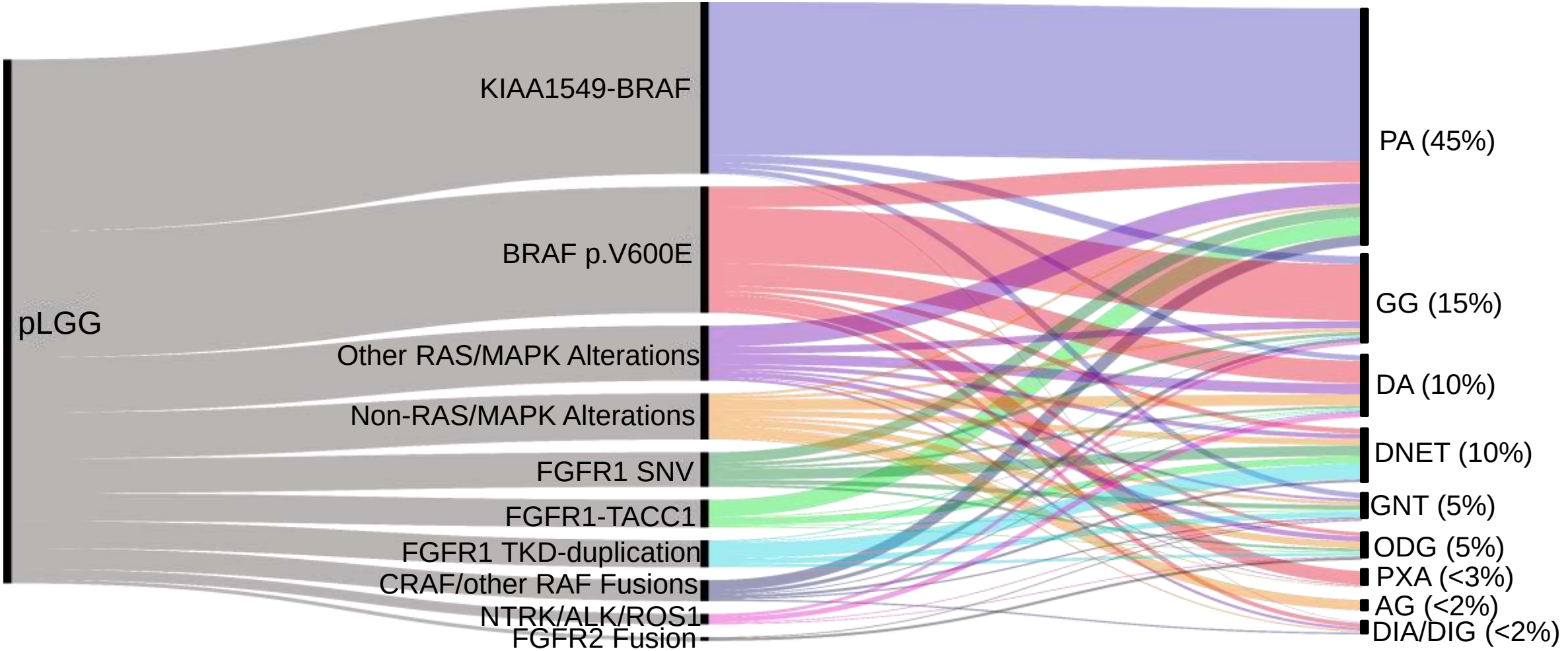


Ryall et al., Cancer Cell, 2020

MOLECULAR VS HISTOLOGY: LOW GRADE GLIOMAS WITH ENRICHED MOLECULAR ALTERATIONS

Tumour	Characteristic Gene
Papillary glioneuronal tumour	*PRKCA*
Rosette-forming glioneuronal tumour	*FGFR1* & *PIK3CA*
Myxoid glioneuronal tumour	*PDFGRA*
Diffuse leptomeningeal glioneuronal tumour	*KIAA1549-BRAF* fusion, 1p del
Astroblastoma, *MN1*-altered	*MN1* fusion
Pleomorphic xanthoastrocytoma	*BRAF* & *CDKN2A/B hom del*
Pilocytic astrocytoma	*KIAA1549-BRAF*, *BRAF*, *NF1*
Angiocentric glioma	*MYB* fusion
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	*MYB*, *MYBL1* fusion
PLNTY	*FGFR2* fusion

MUTATION VS HISTOLOGY IN PAEDIATRIC LOW GRADE GLIOMA – MIX AND MATCH

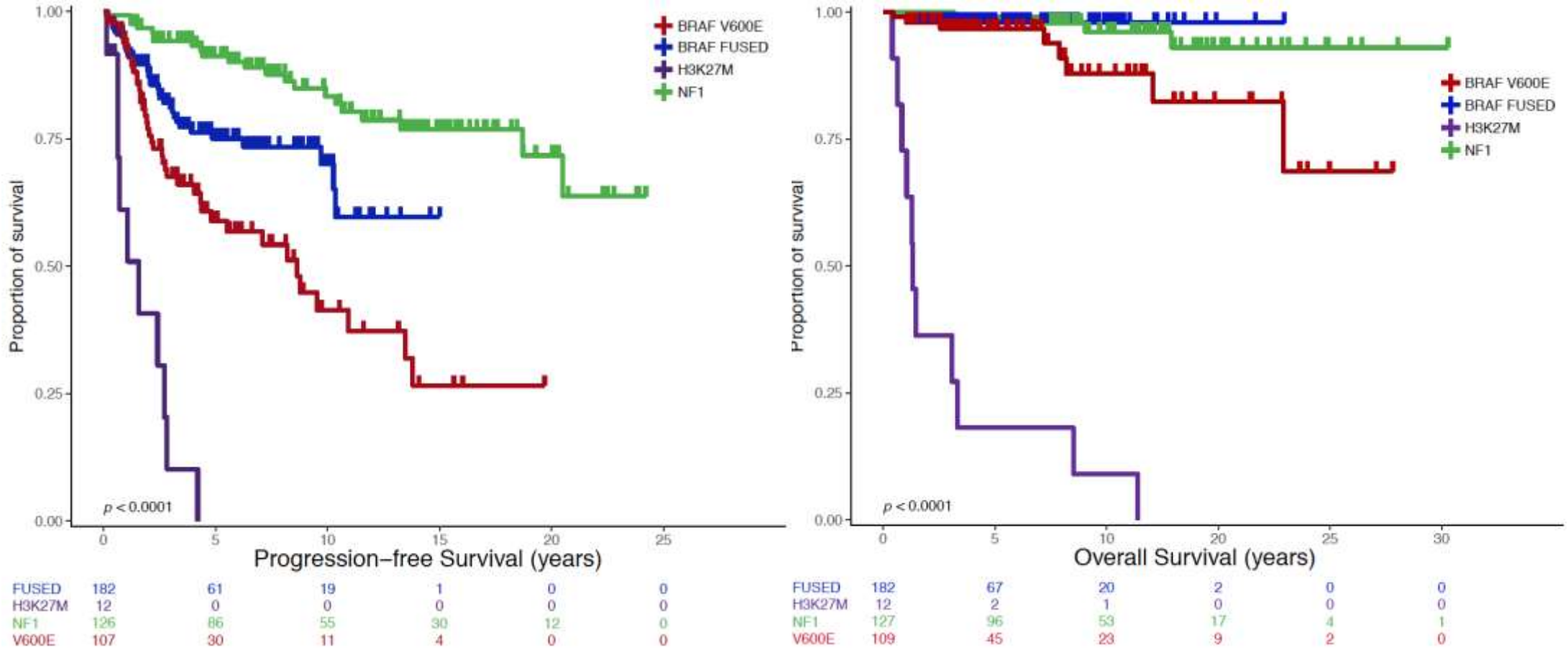


Ryall et al. Acta Neuropath Comms, 2020

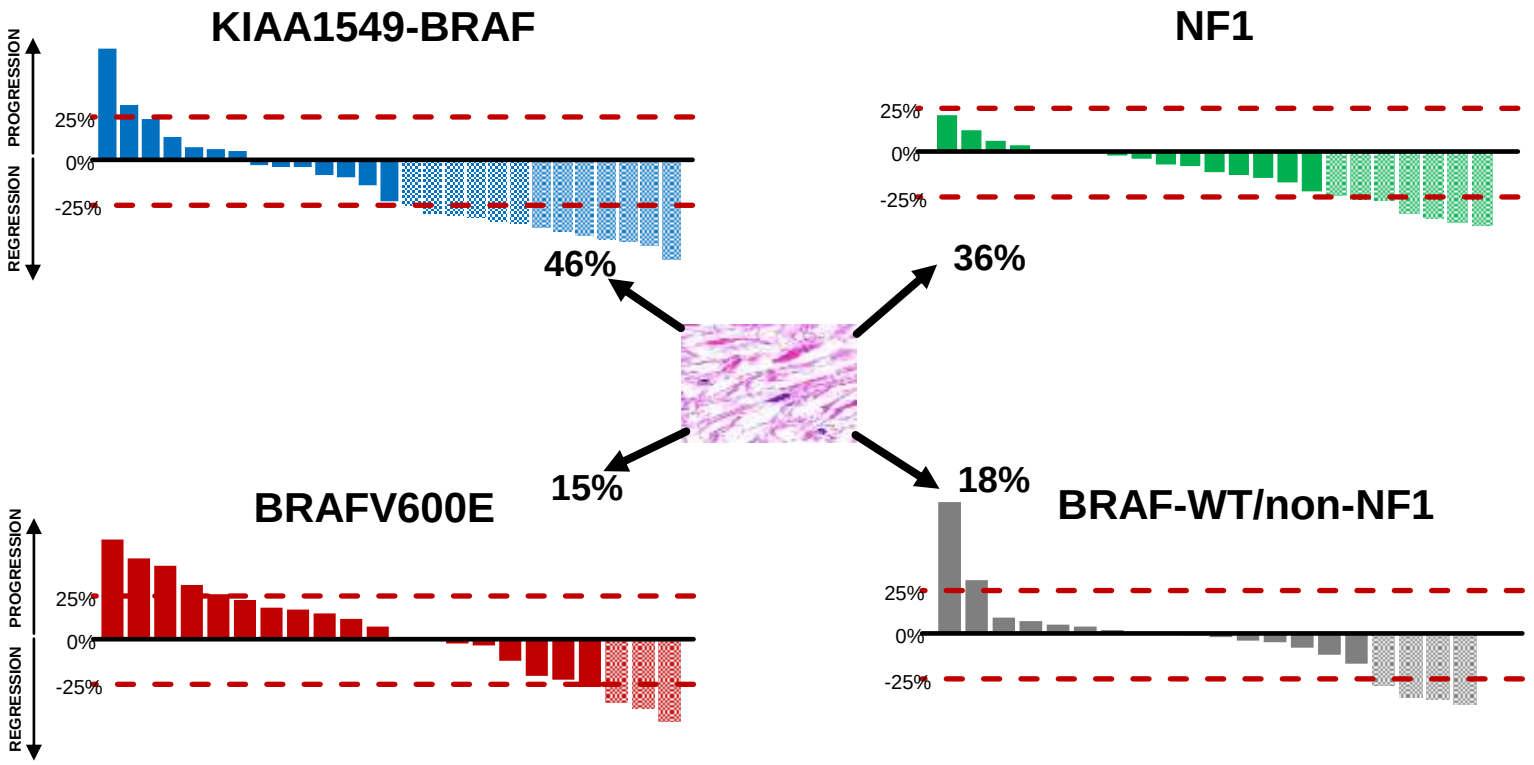
DO I REALLY NEED MOLECULAR TESTING FOR PLGG?

- For morphologically classic entities with gross total resection, histology alone may be sufficient
- Situations where molecular characterisation is helpful:
  - Consideration is being given to radiation and need further prognostic guidance
  - Small biopsy and unsure if low grade vs high grade
  - Growing, incompletely resected lesion with potential for targeted therapeutics

SURVIVAL VARIES BY MOLECULAR STATUS

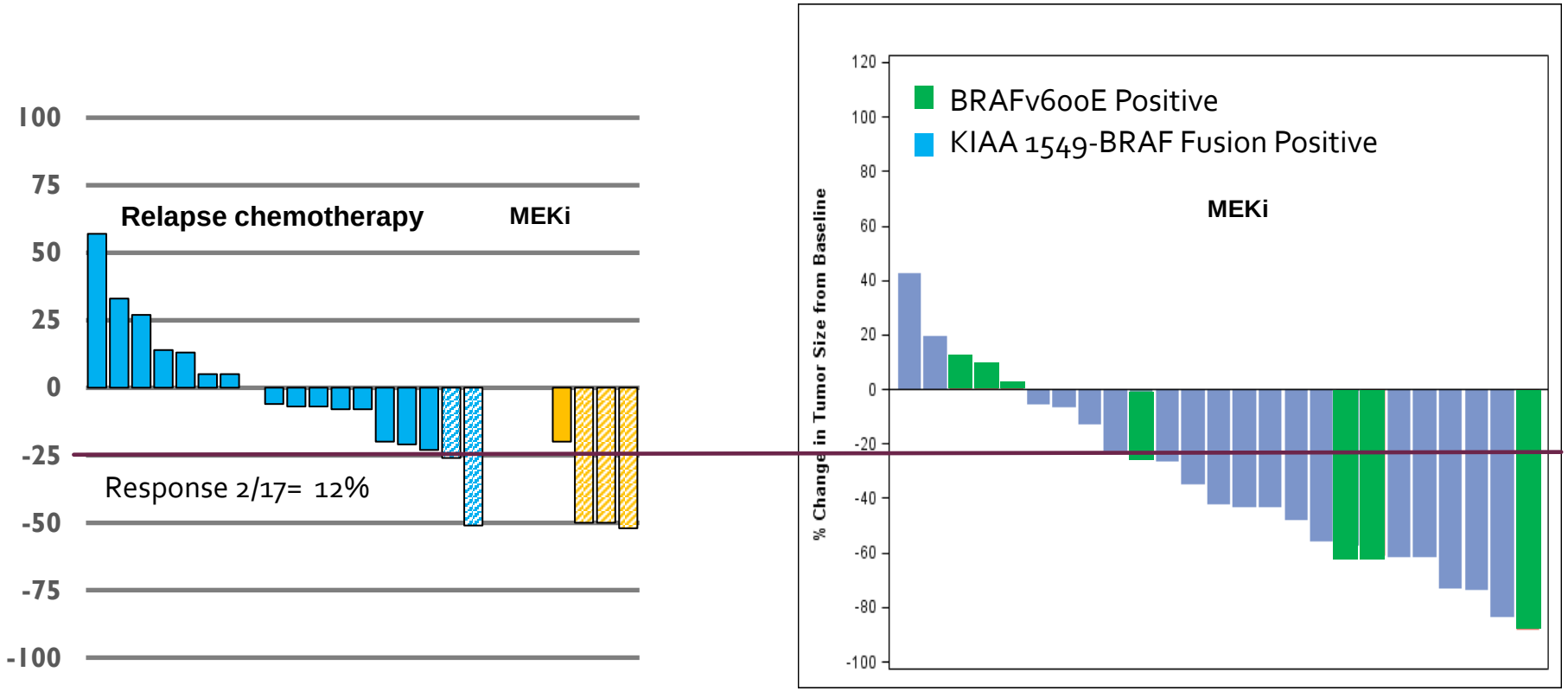


RESPONSE TO CHEMOTHERAPY VARIES BY MOLECULAR STATUS



Fisher Exact test p=0.0226

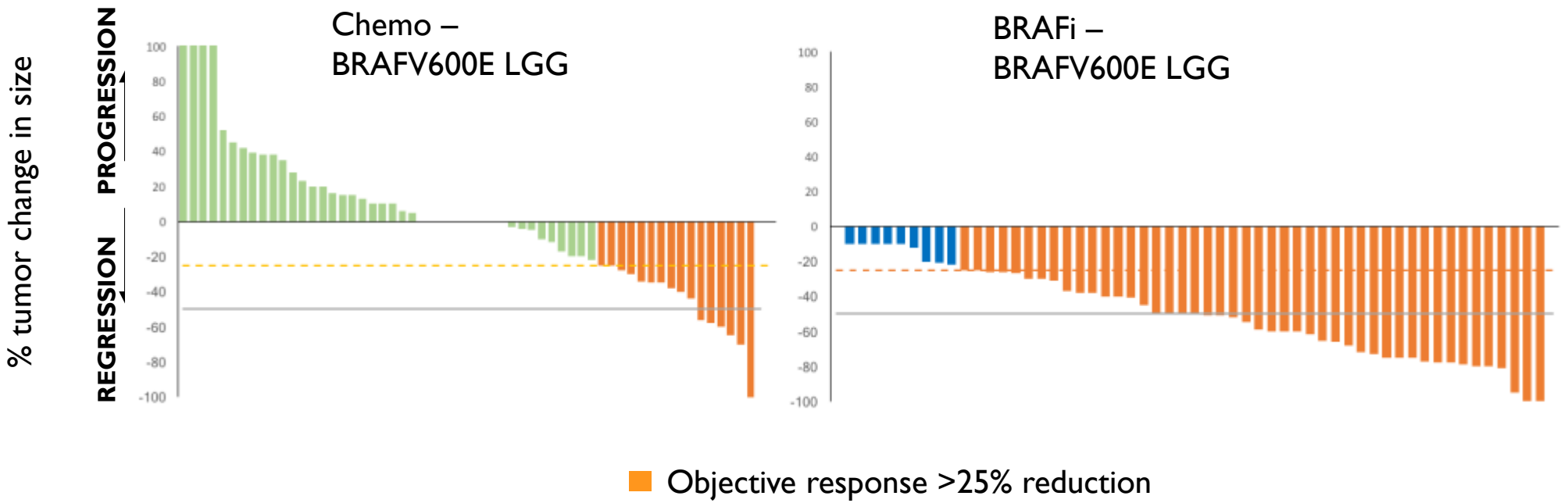
RELAPSED *KIAA1549-BRAF* PATIENTS AND RESPONSE TO CHEMOTHERAPY VS MEKI



Response 16/25= 64%

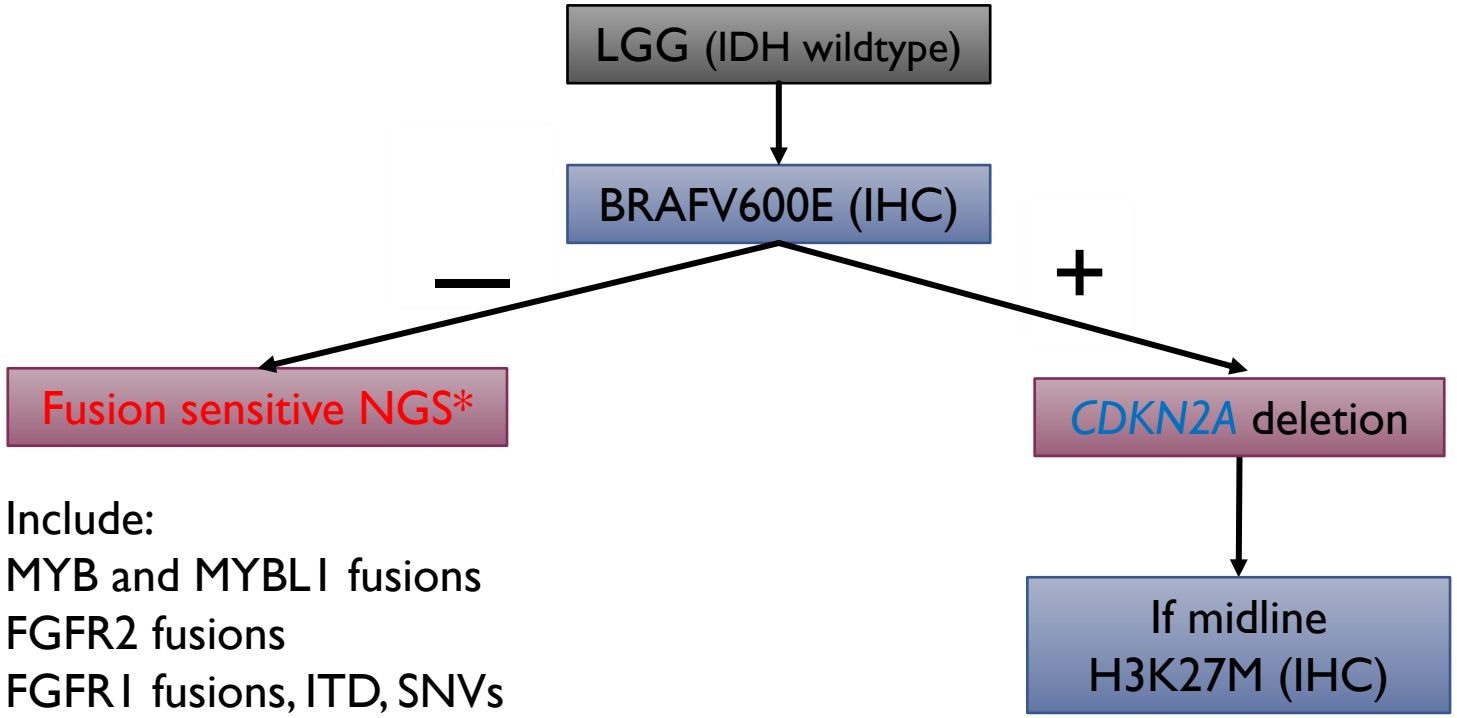
Fangusaro et al. Lancet Oncology, 2019

RESPONSE TO TARGETED THERAPEUTICS MAY BE BETTER THAN TO STANDARD CHEMOTHERAPY

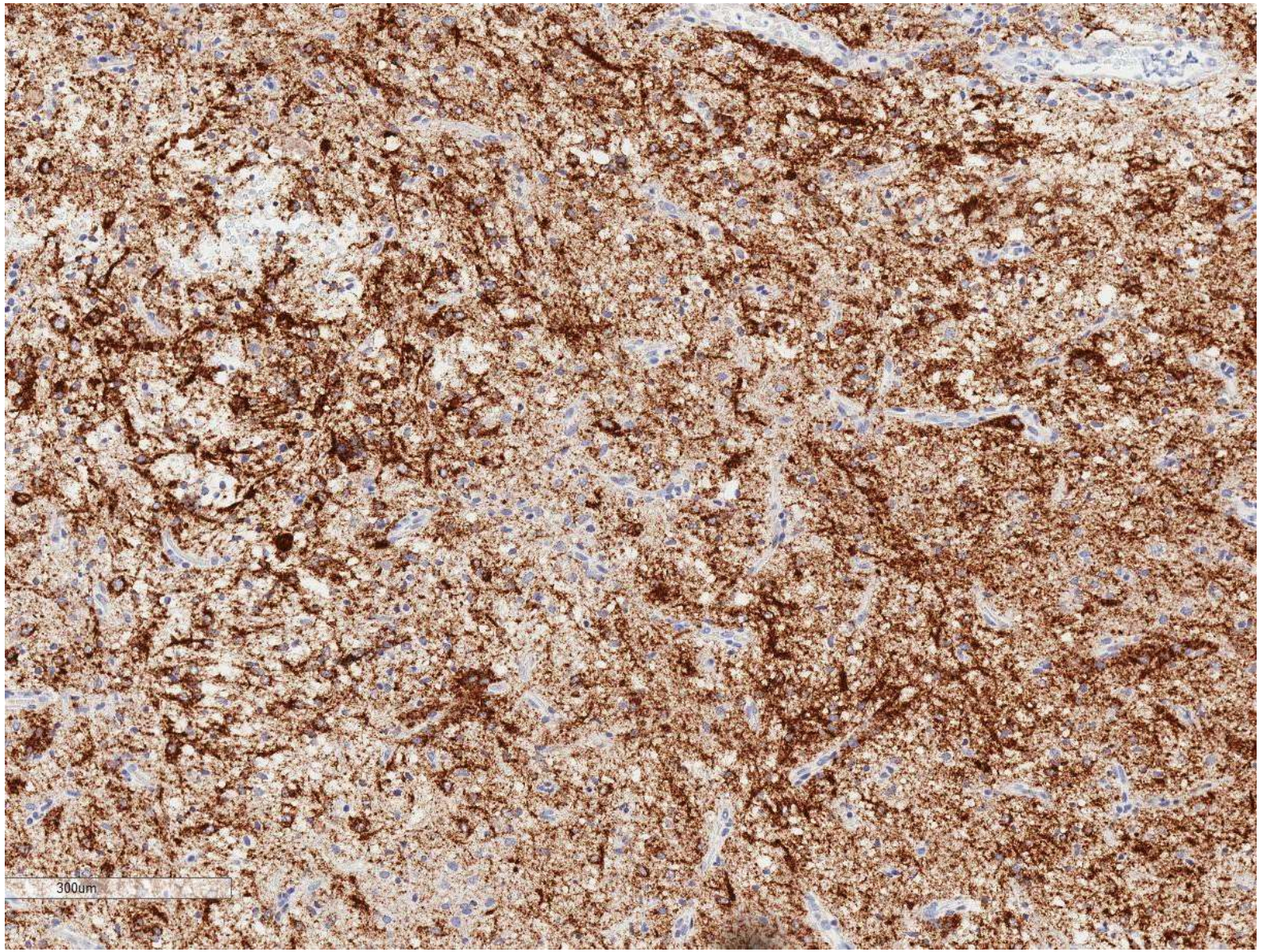


Nobre et al. JCO Precision Oncology, 2020

LGG TESTING STRATEGY



Include:
MYB and MYBL1 fusions
FGFR2 fusions
FGFR1 fusions, ITD, SNVs
MN1 fusions
PRKCA fusions
BRAF fusions and SNVs
PDGFRA SNVs
PIK3CA SNVs



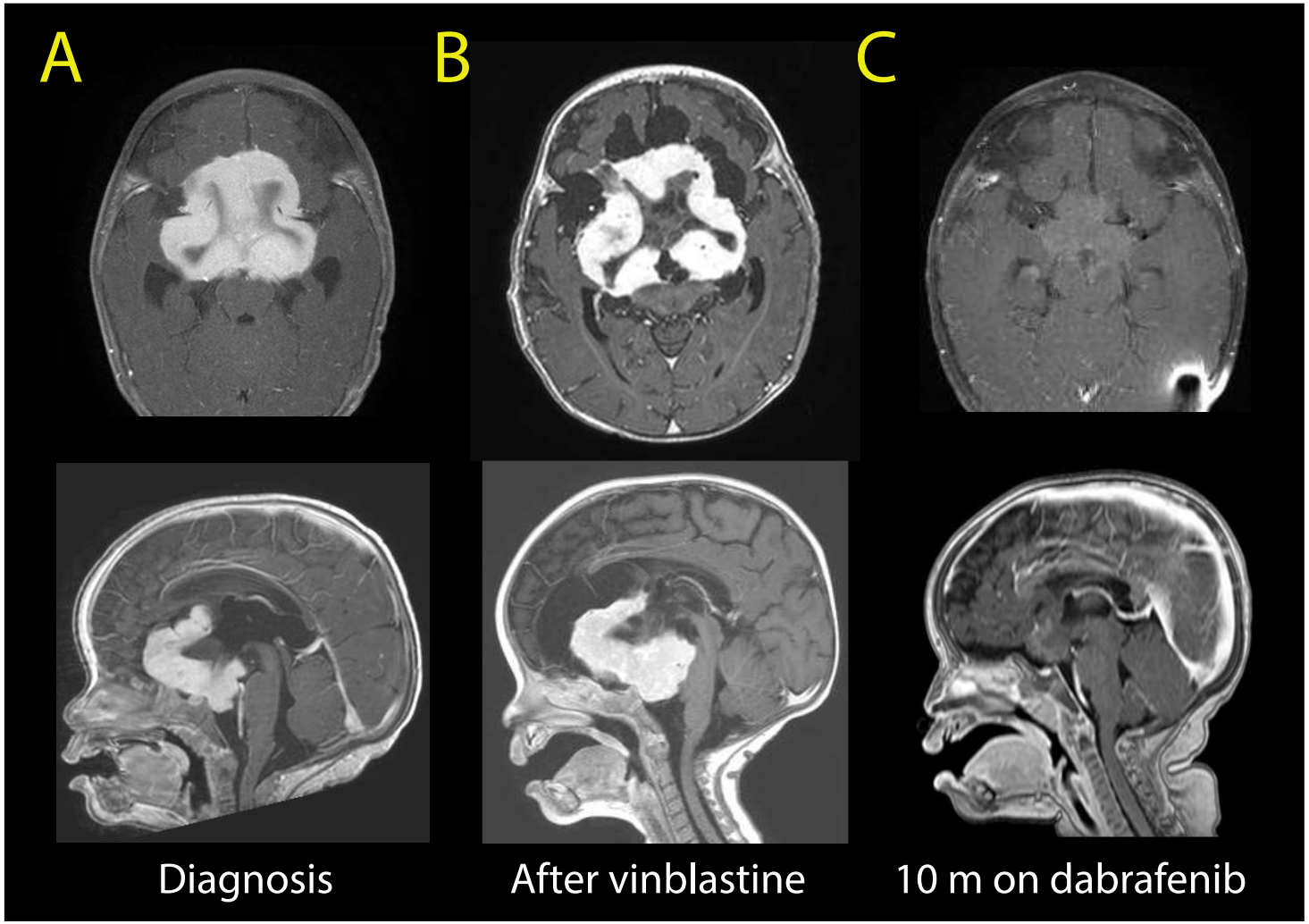
CASE 1- BRAFV600E

INTEGRATED DIAGNOSIS

- Biopsy, Optic pathway/ hypothalamic mass:
  - Ganglioglioma
    - WHO grade 1
    - BRAF p.V600E mutant (IHC)
    - *CDKN2A* not deleted (FISH)

CASE 1

- BRAF inhibitor started when the patient was critically ill in ICU
- Prompt clinical and radiological response
- Improvement of diencephalic syndrome (calorimetry normal), normal vision
- Currently on therapy 6 years later doing well

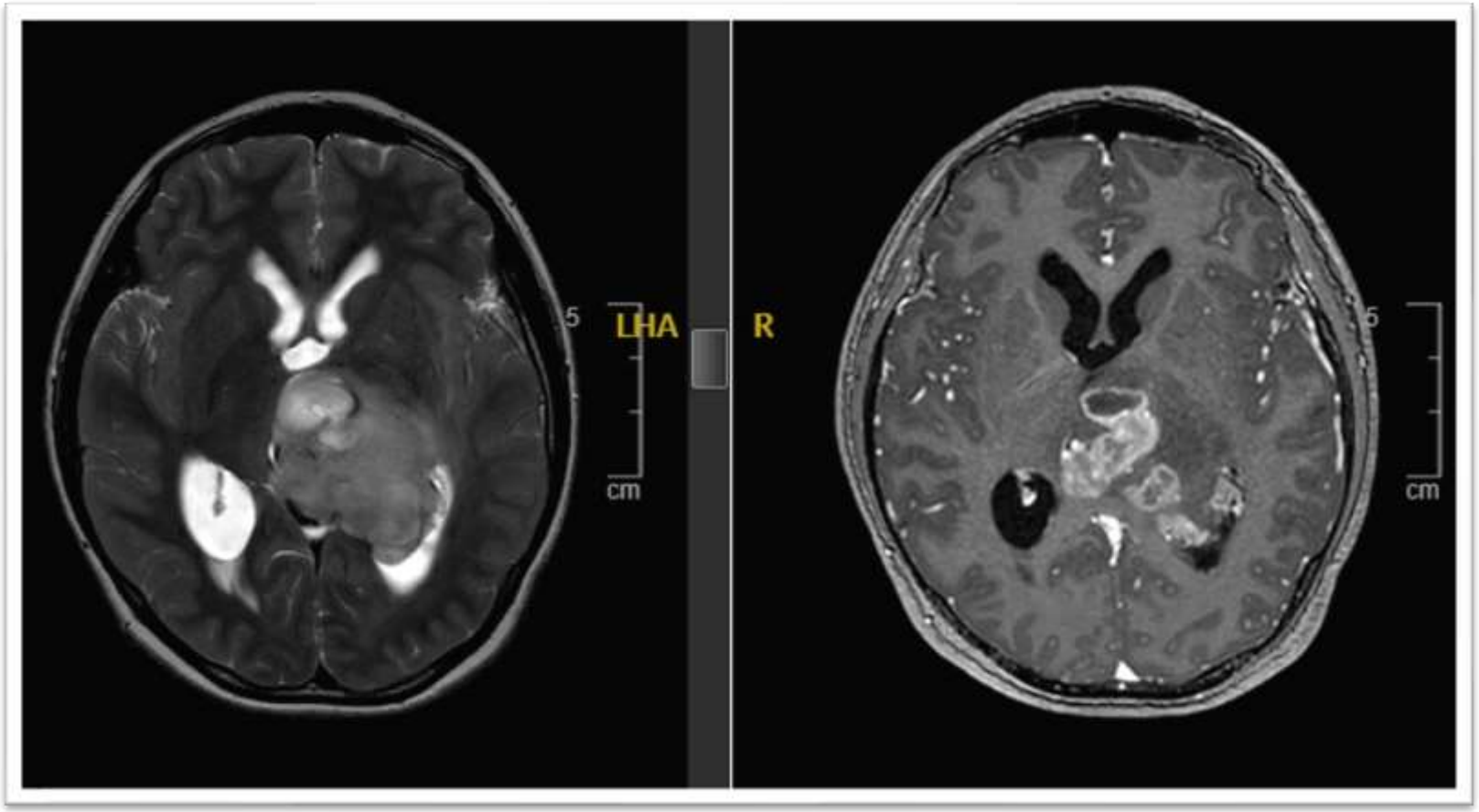


CASE 2

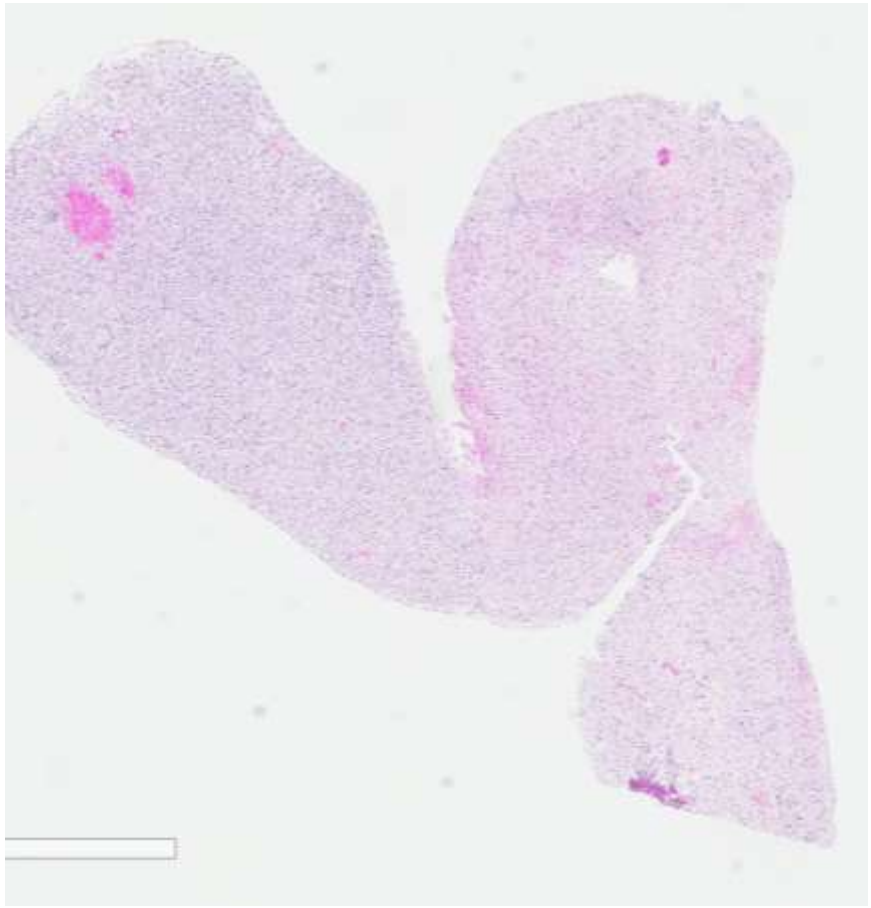
12 yr old female presented with

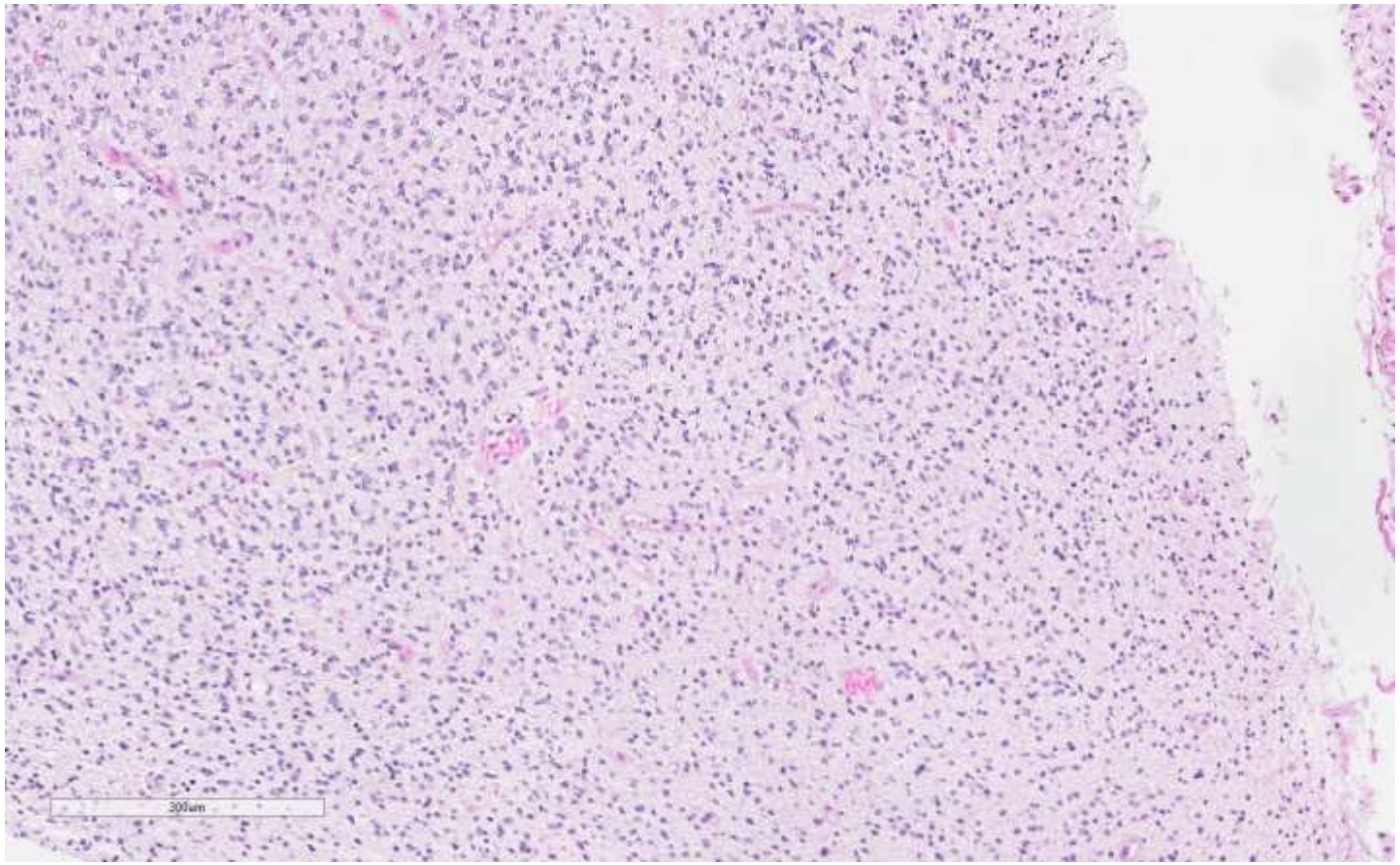
- Headaches and vomiting x 4 week
- Diploplia and blurry vision x 2 weeks

- Examination
  - Bilateral papilledema
  - No other neurological deficit

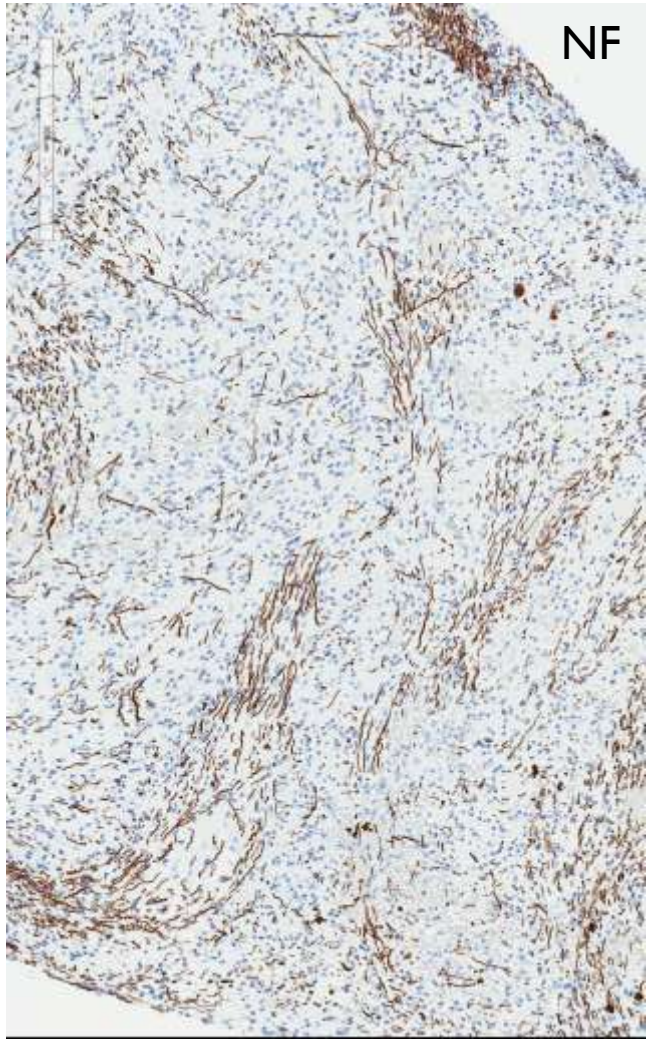


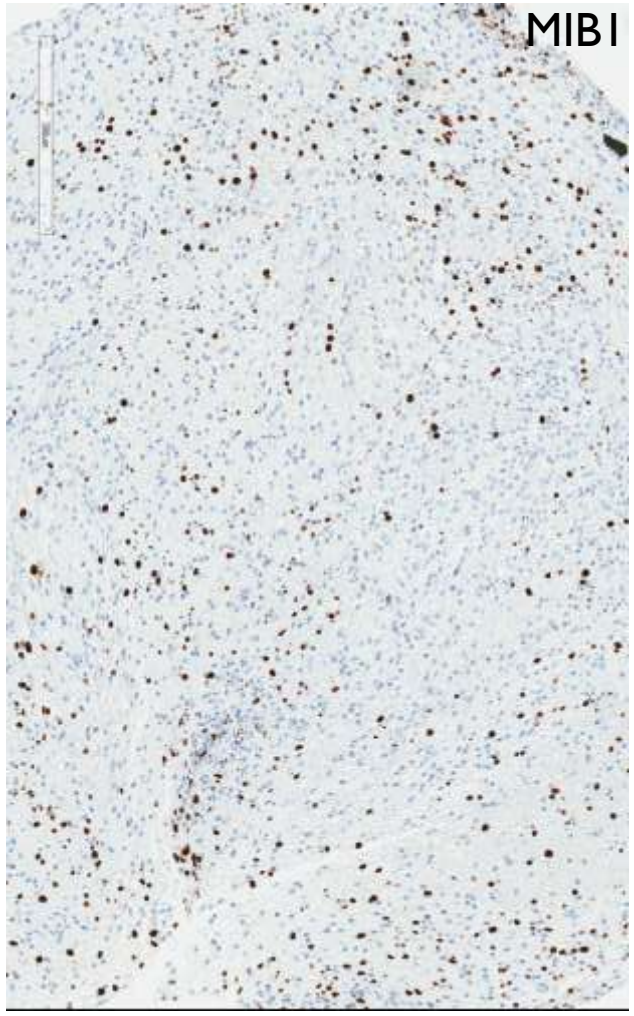
CASE 2 - BIOPSY





CASE 2- IHC

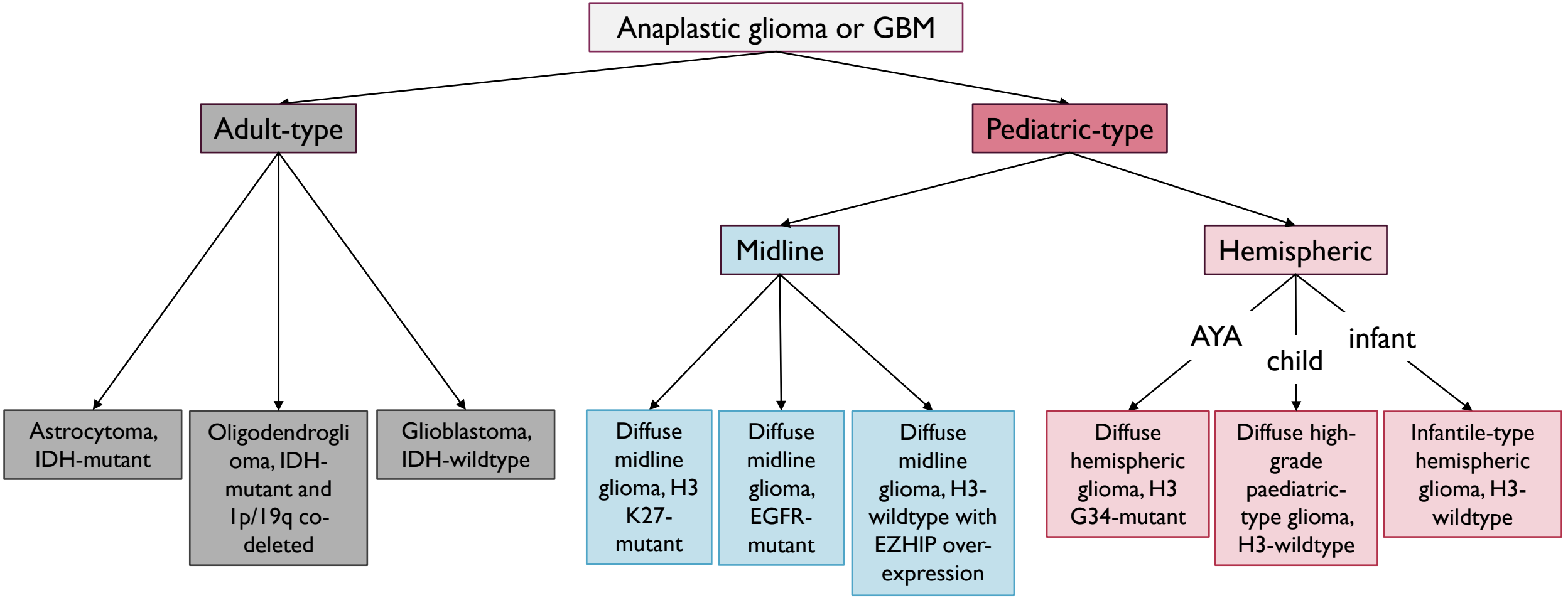




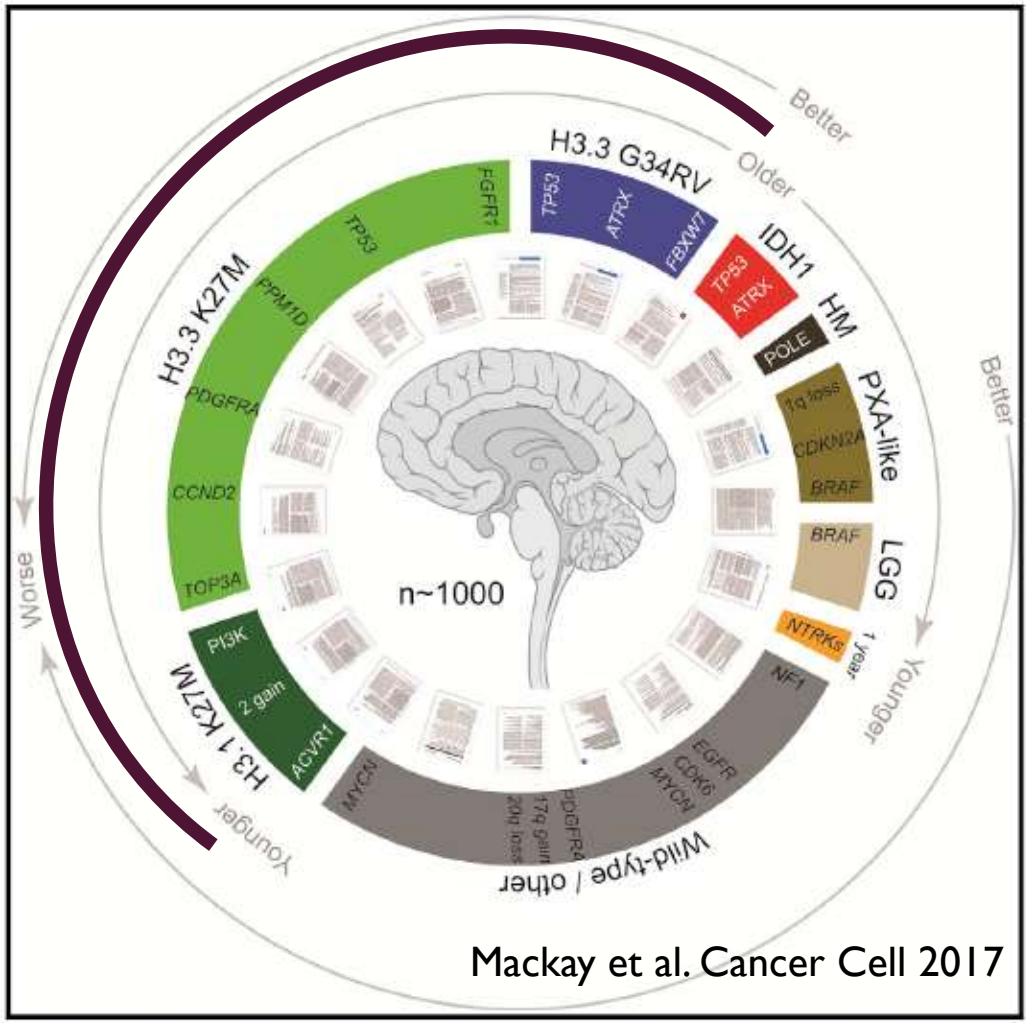
PEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMAS

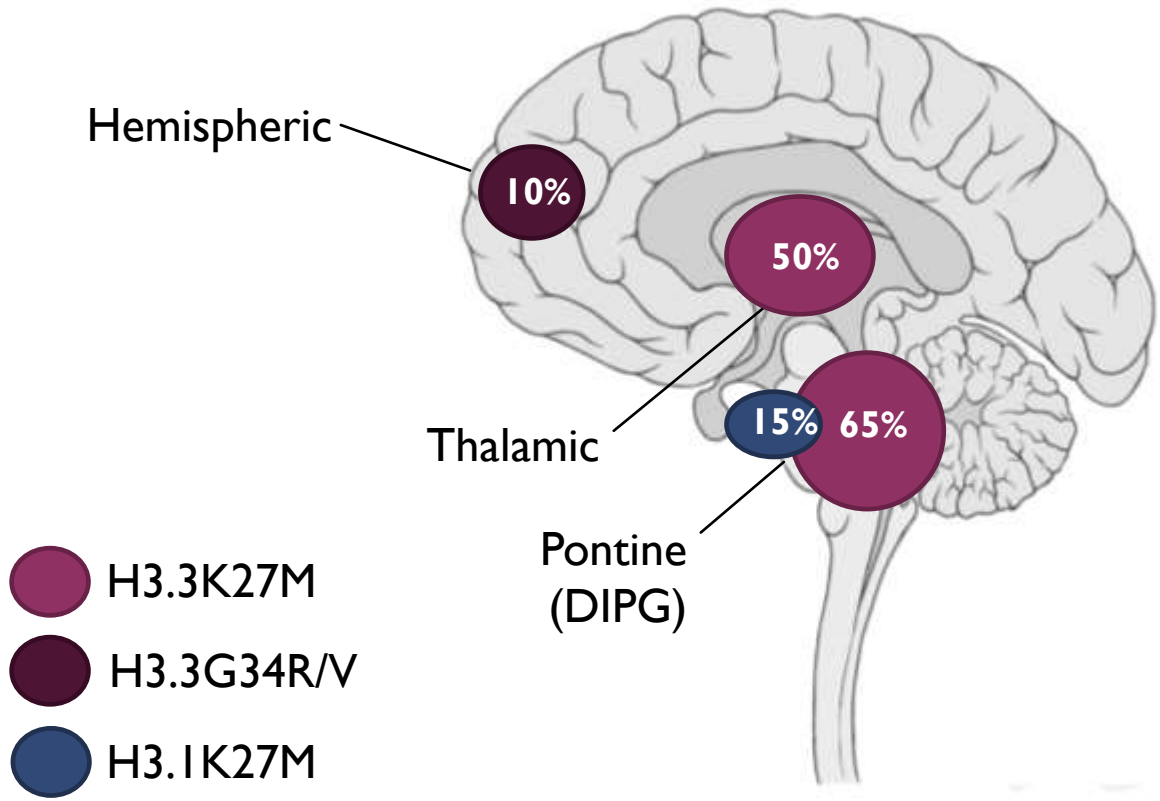
- Less common than low-grade glioma
- Usually are not the result of progression from low-grade counterpart (except BRAFV600E)
- Molecularly distinct from adult-type, by definition IDH WT
- Types defined based on characteristic age, location and molecular alterations

DIFFUSE HIGH-GRADE GLIOMAS: TUMOR TYPES



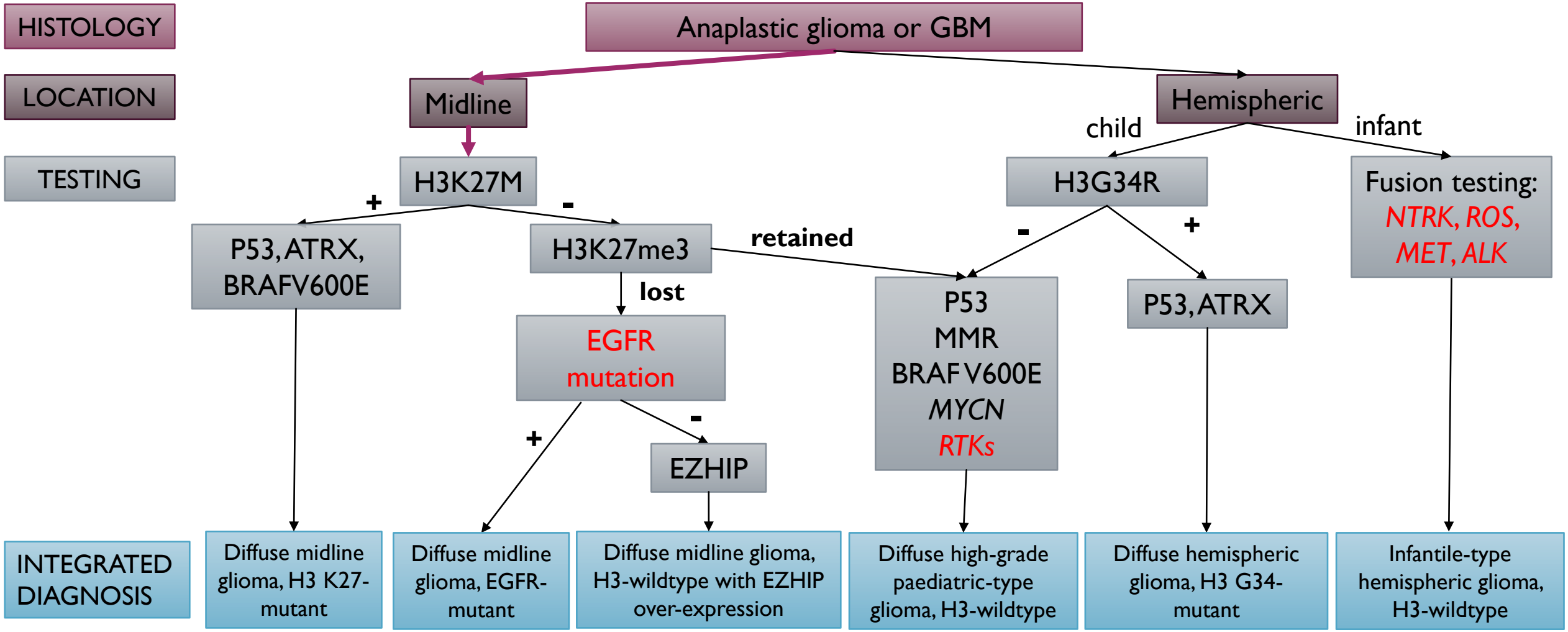
MOLECULAR SPECTRUM OF DIFFUSE HIGH-GRADE PEDIATRIC-TYPE GLIOMAS



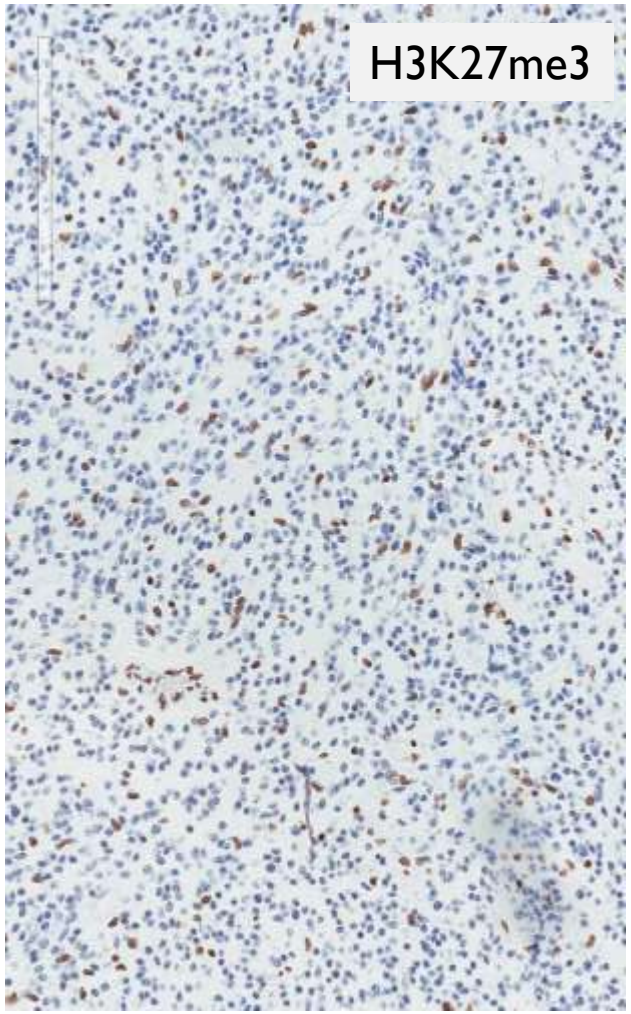


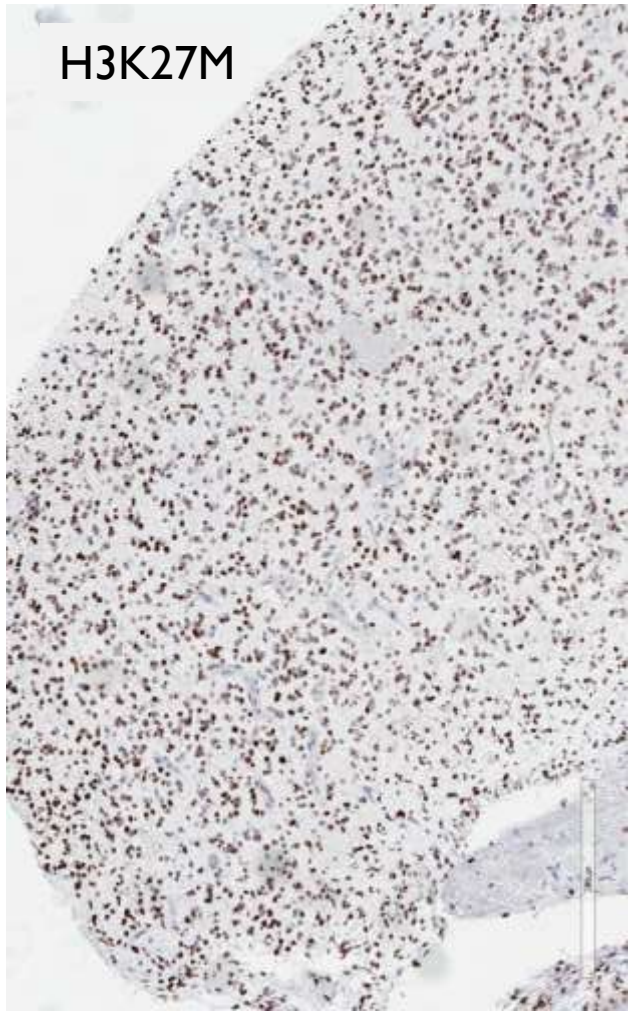
- Histone mutations are most frequent recurrent alterations

PEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMAS : DIAGNOSTIC APPROACH



CASE 2- IHC





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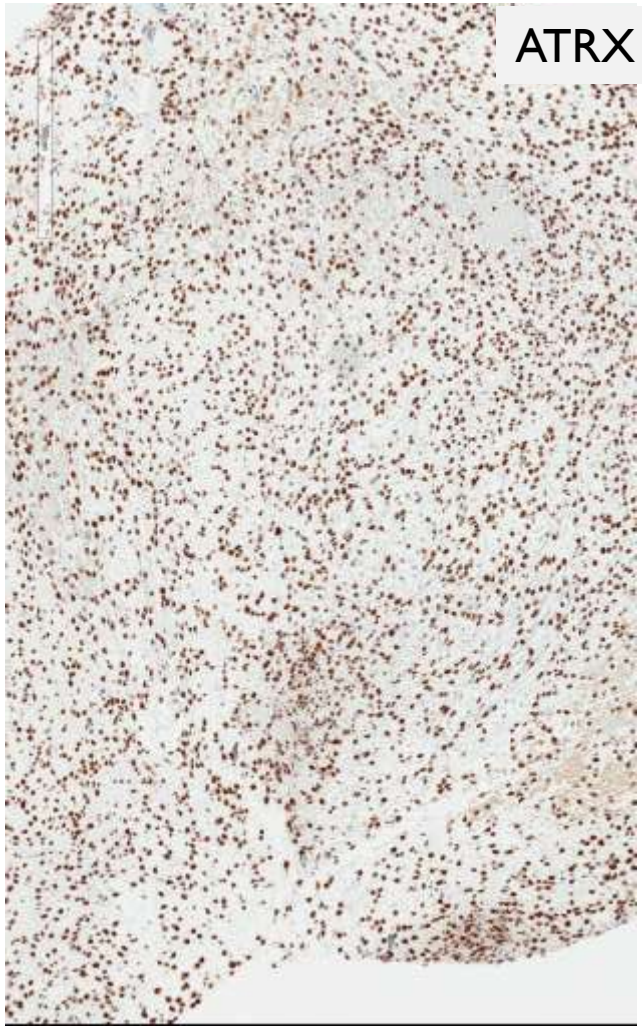
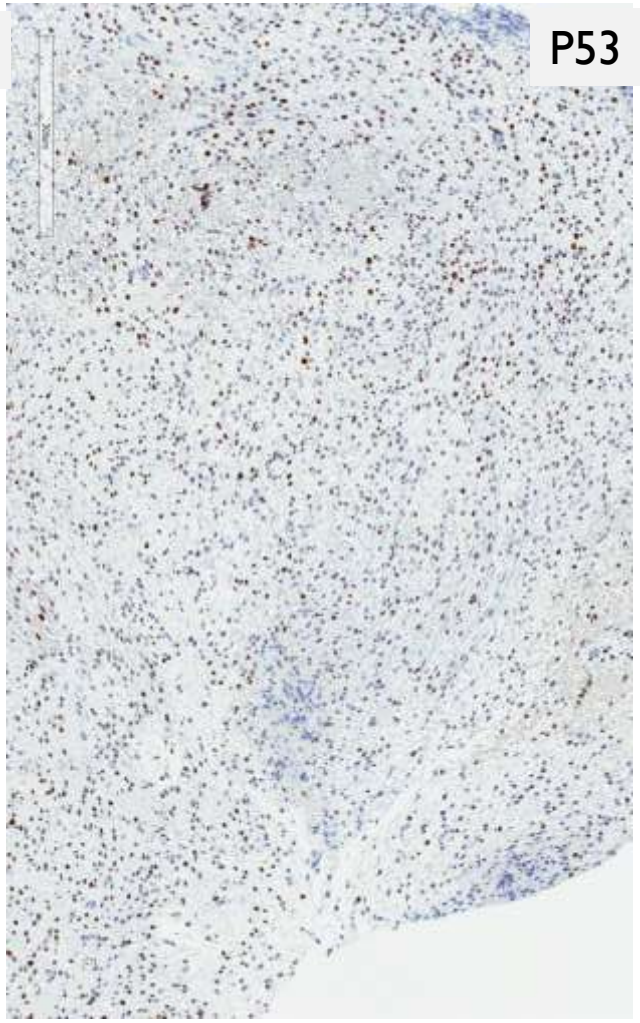
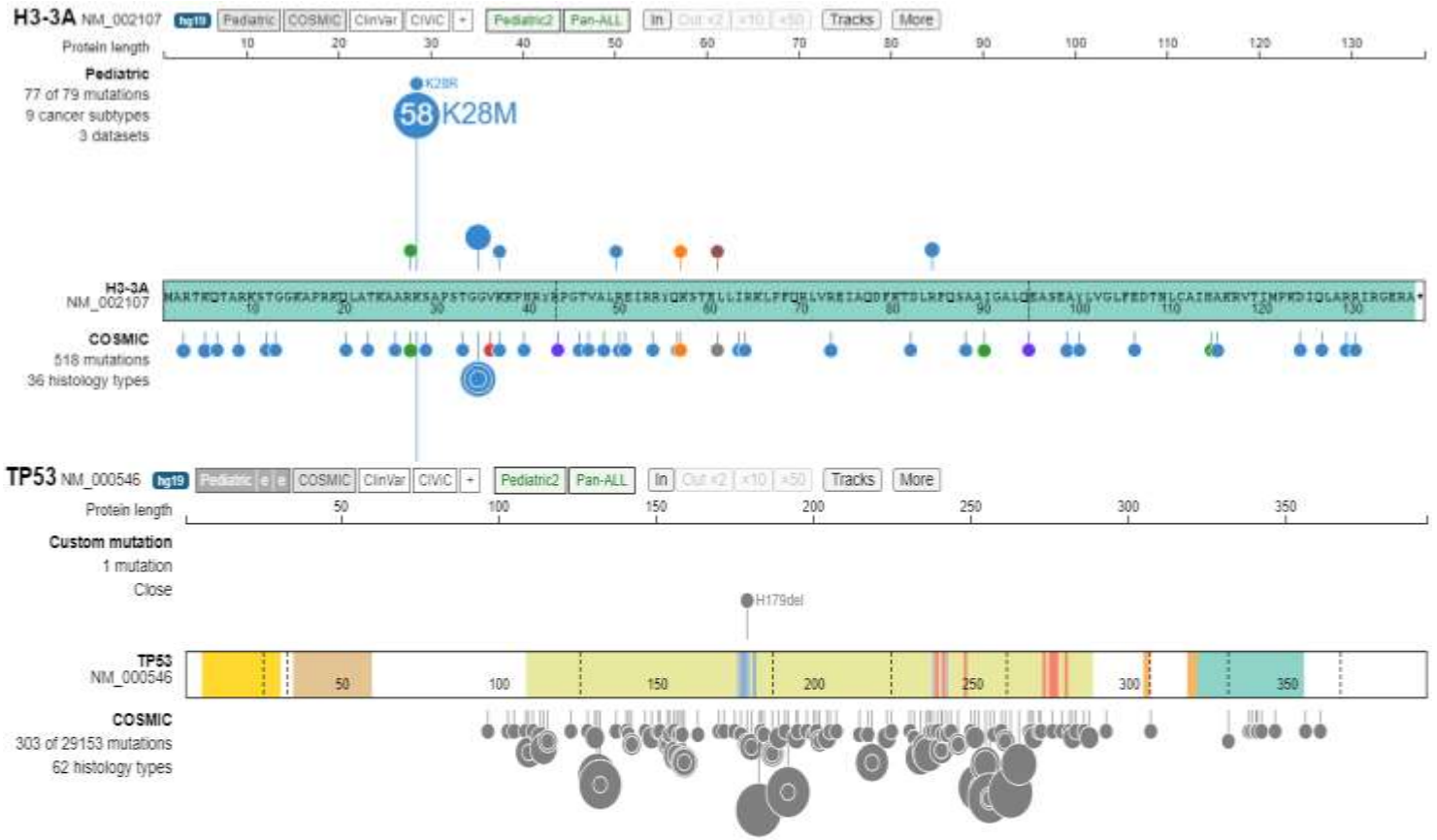




INTEGRATED DIAGNOSIS

- Biopsy, Thalamic mass:
  - Diffuse midline glioma, H3 K27-altered
    - WHO grade 4
    - H3.3 p.K27M (IHC)



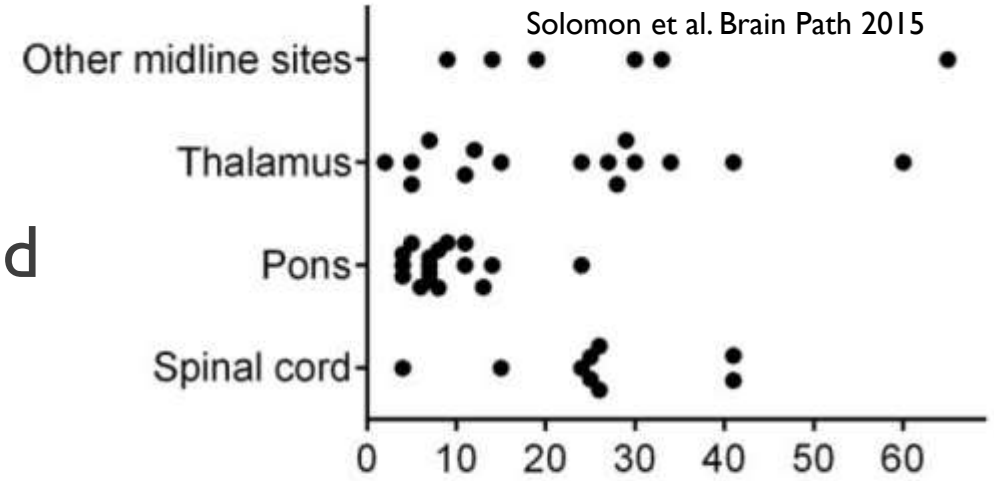
MOLECULAR RESULTS

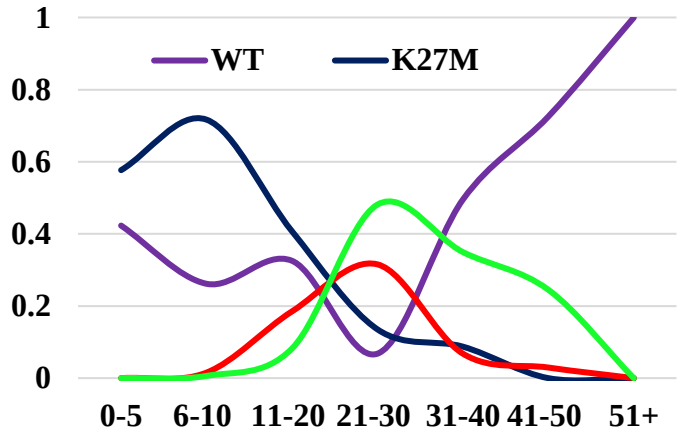
ADDENDED INTEGRATED DIAGNOSIS

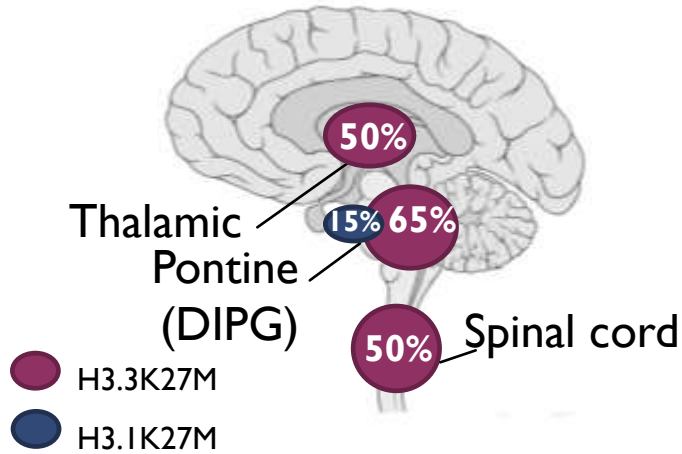
- Biopsy, Thalamic mass:
  - Diffuse midline glioma, H3 K27-altered
    - WHO grade 4
    - H3.3 p.K27M (IHC and NGS)
    - P53 p.H179del (NGS)

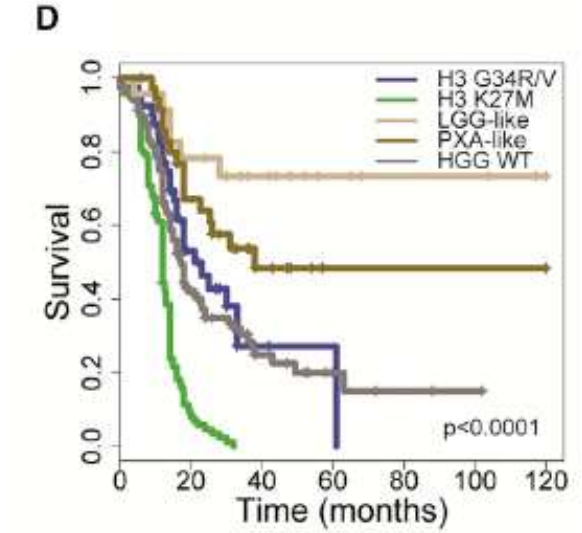
DIFFUSE MIDLINE GLIOMA, H3 K27M-MUTANT

- Enriched in childhood but can occur at any age, particularly outside the pons
- H3.3 and H3.1
- Very poor outcome



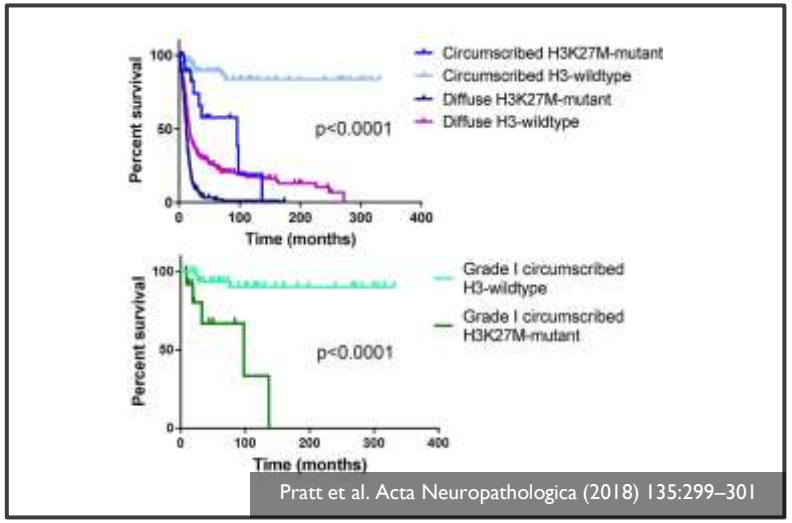




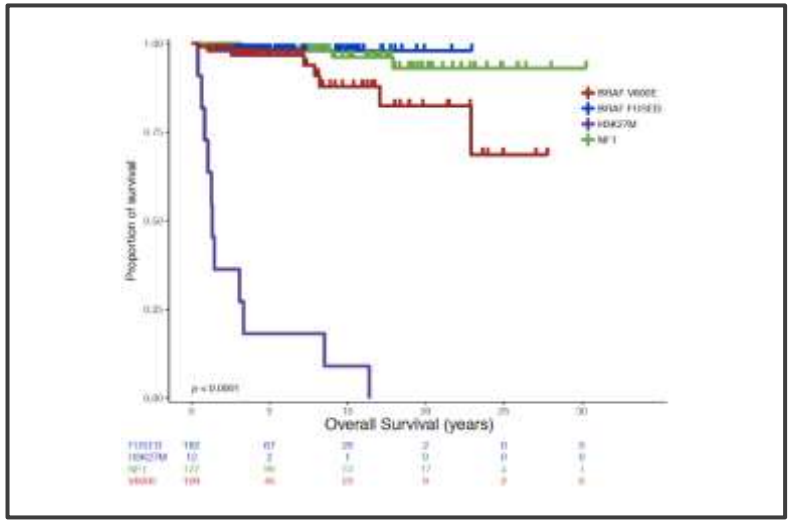


Mackay et al. Cancer Cell 2017

DIFFUSE MIDLINE GLIOMA, H3 K27M-MUTANT



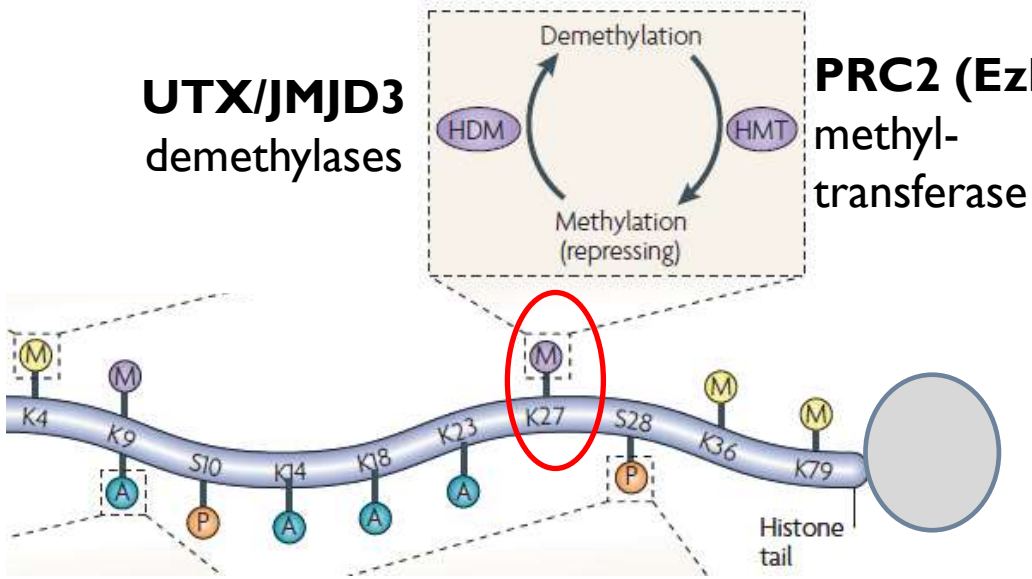
Pratt et al. Acta Neuropathologica (2018) 135:299–301



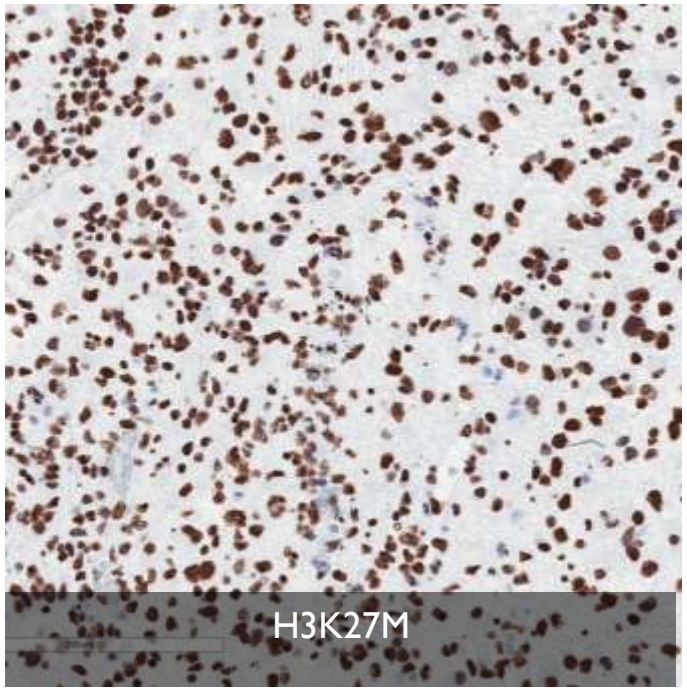
- cIMPACT/ WHO recommendation is to limit this diagnosis to diffuse gliomas
- Even if DA or circumscribed/ grade 1 histology, these are not low-grade gliomas

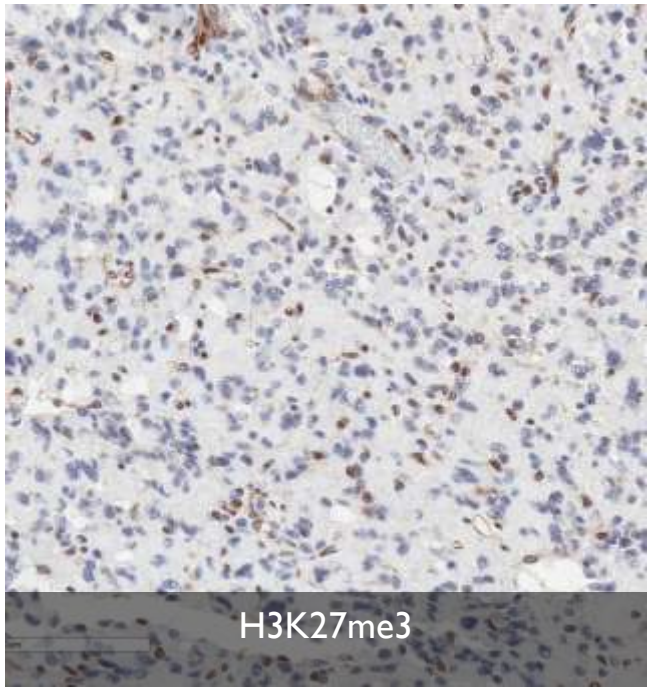
H3K27M INHIBITS PRC2 FUNCTION AND LEADS TO LOSS OF H3K27ME3

UTX/JMJD3
demethylases



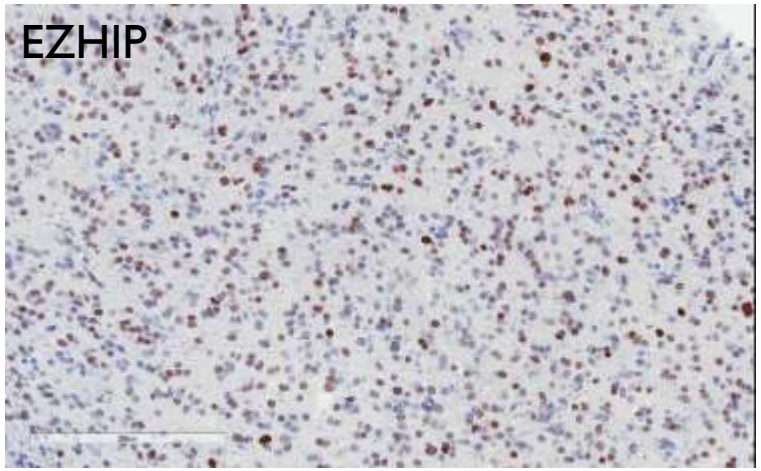
PRC2 (Ezh2)
methyl-
transferase





H3 WILD-TYPE DMG: EZHIP OVER-EXPRESSION

- Some DMGs have loss of H3K27me3 but no H3K27M
- EZHIP inhibits PRC2 through an H3K27M-like mechanism



Molecular heterogeneity and *CXorf67* alterations in posterior fossa group A (PFA) ependymomas *Acta Neuropathol* 136(2):211-26, 2018

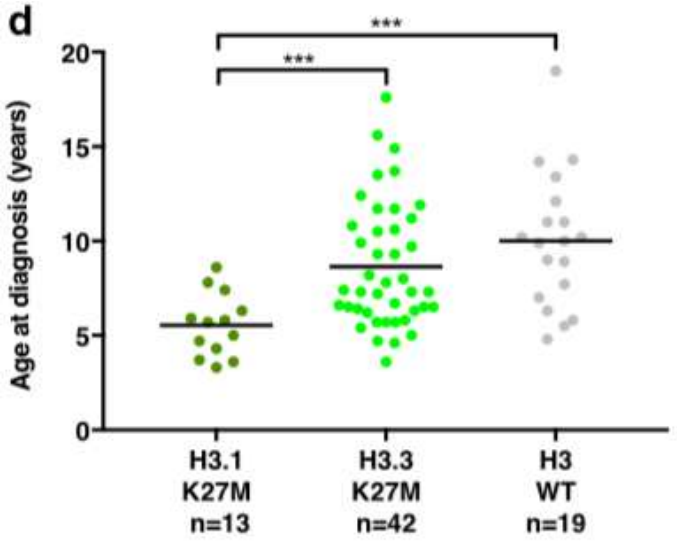
Kristian W. Pajtler,[1,2,3,20] Ji Wen,[4,20] Martin Sill,[1,2,20] Tong Lin,[5,20] Wilda Orisme,[4] Bo Tang,[4] Jens-Martin Hübner,[1,2] Vijay Ramaswamy,[6,7] Sujuan Jia,[4] James D. Dalton,[4] Kelly Haupfear,[4] Hazel A. Rogers,[8] Chandanamali Punchihewa,[4] Ryan Lee,[4] John Easton,[9] Gang Wu,[9] Timothy A. Ritzmann,[8] Rebecca Chapman,[8] Lukas Chavez,[1,2] Fredrick A. Boop,[10] Paul Klimo, Jr.,[10] Noah D. Sabin,[11] Robert Ogg,[11] Stephen C. Mack,[7,12] Brian D. Freibaum,[13] Hong Joo Kim,[13] Hendrik Witt,[1,2,3] David T.W. Jones,[1,2] Baohan Vo,[14] Amar Gajjar,[15] Stan Pounds,[5] Arzu Onar-Thomas,[5] Martine F. Roussel,[14] Jinghui Zhang,[9] J. Paul Taylor,[13,16] Thomas E. Merchant,[17] Richard Grundy,[8] Ruth G. Tatevossian,[4] Michael D. Taylor,[7] Stefan M. Pfister,[1,2,3] Andrey Korshunov,[18,19] Marcel Kool,[1,2,21] and David W. Ellison[4,21,*]

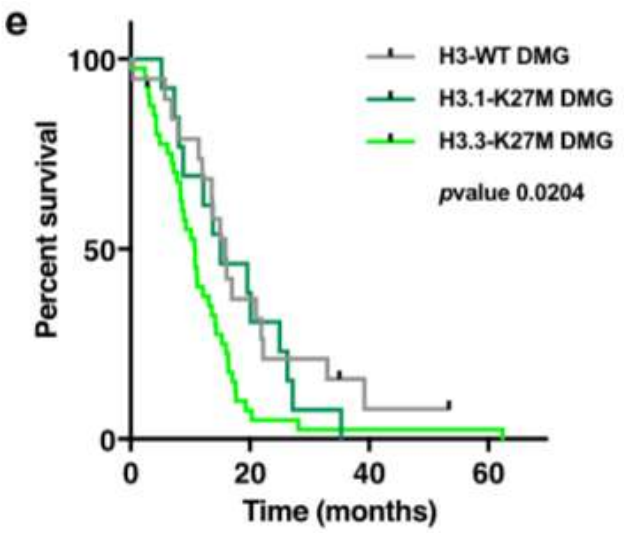
Histone H3 wild-type DIPG/DMG overexpressing *EZHIP* extend the spectrum diffuse midline gliomas with PRC2 inhibition beyond H3-K27M mutation *Acta Neuropathol* 139: 1109–1113, 2020

David Castel[1,2] · Thomas Kergrohen[1,2] · Arnault Tauziède-Espariat[3,4] · Alan Mackay[5] · Samia Ghermaoui[1] · Emmanuèle Lechapt[3,4] · Stefan M. Pfister[6,7,8] · Christof M. Kramm[9] · Nathalie Boddaert[10] · Thomas Blauwblomme[11] · Stéphanie Puget[11] · Kévin Beccaria[1,11] · Chris Jones[5] · David T. W. Jones[6,12] · Pascale Varlet[3,4] · Jacques Grill[1,2] · Marie-Anne Debily[1,13]

H3 WILD-TYPE DMG WITH EZHIP OVER-EXPRESSION

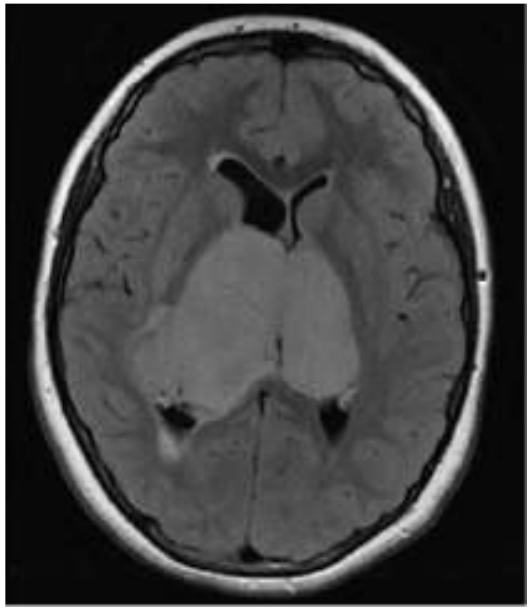
- Outcome and age distribution similar to H3K27M
- These likely belong in DMG, H3 K27M mutant group





Acta Neuropathol 139: 1109–1113, 2020

DMG, EGFR-MUTANT

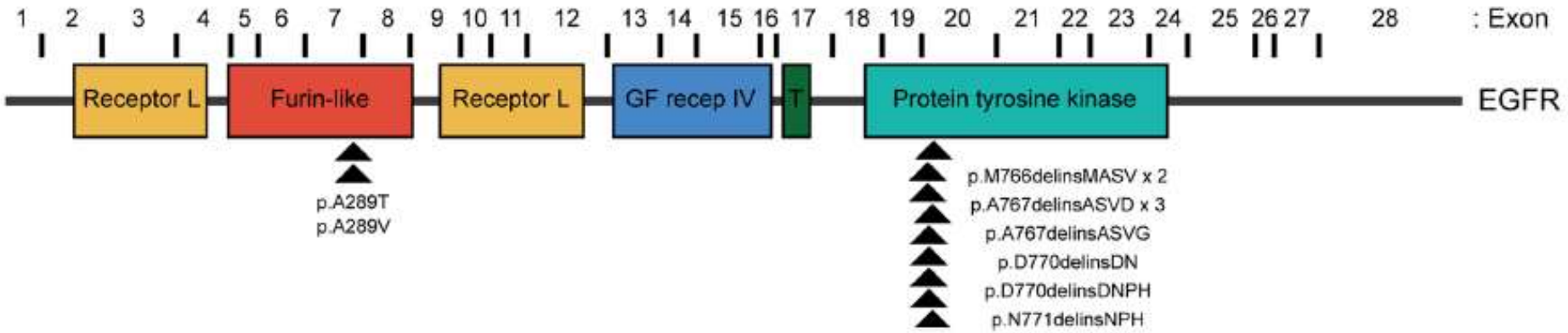


Acta Neuropathologica (2020) 139:1071–1088
https://doi.org/10.1007/s00401-020-02155-5

ORIGINAL PAPER

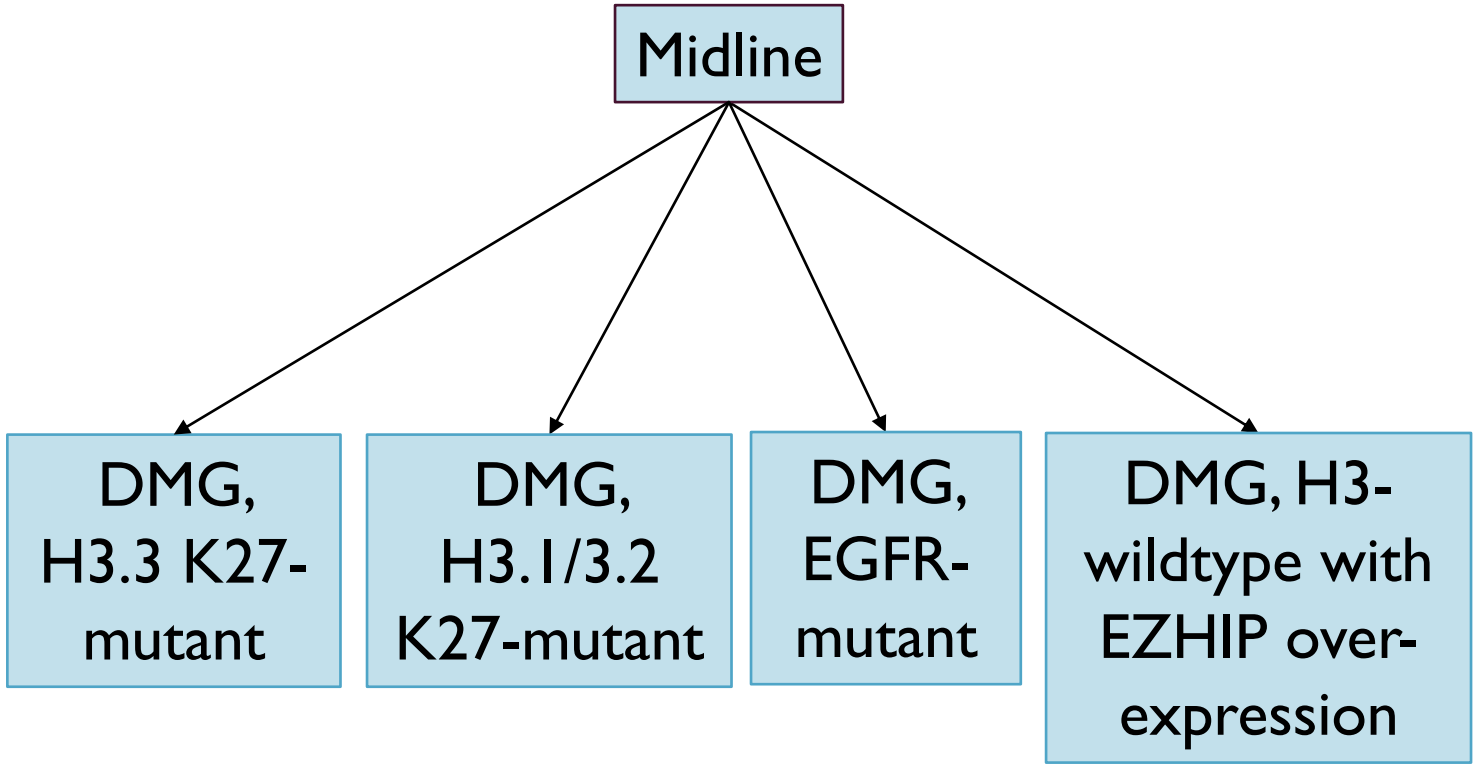
Pediatric bithalamic gliomas have a distinct epigenetic signature and frequent *EGFR* exon 20 insertions resulting in potential sensitivity to targeted kinase inhibition

Gourish Mondal[1] · Julieann C. Lee[1] · Ajay Ravindranathan[1] · Javier E. Villanueva-Meyer[2] · Quynh T. Tran[3] · Sariah J. Allen[3] · Jairo Barreto[1] · Rohit Gupta[1] · Pamela Doo[4] · Jessica Van Ziffle[1,5] · Courtney Onodera[1,5] · Patrick Devine[1,5] · James P. Grenert[1,5] · David Samuel[6] · Rong Li[7] · Laura K. Metrock[8] · Lee-way Jin[9] · Reuben Antony[10] · Mouled Alasharl[11] · Samuel Cheshier[12] · Nicholas S. Whipple[13] · Carol Bruggers[13] · Corey Raffel[14] · Nalin Gupta[14] · Cassie N. Kline[15,16] · Alyssa Reddy[16] · Anu Banerjee[15] · Matthew D. Hall[17] · Minesh P. Mehta[17] · Ziad Khatib[18] · Ossama M. Maher[18] · Carole Brathwaite[19] · Melike Pekmezci[1] · Joanna J. Phillips[1,14] · Andrew W. Bollen[1] · Tarik Tihan[1] · John T. Lucas Jr[20] · Alberto Broniscer[21] · Mitchel S. Berger[14] · Arie Perry[1,14] · Brent A. Orr[3] · David A. Solomon[1,5]



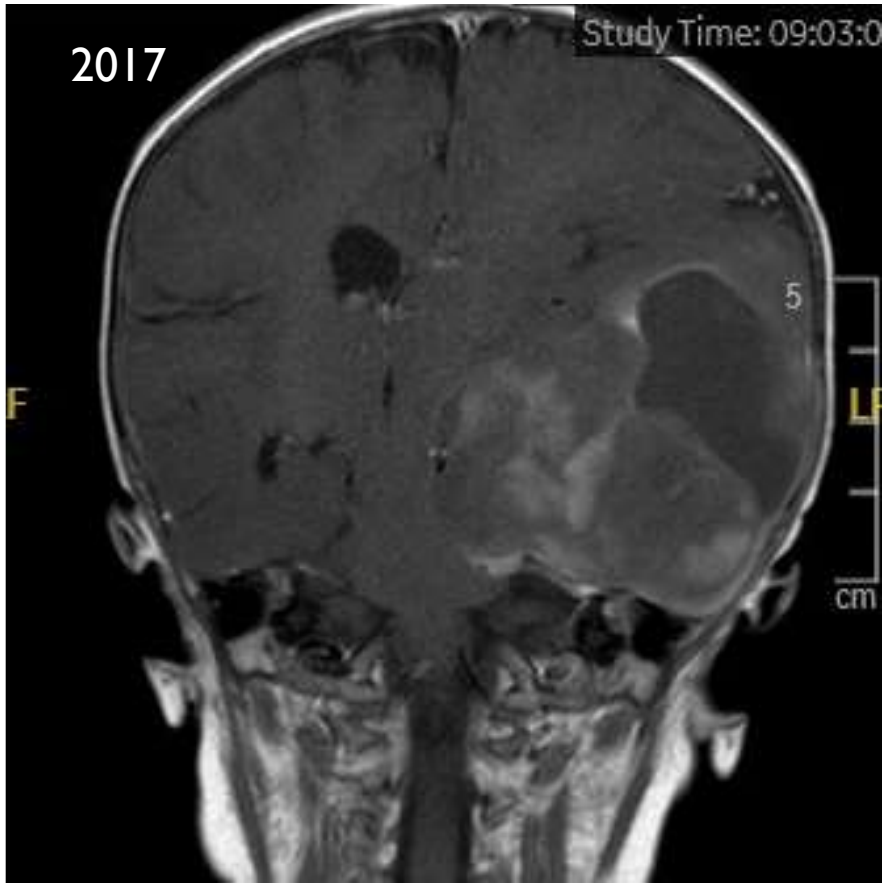
DIFFUSE MIDLINE GLIOMA, H3 K27-ALTERED

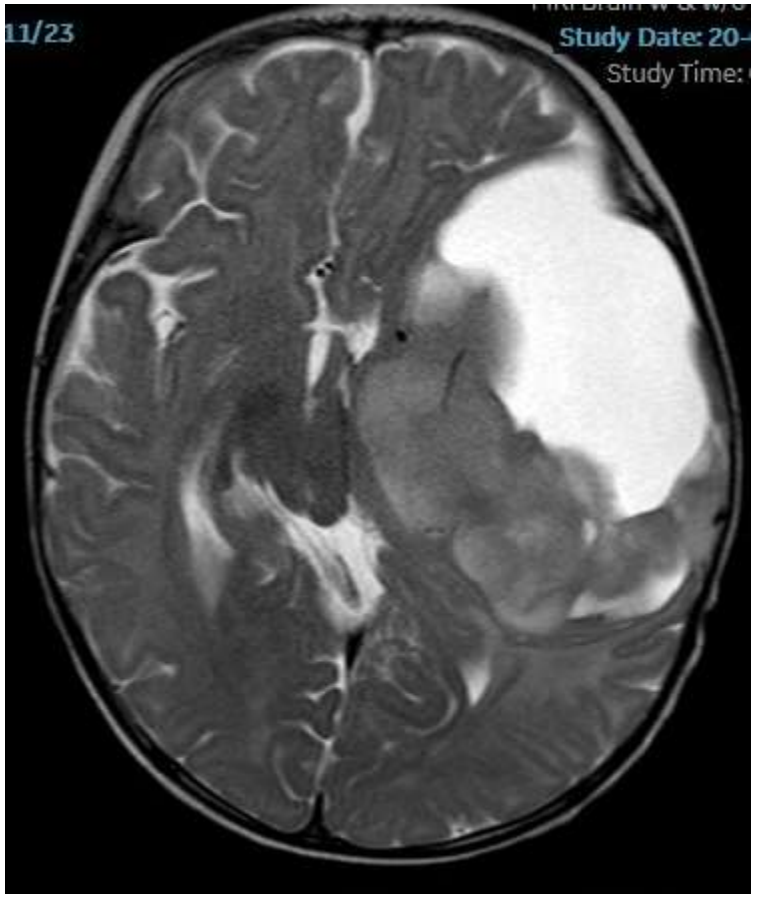
- Category expanded to recognise all diffuse gliomas with H3K27me3 loss



CASE 3

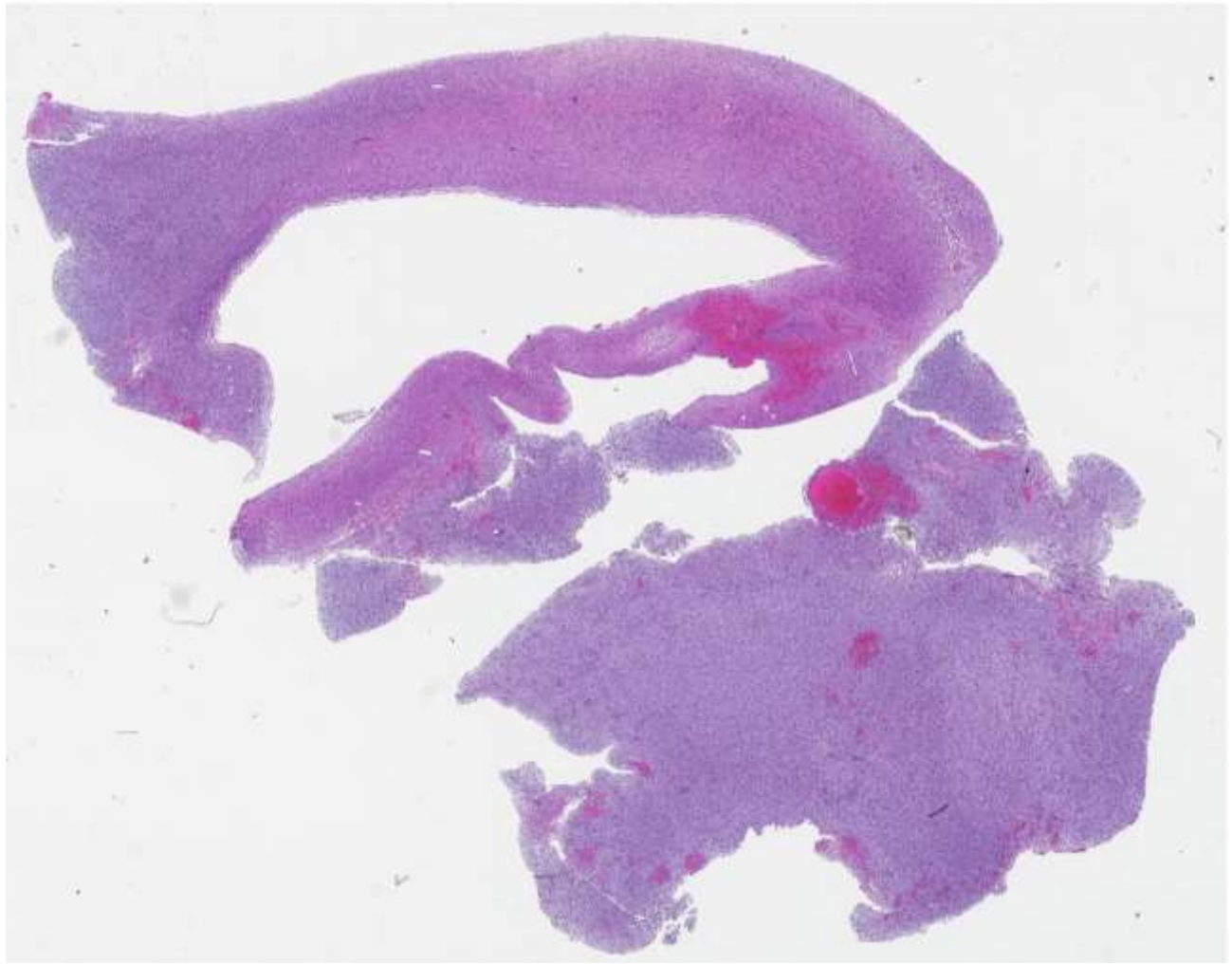
- 7 month-old boy presented with poor feeding and increased head circumference
- Partial resection

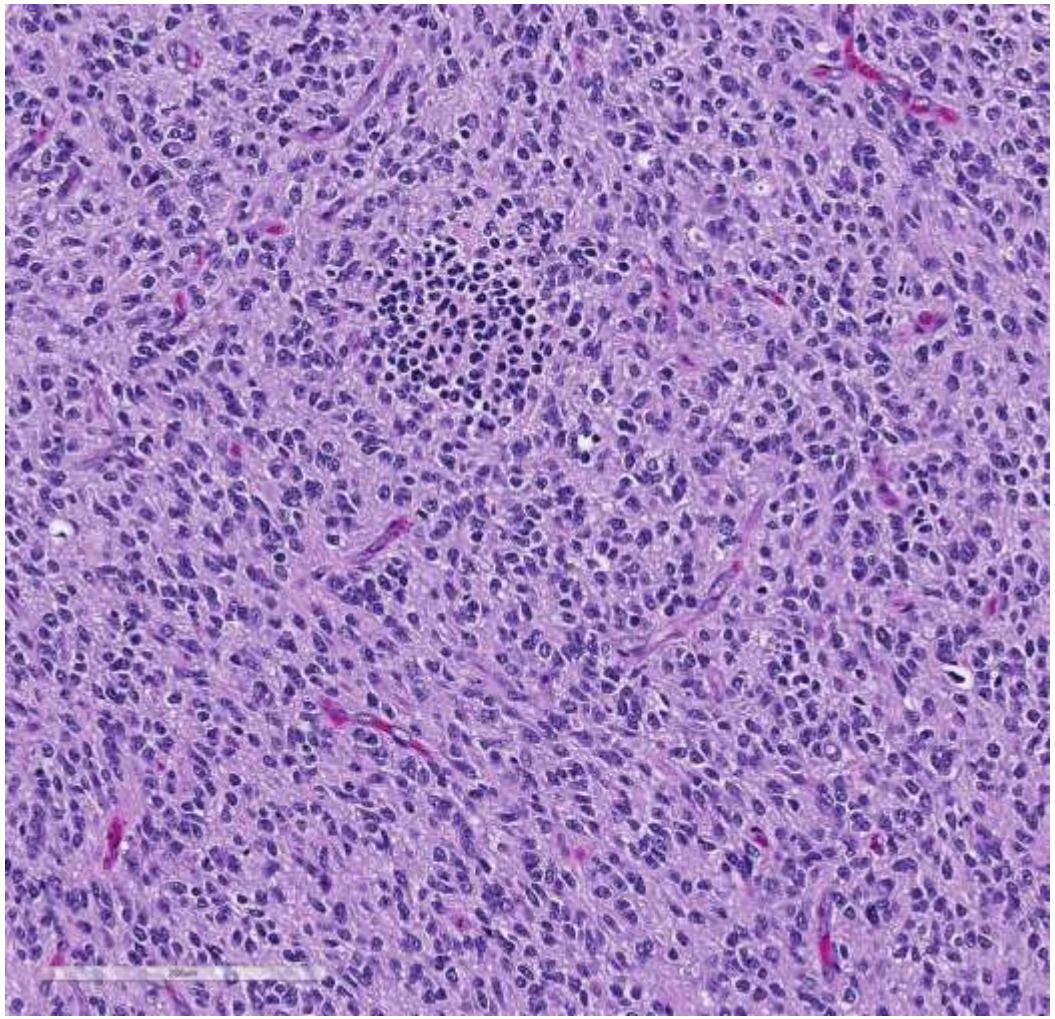




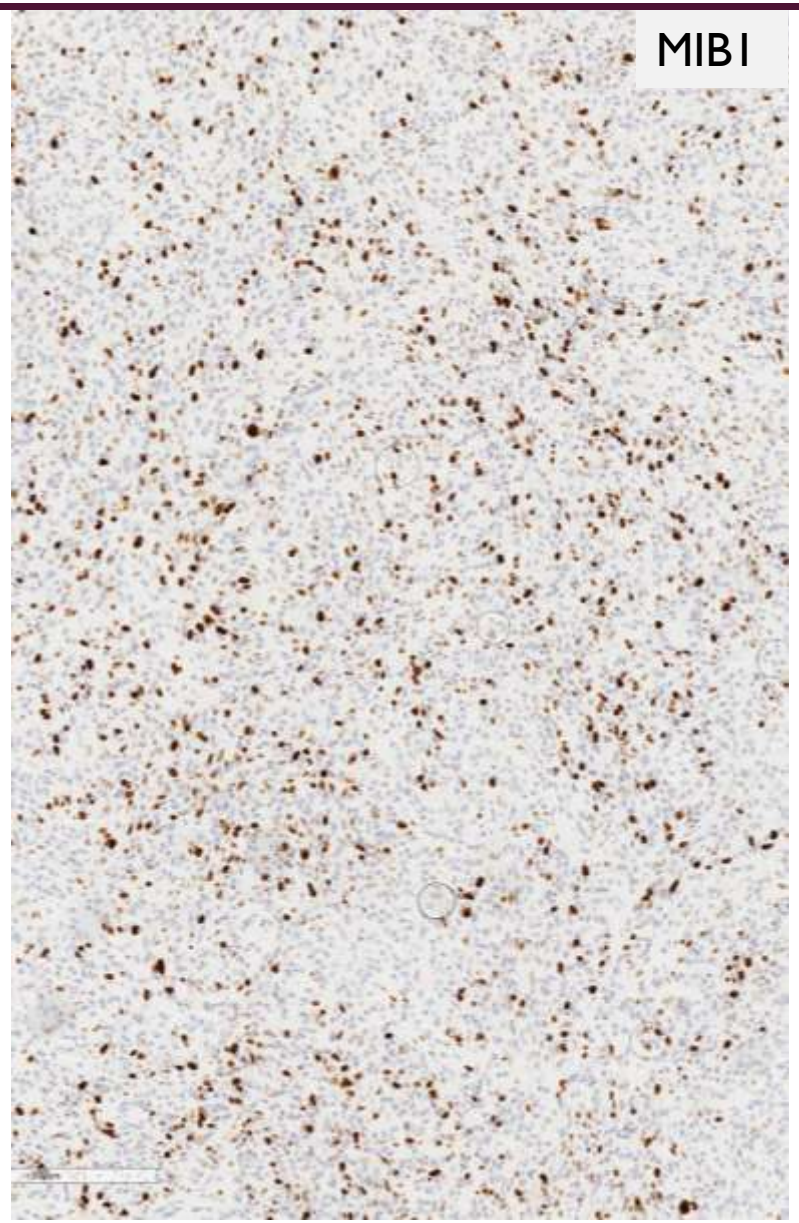
DIGITAL SLIDE

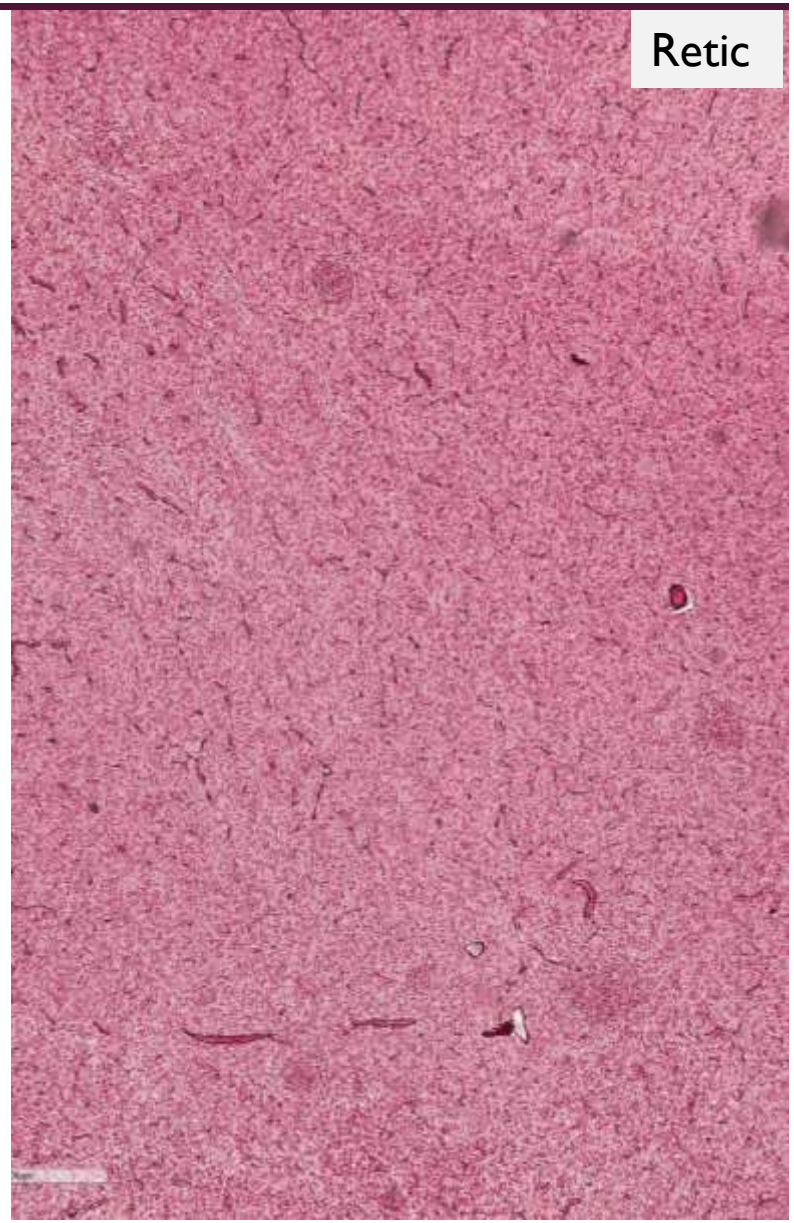
CASE 3 H&E

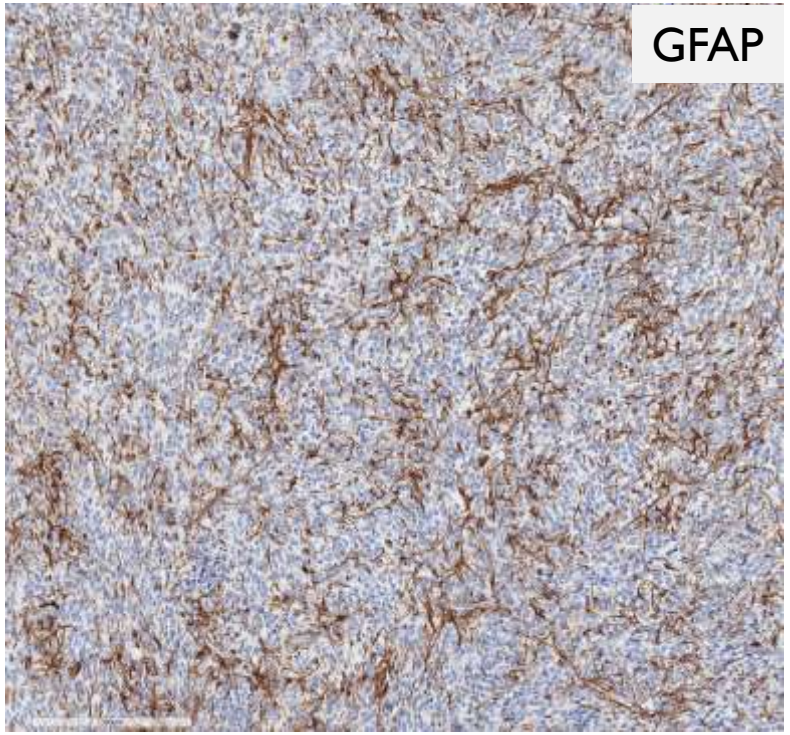


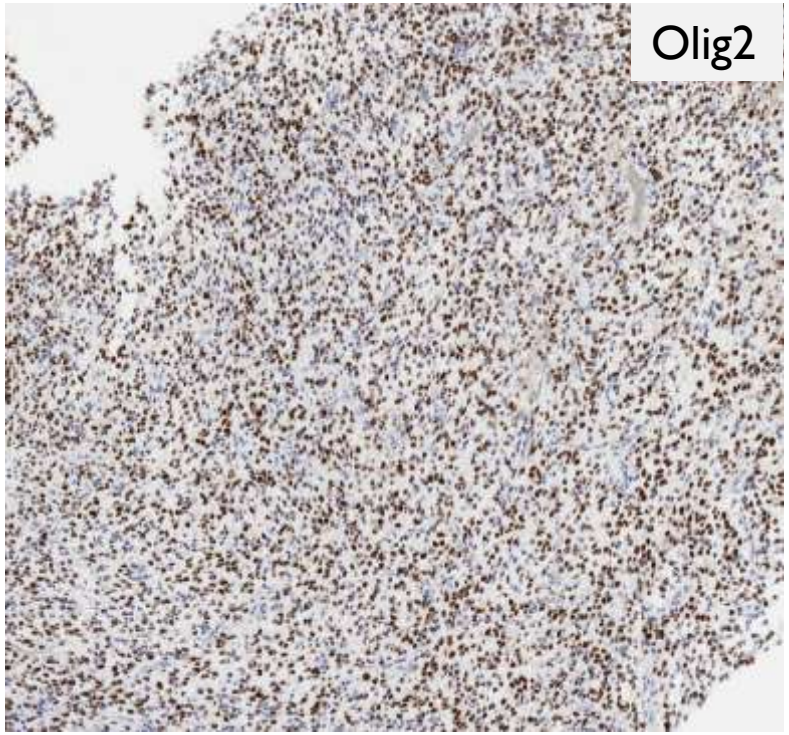


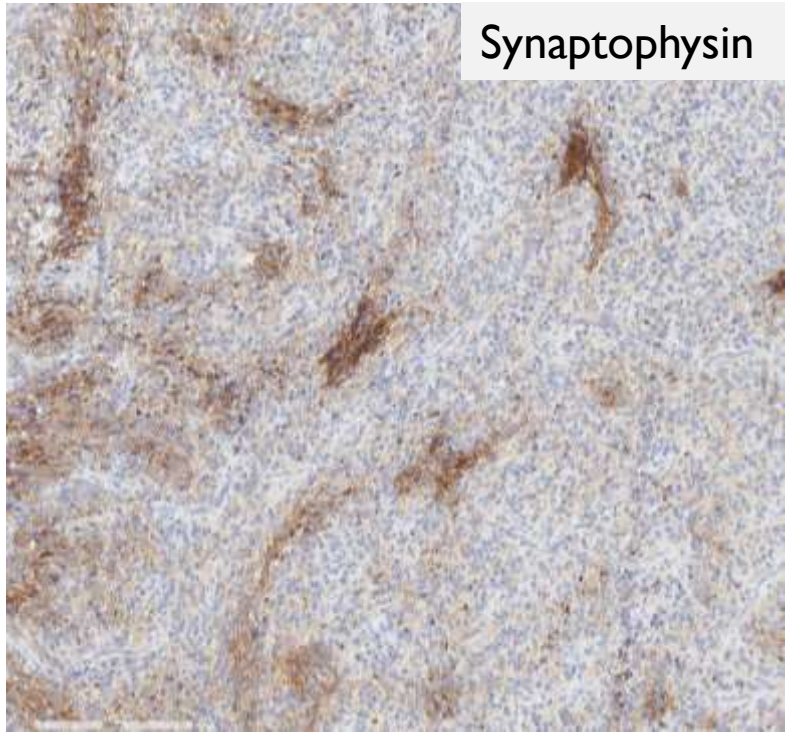
CASE 3





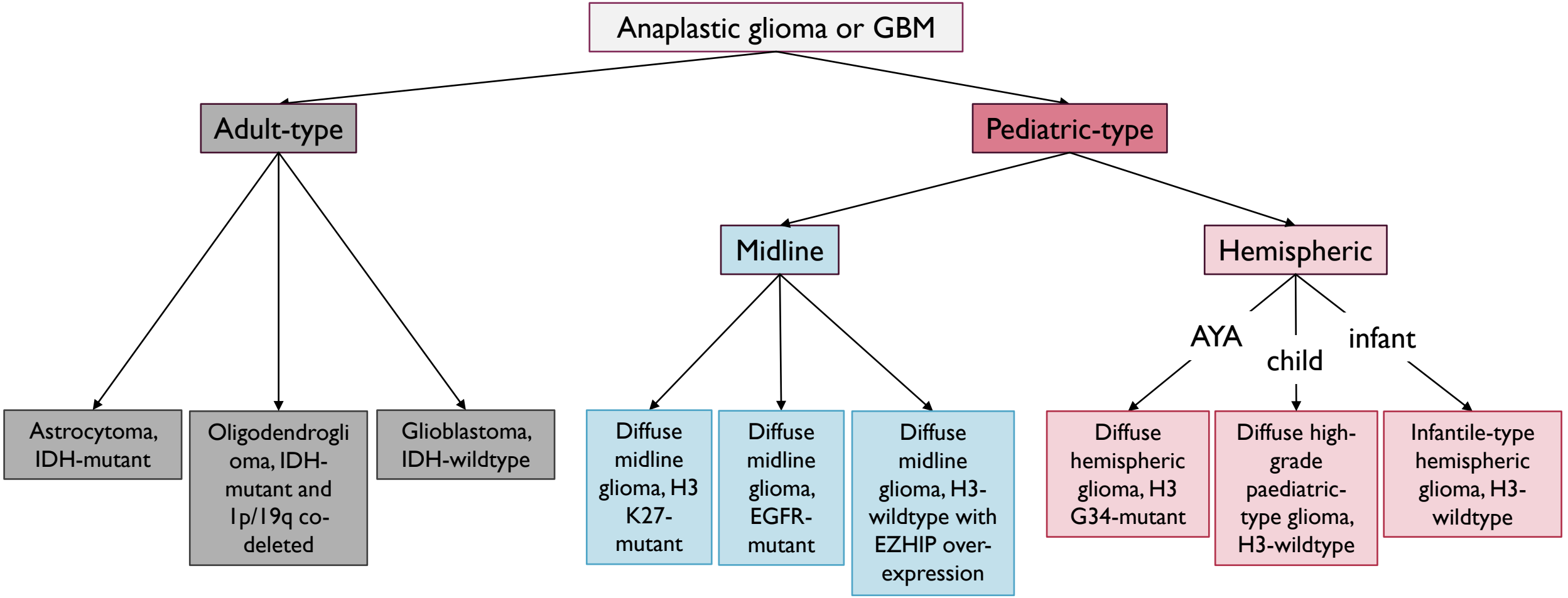




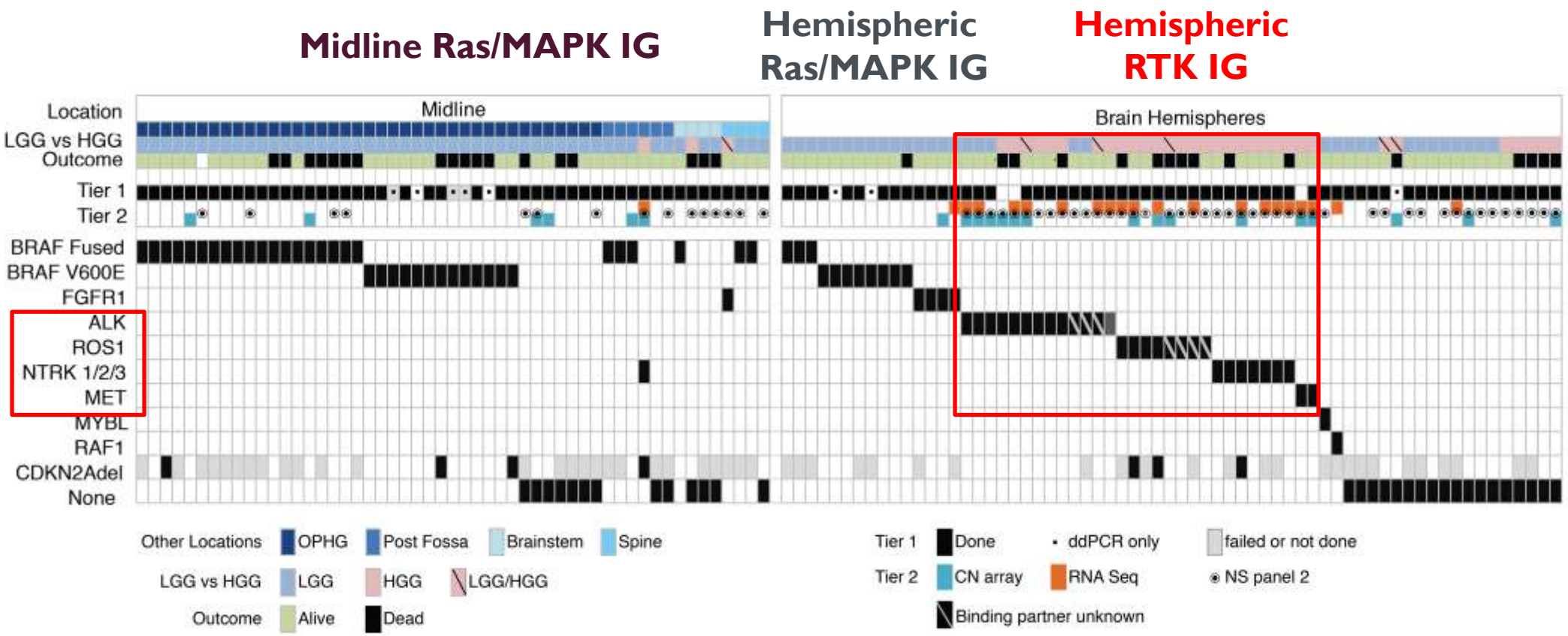


CASE 3 IHC

DIFFUSE HIGH-GRADE GLIOMAS: TUMOR TYPES



3 MAIN SUBGROUPS OF INFANT GLIOMAS



Stucklin, Ryall et al. Nature Commun, 2019

INFANT-TYPE HEMISPHERIC GLIOMA

- Hemispheric, high-grade gliomas arising in early childhood, mostly < 1year
- Typically harbor receptor tyrosine kinase fusions: *NTRK, ALK, ROS1, MET*
- Better outcome than high grade gliomas in older children
- RTK fusions may be therapeutically targeted

CASE 3 MOLECULAR RESULTS

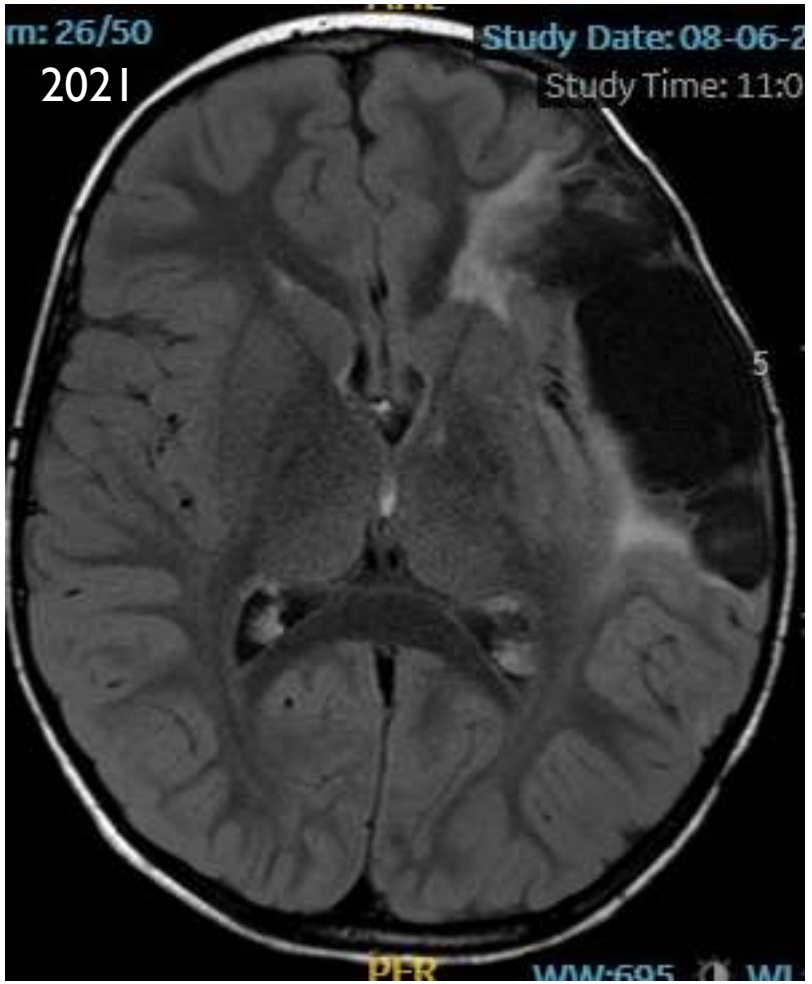
- RNA sequencing revealed *CLIP2-MET* fusion

FINAL INTEGRATED DIAGNOSIS

- Resection, Left hemispheric mass:
  - Infantile hemispheric glioma
    - *CLIP2-MET* fusion positive (RNAseq)

CASE 3

- Treated with chemotherapy (carbo/ vincristine)
- Currently off-treatment, doing well



OBJECTIVES - AT THE END OF THIS TALK YOU SHOULD BE ABLE TO:

1

Approach the workup of a pediatric glioma

2

Apply the changes in the new WHO classification of CNS tumors as it applies to gliomas

3

Integrate molecular and morphologic data to generate a layered neuropathologic diagnosis

QUESTIONS?

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