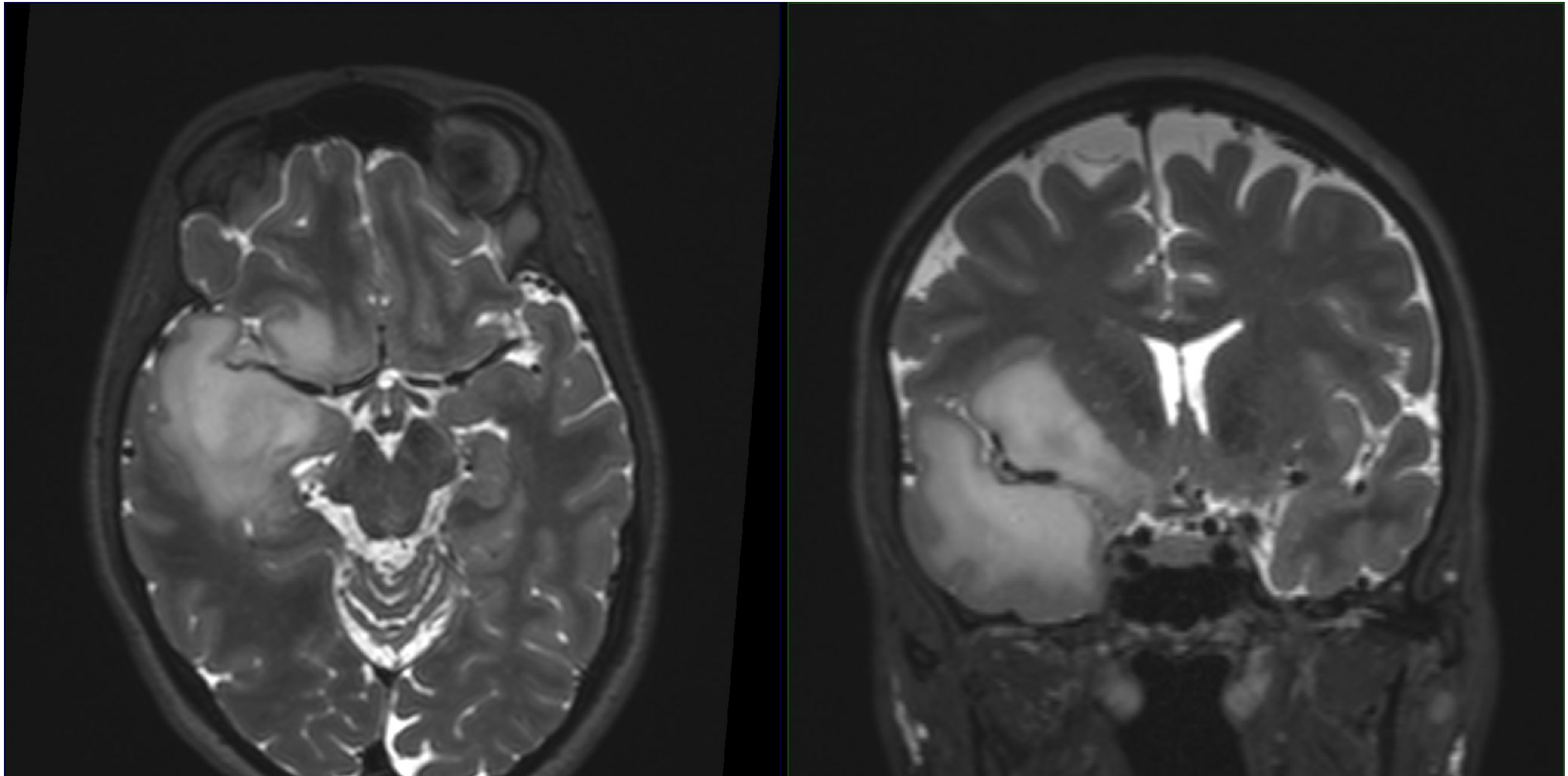
Low Grade Glioma

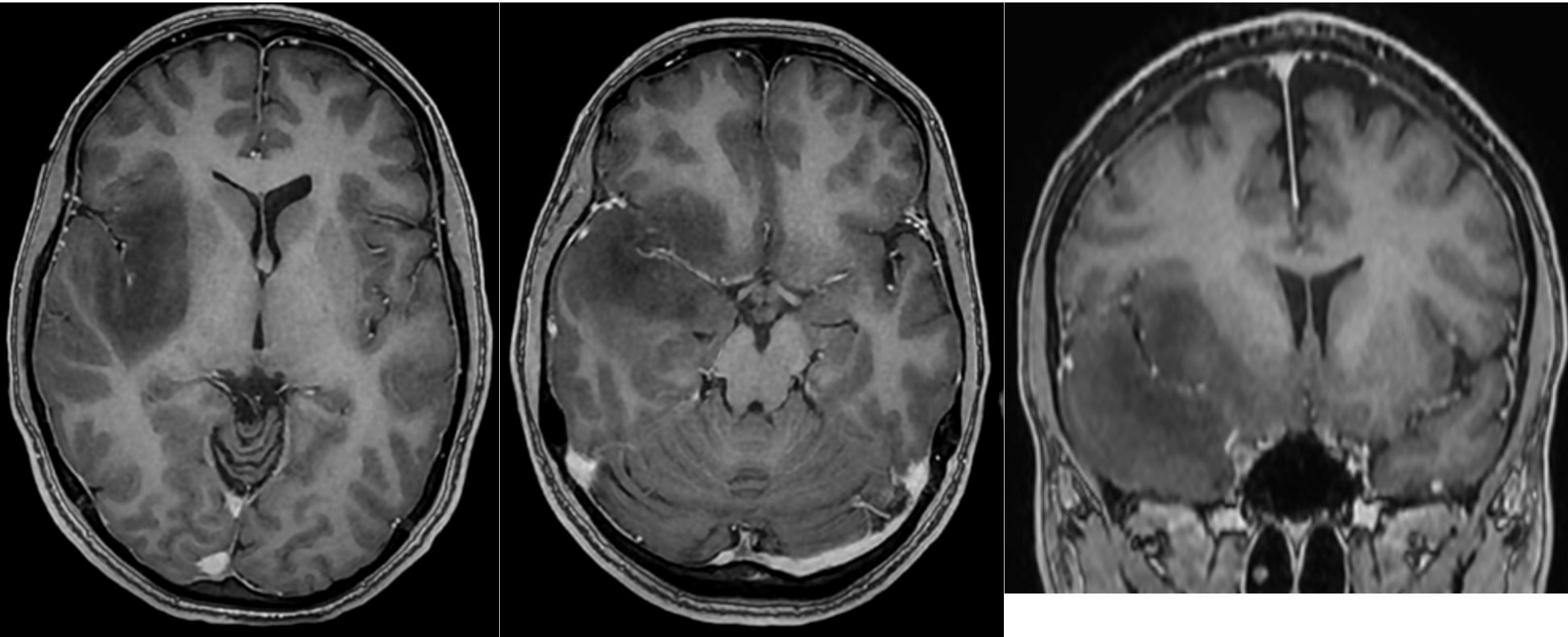
Presentation

- Female in their 30s presented with acute nausea followed by loss of consciousness, ? Seizure episode
- Neuroimaging revealed right frontotemporal/insular nonenhancing lesion
- Right stealth Craniotomy with asleep motor mapping
  - Subtotal resection
  - Tumor involving the insula unable to be resected – mapped to functional areas

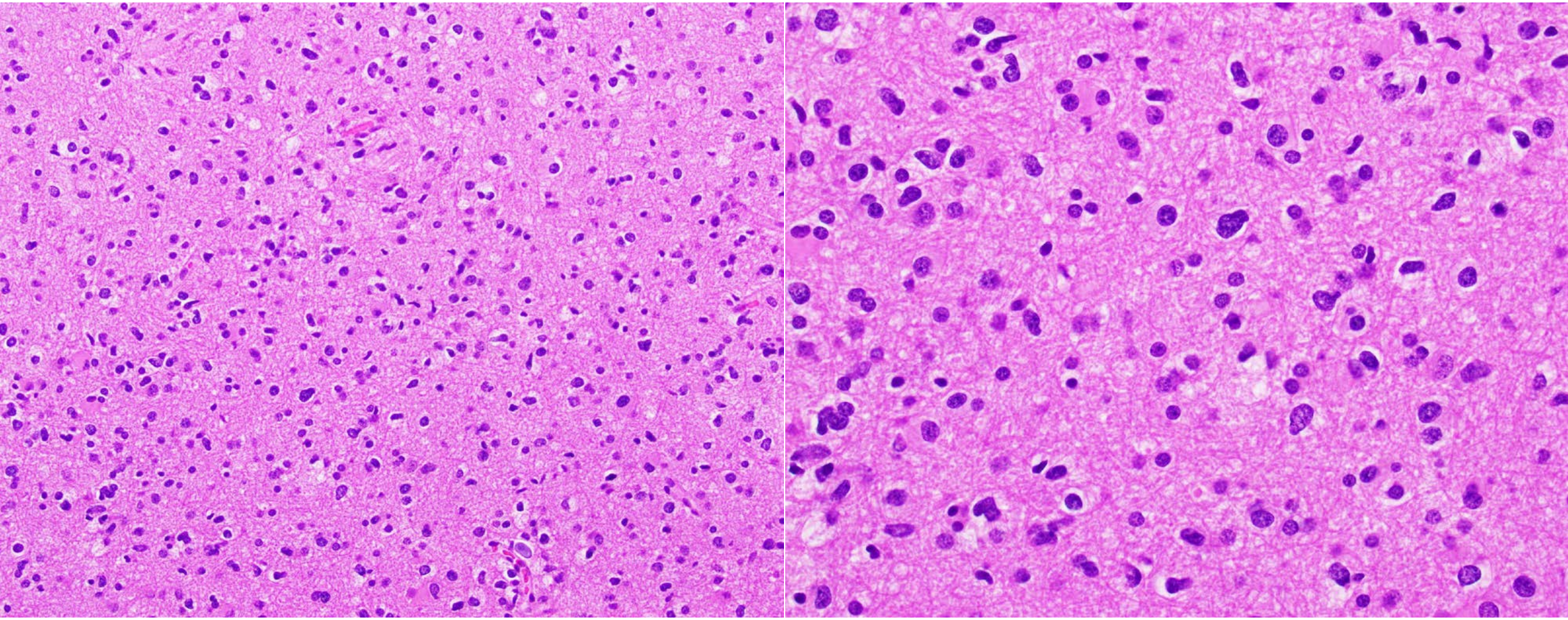
MRI volumetric T2



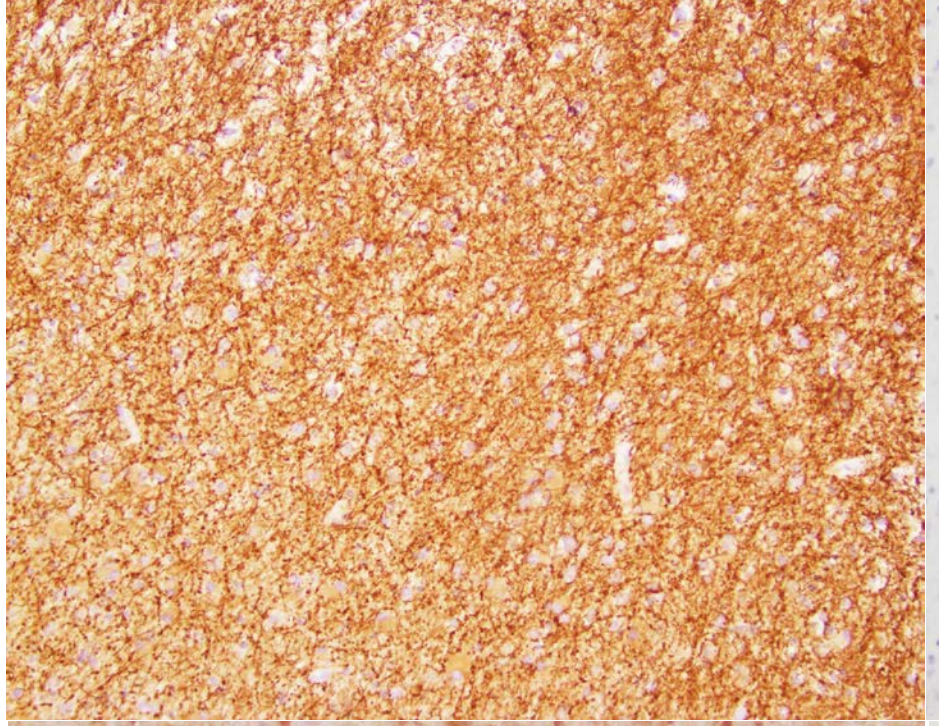
MRI Postcontrast volumetric T1

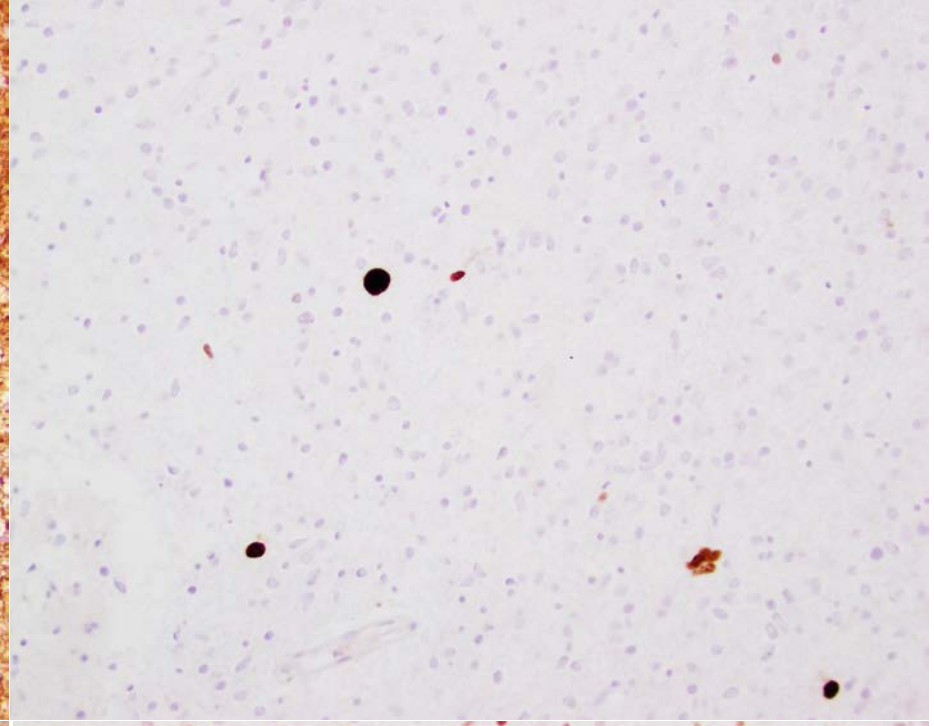


H&E Histology

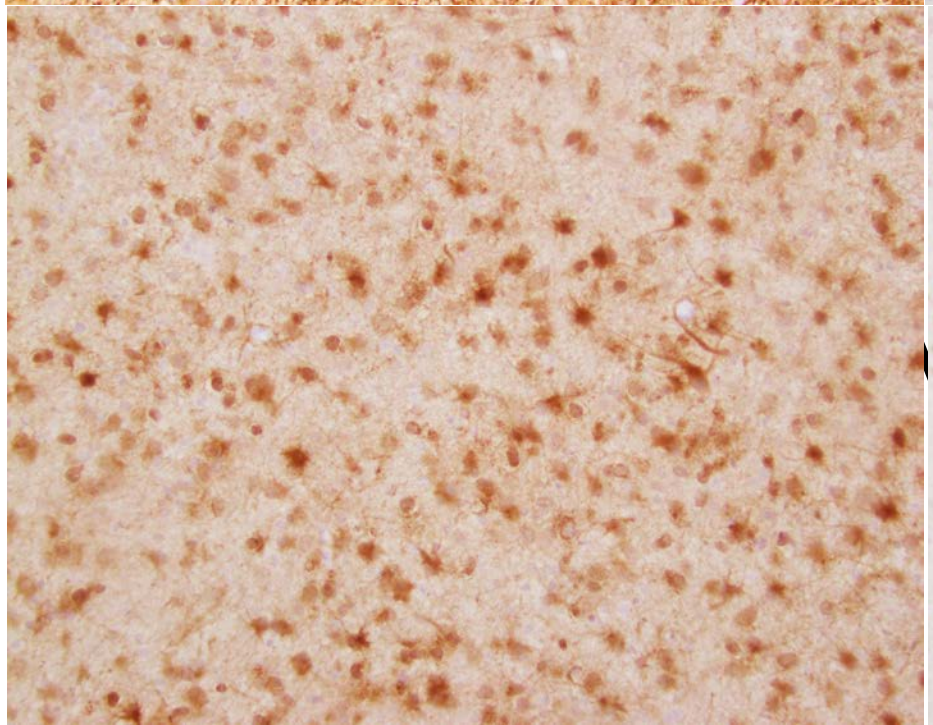


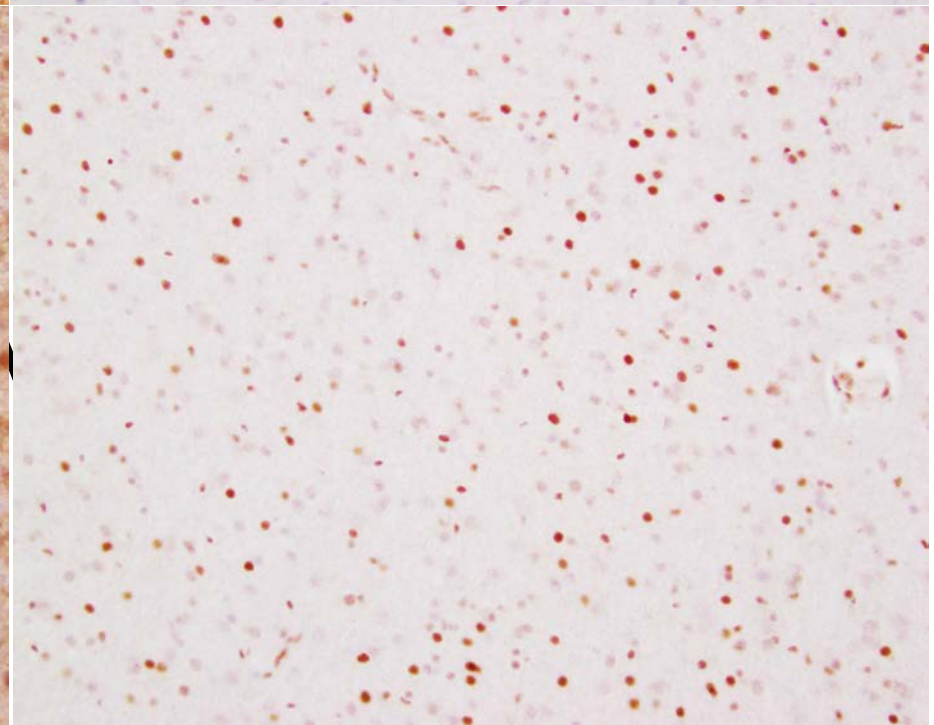
GFAP





IDH1
R132H





- **Genetic Analysis Report**
- **UF HEALTH PATHLABS GATORSEQ700 NGS SCREENING PANEL**

Indication: Suspected Astrocytoma

TMB Status: TMB-low (3.9 mut/Mb)

Comment: CNV dot plot suggests gain of chromosome 7. Whole and arm level chromosome changes are not clinically validated for this test and reported for academic purposes only. Correlation with a clinically validated method (such as FISH) is recommended; if indicated.

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1. Pathogenic variants

IDH1 c.395G>A p.R132H VAF: 37% chr2:g.209113112C>T (Tier 1A)
TP53 c.817C>T p.R273C VAF: 71% chr17:g.7577121G>A (Tier 2C) #

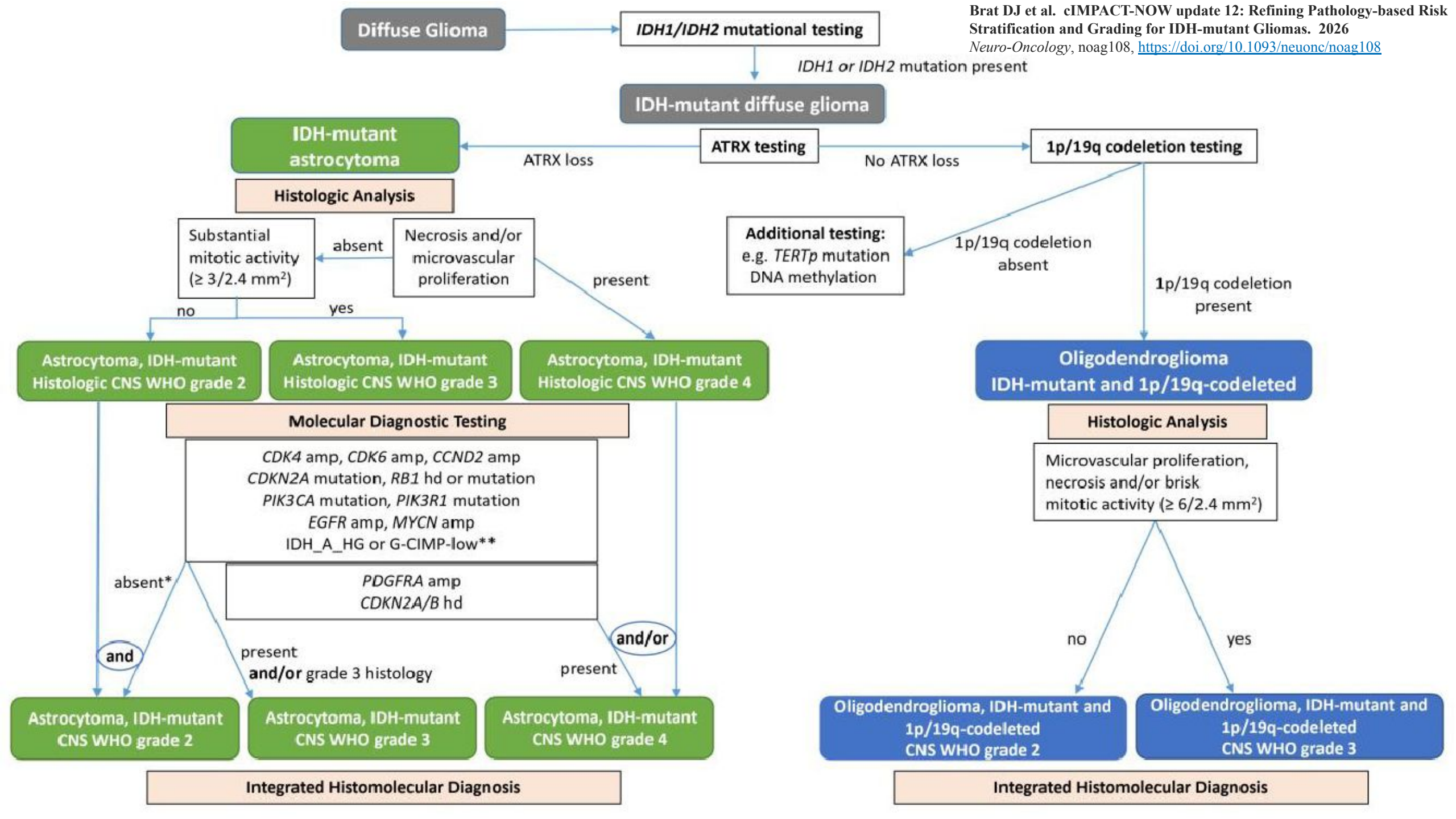
TP53 variant: This assay cannot differentiate germline and somatic (tumor only) variants. Genetic counseling is recommended for the TP53 variant above; if clinically indicated.

Brain, right temporal tumor, craniotomy for resection: (integrated diagnosis)

Astrocytoma, IDH-mutant, CNS WHO Grade 2. (Please see comment.)

- **Histopathological Diagnosis:** Diffuse glioma, adult type.
  - Mitoses are only rarely identified on routine H&E stains.
  - No microvascular proliferation or necrosis are present.
- **Immunohistochemistry:**
  - GFAP – Positive in tumor cells and processes.
  - IDH1 (R132H) - positive for mutation.
  - ATRX – loss of nuclear immunoreactivity in tumor cells.
  - Ki-67 - low proliferation index (1-4% approximately).
- **Molecular study:**
  - (Gatorseq NGS) confirms mutations of *IDH1p.R132H* and *ATRX* while also showing a *TP53* mutation.
  - No homozygous deletions of *CDKN2A/2B* or PDGFRA amplifications are identified.
  - MGMT promoter methylation is not identified.

Brat DJ et al. cIMPACT-NOW update 12: Refining Pathology-based Risk Stratification and Grading for IDH-mutant Gliomas. 2026
Neuro-Oncology, noag108, https://doi.org/10.1093/neuonc/noag108



Treatment landscape for IDH 1/2 mutant Gliomas – prior to 2023

- Oligodendroglioma WHO Grade 2
  - Surgical resection followed
    - Observation*
    - Radiation followed by PCV (vs TMZ)
- Diffuse Astrocytoma WHO Grade 2
  - Surgical resection followed by
    - Observation*
    - Radiation followed by TMZ (vs PCV)

*Decision aided by certain factors such as resection status, age

Weller M et al. Nat Rev Clin Oncol 2021

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

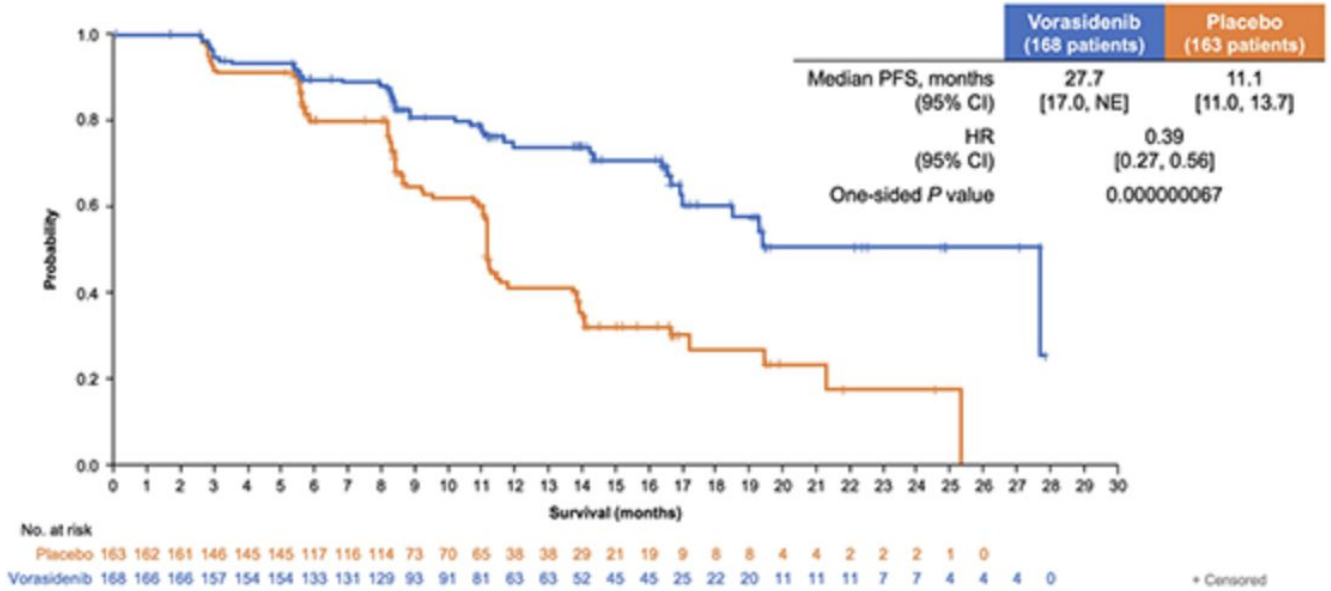
Ingo K. Mellinghoff, M.D., Martin J. van den Bent, M.D., Deborah T. Blumenthal, M.D., Mehdi Touat, M.D., Katherine B. Peters, M.D., Jennifer Clarke, M.D., M.P.H., Joe Mendez, M.D., Shlomit Yust-Katz, M.D., Liam Welsh, M.D., Ph.D., Warren P. Mason, M.D., François Ducray, M.D., Yoshie Umemura, M.D., Burt Nabors, M.D., Matthias Holdhoff, M.D., Andreas F. Hottinger, M.D., Ph.D., Yoshiki Arakawa, M.D., Juan M. Sepulveda, M.D., Wolfgang Wick, M.D., Riccardo Soffietti, M.D., James R. Perry, M.D., Pierre Giglio, M.D., Macarena de la Fuente, M.D., Elizabeth A. Maher, M.D., Steven Schoenfeld, M.S., Dan Zhao, Ph.D., Shuchi S. Pandya, M.D., Lori Steelman, M.S., Islam Hassan, M.D., Patrick Y. Wen, M.D., and Timothy F. Cloughesy, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

- Phase 3 double-blind, randomized study
- Vorasidenib (IDH1/2 inhibitor) vs placebo
  - Glioma IDH 1/2 mutant WHO Grade 2 s/p resection
  - No urgent need to receive radiation or chemotherapy
- Pre-planned interim analysis
  - Vorasidenib had significant improvement in PFS and Time to next intervention (TTNI)

INDIGO Study

Figure 1. Primary Endpoint of PFS per Blinded Independent Review Committee



Abbreviations: BIRC, blinded independent review committee; PFS, progression-free survival.View larger

Updated at ASCO 2026
Vorasidenib arm
Median PFS - 49.9 months
Median TTNI - Not evaluable
NCT04164901

Mellinghoff I et al. N Engl J Med 2023
Cloughesy T et al. J Clin Oncol 2026

Changing our treatment paradigm?

- Low risk Grade 2 gliomas IDH 1/2 mutated
  - Residual disease, no urgency to start chemotherapy or radiation Give Vora
  - Gross total resection, no visible disease, observe vs Vora?
- What do we do for recurrent patients who have not had IDH inhibitors
  - Monotherapy vs combinatorial approaches
- What do we do for Grade 3 patients
  - Role for adding upfront with Chemoradiation?