



HEIDELBERG
UNIVERSITY
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Update on Meningioma Guidelines

Felix Sahm



COI

Honoraria from Bayer, Illumina, Agilent

Co-founder and shareholder of Heidelberg Epignostix GmbH

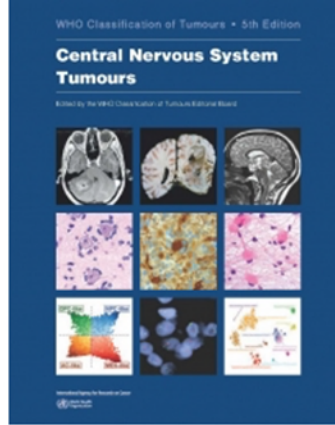
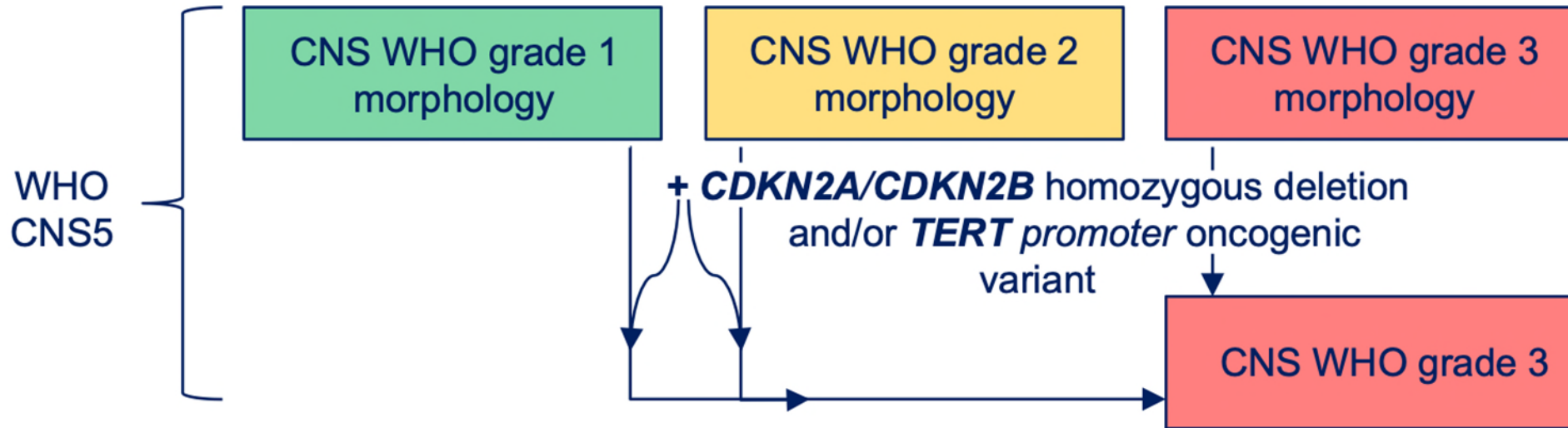
Co-inventor in patents in the field of methylation-based classification

Learning objectives

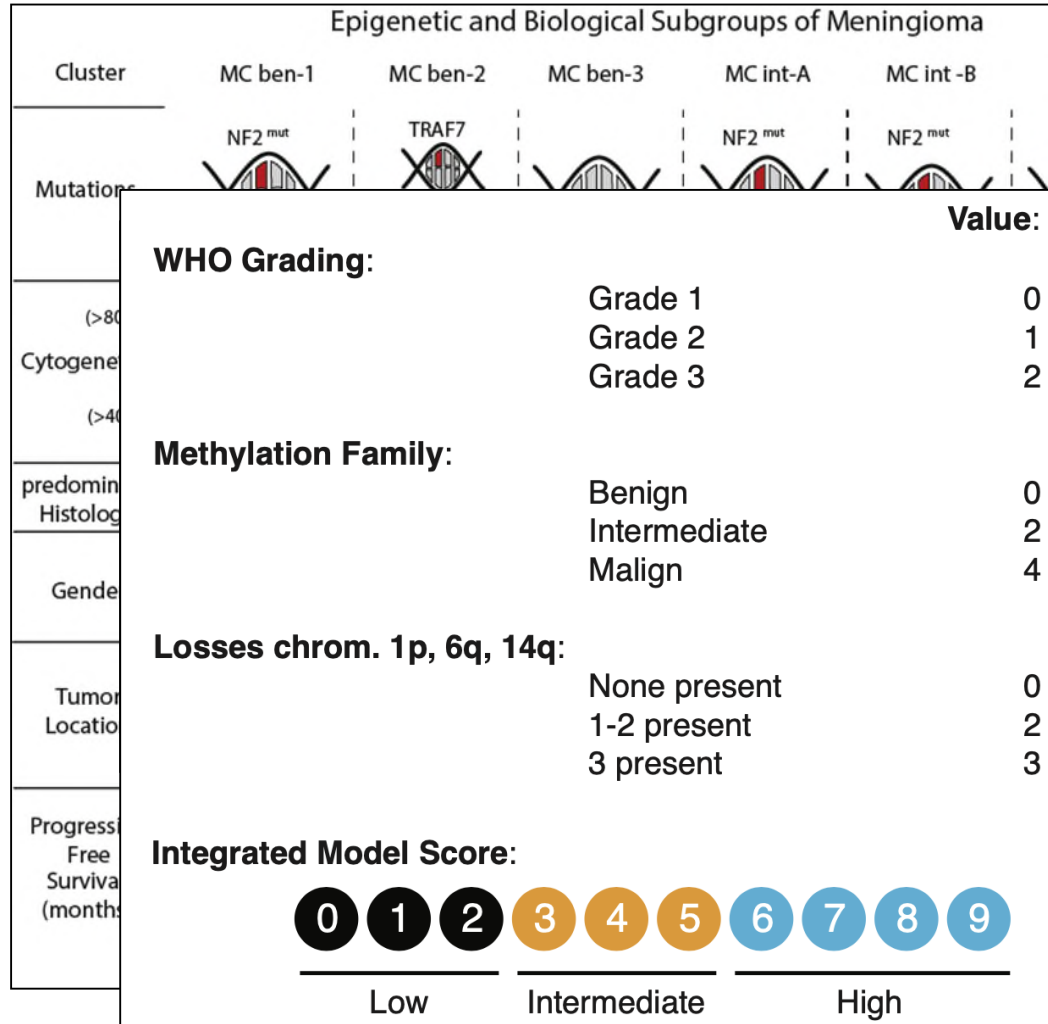
1. Identify molecular markers that distinguish CNS WHO grade 1 and 2 meningioma
2. Describe high-throughput platform results (methylation, RNA) into classification and grading of meningiomas
3. Identify suitable workflows for grading of brain invasive otherwise benign meningiomas



Meningioma Grading WHO 2021



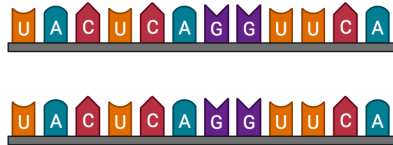
Advanced Molecular Grading



Group	Merlin-intact	Immune-enriched	Hypermitotic
Genetic features	5 gain 6p loss (HLA) 22q neutral (NF2)	6p gain (HLA) 22q loss (NF2)	1p loss 1q gain (USF1) 6p loss (HLA) 9p loss (CDKN2A/B) 14q loss or gain 22q loss (NF2)
Epigenetic and gene expression features	NF2 expression	HLA and meningeal lymphatic gene hypomethylation and expression	FOXM1 expression CDKN2A/B hypermethylation
Cellular features	Merlin Apoptosis	Immune infiltration Meningeal lymphatics	Cell cycle Mitosis
Meningioma cell lines	MSC1 MSC5	M10G DI134 IOMM-Lee CH-157MN	M13C BenMen DI98
WHO grade	Grade 1 81% Grade 2 17% Grade 3 2%	Grade 1 75% Grade 2 19% Grade 3 6%	Grade 1 43% Grade 2 45% Grade 3 12%
LFFR (%)			
OS (%)			

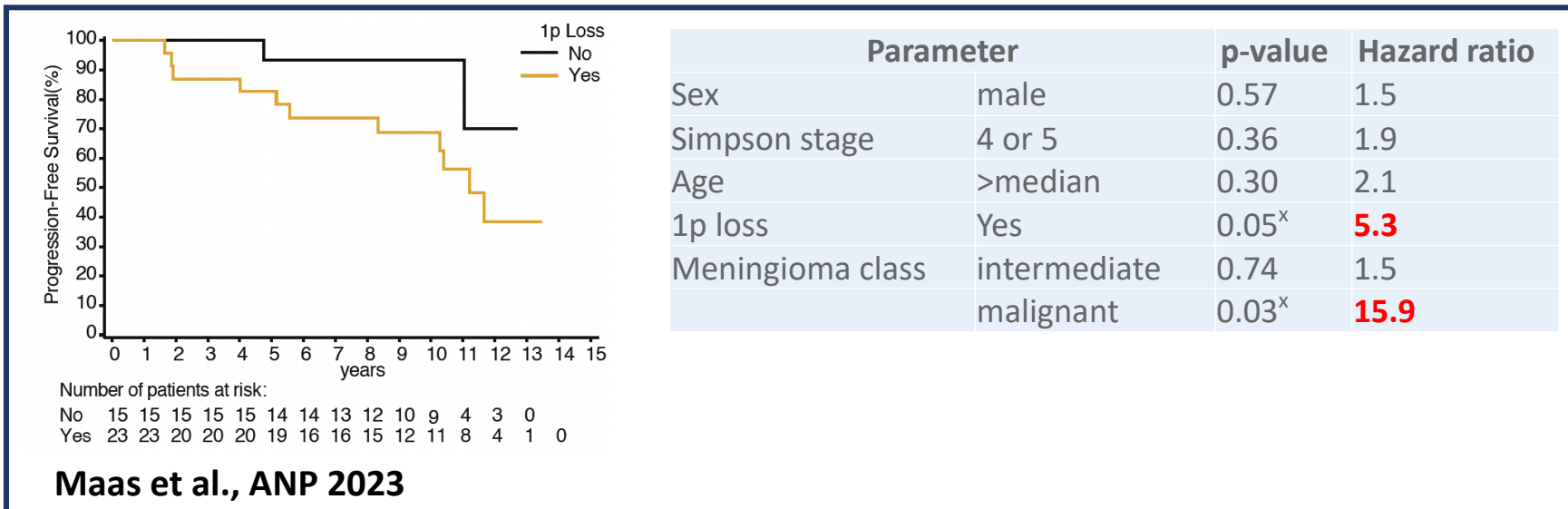
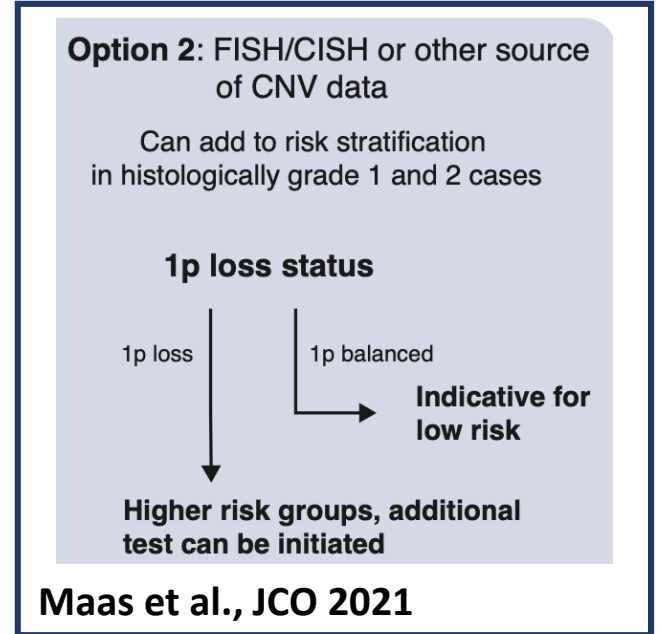
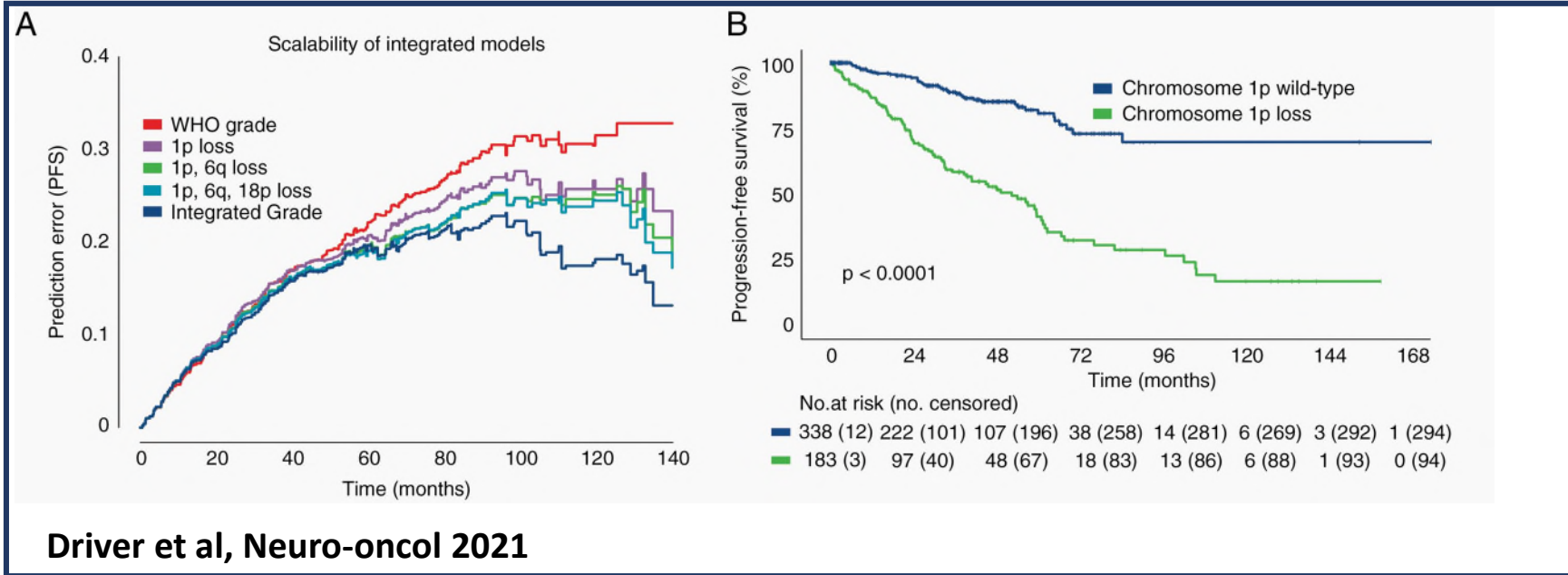
Sahm et al., 2016
Maas et al., 2021
Nassiri et al., 2021
Choudhury et al., 2022

What data to include in grading / reporting?



Most robust single marker

1p



Most robust single marker

1p

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Vol. 60, No. 6
June, 2001
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Chromosome 1p and 14q FISH Analysis in Clinicopathologic Subsets of Meningioma: Diagnostic and Prognostic Implications

DAN X. CAI, MD, PHD, RUMA BANERJEE, BERND W. SCHEITHAUER, MD, CHRISTINE M. LOHSE,
BETTE K. KLEINSCHMIDT-DEMASTERS, MD, AND ARIE PERRY, MD

GENES, CHROMOSOMES & CANCER 9:296–298 (1994)

BRIEF COMMUNICATION

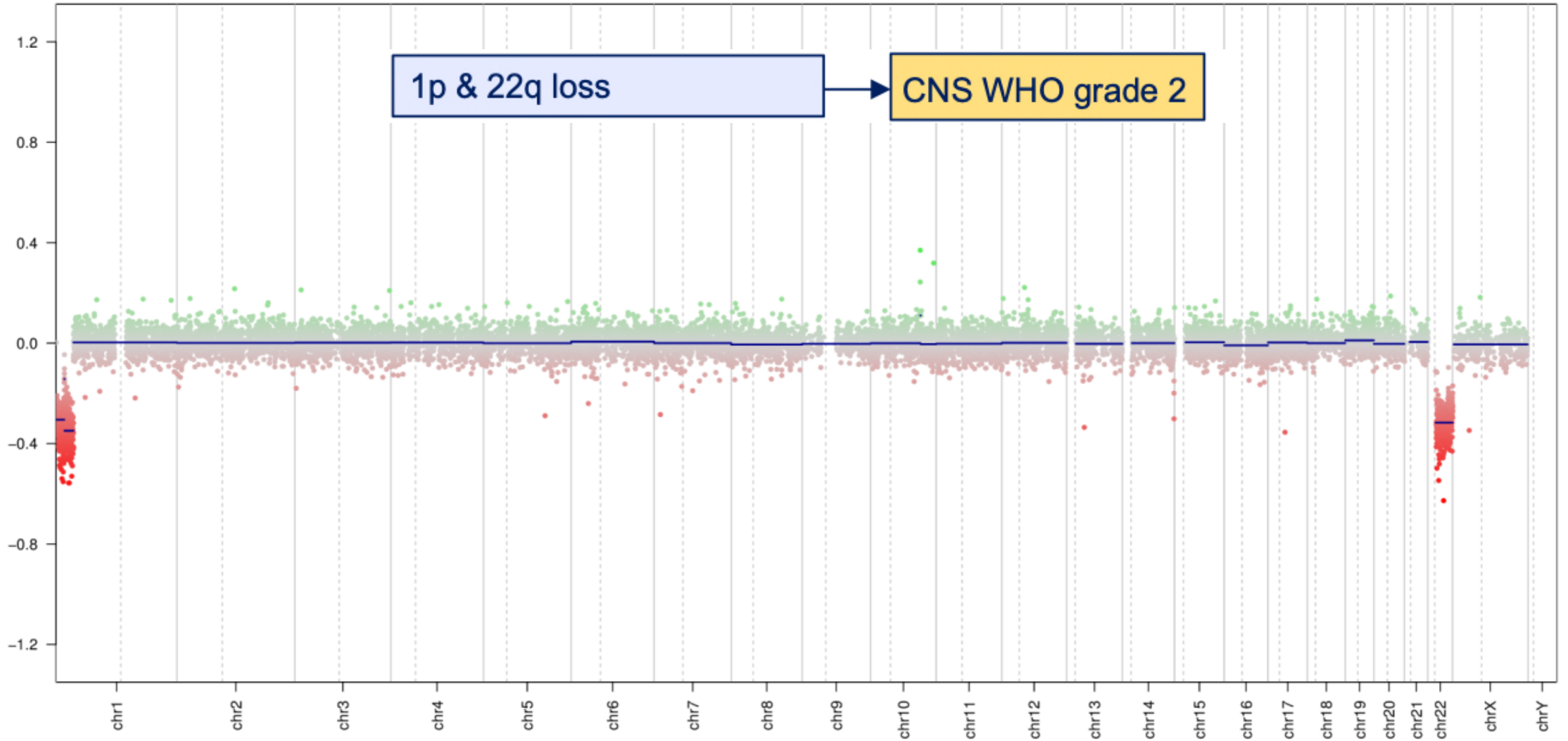
Allelic Loss at 1p Is Associated With Tumor Progression of Meningiomas

**M. Josefa Bello, Jose M. de Campos, M. Elena Kusak, Jesus Vaquero, Jose L. Sarasa, Angel Pestaña,
and Juan A. Rey**

Instituto de Investigaciones Biomédicas (CSIC) (M.J.B., A.P., J.A.R.); Department of Biochemistry, Facultad de Medicina de la U.A.M. (J.A.R.); Departments of Neurosurgery, the Fundación Jiménez Díaz (J.M. de C.), Hospital de la Princesa (M.E.K.), and Clínica Puerta de Hierro (J.V.); and Department of Anatomical Pathology of Fundación Jiménez Díaz (J.L.S.), Madrid, Spain.



New Guideline



cIMPACT8: 1p deletion CNS WHO grade 2



cIMPACT8: When to test?



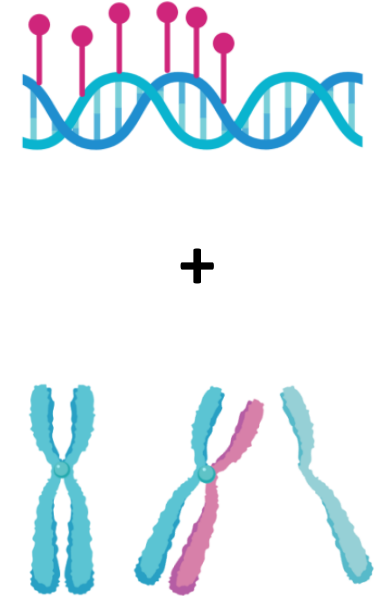
cIMPACT8: Novel Markers

Epigenetic and Biological Subgroups of Meningioma

Cluster	MC ben-1	MC ben-2	MC ben-3	MC int-A	MC int-B	MC mal
Mutations	NF2 mut	TRAF7, NLF4, SMO, AKT1		NF2 mut	NF2 mut, TERT mut	NF2 mut, TERT mut
Cytogenetics (>80%)	22q del.	balanced		22q del.	22q del.	22q del.
Cytogenetics (>40%)			22q del., 5 gain	1p del.	1p, CDKN2A del.	1p, 10, CDKN2A del.
predominant Histology	Fibroblastic Transitional Atypical	Secretory Transitional Meningothelial	Angiomatous Transitional Atypical	Fibroblastic Transitional Atypical	Atypical Anaplastic	Anaplastic
Gender						
Tumor Location						
Progression Free Survival (months)						



Group	Merlin-intact	Immune-enriched	Hypermitotic
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LFFR (%)			
OS (%)			



Clinical outcomes and features

cIMPACT8: Novel Markers

Scenarios where additional molecular testing may be useful

- Features borderline between CNS WHO grade 1 and 2 (e.g. 3 mitotic figures per 1.6 mm² or 2 of the 5 “soft” criteria)
- Brain-invasive, otherwise benign (BIOB) meningioma
- CNS WHO grade 1 meningioma with unexpectedly rapid growth on serial imaging or recurrence
- CNS WHO grade 2 (confirmation, distinguishing from CNS WHO grade 1/3)
- Chordoid, clear cell, rhabdoid or papillary histology

Chromosomal (arm) losses*

1p & 22q loss

CNS WHO grade 2

Multi-layered (integrated) diagnosis (cIMPACT 8)



Morphology: Meningioma with low mitotic activity

Molecular findings: TERT promoter wildtype, CDKN2A/B balanced, 1p and 22q deletion

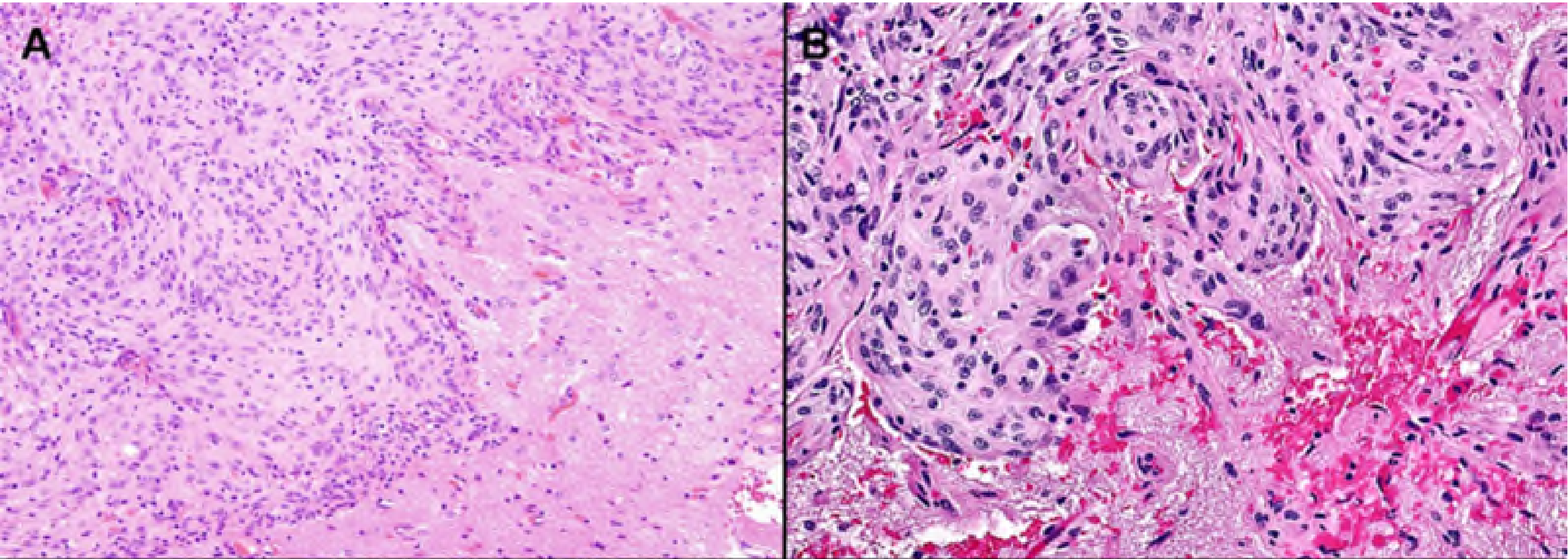
Integrated diagnosis: Atypical meningioma CNS WHO grade 2

Morphology: Meningioma with marginal features of atypia

Molecular findings: no copy-number alterations, MC benign-2

Integrated diagnosis: Meningioma CNS WHO grade 1 with molecular low risk

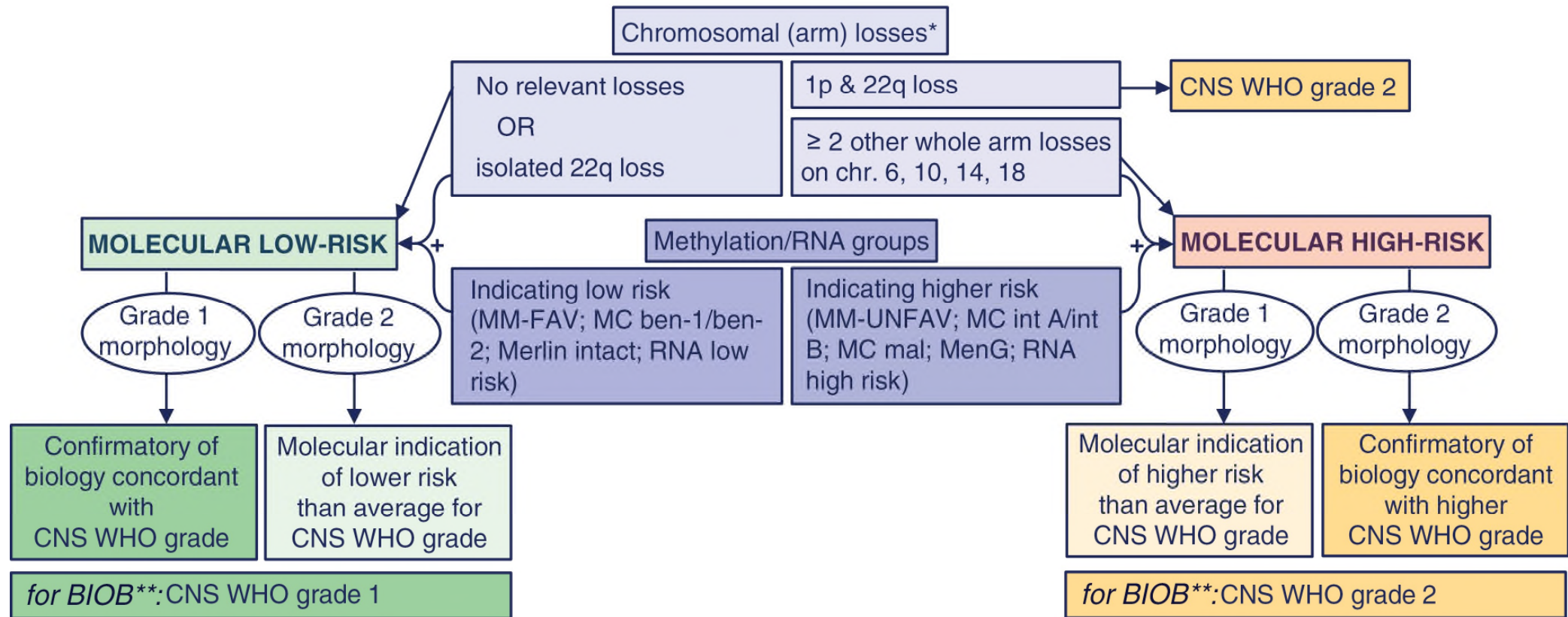
cIMPACT8: Brain Invasion Otherwise Benign



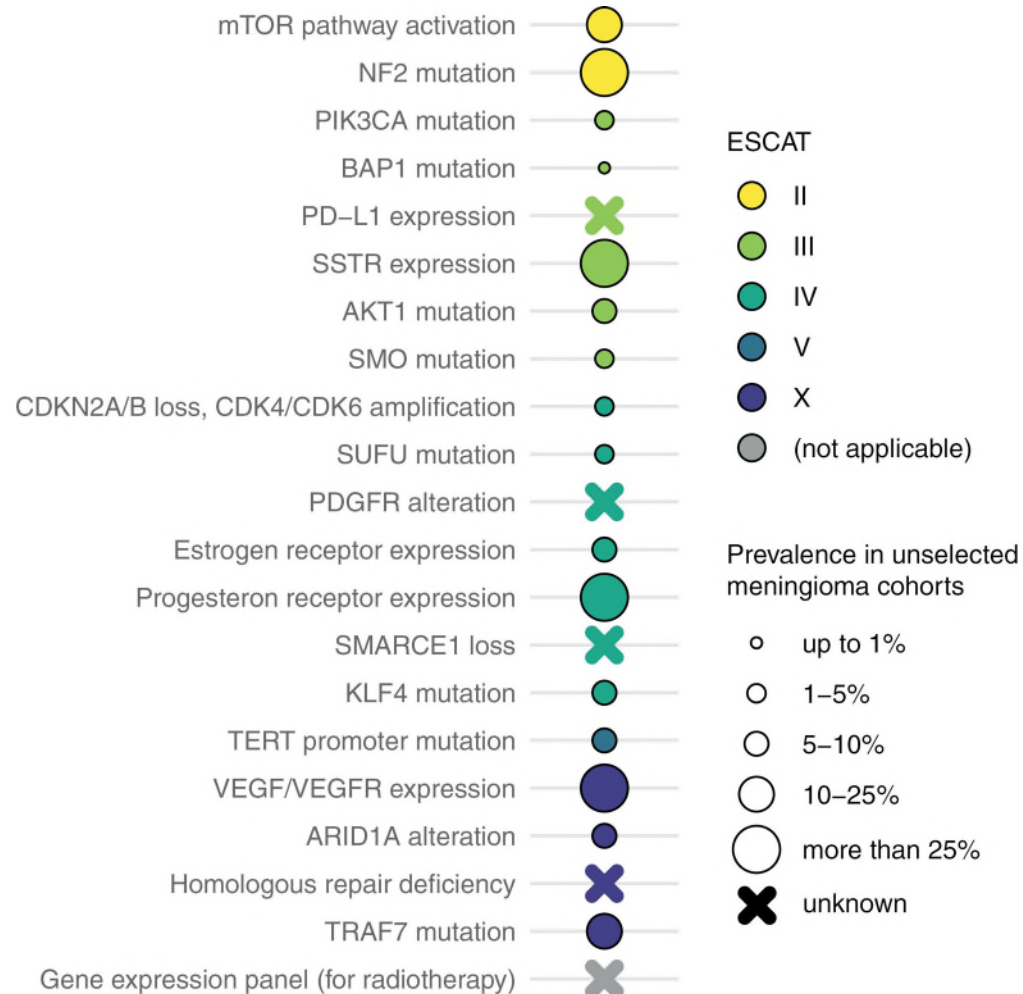
cIMPACT8: Brain Invasion Otherwise Benign

Scenarios where additional molecular testing may be useful

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EANO Meningioma Targeted Treatment Guideline

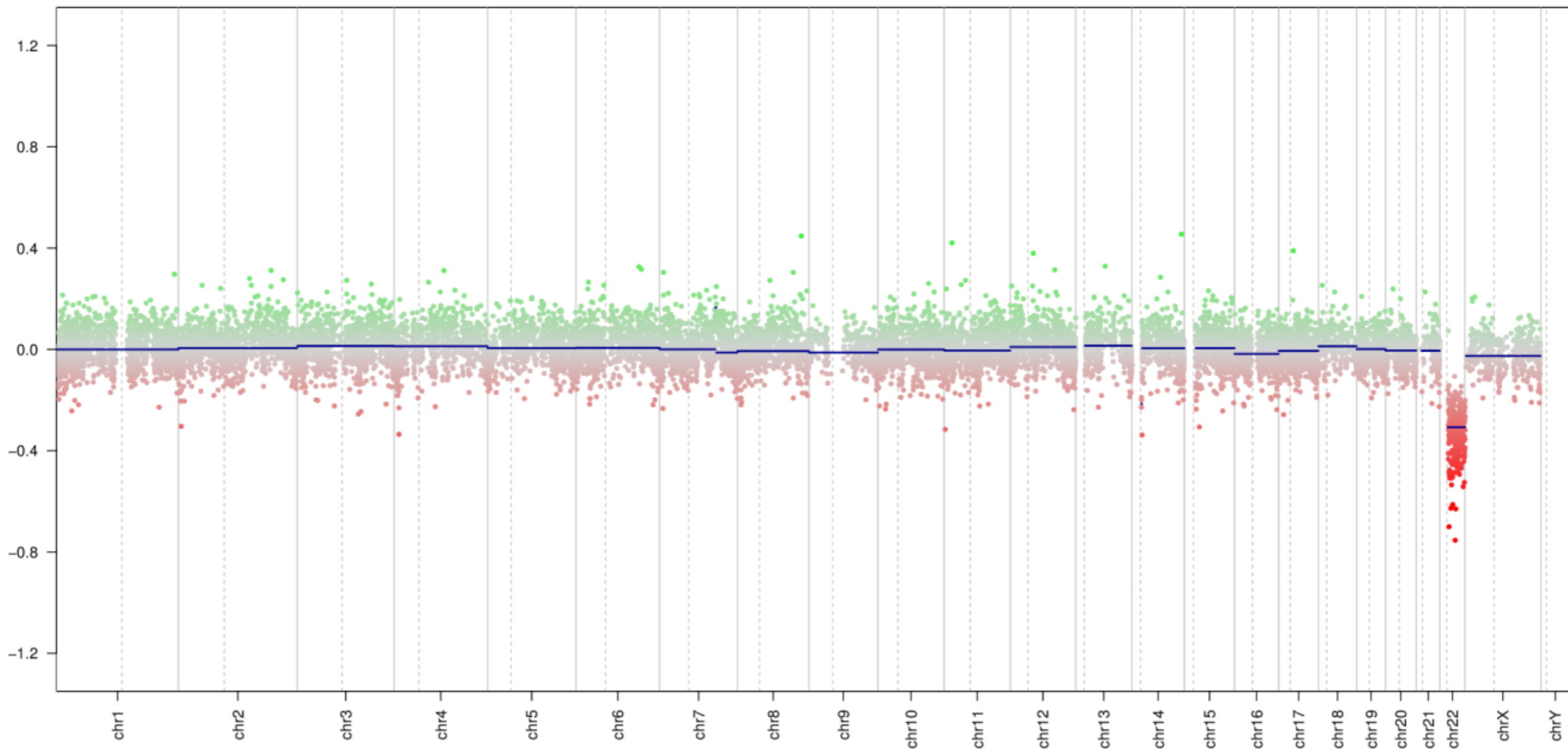


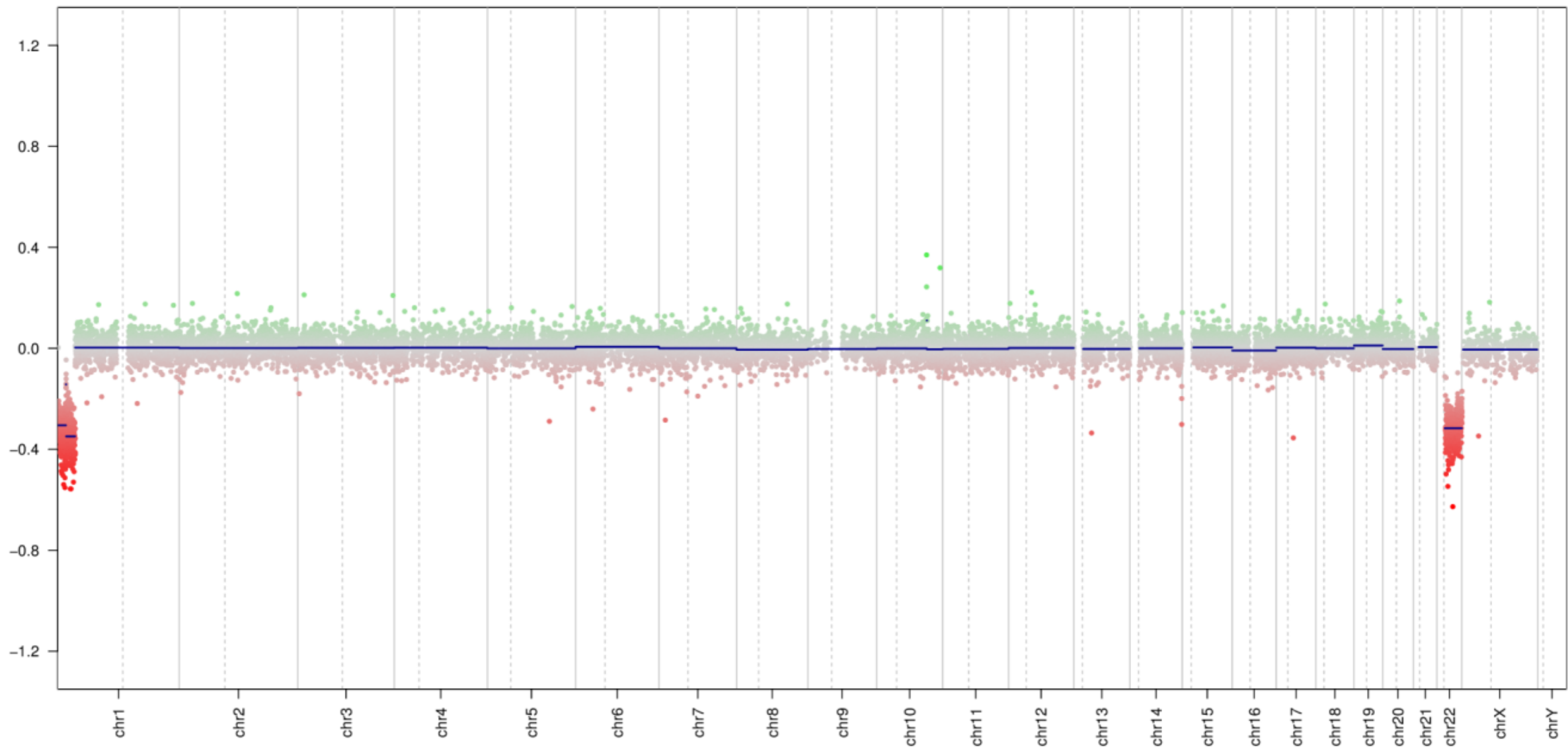
Neuro-Oncology

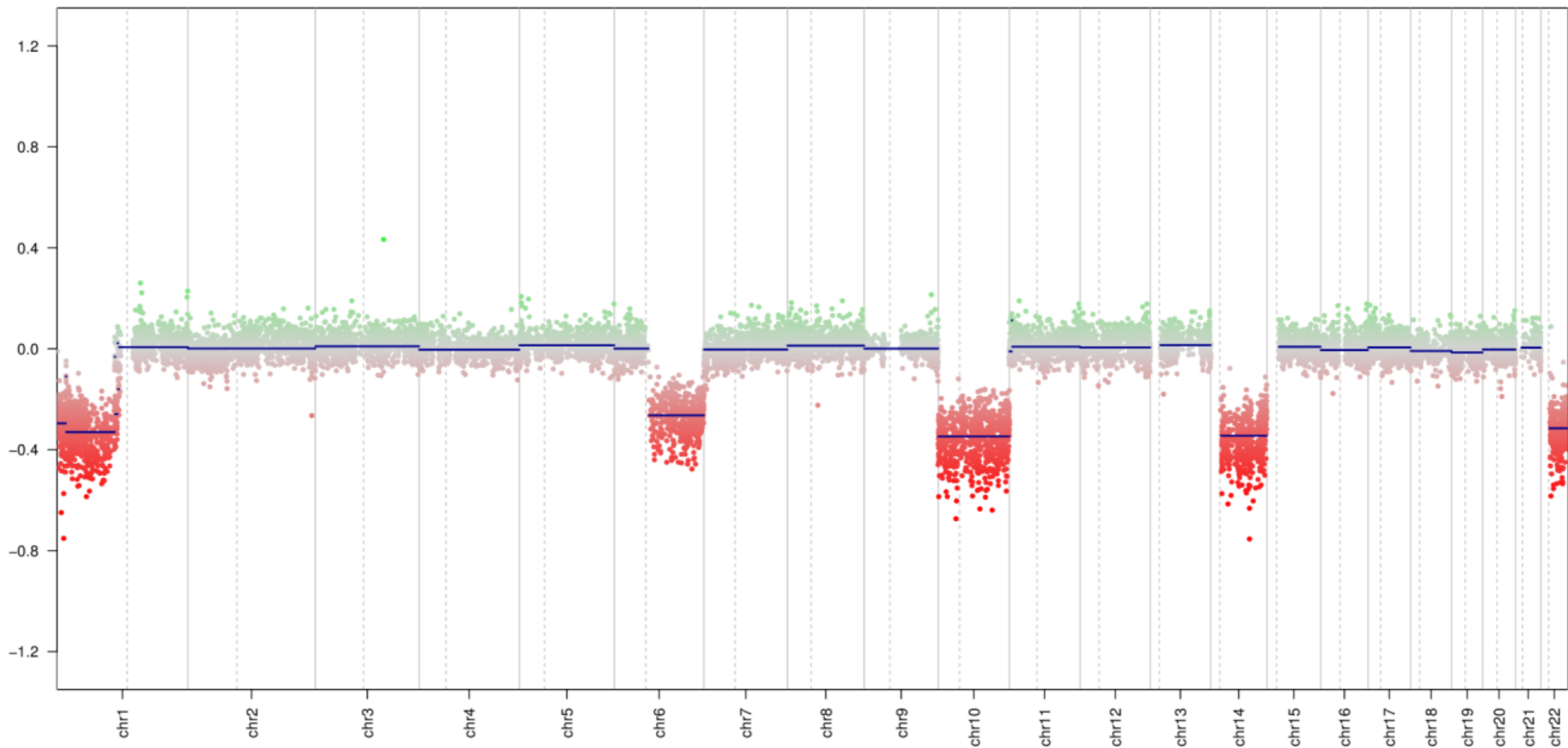
27(4), 869–883, 2025 | <https://doi.org/10.1093/neuonc/noae253> | Advance Access date 23 November 2024

European Association of Neuro-Oncology guideline on molecular testing of meningiomas for targeted therapy selection

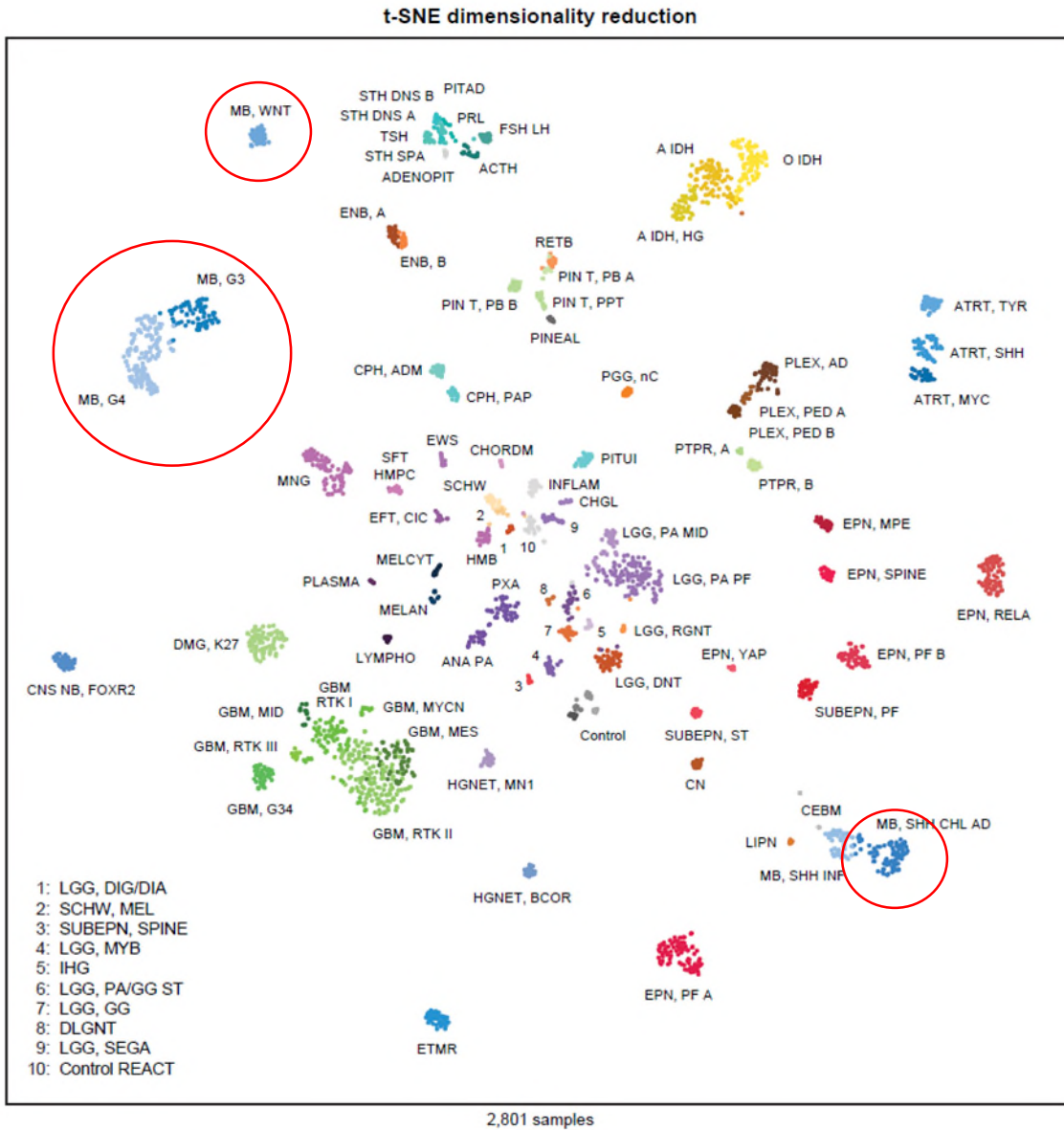
Felix Sahm^o, Luca Bertero^o, Sebastian Brandner^o, David Capper^o, Roland Goldbrunner, Michael D. Jenkinson, Michel Kalamarides, Katrin Lamszus, Nathalie L. Albert^o, Maximilian J. Mair, Anna S. Berghoff, Christian Mawrin, Hans-Georg Wirsching, Sybren L.N. Maas, David R. Raleigh, Guido Reifenberger, Leonille Schweizer^o, Abigail K. Suwala, Ghazaleh Tabatabai^o, Emeline Tabouret^o, Susan Short, Patrick Y. Wen, Michael Weller^o, Emilie Le Rhun^o, Pieter Wesseling, Martin van den Bent, and Matthias Preusser^o



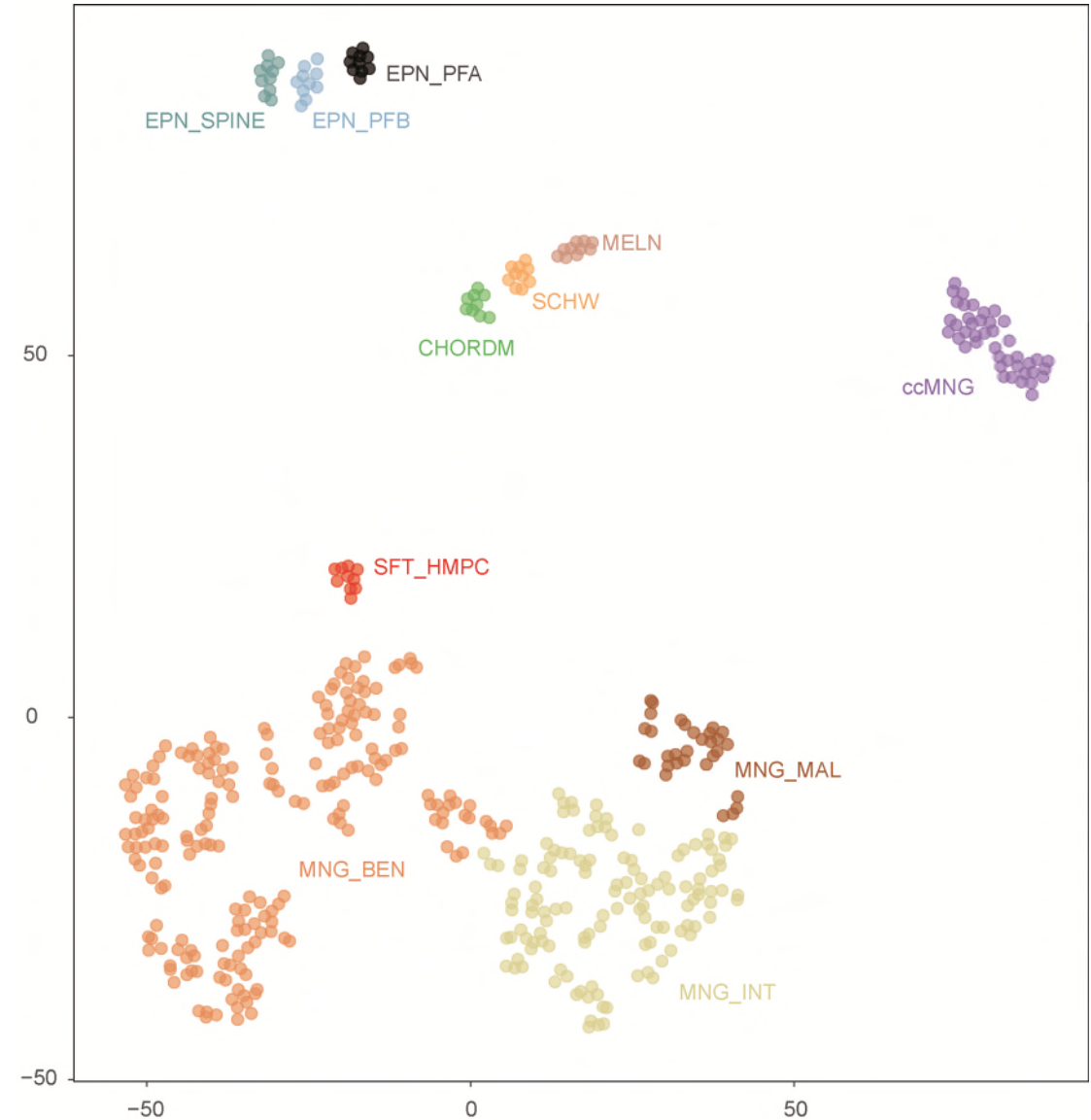




Meningioma Subgroups are not Medulloblastoma Subgroups

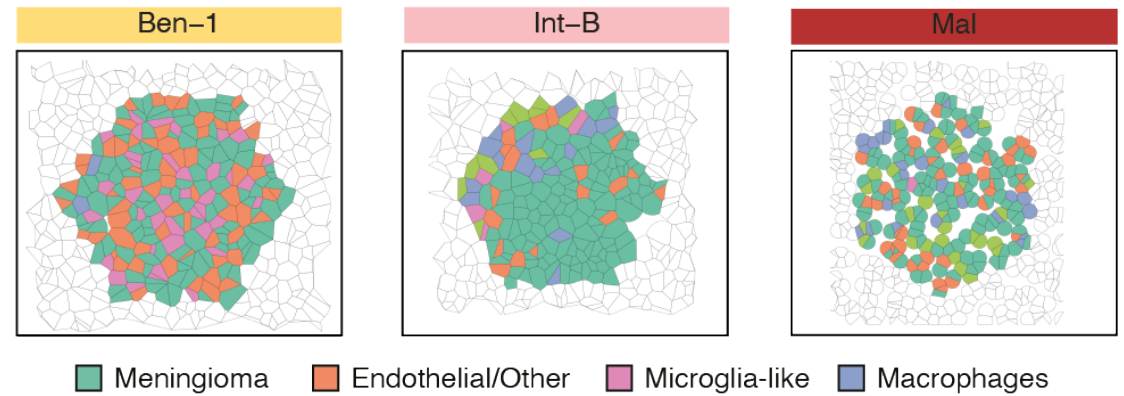
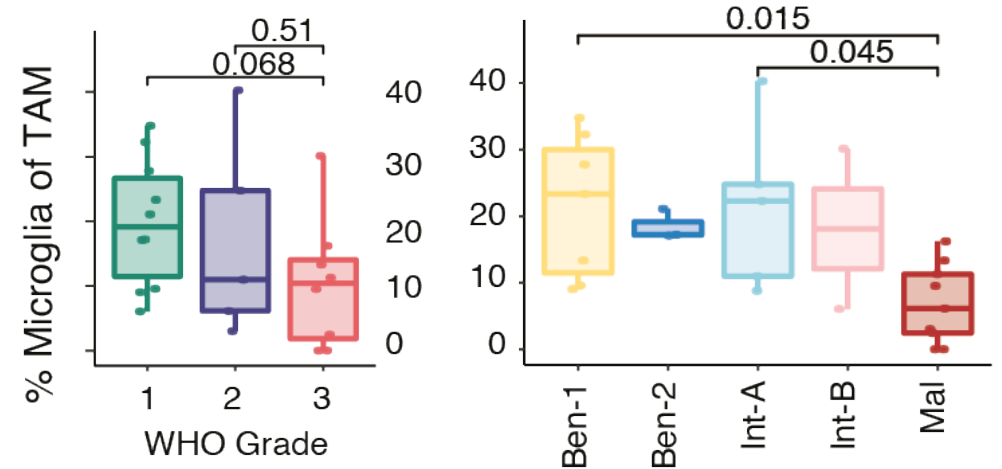
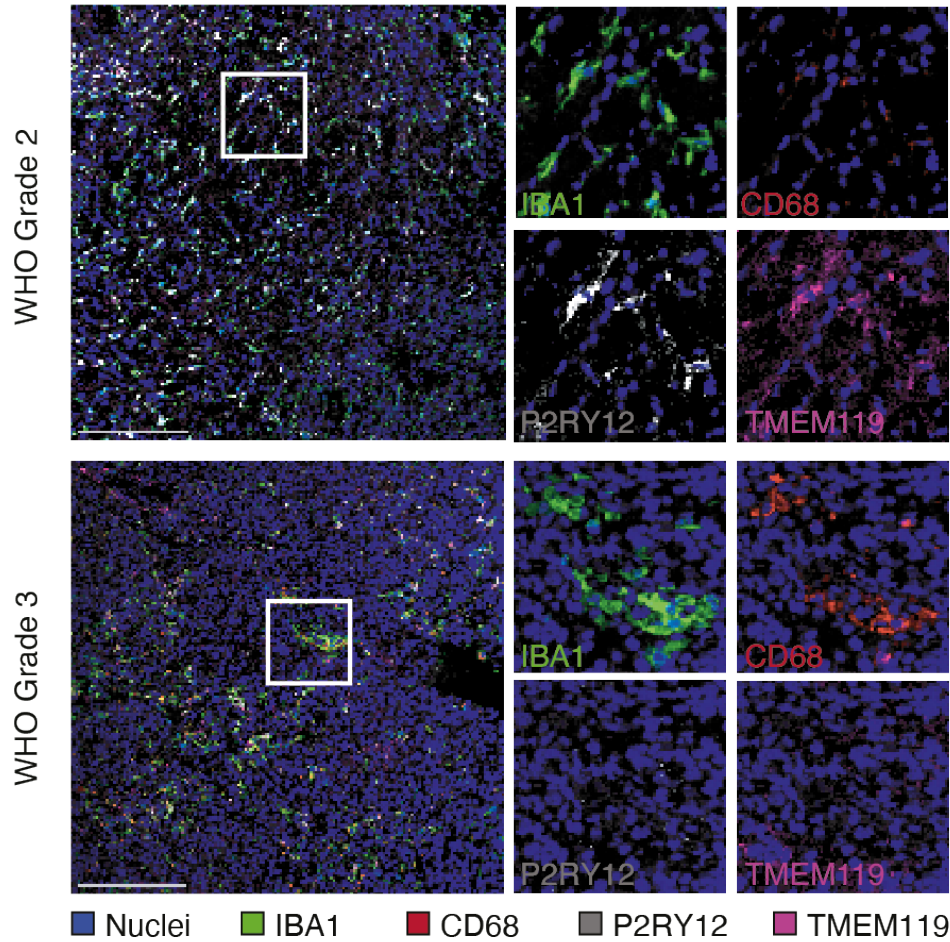


Capper et al., Nature 2018

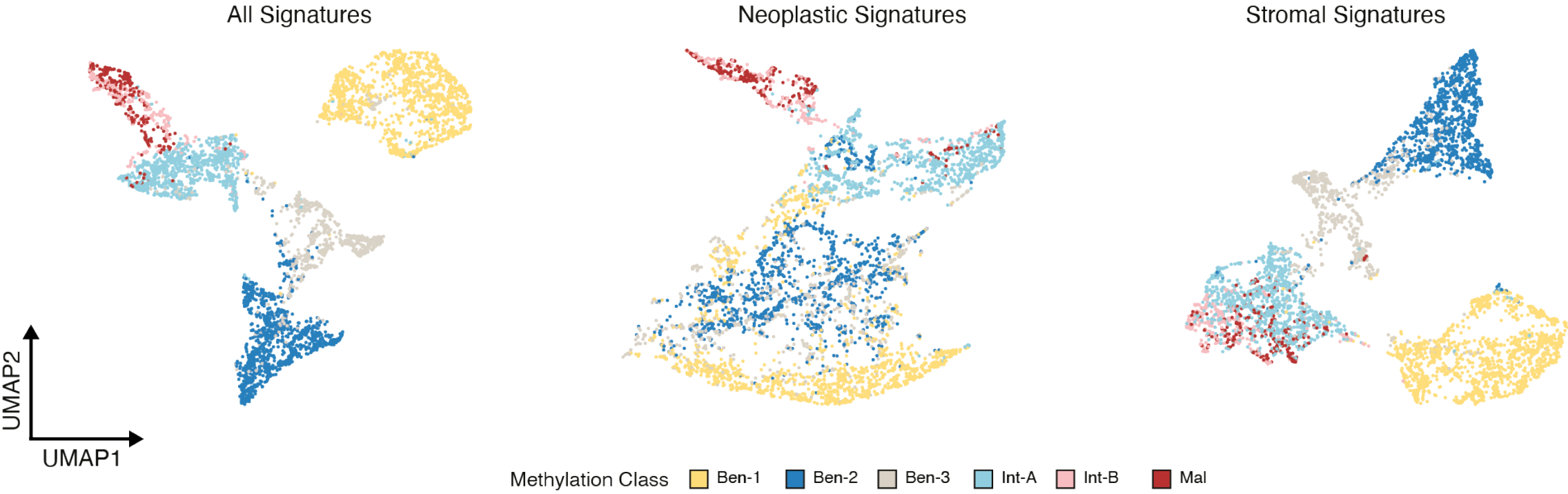


Sievers et al., ANP 2021

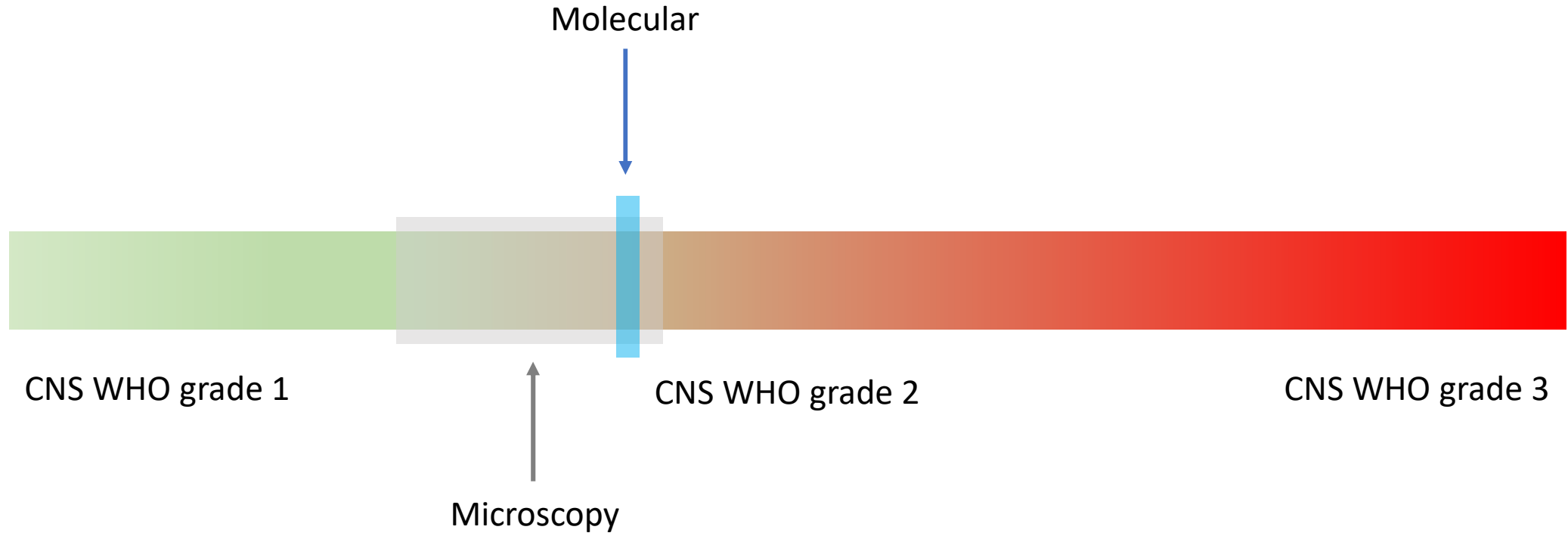
Cellular composition



Cellular composition



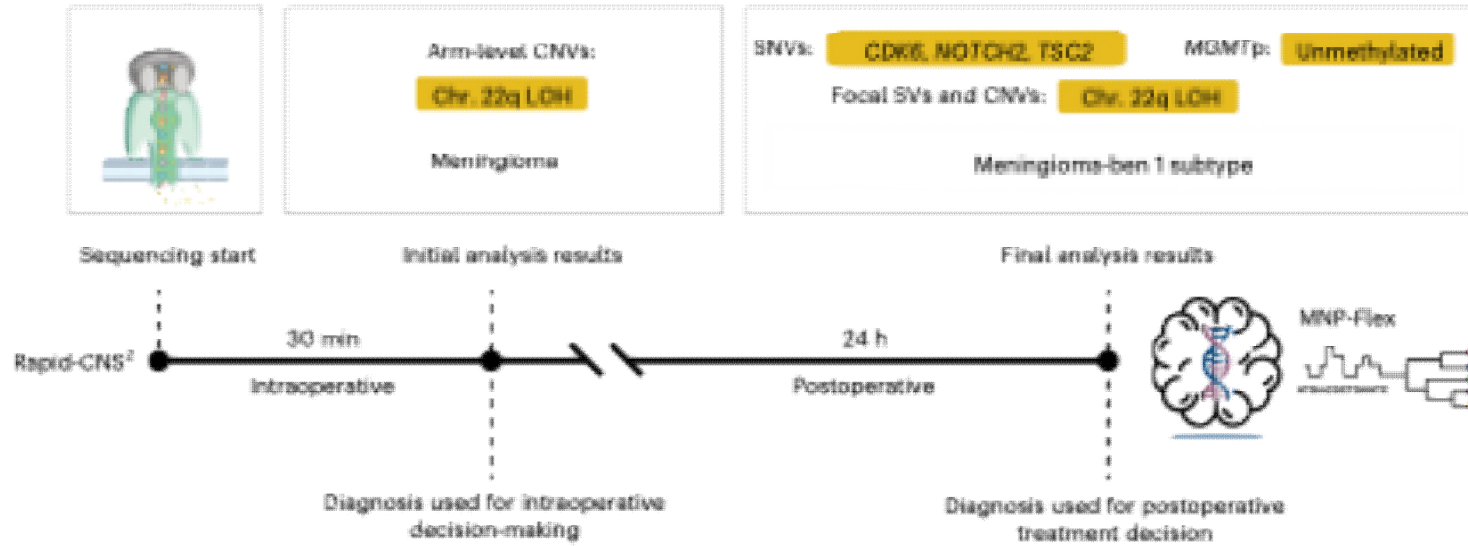
Meningioma continuum



Meningioma continuum

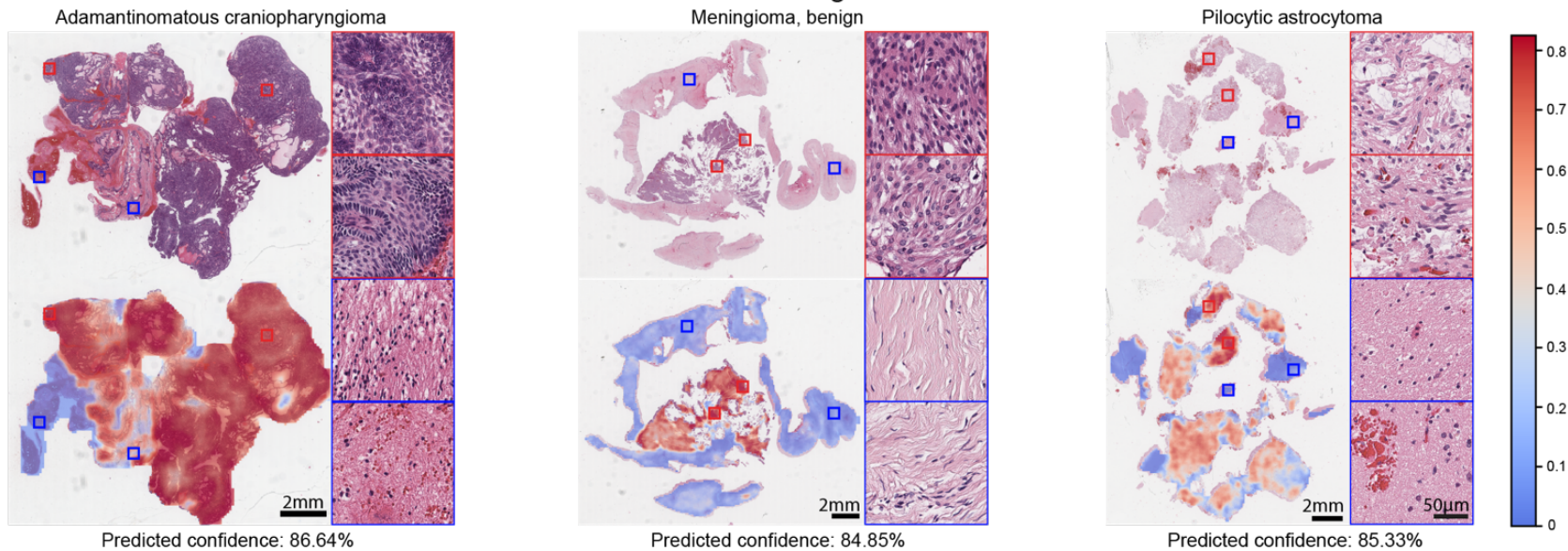


Diagnostic Accessibility

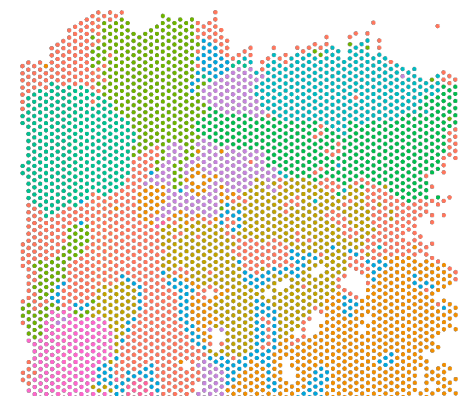
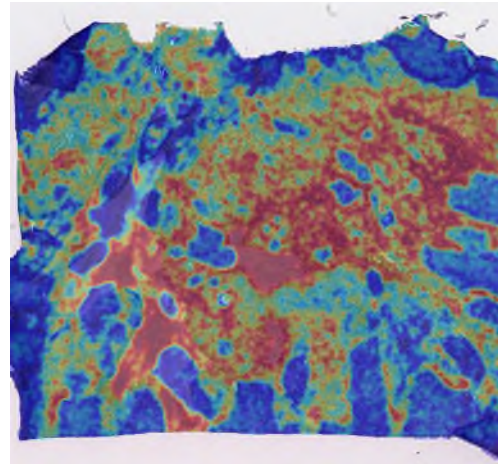
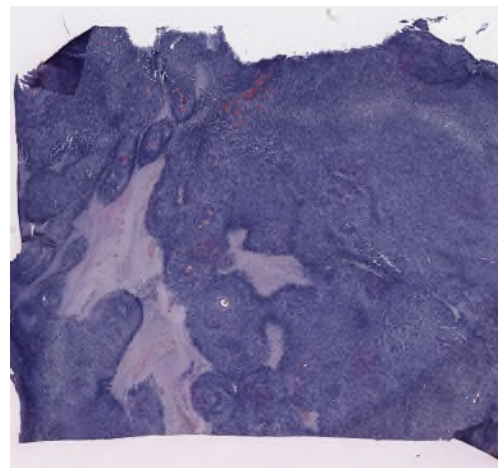
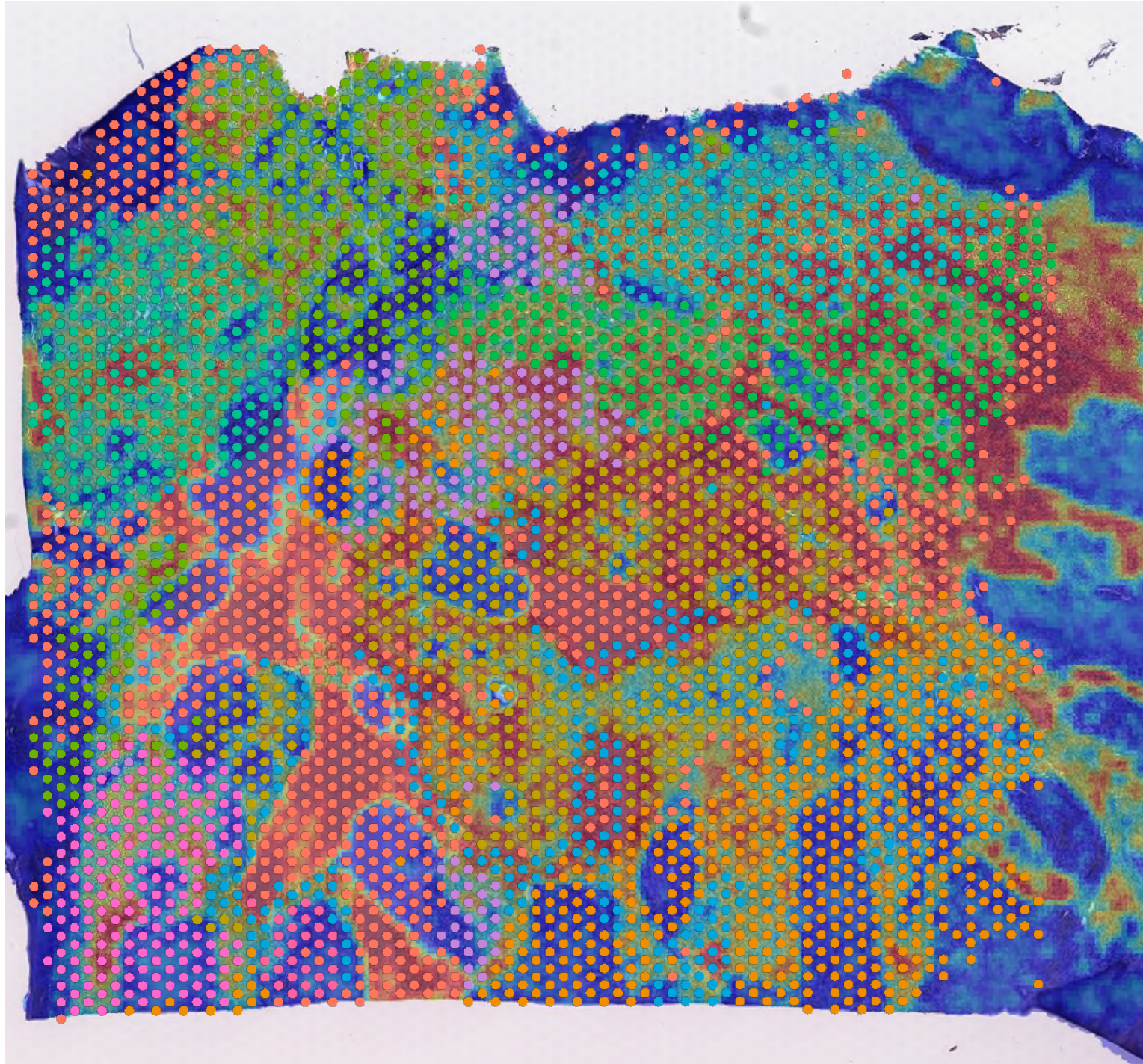


Patel et al., Nat Med 2025

Hetero-assisted histological assessment



Jin et al., accepted



Maas, Zhao et al., in preparation

Neuropathology HD

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Dr. Rolf M. Schwiete Stiftung

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Health + Life Science Alliance
Heidelberg Mannheim



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