Samples and molecular analyses

Meningioma tissue and patient data were collected from the archives of the departments of neurology, neuropathology and neurosurgery in Düsseldorf, Frankfurt, Gießen, Hamburg, Heidelberg, Homburg, Magdeburg, Mannheim, Tübingen (all Germany), Basel, Zurich (Switzerland), Langone Medical Center New York (USA), London (UK), Vienna (Austria), all with ethical approval according to local regulations, or provided with consent for research use via the brain tumor classifier portal www.molecularneuropathology.org [1]. Patients from these centers are part of the discovery cohort, and novel classifier data on methylation files from previously published data constitute the retrospective validation cohort [2,3]. The data from Basel, Gießen, and New York which were submitted constitutively from actual diagnostic cases since 2015, after making the meningioma methylation classification publicly available, serve as the prospective validation cohort. With only two anaplastic meningiomas in the prospective cohort, in line with the all-comer distribution of meningioma cases, this grade was underpowered, and the two cases were excluded. An independent multi-center retrospective set of 184 cases was collected separately and served for validation. DNA methylation data, copy-number calculation thereof, and panel sequencing with the Heidelberg brain tumor panel[4], including all meningioma associated genes reported in previous whole-exome and -genome studies[5-7], were performed as previously described (gene set in Suppl. Table 1)[8]. Hotspot mutations for *AKT1* were determined as p.E17K alterations, for *KLF4* as p.K409Q alterations, for *SMO* as p.L412F or p.W535L alterations and for *PIK3CA* as any mutations in codons 542, 545 and 1047. For *NF2*, stop gain mutations were annotated specifically and known pathogenic single nucleotide variants (SNVs), identified in the Varsome and COSMIC databases, as well as insertions and deletions were annotated separately. Of note, POLR2A was only covered in 35.5% of samples due to an update of the target region during the study but yielded no mutations in these samples. Meningioma methylation classes were determined by a previously reported random-

forest classifier trained for the six established meningioma methylation classes (MC) benign-1, benign-2, benign-3, intermediate-A, intermediate-B, and malignant as introduced before [1,8]. CNVs were calculated from the IDAT files using the R/Bioconductor package conumee (http://bioconductor.org/packages/release/bioc/html/conumee.html) after additional baseline correction using the B allele frequency of single nucleotide polymorphisms that were included on the BeadChip for creation of DNA fingerprints (https://github.com/dstichel/conumee). For each case, the total number of copy-number variations and the integrated length of all copy number variations, were calculated.

Statistics

Fisher's exact test and Wilcoxon Mann-Whitney were used to compare categorical/continuous parameters. Kendall's correlation coefficient was used to assess correlation between CNVs. An oncogenetic tree based on CNVs was estimated according to Szabo and Boucher [9]. Primary endpoint was time to progression or recurrence (TTP) after surgery. Distribution of TTP was estimated by the Kaplan-Meier method and compared between groups with the log-rank test and univariable Cox regression. For prognostic testing, only CNVs with a prevalence >10% were included. The p-values were corrected for multiple testing using Holm correction [10]. Adjusted estimates of each CNV were estimated with a separate multivariable Cox regression model including clinical factors. For this multivariable model, missing value imputation of clinical parameters was performed using the mice algorithm [11] with B=10 imputation runs. Harrell's c-index and integrated Brier score were used to assess discrimination and performance of models and were tested for differences between models. L1-penalized (lasso) Cox regression [12] was used to determine an optimal sparse

combination of CNVs allowing for not more than four non-zero coefficients within the model. Average bootstrapped c-index based on out-of-bag samples from 100 bootstrap runs was calculated. All p-values below 0.05 were considered significant. All analyses were carried out using R 3.6 including add-on packages glmnet, rms and Oncotree. Heatmaps were generated using the ComplexHeatmap package in R [13].

Determination of cut-off for MF/MC allocation

In the previously published brain tumor classifier, a cut-off of >0.9 (classifiable vs non-classifiable samples below) has been suggested. Of the 3,031 cases identified as a meningioma in the brain tumor classifier, 53% had a subsequent meningioma classifier score of >0.9 (Suppl. Figure 12A). Therefore, we investigated if a meningioma classifier score <0.9 influenced the risk for progression and if the integrated risk score could be optimized by accounting for the exact meningioma classifier score or any specific cut-off, instead of using the highest group allocation regardless of score. Only for the benign methylation family, a difference in risk for progression was observed with <0.9 cases having a higher risk for progression (Suppl. Figure 12B). Upon further inspection of the individual methylation classes, this effect is mainly attributed to cases of the ben-3 methylation class (Suppl. Figure 12C). Integration of this information into a modified integrated risk model, where a different number of points was attributed to cases of the ben-3 class, did however not result in increased prediction accuracy over the three clinical cohorts as this difference in prognosis was not observed in the validation cohorts. Thus, a segregation between samples with scores below or above 0.9 is

obsolete and, therefore, the integrated score uses the highest group allocation, irrespective of exact score. In fact, many diffuse glioma samples also obtain brain tumor classifier scores below 0.9. However, with the integration of CNV-derived information, such as an amplification of EGFR, a 7/10 signature or the homozygous loss of CDKN2A/B, a reliable integrated diagnosis can be rendered. This underlines the value of integrating different levels of information.

1. Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. Nature 2018;555:469-74.
2. Olar A, Wani KM, Wilson CD, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. Acta Neuropathol 2017;133:431-44.
3. Sahm F, Schrimpf D, Olar A, et al. TERT Promoter Mutations and Risk of Recurrence in Meningioma. J Natl Cancer Inst 2016;108.
4. Sahm F, Schrimpf D, Jones DT, et al. Next-generation sequencing in routine brain tumor diagnostics enables an integrated diagnosis and identifies actionable targets. Acta Neuropathol 2016;131:903-10.
5. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 2013;339:1077-80.
6. Clark VE, Harmanci AS, Bai H, et al. Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. Nat Genet 2016;48:1253-9.
7. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet 2013;45:285-9.
8. Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 2017;18:682-94.
9. Szabo A, Boucher K. Estimating an oncogenetic tree when false negatives and positives are present. Math Biosci 2002;176:219-36.
10. Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scand J Stat 1979;6:65-70.
11. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software 2011;45(3):1-67.
12. Simon N, Friedman J, Hastie T, Tibshirani R. Regularization Paths for Cox's Proportional Hazards Model via Coordinate Descent. Journal of Statistical Software 2011;39:1-13.
13. Gu Z, Eils R, Schlesner M. Complex heatmaps reveal patterns and correlations in multidimensional genomic data. Bioinformatics 2016;32:2847-9.

Suppl. Table S1: Gene set analyzed in panel sequencing

ABL1	ACVR1	AKT1	AKT2	AKT3	ALK
APC	ARID1A	ARID1B	ARID2	ATM	ATR
ATRX	BCOR	BRAF	BRAF	BRCA1	BRCA2
BRPF1	BRPF3	C11ORF95	CCND1	CCND2	CDH1
CDK4	CDK6	CDKN2A	CDKN2B	CDKN2C	CHEK2
CIC	CREBBP	CSF1R	CTNNB1	D2HGDH	DAXX
DDX3X	DICER1	EGFR	EZH2	FBXW7	FGFR1
FGFR2	FGFR3	FGFR4	FLT3	FOXO3	FUBP1
GABRA6	GNA11	GNAQ	GNAS	H2AFX	H3F3A
HDAC2	HIST1H3B	HIST1H3C	HNF1A	HRAS	IDH1
IDH2	IDO2	JAK2	JAK3	KDM6A (UTX)	KDR
KIAA0182/GSE1	KIT	KLF4	KLK1	KRAS	LDB1
LZTR1	MDM2	MDM4 (MDMX)	MET	MET	MGMT
MLH1	MLL2 (KMT2D)	MPL	MRE11A	MSH2	MSH6
MYB	MYBL1	MYC	MYCN	MYL1	NBN
NDRG2	NF1	NF2	NOTCH1	NOTCH2	NRAS
NTRK2	PDGFRA	PIK3C2G	PIK3CA	PIK3R1	PPM1D
PRKAR1A	PTCH1	PTCH2	PTEN	PTPN11	Rad50
RAF1	RB1	RET	SETD2	SMAD4	SMARCA2
SMARCA4	SMARCB1	SMARCD1	SMARCD2	SMARCE1	SMO
STAG2	SUFU	TBR1	TCF4	TERT	TP53
TRAF7	TSC1	TSC2	VHL	POLR2A*	

***** POLR2A was only covered in 35.5% of samples due to an update of the target region during the study, but yielded no mutations in these samples.

Suppl. Table S2: Patient characteristics of the discovery cohort

	Cohort	Discovery	Retrospective Validation	Prospective Validation
n		514	184	287
Sex (%)	f	340 (66.1)	110 (65.5)	210 (73.2)
	m	174 (33.9)	58 (34.5)	77 (26.8)
age (median [IQR])		58.00 [48.00, 67.00]	61.00 [51.43, 69.85]	59.00 [50.00, 70.00]
Simpson grade (%)	1	80 (47.1)	92 (53.2)	85 (38.8)
	2	58 (34.1)	51 (29.5)	99 (45.2)
	3	20 (11.8)	15 (8.7)	17 (7.8)
	4 or 5	12 (7.1)	15 (8.7)	18 (8.2)
EOR (%)	STR	12 (7.1)	15 (8.7)	33 (11.7)
	GTR	158 (93.0)	158 (91.4)	250 (88.3)
Histology (%)	Anaplastic	61 (11.9)	N/A	0 (0.0)
	Angiomatous	14 (2.7)	N/A	1 (0.8)
	Atypical	181 (35.2)	N/A	53 (42.7)
	Chordoid	23 (4.5)	N/A	6 (4.8)
	Clear	4 (0.8)	N/A	0 (0.0)
	Fibroblastic	28 (5.4)	N/A	6 (4.8)
	Meningioma NOS	50 (9.7)	N/A	1 (0.8)
	Meningothelial	21 (4.1)	N/A	43 (34.7)
	Metaplastic	8 (1.6)	N/A	0 (0.0)
	Microcystic	13 (2.5)	N/A	2 (1.6)
	Psammomatous	23 (4.5)	N/A	1 (0.8)
	Rhabdoid	1 (0.2)	N/A	0 (0.0)
	Secretory	24 (4.7)	N/A	2 (1.6)
	Transitional	63 (12.3)	N/A	9 (7.3)
WHO Grade (%)	1	235 (45.7)	106 (57.6)	190 (66.2)
	2	217 (42.2)	65 (35.3)	97 (33.8)
	3	62 (12.1)	13 (7.1)	0 (0.0)
1p loss (%)	0	271 (52.7)	91 (49.5)	217 (75.6)
	1	243 (47.3)	93 (50.5)	70 (24.4)
Methylation Family (%)	ben	248 (48.2)	83 (45.1)	198 (69.0)
	int	211 (41.1)	84 (45.7)	84 (29.3)
	mal	55 (10.7)	17 (9.2)	5 (1.7)

Methylation Class (%)	ben-1	76 (14.8)	37 (20.1)	65 (22.6)
	ben-2	107 (20.8)	32 (17.4)	113 (39.4)
	ben-3	51 (9.9)	8 (4.3)	17 (5.9)
	int-A	182 (35.4)	72 (39.1)	76 (26.5)
	int-B	39 (7.6)	14 (7.6)	9 (3.1)
	mal	59 (11.5)	21 (11.4)	7 (2.4)
CNV-Lasso Model (%)	none	228 (44.4)	79 (42.9)	182 (63.4)
	1-2 CNVs	232 (45.1)	74 (40.2)	85 (29.6)
	3 CNVs	54 (10.5)	31 (16.8)	20 (7.0)
CNV-Literature Model (%)	None	227 (44.2)	78 (42.4)	181 (63.1)
	1-2 CNVs	196 (38.1)	57 (31.0)	79 (27.5)
	>2 CNVs	91 (17.7)	49 (26.6)	27 (9.4)
Integrated Score (%)	low	235 (45.7)	87 (47.3)	199 (69.3)
	int	179 (34.8)	61 (33.2)	72 (25.1)
	high	100 (19.5)	36 (19.6)	16 (5.6)

IQR – interquartile range, EOR – extent of resection, STR – subtotal resection, GTR – gross total resection, CNV – copy number variation, NOS – not otherwise specified

Suppl. Table S3: Distribution of mutations in the discovery cohort

Variable	Levels	n	%	∑%
NF2 mutation	0	322	81.5	81.5
	1	73	18.5	100.0
	all	395	100.0	
NF2 insertion or deletion	0	339	85.8	85.8
	1	56	14.2	100.0
	all	395	100.0	
AKT1 mutation	0	373	94.4	94.4
	1	22	5.6	100.0
	all	395	100.0	
KLF4 mutation	0	365	92.4	92.4
	1	30	7.6	100.0
	all	395	100.0	
TRAF7 mutation	0	336	85.1	85.1
	1	59	14.9	100.0
	all	395	100.0	
PIK3CA mutation	0	382	96.7	96.7
	1	13	3.3	100.0
	all	395	100.0	
POLR2A mutation	0	109	100.0	100.0
	all	109	100.0	
SMO mutation	0	378	95.7	95.7
	1	17	4.3	100.0
	all	395	100.0	
TRAKL mutation*	0	323	81.8	81.8
	1	72	18.2	100.0
	all	395	100.0	
TERT Promotor mutation	0	372	93.9	93.9
	1	24	6.1	100.0
	all	396	100.0	

*** "**TRAKL" defined as at least 1 mutation in TRAF7, AKT1 and/or KLF4

Suppl. Table S4: Prognostic impact of mutations, CDKN2A/B status and clinical parameters in the discovery cohort

Clinical parameters

Parameter	N	Events	level	ref	HR	LCL	UCL	Waldp	LRTp
Methylation family	514	169	int	ben	4.37	2.90	6.58	<0.001	<0.001
			mal	ben	14.04	8.67	22.76	<0.001	
WHO 2016 Grade	514	169	2	1	2.69	1.84	3.94	<0.001	<0.001
			3	1	7.76	4.98	12.07	<0.001	
WHO 2021 Grade	399	166	2	1	2.39	1.61	3.54	<0.001	<0.001
			3	1	7.18	4.68	11.01	<0.001	
Sex	514	169	m	f	1.60	1.18	2.17	0.003	0.003
age10	482	157			1.02	0.91	1.15	0.684	0.683
ageT	482	157	[50.6, 64.1)	[0.0, 50.6)	0.81	0.55	1.18	0.261	0.120
			[64.1,120.1]	[0.0, 50.6)	1.20	0.81	1.79	0.355	
location	488	161	convexity	basal	1.28	0.85	1.91	0.238	0.192
			posterior fossa	basal	0.71	0.34	1.50	0.369	
			spinal	basal	0.58	0.18	1.91	0.374	
			supratentorial	basal	1.30	0.63	2.66	0.480	
Grouped Simpson grade	170	73	4/5	1-3	2.57	1.32	5.02	0.006	0.013
Simpson grade	170	73	2	1	1.17	0.68	2.03	0.571	0.053
			3	1	1.58	0.79	3.17	0.196	
			4/5	1	2.92	1.42	6.00	0.004	

HR – hazard ratio, LCL – lower confidence limit, UCL – upper confidence limit

Mutations

Parameter	N	Events	level	ref	HR	LCL	UCL	Waldp
NF2 mutation	395	166	1	0	1.17	0.81	1.70	0.397
NF2 insertion or deletion	395	166	1	0	2.01	1.39	2.89	<0.001
AKT1 mutation	395	166	1	0	0.46	0.19	1.11	0.084
KLF4 mutation	395	166	1	0	0.33	0.13	0.80	0.014
TRAF7 mutation	395	166	1	0	0.41	0.23	0.73	0.002
PIK3CA mutation	395	166	1	0	0.53	0.17	1.69	0.284
SMO mutation	395	166	1	0	1.05	0.56	2.00	0.873
TRAKL mutation*	395	166	1	0	0.40	0.24	0.69	<0.001
TERT Promotor mutation	396	166	1	0	4.61	2.87	7.40	<0.001
CDKN2A/B homozygous del	514	169	1	0	7.77	4.59	13.15	<0.001

* **“**TRAKL” defined as at least 1 mutation in TRAF7, AKT1 and/or KLF4

Suppl. Table S5: Prognostic impact of CNVs in the discovery cohort (univariable)

	logrankP	Adj logrankP	Cox HR	Cox p-value	cindex	Adj Cox p-value
loss1p	<0.001	<0.001	4.67 [3.24;6.71]	<0.001	0.68	<0.001
loss6q	<0.001	<0.001	3.35 [2.47;4.55]	<0.001	0.64	<0.001
loss10q	<0.001	<0.001	3.42 [2.46;4.75]	<0.001	0.60	<0.001
loss14q	<0.001	<0.001	2.90 [2.13;3.96]	<0.001	0.61	<0.001
loss18q	<0.001	<0.001	2.87 [2.10;3.93]	<0.001	0.60	<0.001
gain1q	<0.001	<0.001	3.09 [2.18;4.39]	<0.001	0.58	<0.001
loss4p	<0.001	<0.001	2.46 [1.74;3.49]	<0.001	0.58	<0.001
loss22q	<0.001	<0.001	2.76 [1.86;4.10]	<0.001	0.60	<0.001
loss7p	<0.001	<0.001	2.24 [1.58;3.19]	<0.001	0.56	<0.001
loss6p	<0.001	<0.001	2.36 [1.59;3.49]	<0.001	0.55	<0.001
loss19p	<0.001	<0.001	2.30 [1.54;3.45]	<0.001	0.55	<0.001
loss4q	<0.001	<0.001	2.07 [1.45;2.96]	<0.001	0.56	<0.001
loss18p	<0.001	<0.001	1.99 [1.42;2.80]	<0.001	0.55	<0.001
loss2p	0.001	0.011	1.84 [1.26;2.70]	0.002	0.54	0.013
loss3p	0.047	0.328	1.46 [1.00;2.13]	0.048	0.52	0.337
gain17q	0.056	0.335	1.54 [0.98;2.42]	0.059	0.52	0.351
loss1q	0.089	0.446	0.62 [0.35;1.08]	0.093	0.52	0.465
gain20q	0.753	1.000	1.07 [0.68;1.70]	0.759	0.51	1.000
gain20p	0.754	1.000	0.92 [0.57;1.51]	0.751	0.50	1.000
loss8p	0.879	1.000	1.04 [0.63;1.72]	0.880	0.51	1.000
loss21p	0.888	1.000	1.03 [0.69;1.55]	0.883	0.51	1.000
SumCNV	NA	NA	1.06 [1.04;1.08]	<0.001	0.67	<0.001

HR – hazard ratio

Suppl. Table S6: Prognostic impact in the discovery cohort of CNVs adjusted for WHO 2016 Grade/Age/Sex/Location

	N	HR	p-value	adj p-value
loss1p	514	3.68 [2.45;5.51]	<0.001	<0.001
loss6q	514	2.36 [1.70;3.29]	<0.001	<0.001
loss10q	514	2.39 [1.65;3.46]	<0.001	<0.001
loss7p	514	2.04 [1.42;2.93]	<0.001	0.002
gain1q	514	2.00 [1.38;2.89]	<0.001	0.004
loss18q	514	1.79 [1.26;2.53]	0.001	0.017
loss19p	514	2.01 [1.31;3.08]	0.001	0.021
loss22q	514	2.03 [1.31;3.13]	0.001	0.021
loss14q	514	1.74 [1.23;2.47]	0.002	0.026
loss2p	514	1.82 [1.23;2.70]	0.003	0.037
SumCNV	514	1.03 [1.01;1.05]	0.012	0.143
loss6p	514	1.70 [1.12;2.56]	0.012	0.143
loss4p	514	1.43 [0.98;2.07]	0.063	0.626
loss4q	514	1.32 [0.90;1.93]	0.152	1.000
loss1q	514	0.66 [0.37;1.18]	0.162	1.000
gain20p	514	0.72 [0.44;1.19]	0.203	1.000
gain20q	514	0.82 [0.51;1.31]	0.414	1.000
loss18p	514	1.13 [0.78;1.64]	0.525	1.000
loss8p	514	0.86 [0.51;1.42]	0.550	1.000
gain17q	514	1.08 [0.68;1.72]	0.746	1.000
loss3p	514	0.97 [0.66;1.44]	0.883	1.000
loss21p	514	0.97 [0.64;1.47]	0.884	1.000

Suppl. Table S7: Patient characteristics arranged for proposed WHO 2021 grading in the discovery cohort

Only patients for whom new WHO grading could be assessed are analyzed:

- all WHO grade 3 (no change in grading)
- WHO grade 1/2 and TERT mutation/CDKN2A/B homozygous deletion determined
- In case of TERT mutation or CDKN2A/B homozygous deletion and WHO grade 1/2, patients are upstaged to WHO grade 3

Variable	Levels	n1	%1	n2	%2	n3	%3	nall	%all
WHO 2021 Grade	1	167	100.0	0	0.0	1	1.4	168	42.1
	2	0	0.0	158	100.0	11	14.9	169	42.4
	3	0	0.0	0	0.0	62	83.8	62	15.5
	all	167	100.0	158	100.0	74	100.0	399	100.0
Methylation family	ben	121	72.5	52	32.9	9	12.2	182	45.6
	int	46	27.5	95	60.1	27	36.5	168	42.1
	mal	0	0.0	11	7.0	38	51.4	49	12.3
	all	167	100.0	158	100.0	74	100.0	399	100.0

Suppl. Table S8: Prognostic impact of CNVs in the discovery cohort adjusted for proposed amendments to WHO 2021 Grade 3 (TERT promotor status, CDKN2A/B status)/Age/Sex/Location

	N	HR	p-value	Adj p-value
loss1p	399	3.43 [2.27;5.19]	<0.001	<0.001
loss6q	399	2.16 [1.55;3.02]	<0.001	<0.001
loss10q	399	2.05 [1.39;3.01]	<0.001	0.005
gain1q	399	1.97 [1.36;2.85]	<0.001	0.006
loss19p	399	2.15 [1.40;3.29]	<0.001	0.009
loss7p	399	1.81 [1.25;2.62]	0.002	0.026
loss22q	399	2.01 [1.28;3.13]	0.002	0.035
loss2p	399	1.83 [1.24;2.72]	0.002	0.037
loss14q	399	1.61 [1.13;2.29]	0.009	0.123
loss18q	399	1.57 [1.10;2.25]	0.013	0.174
loss6p	399	1.61 [1.07;2.44]	0.024	0.284
SumCNV	399	1.02 [1.00;1.05]	0.053	0.582
loss4p	399	1.37 [0.94;1.99]	0.102	1.000
gain20p	399	0.74 [0.45;1.22]	0.234	1.000
loss1q	399	0.71 [0.40;1.26]	0.244	1.000
loss4q	399	1.24 [0.85;1.81]	0.273	1.000
loss21p	399	0.85 [0.55;1.31]	0.452	1.000
gain20q	399	0.84 [0.52;1.34]	0.455	1.000
loss8p	399	0.82 [0.49;1.37]	0.456	1.000
gain17q	399	1.13 [0.71;1.80]	0.616	1.000
loss18p	399	1.04 [0.72;1.52]	0.823	1.000
loss3p	399	0.96 [0.65;1.42]	0.825	1.000

Suppl. Table S9: Prognostic impact of CNVs in the discovery cohort adjusted for WHO 2016 Grade/Methylation Family/Age/Sex/Location

	N	HR	p.value	adj.Pvalue
loss1p	514	2.57 [1.64;4.05]	<0.001	<0.001
loss6q	514	1.67 [1.19;2.34]	0.003	0.064
loss10q	514	1.67 [1.14;2.45]	0.009	0.175
loss7p	514	1.63 [1.13;2.34]	0.009	0.175
loss2p	514	1.62 [1.09;2.41]	0.017	0.301
loss19p	514	1.60 [1.04;2.45]	0.032	0.541
loss18q	514	1.46 [1.03;2.09]	0.035	0.554
gain1q	514	1.46 [1.00;2.12]	0.049	0.730
loss6p	514	1.45 [0.96;2.19]	0.075	1.000
loss3p	514	0.69 [0.46;1.04]	0.077	1.000
loss1q	514	0.64 [0.36;1.15]	0.138	1.000
loss14q	514	1.22 [0.85;1.76]	0.283	1.000
gain20p	514	0.77 [0.47;1.27]	0.301	1.000
loss22q	514	1.20 [0.76;1.90]	0.437	1.000
loss4p	514	1.15 [0.78;1.67]	0.481	1.000
SumCNV	514	1.01 [0.98;1.04]	0.526	1.000
gain20q	514	0.87 [0.54;1.38]	0.549	1.000
loss18p	514	0.90 [0.61;1.32]	0.578	1.000
loss8p	514	0.89 [0.53;1.50]	0.667	1.000
loss21p	514	0.92 [0.60;1.42]	0.721	1.000
gain17q	514	0.96 [0.61;1.53]	0.866	1.000
loss4q	514	0.99 [0.66;1.48]	0.961	1.000

Suppl. Table S10: Prognostic value of a combination of CNVs (lasso selected CNV combination) in the discovery cohort

	coef
loss1p	1.15
loss6q	0.54
loss14q	0.53

Suppl. Table S11: Prediction accuracy comparison in cases in the discovery cohort with WHO 2021 grading available

A. Pairwise test on c-indices

Parameter 1	Parameter 2	cindex.1	cindex.2	p-value
WHO 2016 Grade	WHO 2021 Grade	0.683	0.697	0.053
WHO 2016 Grade	Methylation family	0.683	0.719	0.065
WHO 2016 Grade	CNV-Lasso model	0.683	0.701	0.448
WHO 2016 Grade	CNV-Literature model	0.683	0.709	0.251
WHO 2021 Grade	Methylation family	0.697	0.719	0.241
WHO 2021 Grade	CNV-Lasso model	0.697	0.701	0.857
WHO 2021 Grade	CNV-Literature model	0.697	0.709	0.580
Methylation family	CNV-Lasso model	0.719	0.701	0.333
Methylation family	CNV-Literature model	0.719	0.709	0.578
CNV-Lasso model	CNV-Literature model	0.701	0.709	0.313

B. Integrated prediction error (Brier score) at 5 and 10 years in cases with WHO 2021 grading in the discovery cohort

	IBS[0;time=60)	IBS[0;time=120)
Reference	0.174	0.211
WHO 2016 Grade	0.149	0.178
WHO 2021 Grade	0.146	0.174
CNV-Lasso model	0.150	0.172
CNV-Literature model	0.150	0.170
Methylation family	0.141	0.158

C. p-value of test on difference in prediction error (IBS) in cases with WHO 2021 grading

	5yrs	10yrs
WHO 2016 Grade vs WHO 2021 Grade	0.0264	0.1860
WHO 2016 Grade vs CNV-Lasso model	0.2684	0.0733
WHO 2016 Grade vs CNV-Literature model	0.1247	0.0552
WHO 2016 Grade vs Methylation family	0.0106	0.0003
WHO 2021 Grade vs CNV-Lasso model	0.5344	0.1956
WHO 2021 Grade vs CNV-Literature model	0.3883	0.1600
WHO 2021 Grade vs Methylation family	0.0362	0.0012
CNV-Lasso model vs CNV-Literature model	0.3776	0.8756
CNV-Lasso model vs Methylation family	0.1441	0.1216
CNV-Literature model vs Methylation family	0.1964	0.2124

Suppl. Table S12: Prediction accuracy comparison in all cases in the discovery cohort

A. Pairwise test on c-indices

Parameter 1	Parameter 2	cindex.1	cindex.2	p-value
WHO 2016 Grade	Methylation family	0.699	0.721	0.267
WHO 2016 Grade	CNV-Lasso model	0.699	0.706	0.746
WHO 2016 Grade	CNV-Literature model	0.699	0.715	0.449
Methylation family	CNV-Lasso model	0.721	0.706	0.446
Methylation family	CNV-Literature model	0.721	0.715	0.785
CNV-Lasso model	CNV-Literature model	0.706	0.715	0.240

B. Integrated prediction error (Brier score) at 5 and 10 years

	IBS[0;time=60)	IBS[0;time=120)
Reference	0.166	0.207
WHO 2016 Grade	0.144	0.175
CNV-Lasso model	0.144	0.168
CNV-Literature model	0.144	0.167
Methylation family	0.136	0.156

C. p-value of test on difference in prediction error (IBS) in the discovery cohort

	5yrs	10yrs
WHO 2016 Grade vs CNV-Lasso model	0.2145	0.0707
WHO 2016 Grade vs CNV-Literature model	0.0899	0.0600
WHO 2016 Grade vs Methylation family	0.0156	0.0005
CNV-Lasso model vs CNV-Literature model	0.0421	0.2956
CNV-Lasso model vs Methylation family	0.1829	0.1419
CNV-Literature model vs Methylation family	0.3760	0.3612

Suppl. Table S13: Cox regression model comparing the different prediction models in the discovery cohort

	coef	HR = exp(coef)	95% CI	*p*-value
WHO 2016 Grade 2	0.34	1.41	[0.94, 2.13]	0.10
WHO 2016 Grade 3	0.90	2.46	[1.44, 4.20]	0.001
MF intermediate	0.84	2.32	[1.43, 3.77]	0.00067
MF malignant	1.57	4.79	[2.60, 8.83]	< 0.0001
CNV-Lasso 1-2 CNVs	0.75	2.12	[1.29, 3.47]	0.0028
CNV-Lasso 3 CNVs	1.20	3.32	[1.85, 5.95]	< 0.0001

Suppl. Table S14: Prediction accuracy of the integrated model compared to the other models in the discovery cohort

A. Pairwise test on c-indices

Parameter 1	Parameter 2	cindex.1	cindex.2	p-value
WHO 2016 Grade	Integrated model	0.699	0.744	0.005
Methylation family	Integrated model	0.721	0.744	0.058
CNV-Lasso model	Integrated model	0.706	0.744	0.008
CNV-Literature model	Integrated model	0.715	0.744	0.044

B. Integrated prediction error (Brier score) at 5 and 10 years

	IBS[0;time=60)	IBS[0;time=120)
Reference	0.166	0.207
Integrated model	0.134	0.155

C. P-value of test on difference in prediction error (IBS) in all cases

	5yrs	10yrs
WHO 2016 Grade vs Integrated model	0.0015	0.0001
CNV-Lasso model vs Integrated model	0.0012	0.0029
CNV-Literature vs Integrated model	0.0011	0.0027
Methylation family vs Integrated model	0.0511	0.1462

D. Pairwise test on c-indices in cases with WHO 2021 grading available

Parameter 1	Parameter 2	cindex.1	cindex.2	p-value
WHO 2021 Grade	Integrated model	0.697	0.739	0.004

E. Integrated prediction error (Brier score) at 5 and 10 years

	IBS[0;time=60)	IBS[0;time=120)
Reference	0.174	0.211
Integrated model	0.139	0.156

F. P-value of test on difference in prediction error (IBS) in cases with WHO 2021 grading available

	5yrs	10yrs
WHO 2021 Grade vs Integrated model	0.0021	0.0001

Suppl. Table S15: Prediction accuracy of the integrated model compared to the other models in the retrospective cohort

A. Pairwise test on c-indices

Parameter 1	Parameter 2	cindex.1	cindex.2	p-value
WHO 2016 Grade	Methylation family	0.673	0.685	0.666
WHO 2016 Grade	CNV-Lasso model	0.673	0.698	0.426
WHO 2016 Grade	CNV-Literature model	0.673	0.701	0.318
WHO 2016 Grade	Integrated model	0.673	0.732	0.018
Methylation family	CNV-Lasso model	0.685	0.698	0.638
Methylation family	CNV-Literature model	0.685	0.701	0.501
Methylation family	Integrated model	0.685	0.732	0.011
CNV-Lasso model	CNV-Literature model	0.698	0.701	0.757
CNV-Lasso model	Integrated model	0.698	0.732	0.027
CNV-Literature model	Integrated model	0.701	0.732	0.037

B. Integrated prediction error (Brier score) at 5 and 10 years

	IBS[0;time=60)	IBS[0;time=120)
Reference	0.132	0.183
WHO 2016 Grade	0.117	0.158
CNV-Lasso model	0.111	0.151
CNV-Literature model	0.111	0.154
Methylation family	0.115	0.152
Integrated model	0.104	0.138

C. P-value of test on difference in prediction error (IBS)

	5yrs
WHO 2016 Grade vs Integrated model	0.045
CNV-Lasso model vs Integrated model	0.238
CNV-Literature vs Integrated model	0.182
Methylation family vs Integrated model	0.016

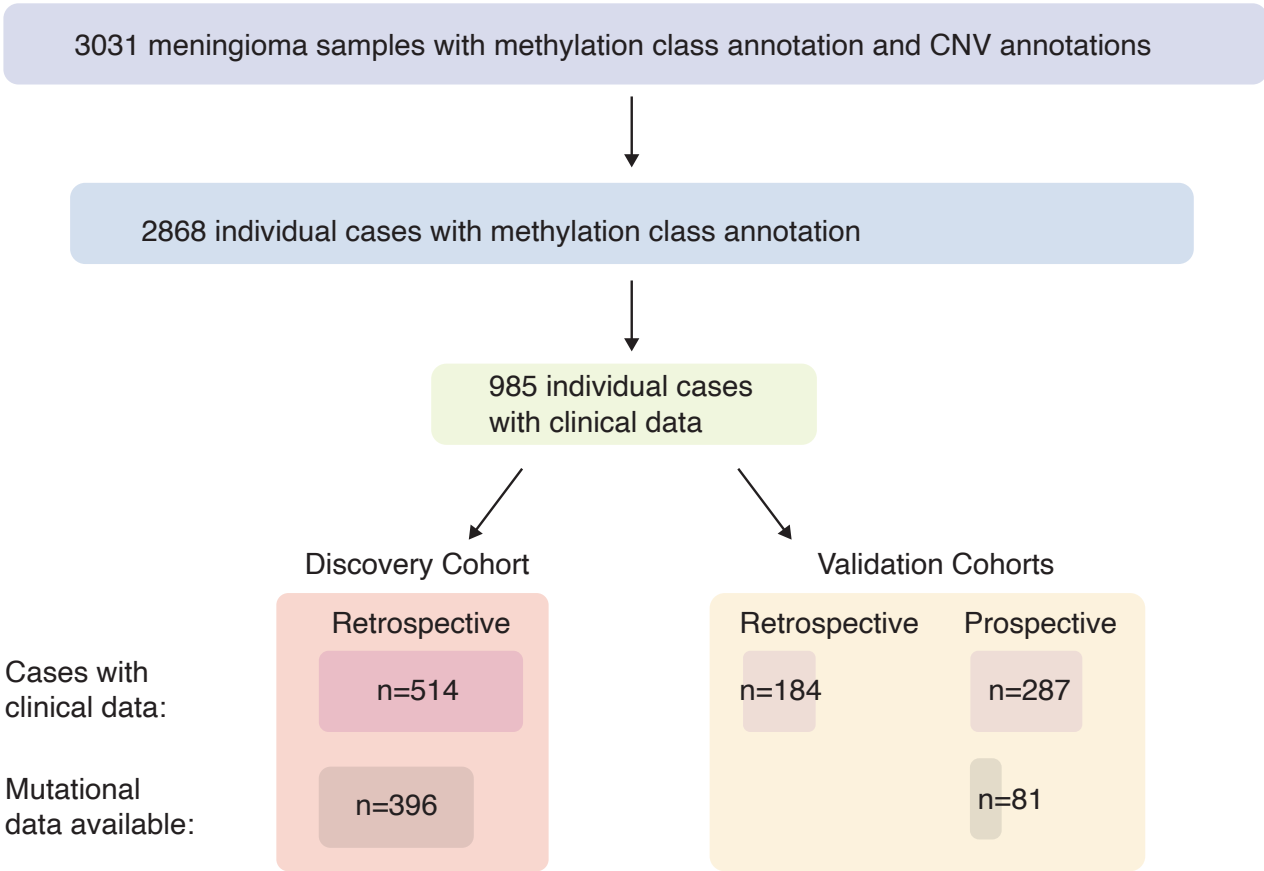
Suppl. Table S16: Prediction accuracy of the integrated model compared to the other models in the prospective cohort

A. Pairwise test on c-indices

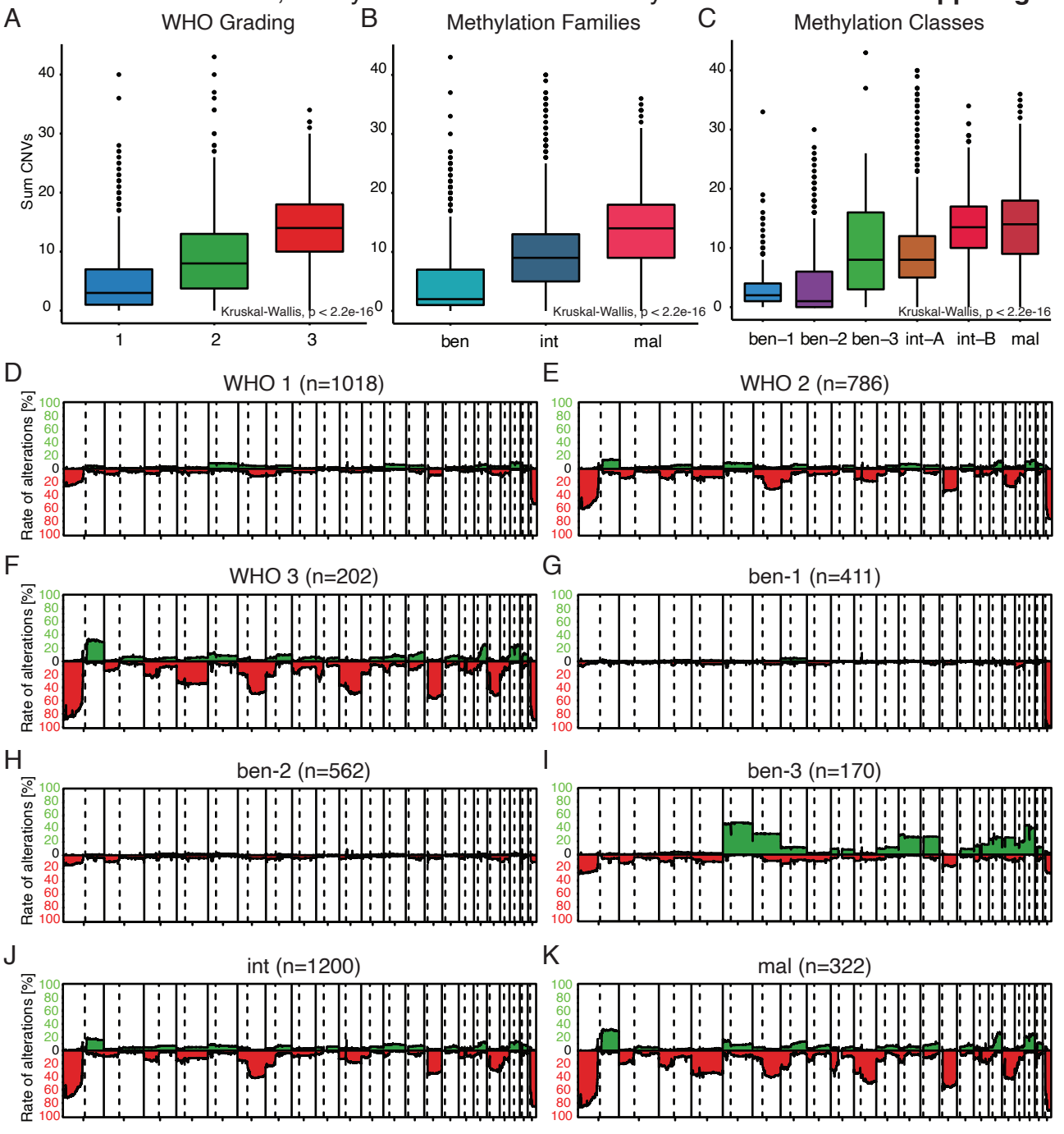
Parameter 1	Parameter 2	cindex.1	cindex.2	p-value
WHO 2016 Grade	CNV-Literature model	0.599	0.652	0.349
WHO 2016 Grade	CNV-Lasso model	0.599	0.629	0.635
WHO 2016 Grade	Methylation family	0.599	0.596	0.970
WHO 2016 Grade	Integrated model	0.599	0.665	0.238
CNV-Literature model	CNV-Lasso model	0.652	0.629	0.497
CNV-Literature model	Methylation family	0.652	0.596	0.337
CNV-Literature model	Integrated model	0.652	0.665	0.481
CNV-Lasso model	Methylation family	0.629	0.596	0.515
CNV-Lasso model	Integrated model	0.629	0.665	0.278
Methylation family	Integrated model	0.596	0.665	0.113

B. Integrated prediction error (Brier score) at 5 and 10 years

	IBS[0;time=60)
Reference	0.087
WHO 2016 Grade	0.082
CNV-Lasso model	0.082
CNV-Literature model	0.081
Methylation family	0.078
Integrated model	0.081

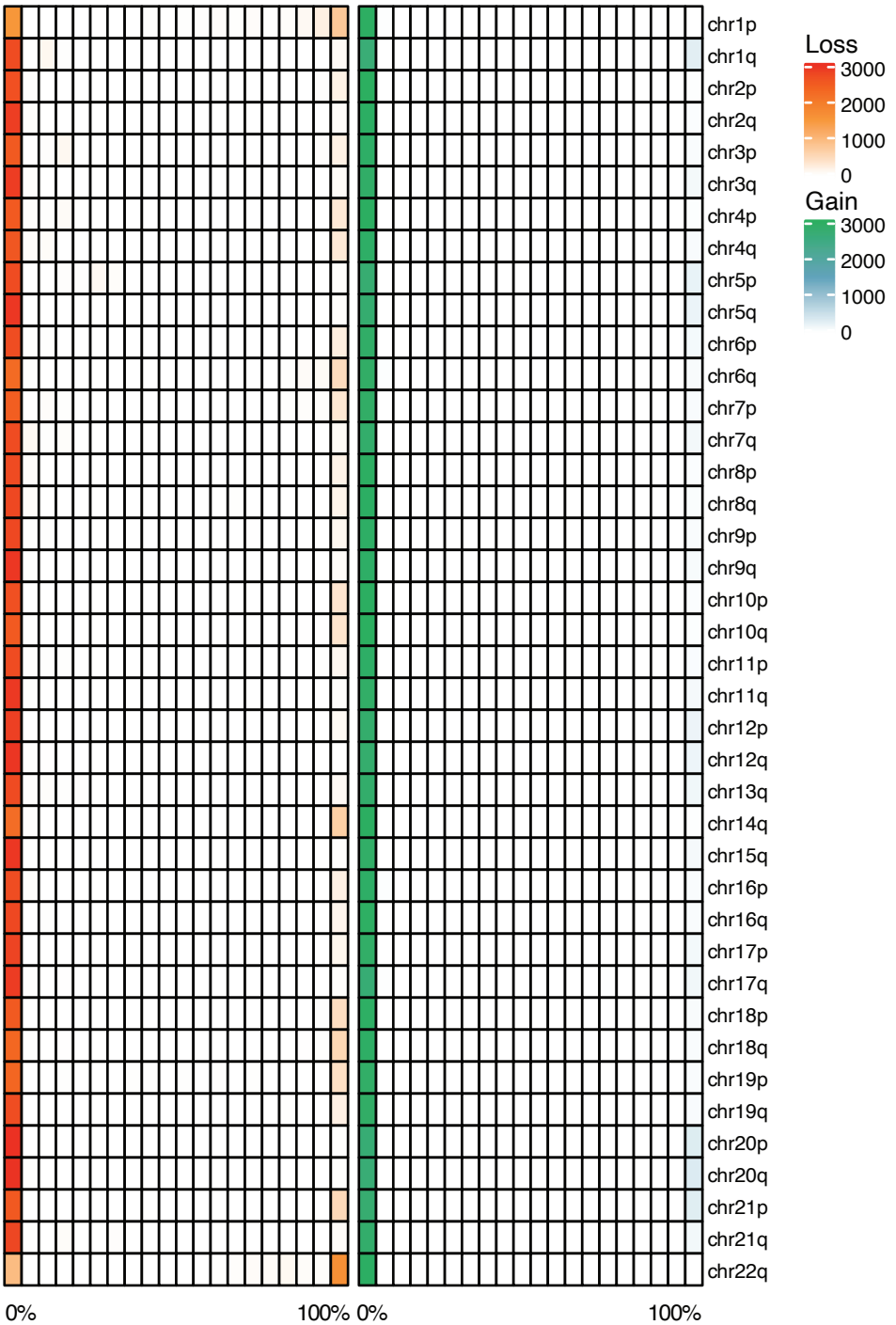

3031 meningioma samples with methylation class annotation and CNV annotations
2868 individual cases with methylation class annotation
985 individual cases with clinical data
Discovery Cohort
Validation Cohorts
Retrospective
Retrospective
Prospective
Cases with clinical data:
n=514
n=184
n=287
Mutational data available:
n=396
n=81

CNVs In WHO Grades, Methylation Families And Methylation Classes **Suppl. Fig 2**



Chromosomal alterations in all cases

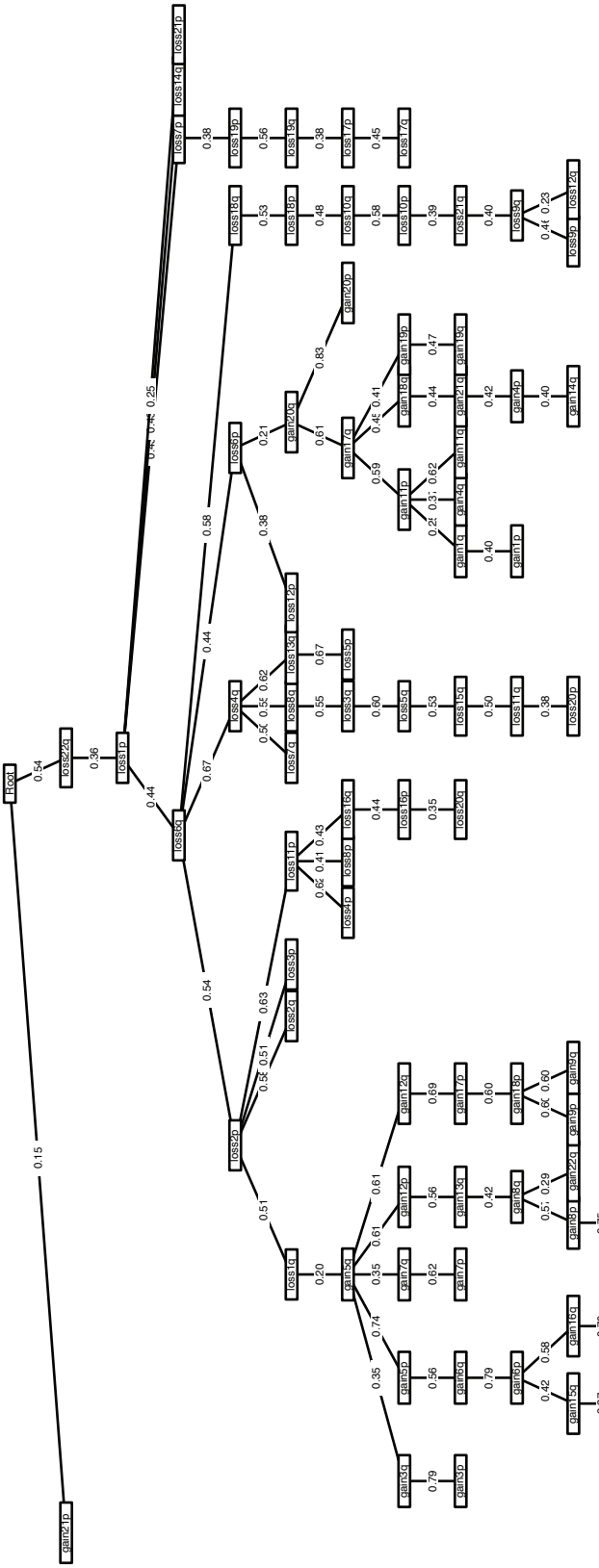
Suppl. Fig. 3



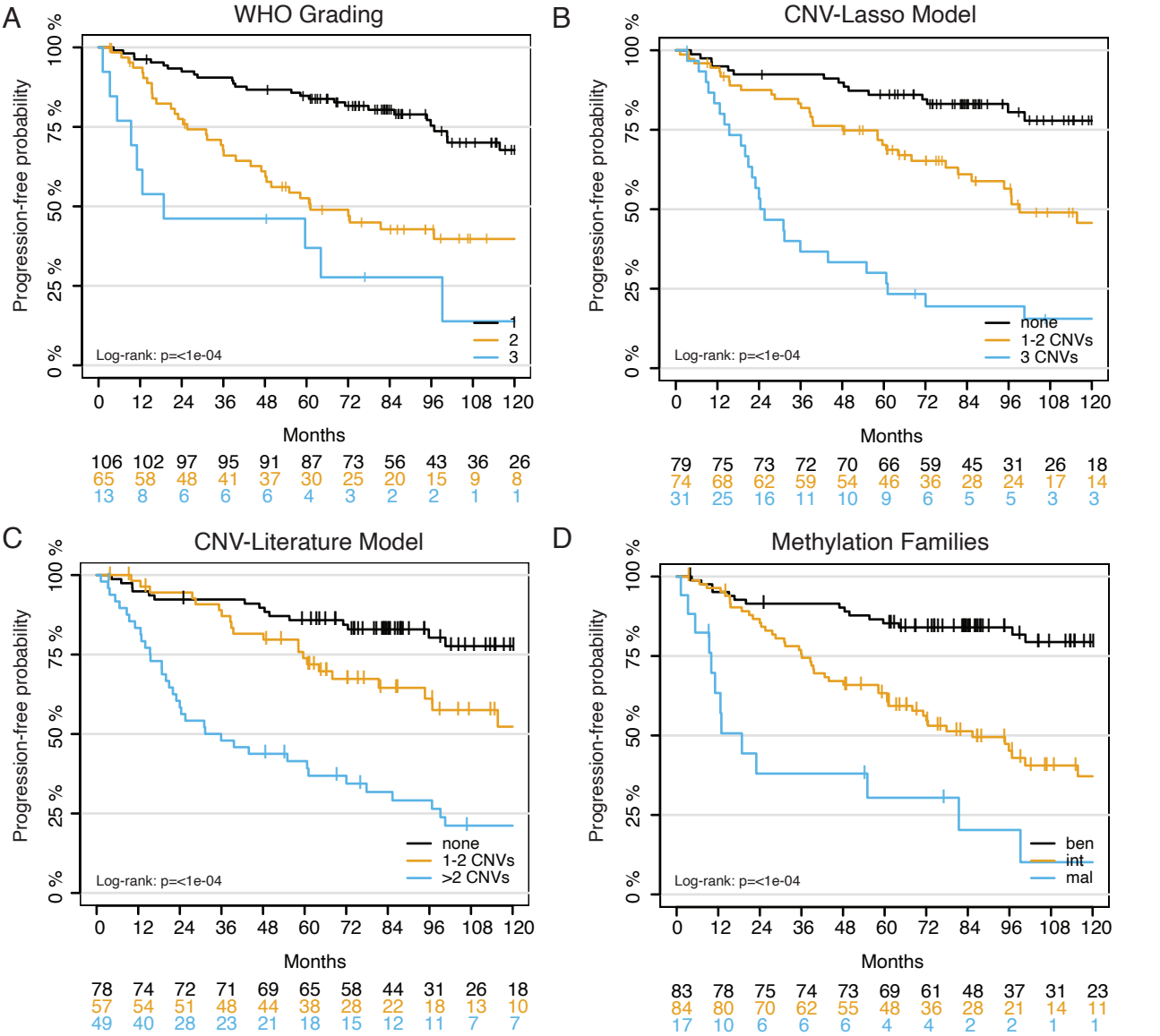
Discovery cohort

Suppl. Fig. 4

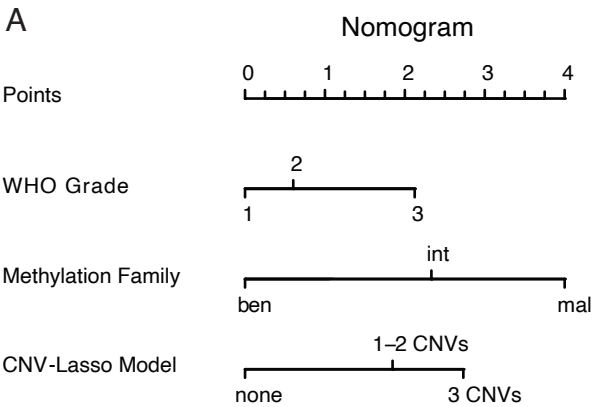
Suppl. Fig. 5

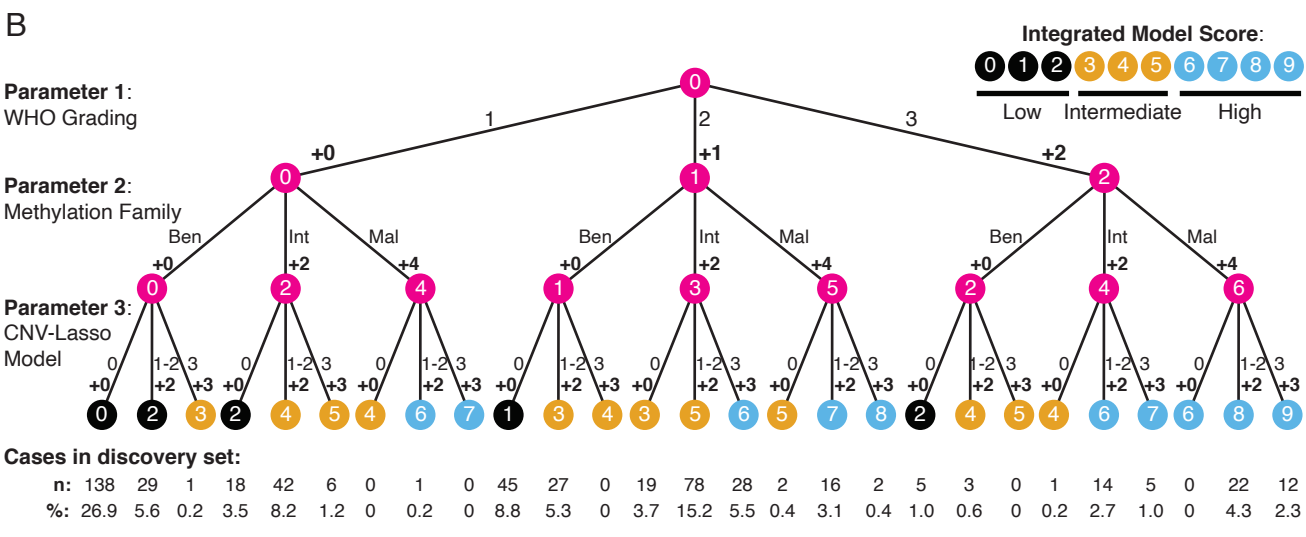

Root
loss21p
loss22p
loss1p
loss8q
loss4q
loss8q
loss13q
loss12p
loss5q
loss5p
loss15q
loss16p
loss20q
loss11p
loss24p
loss9p
loss2q
loss3p
loss1q
gain5q
loss8p
loss14q
loss24p
loss7p
loss19p
loss13p
loss17p
loss17q
loss18q
loss18p
loss10q
loss10p
loss21q
loss9q
loss9p
loss12q
gain24p
gain20q
gain7q
gain19q
gain19p
gain21q
gain19q
gain1p
gain4q
gain11q
gain4p
gain14q
gain1q
gain1p
gain12q
gain12p
gain13q
gain17p
gain13p
gain8q
gain22q
gain9q
gain7q
gain7p
gain8p
gain9p
gain3q
gain3p
gain6q
gain8p
gain16q
gain16p
gain15q
gain2q
gain23q
gain10q

Suppl. Fig. 6


A
WHO Grading
Progression-free probability
100 %
75 %
50 %
25 %
0 %
Log-rank: p=<1e-04
1
2
3
0 12 24 36 48 60 72 84 96 108 120
Months
106 102 97 95 91 87 73 56 43 36 26
65 58 48 41 37 30 25 20 15 9 8
13 8 6 6 6 4 3 2 2 1 1
B
CNV-Lasso Model
Progression-free probability
100 %
75 %
50 %
25 %
0 %
Log-rank: p=<1e-04
none
1-2 CNVs
3 CNVs
0 12 24 36 48 60 72 84 96 108 120
Months
79 75 73 72 70 66 59 45 31 26 18
74 68 62 59 54 46 36 28 24 17 14
31 25 16 11 10 9 6 5 5 3 3
C
CNV-Literature Model
Progression-free probability
100 %
75 %
50 %
25 %
0 %
Log-rank: p=<1e-04
none
1-2 CNVs
>2 CNVs
0 12 24 36 48 60 72 84 96 108 120
Months
78 74 72 71 69 65 58 44 31 26 18
57 54 51 48 44 38 28 22 18 13 10
49 40 28 23 21 18 15 12 11 7 7
D
Methylation Families
Progression-free probability
100 %
75 %
50 %
25 %
0 %
Log-rank: p=<1e-04
ben
int
mal
0 12 24 36 48 60 72 84 96 108 120
Months
83 78 75 74 73 69 61 48 37 31 23
84 80 70 62 55 48 36 28 21 14 11
17 10 6 6 6 4 4 2 2 1 1

Integrated Risk Model and Discovery cohort Score Distribution **Suppl. Fig. 7**



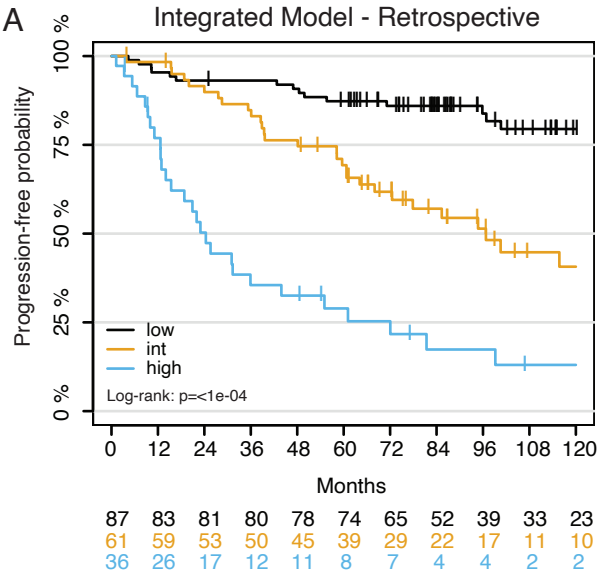


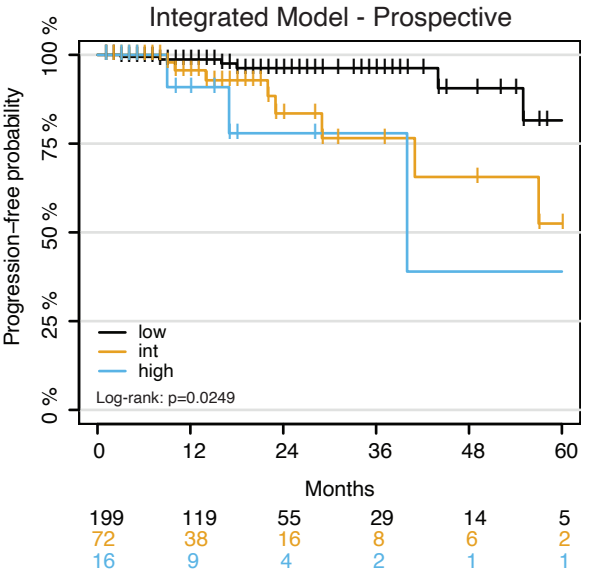
Cases in discovery set:

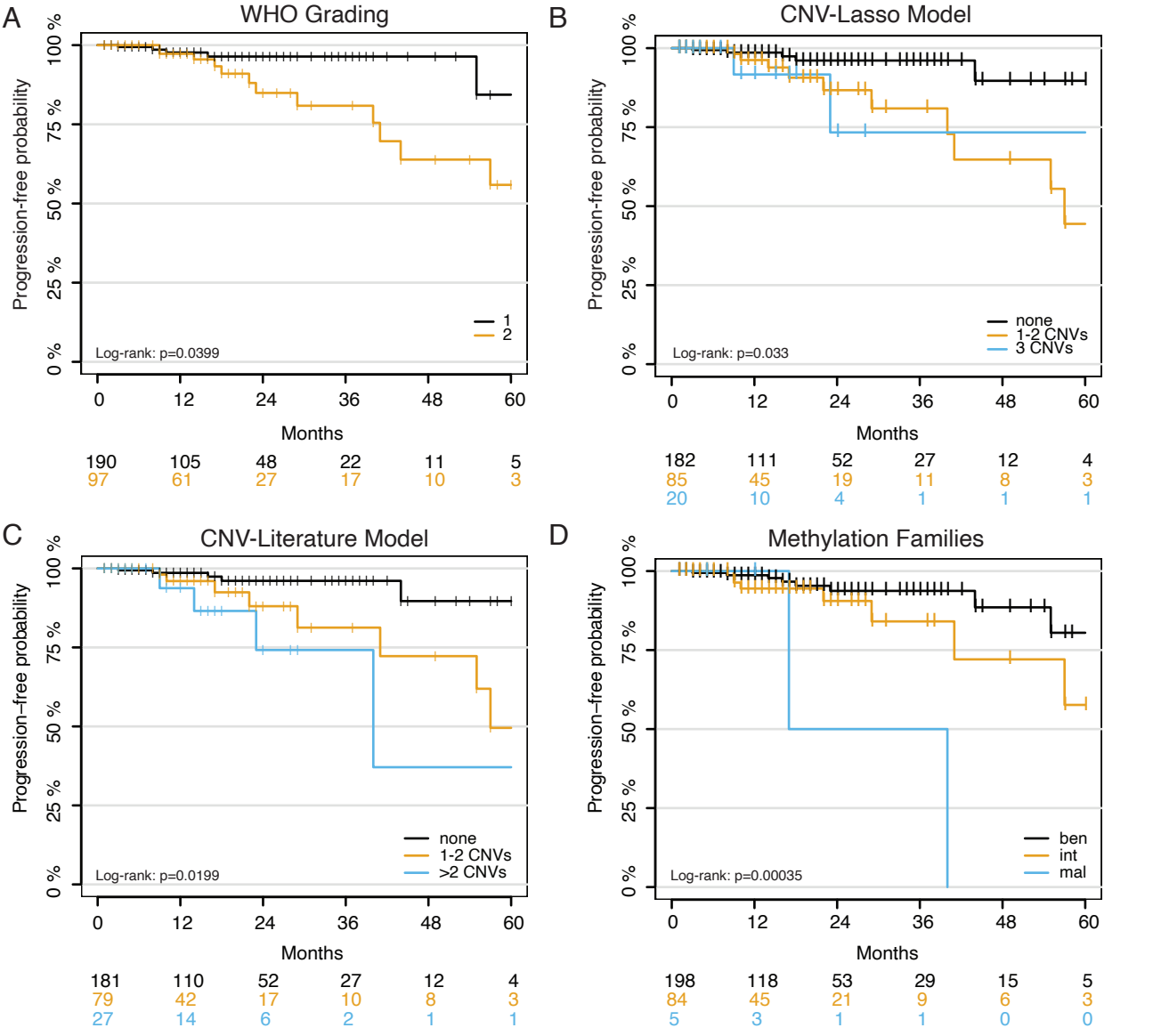
n:	138	29	1	18	42	6	0	1	0	45	27	0	19	78	28	2	16	2	5	3	0	1	14	5	0	22	12
%:	26.9	5.6	0.2	3.5	8.2	1.2	0	0.2	0	8.8	5.3	0	3.7	15.2	5.5	0.4	3.1	0.4	1.0	0.6	0	0.2	2.7	1.0	0	4.3	2.3

Retrospective and prospective validation cohorts

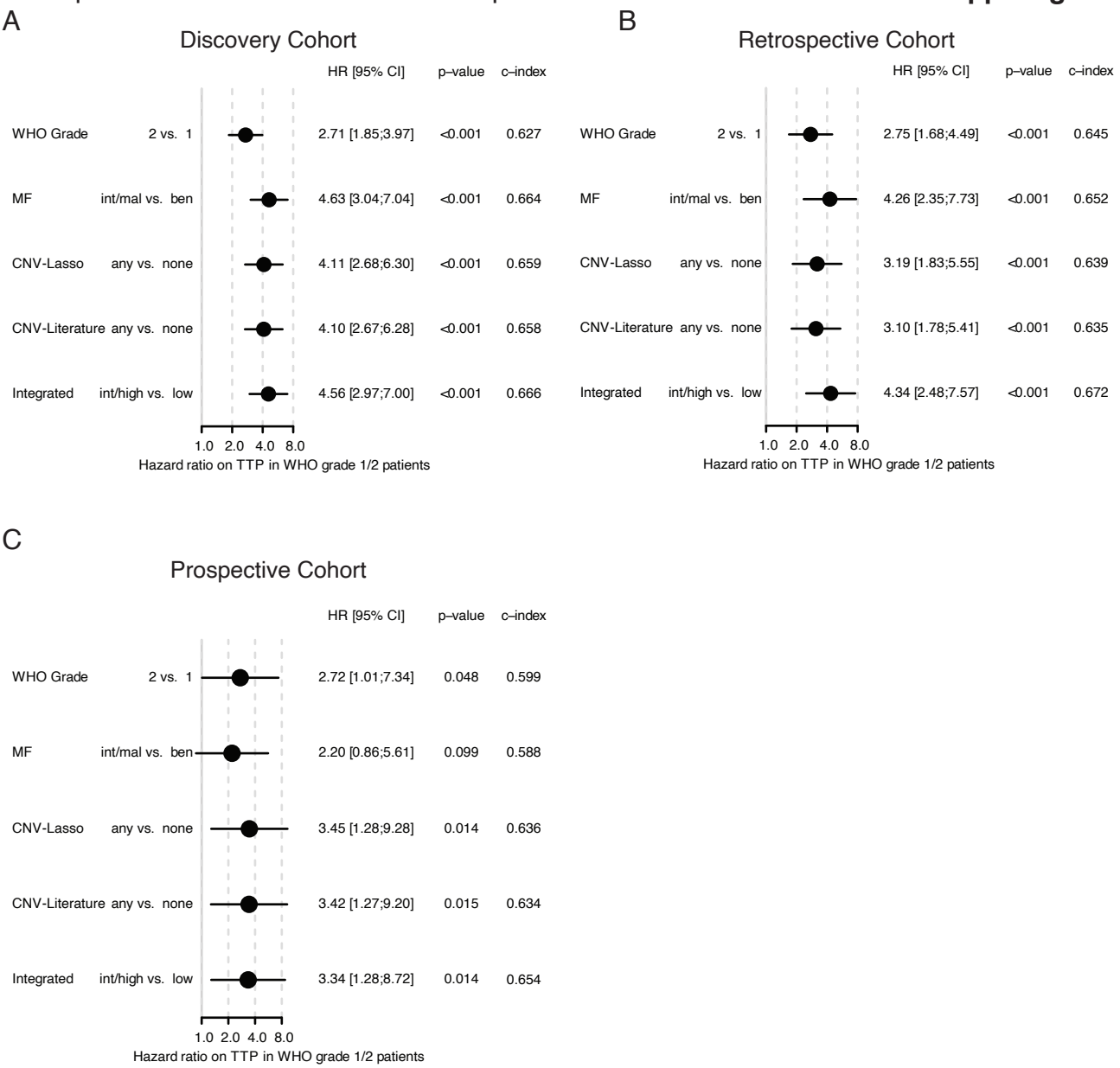
Suppl. Fig. 8



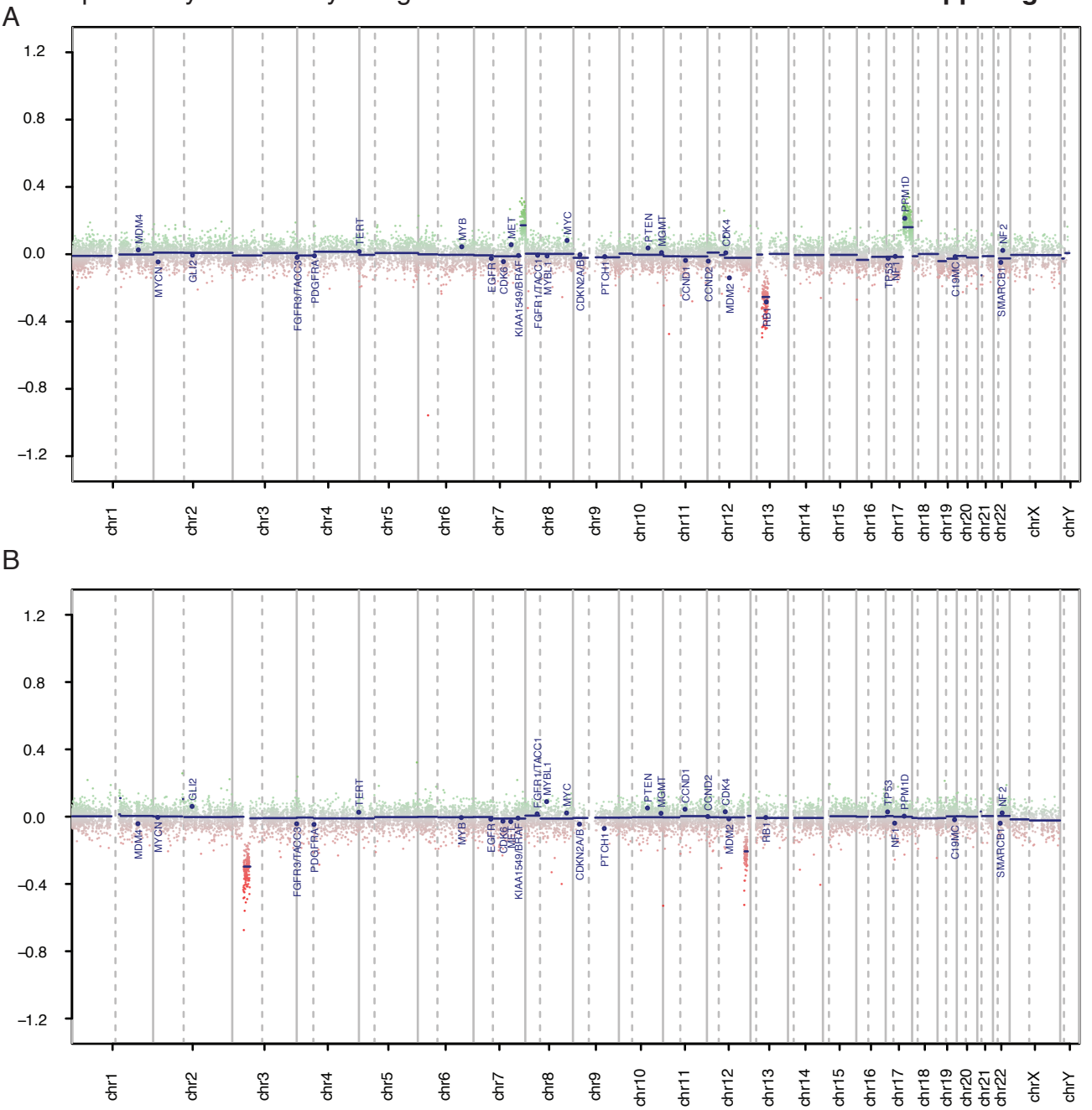



A
WHO Grading
Progression-free probability
100 %
75 %
50 %
25 %
0 %
1
2
Log-rank: p=0.0399
0
12
24
36
48
60
Months
190 105 48 22 11 5
97 61 27 17 10 3
B
CNV-Lasso Model
Progression-free probability
100 %
75 %
50 %
25 %
0 %
none
1-2 CNVs
3 CNVs
Log-rank: p=0.033
0
12
24
36
48
60
Months
182 111 52 27 12 4
85 45 19 11 8 3
20 10 4 1 1 1
C
CNV-Literature Model
Progression−free probability
100 %
75 %
50 %
25 %
0 %
none
1-2 CNVs
>2 CNVs
Log-rank: p=0.0199
0
12
24
36
48
60
Months
181 110 52 27 12 4
79 42 17 10 8 3
27 14 6 2 1 1
D
Methylation Families
Progression−free probability
100 %
75 %
50 %
25 %
0 %
ben
int
mal
Log-rank: p=0.00035
0
12
24
36
48
60
Months
198 118 53 29 15 5
84 45 21 9 6 3
5 3 1 1 0 0

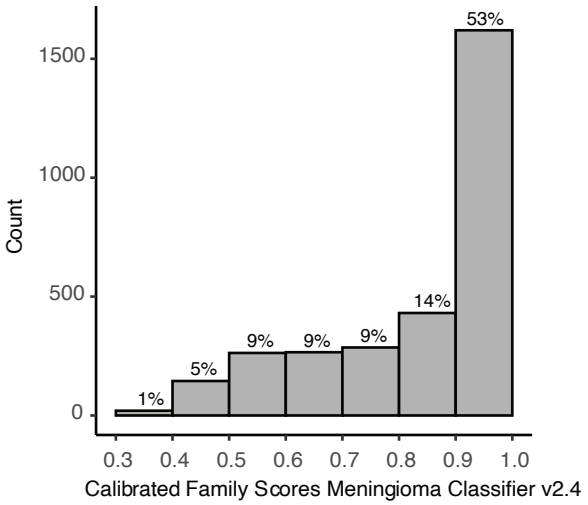
Risk prediction in WHO Grade 1 and 2 patients



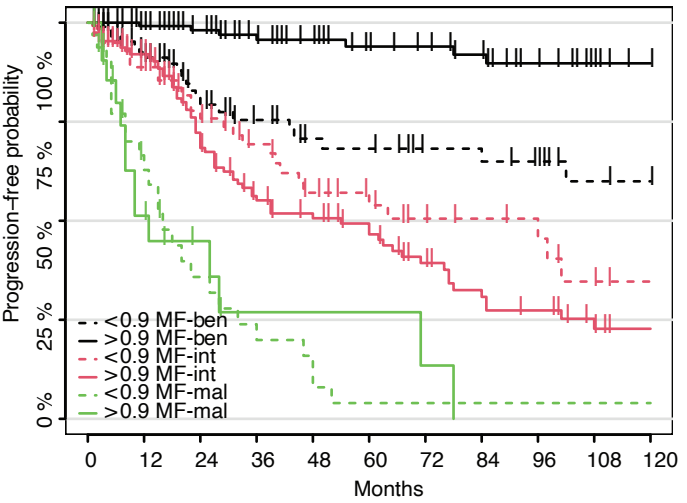
Example methylation family malignant cases with limited CNVs **Suppl. Fig. 11**



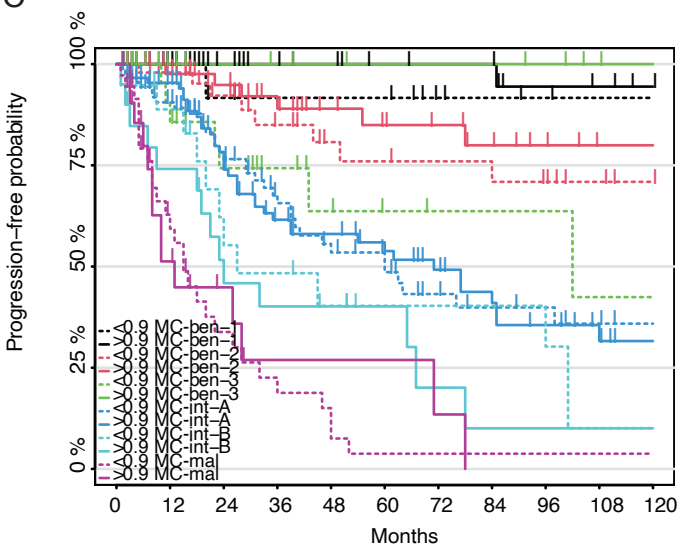
A


Count
1500
1000
500
0
1%
5%
9%
9%
9%
14%
53%
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Calibrated Family Scores Meningioma Classifier v2.4

B


Progression–free probability
100 %
75 %
50 %
25 %
0 %
<0.9 MF-ben
>0.9 MF-ben
<0.9 MF-int
>0.9 MF-int
<0.9 MF-mal
>0.9 MF-mal
0
12
24
36
48
60
72
84
96
108
120
Months

C

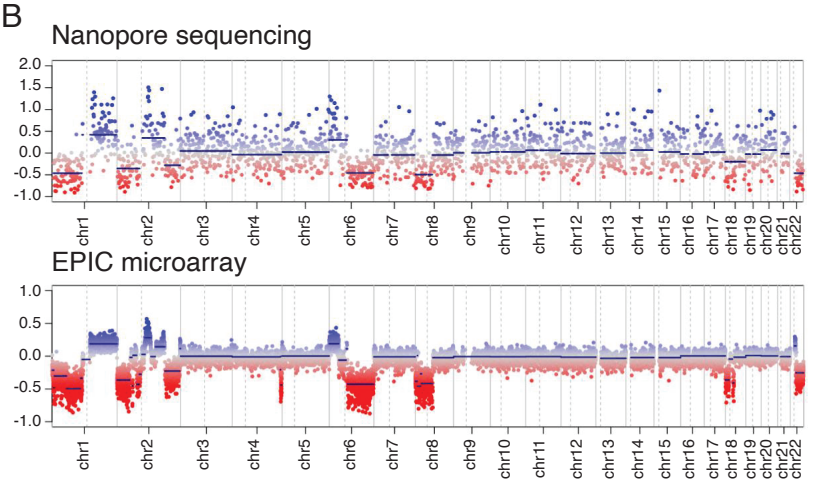

Progression–free probability
100 %
75 %
50 %
25 %
0 %
<0.9 MC-ben–1
>0.9 MC-ben–1
<0.9 MC-ben–2
>0.9 MC-ben–2
<0.9 MC-ben–3
>0.9 MC-ben–3
<0.9 MC-int–A
>0.9 MC-int–A
<0.9 MC-int–B
>0.9 MC-int–B
<0.9 MC-mal
>0.9 MC-mal
0
12
24
36
48
60
72
84
96
108
120
Months

Comparison of microarray and nanopore sequencing **Suppl. Fig. 13**

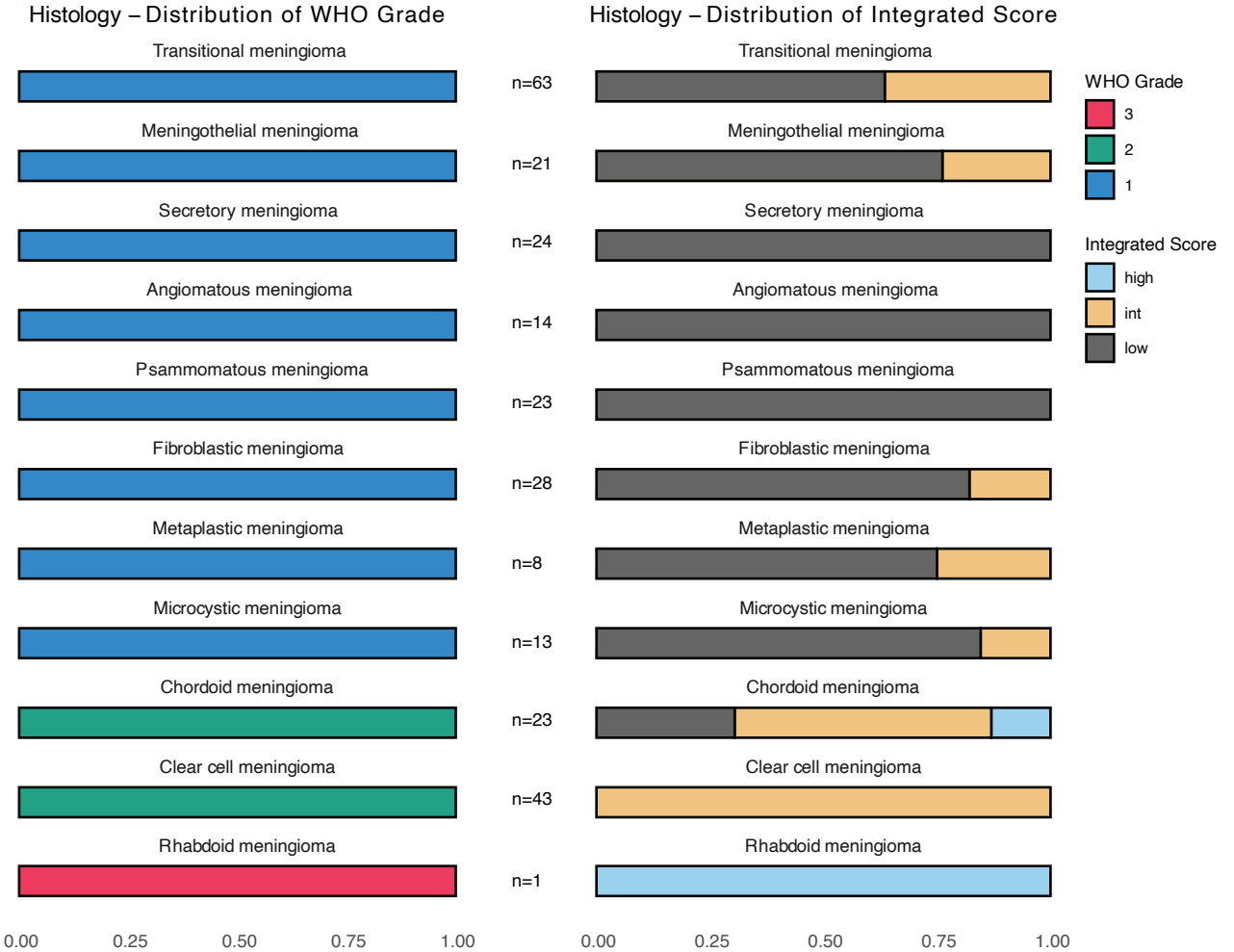
A

EPIC microarray \ Nanopore sequencing	ben-1	ben-2	int-A
N=22			
ben-1	11		
ben-2	2	8	
int-A			1

B



Suppl. Fig. 14


Histology – Distribution of WHO Grade
Transitional meningioma
n=63
Meningothelial meningioma
n=21
Secretory meningioma
n=24
Angiomatous meningioma
n=14
Psammomatous meningioma
n=23
Fibroblastic meningioma
n=28
Metaplastic meningioma
n=8
Microcystic meningioma
n=13
Chordoid meningioma
n=23
Clear cell meningioma
n=43
Rhabdoid meningioma
n=1
0.00
0.25
0.50
0.75
1.00
Histology – Distribution of Integrated Score
Transitional meningioma
Meningothelial meningioma
Secretory meningioma
Angiomatous meningioma
Psammomatous meningioma
Fibroblastic meningioma
Metaplastic meningioma
Microcystic meningioma
Chordoid meningioma
Clear cell meningioma
Rhabdoid meningioma
0.00
0.25
0.50
0.75
1.00
WHO Grade
3
2
1
Integrated Score
high
int
low

Case Re-distribution From WHO Grade To Integrated Score

Suppl. Fig. 15