

Supplementary Information

Table S1. Cohorts, platforms, endpoints, program-gene availability, and models.

Cohort	Platform	n (composition)	Role	Endpoint(s)	Program genes available	Scaling	Primary model(s) & covariates
GSE136661 [2]	RNA-seq (HTSeq counts)	160 (Disc 97 / Val 48 / Recur 15; WHO I/II/III)	Discovery	program definition (WHO I vs II)	all (definition set)	VST	DESeq2 WHO I vs II → 200-gene program
GSE16581	Microarray (GPL570)	68 (WHO I/II/III = 43/19/6; 10 recurrences)	External association testing	grade; recurrence; OS	142/200 (up 60 / dn 82)	within-cohort gene-wise z; rank sensitivity	grade ANOVA; Firth recurrence ~ score + grade; proliferation LRT; Cox OS
GSE74385	Illumina HT-12 (illuminaHumanv4.db; max-mean probe collapse)	62 total; 54 known outcome (23 non-recurrent / 22 recurrent / 9 malignant progression / 8 outcome-unknown; WHO I/II/III = 20/14/28)	External association testing	recurrence and malignant progression separated	160/200 (up 67 / dn 93)	within-cohort gene-wise z; rank sensitivity	Firth endpoint ~ score + grade + batch; composite sensitivity; grade-I flagged batch-confounded
GSE183655	scRNA (10x)	10 samples / 63,628 cells	Architecture atlas	cell-type resolution	—	AddModuleScore	compartment annotation; descriptive CellChat (Supplementary)
GSE206647	scRNA (10x)	16 tumor patients (+2 normal) / 163,897 cells; WHO I/II/III = 8/4/4	Single-cell grade reproduction	grade-association	159/200 (up 67 / dn 92)	per-patient pseudobulk z; AddModuleScore	per-patient pseudobulk Spearman/ANOVA (primary); cell-level mixed model (patient random intercept; cell-cycle/depth/ribo/mito covariates); patient-wise CopyKAT sensitivity; supplementary Geneformer benchmark on 1,800-cell grade-balanced subsample

Table S2. WHO-grade-associated program genes. The 200 genes defining the WHO-grade-associated program, including Ensembl ID, available gene symbol, program direction, rank within up/down program genes, baseMean, log2FoldChange, Wald statistic, p value and adjusted p value. Because the complete 200-row table is not legible within a manuscript page, it is provided in the accompanying supplementary table workbook (worksheet “Table S2”).

6 **Table S3. GSE206647 per-patient tumor/tumor-like pseudobulk scores.** Per-sample grade, program score and tumor/tumor-like cell count used for the primary pseudoreplication-free single-cell
7 grade-association test. The complete table is reproduced below.

GEO sample	WHO grade	score	Tumor cells
GSM7476436	Normal	-0.770395022760716	319
GSM7476437	Normal	-1.56298328884232	1147
GSM7476438	I	-0.28625573688169	4485
GSM7476439	I	-1.01183440375878	1895
GSM7476440	I	-1.04248438097838	4412
GSM7476441	I	0.19397695411509	3942
GSM7476442	I	-1.30779201143025	9542
GSM7476443	I	-0.192224474151945	2530
GSM7476444	I	-0.0526805985043967	9088
GSM7476445	I	-0.919872396954934	3310
GSM7476446	II	1.28914462476548	5650
GSM7476447	II	0.48599065729552	3962
GSM7476448	II	0.58106601845005	2181
GSM7476449	II	0.67585478634272	2620
GSM7476450	III	1.03746337254164	5607
GSM7476451	III	0.975439099373594	3611
GSM7476452	III	0.954689497057076	441
GSM7476453	III	0.952897304322244	6975

8 **Table S4. Clinically exposed drug-signature reversal candidates and evidence adjudication.** Present-project L1000FWD rank, score, perturbation context, market/clinical status, independent
9 meningioma evidence, decision and caveat. The complete table is reproduced below. The raw query and all 50 opposing signatures are retained with the analysis code.

candidate	I1000 opposite rank	I1000 score	cell line	time h	dose	market or clinical status	meningioma cross validation	decision	key caveat	source
Etoposide	1	-0.119565217391304	MCF7	24	10.0	marketed oncology drug	meningioma cell-line evidence includes surviving drug-resistant stem-like cells	deprioritise	strongest current reversal but single MCF7 signature; nonspecific cytotoxicity/resistance concern	https://pmc.ncbi.nlm.nih.gov/articles/PMC5521079/
Amsacrine	2	-0.119565217391304	MCF7	24	10.0	clinically used/marketed in some jurisdictions for acute leukaemia	no direct meningioma validation identified	deprioritise	strongest current reversal but single MCF7 signature and substantial systemic toxicity	https://maayanlab.cloud/dmoa/report/BRD-K98490050
ESTRADIOL BENZOATE	4	-0.108695652173913	VCAP	24	10.0	marketed hormonal drug in some jurisdictions	no therapeutic meningioma validation identified	exclude	estrogenic exposure is not a rational unselected meningioma therapy	
Danazol	10	-0.0978260869565217	VCAP	24	10.0	marketed hormonal drug	no therapeutic meningioma validation identified	exclude	hormonal pharmacology and meningioma context make repurposing unattractive despite reversal	
itraconazole	22	-0.0869565217391304	VCAP	24	10.0	marketed antifungal; oncology repurposing studied clinically	no direct meningioma validation identified	exploratory	weak single-VCAP reversal; mechanistic and tumour-exposure validation required	https://clinicaltrials.gov/study/NCT02357836
Perhexiline maleate	24	-0.0869565217391304	MCF7	24	10.0	marketed for angina in limited jurisdictions	no direct meningioma validation identified	exploratory	weak single-MCF7 reversal; metabolic mechanism is conceptually relevant to OXPHOS but hepatotoxicity and exposure are concerns	https://pubchem.ncbi.nlm.nih.gov/compound/Perhexiline
AMIODARONE HYDROCHLORIDE	29	-0.0869565217391304	HT29	24	10.0	marketed antiarrhythmic	no direct meningioma validation identified	deprioritise	weak single-HT29 reversal and major chronic toxicity	
Cyclosporin A	34	-0.0869565217391304	PC3	24	10.0	marketed immunosuppressant	no direct meningioma validation identified	exclude	immunosuppression is translationally unattractive for an unvalidated anticancer signal	
Norethindrone	41	-0.0869565217391304	VCAP	24	10.0	marketed progestin	no therapeutic meningioma validation identified	exclude	progestin exposure is a safety concern in meningioma	
Retinoic acid	43	-0.0869565217391304	MCF7	6	40.0	marketed as tretinoin/all-trans retinoic acid	in vitro meningioma evidence: reduced invasion/migration and increased matrix adhesion	literature-supported hypothesis	weak single-MCF7 reversal, but orthogonal meningioma-specific experimental support makes it testable	https://doi.org/10.1038/sj.bjc.6690705
oxymetholone	45	-0.0869565217391304	VCAP	24	10.0	marketed androgen/anabolic steroid	no therapeutic meningioma validation identified	exclude	hormonal toxicity and absent meningioma evidence	
mirtazapine	50	-0.0760869565217391	VCAP	24	10.0	marketed antidepressant	no direct meningioma validation identified	deprioritise	weakest listed single-VCAP reversal and no mechanistic support	

10 **Table S5. Patient-level candidate-marker evidence matrix.** For each of the 200 program genes: discovery rank and DESeq2 statistics, GSE206647 tumor/tumor-like pseudobulk grade Spearman
11 (rho, p, BH-FDR), tumor-versus-other-cell expression specificity, directional concordance in GSE16581/GSE74385, and a transparent internal-evidence score used only for ranking (not statistical
12 inference). Because the complete 200-row, 22-column matrix is not legible within a manuscript page, it is provided in the accompanying supplementary table workbook (worksheet “Table S5”).

13 **Table S6. CopyKAT tumor-annotation sensitivity analysis.** Per-patient CopyKAT input counts, aneuploid tumor/tumor-like fraction, eligibility for an aneuploid pseudobulk, and paired program
14 scores from all classified tumor/tumor-like versus CopyKAT-aneuploid cells in the patient-balanced subsample. One WHO I patient had no CopyKAT-aneuploid tumor/tumor-like cells and is retained
15 with a missing restricted score. Across the 15 eligible patients the CopyKAT-aneuploid fraction ranged from 0.576 to 0.983 (median $\approx$ 0.900); because the CopyKAT-aneuploid pseudobulk is a nested
16 subset of the broader tumor/tumor-like pseudobulk, the correlation of 0.993 between the two is a robustness check rather than an independent confirmation. The complete table is reproduced below.

GEO sample	WHO grade	n copykat tumour	n copykat aneuploid tumour	aneuploid fraction	WHO grade (ordinal)	cnv eligible	broad balanced pseudobulk score	copykat aneuploid pseudobulk score
GSM7476438	I	1431	1406	0.982529699510832	1	TRUE	-0.501894449732101	-0.497853901357039
GSM7476439	I	1423	1280	0.89950808151792	1	TRUE	-1.22396993669963	-1.16355765582534
GSM7476440	I	1370	992	0.724087591240876	1	TRUE	-1.30849906627072	-1.40965978633615
GSM7476441	I	1247	1001	0.802726543704892	1	TRUE	-0.0362442484678432	-0.100997393677239
GSM7476442	I	1341	1014	0.756152125279642	1	TRUE	-1.54086086385735	-1.6602820194927
GSM7476443	I	1362	1276	0.936857562408223	1	TRUE	-0.37258800623287	-0.363013609585549
GSM7476444	I	1389	1331	0.958243340532757	1	TRUE	-0.323042633021712	-0.280889181723198
GSM7476445	I	1436	0	0	1	FALSE	NA	NA
GSM7476446	II	1342	951	0.708643815201192	2	TRUE	1.06428717674499	1.07996334795822
GSM7476447	II	1473	1405	0.953835709436524	2	TRUE	0.313260716288031	0.351657810513491
GSM7476448	II	1436	1070	0.745125348189415	2	TRUE	0.422657996281497	0.326577363363066
GSM7476449	II	1453	1382	0.951135581555403	2	TRUE	0.498676711795669	0.551738085224745
GSM7476450	III	1340	1188	0.886567164179105	3	TRUE	0.862285247011332	0.98845017103462
GSM7476451	III	1456	1404	0.964285714285714	3	TRUE	0.705735584296212	0.704339325984766
GSM7476452	III	420	242	0.576190476190476	3	TRUE	0.730417897713833	0.78230376184643
GSM7476453	III	1433	1387	0.967899511514306	3	TRUE	0.709777874150671	0.691223682071869

17 **Table S6b. Complementary chromosome-arm expression-dosage proxy.** For each of the 16 GSE206647 tumors, the per-patient tumor-cell pseudobulk relative expression of chromosome 22q
18 (referenced to the two normal-meninges samples; an arm scored as lost below -0.1) and the broad autosomal-arm loss burden. Lower relative chr22q dosage was seen in 13 of 16 tumors and the
19 broad-loss burden increased modestly with grade (Spearman $\rho=0.40$), qualitatively consistent with the canonical meningioma copy-number pattern. This is an expression-inferred dosage proxy
20 computed from the same expression data and annotations — complementary context, not a CopyKAT copy-number reconstruction and not DNA-based confirmation. The complete table is reproduced
21 below.

GEO sample		WHO grade	chr22q rel	broad loss burden	
GSM7476438	I		-0.438280298575854	39	
GSM7476439	I		-0.137067751204072	38	
GSM7476440	I		0.226856386408184	0	
GSM7476441	I		-0.147972267733333	2	
GSM7476442	I		0.0253646316508472	1	
GSM7476443	I		-0.303114108057326	6	
GSM7476444	I		-0.197884256739793	4	
GSM7476445	I		0.0691392828970759	0	
GSM7476446	II		-0.362990510878434	31	
GSM7476447	II		-0.228067120515508	8	
GSM7476448	II		-0.237583225250567	17	
GSM7476449	II		-0.286296535225452	20	
GSM7476450	III		-0.326792752767689	13	
GSM7476451	III		-0.16891475949563	7	
GSM7476452	III		-0.102294989380923	26	
GSM7476453	III		-0.294027243222727	21	

22 **Table S7. Endpoint dictionary and sample-exclusion flow.** The table below defines each analyzed endpoint, its eligible population, exclusions and inferential role. Recurrence, malignant
23 progression and overall survival were not combined except in the explicitly labeled GSE74385 composite sensitivity analysis.

Dataset / analysis	Starting material	Endpoint or role	Included observations	Exclusions / restrictions	Inferential status
GSE136661 program definition	160 tumors (Discovery 97 / Validation 48 / Recurrence 15)	WHO I versus II grade contrast	116 WHO I and 29 WHO II primary tumors	WHO III and recurrence-cohort samples were not used to select program genes	Discovery; WHO I/II display is in-sample
GSE136661 held-out display	Samples not used in the WHO I/II contrast	Grade extrapolation and recurrence-cohort projection	Available WHO III and recurrence-cohort samples	Not used for program selection	Descriptive / held-out projection
GSE16581 recurrence	68 tumors	Documented recurrence (yes/no)	All 68; 10 recurrence events	No additional sample exclusion; clinical covariates beyond grade were unavailable	External retrospective association; Firth model adjusted for grade
GSE16581 overall survival	68 tumors	Overall survival time and event	Samples with available survival fields; approximately 10 events	Event-limited; not a recurrence-free-survival endpoint	Secondary and underpowered
GSE74385 recurrence-only	62 tumors	Recurrent versus non-recurrent	45 tumors: 22 recurrent and 23 non-recurrent	Nine malignant-progression tumors and eight 3NA outcome-unknown tumors excluded	Primary GSE74385 recurrence analysis; adjusted for grade and batch
GSE74385 malignant progression	62 tumors	Malignant progression versus non-recurrent	32 tumors: 9 malignant progression and 23 non-recurrent	Recurrent and 3NA outcome-unknown tumors excluded	Exploratory secondary endpoint
GSE74385 composite sensitivity	62 tumors	Recurrence or malignant progression versus non-recurrent	54 known-outcome tumors	Eight 3NA outcome-unknown tumors excluded	Sensitivity analysis only
GSE74385 grade-I view	WHO I subset	Recurrence pattern within grade I	Available WHO I tumors	Processing batch was fully confounded with recurrence	Descriptive; no within-grade-I inferential claim
GSE183655 architecture atlas	10 samples / 63,628 QC cells	Cell-type architecture and descriptive program projection	All QC cells used for atlas description	No recurrence or grade inference performed	Descriptive
GSE206647 grade pseudobulk	16 tumors plus 2 normal meninges / 163,897 QC cells	Ordinal WHO grade association	Sixteen grade-labeled tumor patients	Two normal meninges excluded from tumor-grade inference; cells aggregated by patient	Primary single-cell reproduction

Dataset / analysis	Starting material	Endpoint or role	Included observations	Exclusions / restrictions	Inferential status
GSE206647 CopyKAT sensitivity	16 tumor patients	Grade association in CopyKAT-aneuploid tumor/tumor-like cells	Fifteen patients with at least 10 eligible aneuploid cells	One WHO I patient lacked an eligible aneuploid pseudobulk	Supportive expression-inferred CNV sensitivity analysis
Geneformer secondary benchmark	16 tumor patients	Patient-level grade representation	1,800 grade-balanced cells retained within 16 patients; inference at patient level	No cell-weighted inference; no external patient cohort	Exploratory secondary benchmark

Table S8. REMARK/STROBE-informed reporting checklist. This secondary analysis of public molecular cohorts is not a prospective biomarker trial. The checklist documents the applicable elements of REMARK and STROBE without implying formal compliance with items that require prospective recruitment or clinical follow-up unavailable in GEO.

Reporting domain	Where addressed	Status / limitation
Study objectives and prespecified contribution	Introduction; Methods	Grade-associated program with retrospective recurrence association; not a deployable predictor
Data sources and study setting	Methods: Datasets; Table S1	GEO accessions, platforms and cohort roles reported
Eligibility and sample selection	Methods: Datasets; Table S7	Dataset-specific inclusions and exclusions reported; no prospective recruitment
Outcome definitions	Methods: Datasets; Table S7	Recurrence, malignant progression and overall survival kept distinct
Candidate-program definition	Methods: Grade-associated program	Fixed 200-gene selection rule and discovery contrast reported
Assay and preprocessing methods	Methods; docs/RUN_ORDER.md	Platform transformations, probe collapse, scaling and single-cell QC reported
Blinding	Not applicable	Public retrospective datasets; analyses were computational and labels were required for modeling
Study-size rationale	Results; Limitations	All eligible public samples used; no prospective power calculation; event limitations disclosed
Missing data and exclusions	Methods: Datasets; Table S7	Eight 3NA outcomes excluded; unavailable clinical covariates listed
Confounding and bias	Methods: Cross-cohort scoring; Discussion: Limitations	Grade and batch adjustment, endpoint separation and known residual confounding reported
Statistical methods	Methods	Firth regression, Cox models, ANOVA, Spearman tests, mixed models and nested validation described
Multiplicity	Methods: program and target scoring	DESeq2/BH-FDR used where applicable; exploratory analyses labeled
Internal and external association testing	Results; Table S1	Independent bulk cohorts and a separate grade-stratified single-cell cohort used; no prospective clinical validation
Effect estimates and uncertainty	Results; Figure legends	Odds ratios, confidence intervals, p values and event limitations reported
Model performance	Results	AUCs labeled retrospective; no calibration or clinical threshold claimed
Sensitivity analyses	Results; Figures S2-S4; Tables S6-S7 and S9	Common-gene, rank-score, endpoint, CopyKAT, rare-event and aggregation-order sensitivity analyses reported
Biological interpretation	Results; Discussion	Candidate markers and pathways framed as hypotheses requiring orthogonal validation
Generalizability	Discussion: Limitations	Cross-platform reproducibility shown; missing clinical covariates and small cohorts constrain clinical generalization
Data and code availability	Data availability	GEO accessions, public repository and project-specific Zenodo DOI reported
Funding and competing interests	Declarations	Funding sources and no competing interests reported

26 **Table S9. GSE16581 rare-event Firth stability analysis.** Canonical and leave-one-recurrence-event-out odds ratios, 2,000-bootstrap coefficient summary, profile-likelihood and Wald intervals,
 27 grade-only/program-only/grade-plus-program model comparison, categorical-versus-ordinal grade coding, grade-specific event counts and exploratory within-grade summaries. The complete table is
 28 reproduced below.

analysis	term	estimate	95% CI lower	95% CI upper	p value	note
canonical	program OR per 1-SD	14.74	2.773	224.1	0.0001634	grade-adjusted (categorical) Firth; manuscript headline
LOEO_summary	OR per 1-SD (min/median/max)	14.23	10.9	18.54	0.0008984	leave-one-recurrence-event-out; p column = worst-case p
bootstrap	program OR per 1-SD	17.55	4.452	1419	0	2000 resamples; p column = P(coef<=0); finite coefficient fits 2000/2000
CI_profile	program OR per 1-SD	14.74	2.773	224.1	0.0001634	profile-likelihood CI (reported)
CI_wald	program OR per 1-SD	14.74	2.322	93.55	0.0001634	Wald symmetric CI (for contrast only)
model_grade_only	penalized log-likelihood	-18.62	NA	NA	NA	Firth model: recurrence ~ categorical grade
model_program_only	program OR per 1-SD	22.94	4.919	327.4	3.651e-08	no grade covariate
model_grade_categorical	program OR per 1-SD	14.74	2.773	224.1	0.0001634	grade as factor (canonical)
model_grade_ordinal	program OR per 1-SD	12.75	2.8	169.3	0.0001234	grade as ordinal 1/2/3
model_add_program_PLR	penalized-likelihood-ratio chi-square	14.21	NA	NA	0.0001634	nested comparison: grade-only vs categorical-grade + program
within_grade_1	exploratory within-grade program OR per full-cohort 1-SD	NA	NA	NA	NA	n=43; recurrence events=1; non-events=42; median score recurrent=0.752, non-recurrent=-0.223; effect not estimated because one outcome group had <3 observations
within_grade_2	exploratory within-grade program OR per full-cohort 1-SD	7.572	1.408	175.1	0.01292	n=19; recurrence events=5; non-events=14; median score recurrent=1.234, non-recurrent=0.404; exploratory Firth estimate shown
within_grade_3	exploratory within-grade program OR per full-cohort 1-SD	NA	NA	NA	NA	n=6; recurrence events=4; non-events=2; median score recurrent=1.868, non-recurrent=-0.019; effect not estimated because one outcome group had <3 observations
LOEO_detail	drop event 1	11.74	2.371	175.5	0.0004812	one recurrence event removed
LOEO_detail	drop event 2	14.15	2.454	223.4	0.0006208	one recurrence event removed
LOEO_detail	drop event 3	18.54	3.006	392.2	0.000134	one recurrence event removed
LOEO_detail	drop event 4	11.13	2.554	157.3	0.0002017	one recurrence event removed
LOEO_detail	drop event 5	15.82	2.814	270.5	0.0001819	one recurrence event removed
LOEO_detail	drop event 6	10.9	2.16	197.2	0.0008984	one recurrence event removed
LOEO_detail	drop event 7	14.89	2.683	227.2	0.0002489	one recurrence event removed
LOEO_detail	drop event 8	14.32	2.575	227.8	0.0002569	one recurrence event removed
LOEO_detail	drop event 9	14.9	2.751	225.5	0.0002362	one recurrence event removed
LOEO_detail	drop event 10	12.51	2.517	168.4	0.0003234	one recurrence event removed

29 **Table S9b. GSE74385 recurrence-only rare-event sensitivity.** Firth models for the GSE74385 recurrence-only set (n=45, 22 events): the full model (score + grade + batch; OR per 1-SD 5.18, 95%
30 CI 1.40–25.83) and parsimonious/nested comparisons (score-only OR 5.23, 95% CI 2.06–18.76; score-plus-grade OR 5.37, 95% CI 1.56–25.46), with estimated-coefficient counts. Leave-one-
31 recurrence-event-out refitting gives OR range 3.59–9.70 (median 5.01; all finite). The association is directionally stable and positive across specifications. The complete table is reproduced below.

model	or score	95% CI lower	95% CI upper	p score	n coeffs	n	events
full(score+grade+batch)	5.17990156288314	1.40349195059322	25.8310409563737	0.0118143080718828	5	45	22
score_only	5.23063884755235	2.06424048728675	18.7577741779113	6.44141515375729e-05	2	45	22
score_grade(no batch)	5.36674793064093	1.56186509088657	25.4612543742466	0.00562762253253823	4	45	22
grade_batch(no score)	NA	NA	NA	NA	4	45	22

32 **Table S9c. Effective model degrees of freedom, both recurrence cohorts.** Recurrence model, n, events, grade/batch factor coding (grade reference WHO I; batch reference batch 1), and effective
33 model degrees of freedom (number of estimated coefficients: 4 for the GSE16581 score-plus-grade model; 5 for the GSE74385 score-plus-grade-plus-batch model). The complete table is reproduced
34 below.

cohort	recurrence model	n	events	grade coding	batch coding	estimated coefficients	effective model df
GSE16581	event ~ score + grade	68	10	factor (ref WHO I)	none	4	4
GSE74385	event ~ score + grade + batch	45	22	factor (ref WHO I)	factor (ref batch 1)	5	5

35 **Table S10. Patient-resolved tumor-cell metaprograms in lineage-filtered GSE206647 cells.** For each reproducible metaprogram recovered by cross-patient NMF clustering: member-patient count,
36 class, top signature genes, patient-level correlation with the program score (Spearman rho over the 15 NMF-eligible patients), the descriptive cell-level correlation, and patient-level WHO-grade
37 association (rho, p, and Benjamini–Hochberg FDR across the 12 metaprograms). Tables S10a and S10b are reproduced below.

38 **Table S10a. Metaprogram summary.**

metaprogram	class	n patients	Program rho (15 patients)	Program rho (cells; descriptive)	grade rho	Grade p value	Grade BH-FDR	Top genes
MP5	Proliferation (cell-cycle)	6	0.568	0.197	0.677	0.00393	0.0094	H2AFZ, HMGB2, NUSAP1, TOP2A, SMC4, TUBA1B, CKS1B, HMGN2, STMN1, UBE2C, H2AFV, TUBB, BIRC5, HIST1H4C, ARL6IP1, CENPF, CKS2, PTTG1, UBE2T, CDKN3
MP6	Immune-like	5	0.589	0.328	0.518	0.04	0.0735	CCL4, CCL4L2, CD74, HLA-DRA, HLA-DPA1, HLA-DRB1, IER3, CCL3, BTG1, CCL3L1, CXCL8, G0S2, HLA-DPB1, HLA-DQA1, IL1B, HLA-DRB5, MT2A, SPP1, PLAUR, SOD2
MP1	Other	15	0.029	0.122	0.243	0.365	0.4867	BTG2, NR4A1, KLF6, ATF3, KLF4, ZFP36, IRF1, EGR1, CEBPD, GADD45B, FOSB, NFKBIZ, IER2, NFKBIA, PPP1R15A, SOCS3, CCNL1, KLF2, JUNB, DUSP1
MP12	Other	3	0.204	0.264	0.07	0.796	0.8684	BAX, BBC3, BTG3, CDKN1A, DDB2, FDXR, GADD45A, GDF15, H1FX, MDM2, MEST, MMP2, NUPR1, PGF, PHLDA3, NINJ1, AEN, CAVIN2, HSPA1A, HSPA1B
MP3	Other	9	0.1	-0.067	-0.045	0.869	0.869	LDHA, SLPI, NDUFA4L2, FTH1, KRT18, FTL, GAPDH, IGFBP6, MT2A, WFDC2, MT1X, IGFBP3, CKB, GSN, PGK1, CAV1, TAGLN2, APOD, CEBPB, NUPR1
MP4	Other	8	-0.061	-0.219	-0.179	0.507	0.6084	CLIC3, NOV, NDUFA4L2, TNNC1, CRIP2, IGFBP6, SLPI, CCND1, CKB, CRABP2, SH3BGRL3, TAGLN2, ADIRF, C19orf33, S100A6, ASS1, EZR, CD177, KLF2, TUBA1B
MP9	Other	3	-0.089	-0.089	-0.409	0.116	0.174	ACTA2, MYL9, PERP, TAGLN, TPM1, TPM2, TPM4, ACTG2, CALD1, CSRP1, CTGF, GLIPR1, APOD, NPW, PDLIM7, APOC1, GPX4, LGALS1, ACTB, CNN1
MP8	Other	3	-0.589	-0.43	-0.511	0.0429	0.0735	CRABP1, SLC26A2, APOE, DNASE1L3, GJB6, IFI27, IFI27L2, ISYNA1, ITM2C, PTGDS, GJB2, PLTP, RETREG1, TMEM205, AKAP12, CLEC3B, DNPH1, FN1, FXYD1, ISLR
MP10	ECM/mesenchymal	3	-0.786	-0.409	-0.677	0.00393	0.0094	APOE, OGN, PTN, SPARCL1, IGFBP2, IGFBP6, CLU, CLDN11, APOD, GJB2, PTGDS, CLEC3B, CRABP1, ITM2A, ATP1A2, IFI27, ISLR, MGP, PLTP, RAMP2
MP7	ECM/mesenchymal	4	-0.729	-0.584	-0.697	0.00271	0.0094	CEMIP, COL3A1, SULF1,

metaprogram	class	n patients	Program rho (15 patients)	Program rho (cells; descriptive)	grade rho	Grade p value	Grade BH-FDR	Top genes
MP11	ECM/mesenchymal	3	-0.704	-0.482	-0.703	0.00238	0.0094	SLC26A2, NOV, CRIM1, LTBP2, NEAT1, SLC12A2, HLA-DRA, VCAN, CTGF, KIAA1324L, MT-ND6, ABLIM1, COL1A1, KCNQ1OT1, AHNAK, EGFL6, ITIH5
MP2	ECM/mesenchymal	10	-0.646	-0.491	-0.741	0.00101	0.0094	TNNT2, TNNC1, APOE, NOV, TAGLN, ADIRF, IFI27, OMD, SLC47A1, WNT6, CRABP2, FGL2, MYL9, SLC26A2, SLC4A4, CLDN11, FAM107A, ID1, CCND1, EPHX1
								IGFBP7, MGP, COL1A1, IFI27, IFI6, DCN, TIMP3, TIMP1, BGN, FBLN1, TAGLN, COL3A1, SFRP4, VCAN, MFAP4, GSN, PENK, SAT1, OLFML3, COL8A1

39 Table S10b. Per-patient lineage-filtering summary.

GEO sample	WHO grade	n pre	n post	removed pct	dropped
GSM7476436	Normal	319	273	14.4	FALSE
GSM7476437	Normal	1147	983	14.3	FALSE
GSM7476438	I	4485	3480	22.4	FALSE
GSM7476439	I	1895	1831	3.4	FALSE
GSM7476440	I	4412	3237	26.6	FALSE
GSM7476441	I	3942	2222	43.6	FALSE
GSM7476442	I	9542	8143	14.7	FALSE
GSM7476443	I	2530	1338	47.1	FALSE
GSM7476444	I	9088	6110	32.8	FALSE
GSM7476445	I	3310	1761	46.8	FALSE
GSM7476446	II	5650	5289	6.4	FALSE
GSM7476447	II	3962	3494	11.8	FALSE
GSM7476448	II	2181	1547	29.1	FALSE
GSM7476449	II	2620	2371	9.5	FALSE
GSM7476450	III	5607	4718	15.9	FALSE
GSM7476451	III	3611	3102	14.1	FALSE
GSM7476452	III	441	130	70.5	FALSE
GSM7476453	III	6975	6408	8.1	FALSE

40 **Table S11. Cohort characteristics.** Per-dataset assay/platform, role in the study, sample size, WHO-grade distribution, WHO edition/diagnostic era, central pathology-review status, recurrence
41 definition and event counts, follow-up availability, extent of resection, radiotherapy, Ki-67, histological subtype, molecular class, specimen status, processing batch and the covariates actually used,
42 with “not reported” stated explicitly where public metadata are silent. The complete table is reproduced below.

characteristic	GSE136661	GSE16581	GSE74385	GSE183655	GSE206647
assay_platform	RNA-seq (HTSeq counts)	Affymetrix microarray (GPL570)	Illumina microarray (GPL10558; illuminaHumanv4)	single-cell RNA-seq (10x)	single-cell RNA-seq (10x)
role_in_study	program definition (WHO I vs II primaries)	external recurrence-association cohort	external recurrence-association cohort (batch-adjusted)	single-cell architecture / CellChat	grade-stratified single-cell reproduction + metaprograms
n_samples	160 (Discovery 97, Validation 48, Recurrence 15)	68	62 (recurrence-only analysis 45; composite 54; 8 grade-III unknown-outcome excluded)	10 samples (63,628 QC cells)	16 tumors + 2 normal meninges (163,897 QC cells)
WHO_grade_distribution_I_II_III	I/II/III present (WHO I vs II used for definition)	43 / 19 / 6	20 / 14 / 28	not grade-stratified (6 tumors + dura/interface)	8 / 4 / 4 (tumors)
WHO_edition_or_diagnostic_era	reported by Patel et al. 2019 (pre-2021 WHO era)	earlier-era diagnoses (pre-2016 WHO); exact edition not reported	reported by Schmidt et al. era (pre-2021 WHO); exact edition not reported	Choudhury et al. 2022 (pre-2021/2021 WHO era)	Ke et al. 2024 (2021 WHO era)
central_pathology_review	not reported in public metadata	not reported	not reported	not reported	not reported
recurrence_definition	recurrence-cohort label provided (n=15); not used for association	binary recurrence status (clinical follow-up)	binary recurrence vs non-recurrence; malignant progression annotated separately	not applicable	not applicable (grade-stratified, no outcome labels)
recurrence_events	not used for association testing	10 (within grade I/II/III = 1 / 5 / 4)	22 (recurrence-only, n=45); composite 31/54	not applicable	not applicable
follow_up_availability	not reported	overall survival available; follow-up duration limited	outcome status available; time-to-event not provided	not applicable	not applicable
extent_of_resection	not reported	not reported	not reported	not reported	not reported
radiotherapy	not reported	not reported	not reported	not reported	not reported
Ki67	not reported	not reported	not reported	not reported	not reported
histological_subtype	not consistently reported	not consistently reported	not consistently reported	not consistently reported	not consistently reported
molecular_class	not reported	not reported	not reported	not reported	not reported
specimen_status	primary tumors (grade I/II used)	primary tumors	primary and recurrent tumors	fresh surgical tumor/dura/interface	fresh surgical tumor + normal meninges
processing_batch	cohort labels (Discovery/Validation/Recurrence)	not reported	processing batch recorded (batch 1 / batch 2); confounded with recurrence within WHO grade I (Table S12)	per-sample	per-sample (GSM)
available_covariates_used	WHO grade	WHO grade; overall survival	WHO grade; processing batch	cell type	WHO grade; cell type; S/G2M scores; library/ribo/mito content
reference	Patel et al. PNAS 2019 [2]	GSE16581 (GEO)	GSE74385 (GEO)	Choudhury et al. Nat Genet 2022 [4]	Ke et al. Neuro Oncol 2024 [9]

43 **Table S12. GSE74385 grade × batch × outcome contingency; GSE16581 within-grade recurrence counts are reported in this caption.** The grade-stratified processing-batch-by-outcome
44 distribution for GSE74385 shows that, within WHO grade I, all four recurrences fall in one processing batch and all thirteen non-recurrences in the other, so the grade-I recurrence signal is fully
45 confounded by batch and is used only as hypothesis-generating. The table reproduced below contains the GSE74385 contingency counts only. For contextual comparison, GSE16581 recurrence
46 events were distributed within grade as 1/5/4 across WHO grades I/II/III (10 events total).

WHO grade		batch	outcome	Count
1	1		MalignantProgression	3
1	1		NonRecur	13
1	2		Recurrent	4
2	1		MalignantProgression	4
2	1		NonRecur	2
2	1		Recurrent	2
2	2		MalignantProgression	2
2	2		NonRecur	4
3	1		NonRecur	4
3	1		Recurrent	16

47 **Table S13. Per-patient single-cell filtering and analysis eligibility.** For every GSE206647 tumor, the number of tumor/tumor-like cells before and after lineage-marker exclusion (removal fraction
 48 3.4–70.5%), NMF eligibility (≥ 200 lineage-filtered cells; 15/16 eligible, GSM7476452 excluded), CopyKAT-aneuploid count and eligibility (≥ 10 aneuploid cells; 15/16 eligible, GSM7476445
 49 excluded — a different patient), and the balanced-pseudobulk aneuploid fraction (as in Table S6). The complete table is reproduced below. The primary metaprogram-construction settings were NMF
 50 rank range $k=4-9$, a minimum of three member patients per reproducible metaprogram, and average-linkage Jaccard clustering at cut height 0.90. Robustness to these choices was assessed by a
 51 factorial sensitivity analysis over 27 settings — NMF rank ranges 3–8, 4–9 and 5–10, minimum recurrence of 2, 3 or 4 patients, and clustering cut heights 0.85, 0.90 and 0.95 (Table S13d) — and the
 52 cell-cycle metaprogram signature was additionally recovered under a more stringent lineage-exclusion rule (Jaccard overlap 0.82).

GEO sample	WHO grade	n tumor pre filter	n tumor post filter	lineage removed pct	NMF eligible (≥ 200 cells)	n copykat aneuploid	CopyKAT eligible (≥ 10 cells)	aneuploid fraction balanced pseudobulk
GSM7476438	I	4485	3480	22.4	TRUE	1441	TRUE	0.983
GSM7476439	I	1895	1831	3.4	TRUE	1280	TRUE	0.9
GSM7476440	I	4412	3237	26.6	TRUE	997	TRUE	0.724
GSM7476441	I	3942	2222	43.6	TRUE	1005	TRUE	0.803
GSM7476442	I	9542	8143	14.7	TRUE	1023	TRUE	0.756
GSM7476443	I	2530	1338	47.1	TRUE	1291	TRUE	0.937
GSM7476444	I	9088	6110	32.8	TRUE	1343	TRUE	0.958
GSM7476445	I	3310	1761	46.8	TRUE	0	FALSE	0
GSM7476446	II	5650	5289	6.4	TRUE	955	TRUE	0.709
GSM7476447	II	3962	3494	11.8	TRUE	1414	TRUE	0.954
GSM7476448	II	2181	1547	29.1	TRUE	1071	TRUE	0.745
GSM7476449	II	2620	2371	9.5	TRUE	1410	TRUE	0.951
GSM7476450	III	5607	4718	15.9	TRUE	1204	TRUE	0.887
GSM7476451	III	3611	3102	14.1	TRUE	1506	TRUE	0.964
GSM7476452	III	441	130	70.5	FALSE	329	TRUE	0.576
GSM7476453	III	6975	6408	8.1	TRUE	1484	TRUE	0.968

53 **Table S13b. GSE74385 program-size sensitivity.** Program-size dependence of the GSE74385 recurrence-only retrospective AUC, increasing monotonically from 0.77 at 50 genes to 0.87 at 500
54 genes. The complete table is reproduced below.

size	n up	n down	n	events	recurrence auc	grade spearman
50	22	23	45	22	0.768774703557312	0.59330901011512
100	41	48	45	22	0.778656126482213	0.622041993974862
200	86	97	45	22	0.839920948616601	0.649636501115632
300	118	144	45	22	0.847826086956522	0.707265108366397
500	184	230	45	22	0.865612648221344	0.691651713363368

55 **Table S13c. Up/down component decomposition.** Separate scoring of the 100 up- and 100 down-program genes in GSE136661 (VST bulk) and in the GSE206647 tumor-cell pseudobulk. Both
 56 components track WHO grade (GSE136661 |Spearman rho|: up 0.63, down 0.58; GSE206647: up 0.88, down 0.58), and at the patient level the summed-count tumor-cell pseudobulk composite is
 57 more strongly anticorrelated with ECM/mesenchymal metaprograms (rho −0.63 to −0.68) than correlated with the cell-cycle metaprogram (rho +0.49), supporting the neutral description of the axis as
 58 proliferation-associated and ECM/mesenchymal-down rather than proliferation-dominated. This pseudobulk-composite correlation is distinct from the rho=0.57 obtained from per-cell
 59 AddModuleScore values averaged within patient in Table S10. The summary statistics are reproduced below; the complete 176-row per-sample decomposition is provided in the accompanying
 60 supplementary table workbook (worksheet “Table S13c”).

analysis	Component or metaprogram	variance	Spearman rho	comparison
GSE136661 VST bulk	Up component	0.291	0.628	WHO grade
GSE136661 VST bulk	Down component	0.373	-0.577	WHO grade
GSE136661 VST bulk	Composite score	1.146	0.648	WHO grade
GSE206647 tumor-cell pseudobulk	Up component	0.260	0.882	WHO grade
GSE206647 tumor-cell pseudobulk	Down component	0.254	-0.575	WHO grade
GSE206647 tumor-cell pseudobulk	Composite score	0.773	0.869	WHO grade
GSE206647 patient-level metaprograms	Cell-cycle MP5		0.489	Composite score
GSE206647 patient-level metaprograms	ECM/mesenchymal MP2		-0.625	Composite score
GSE206647 patient-level metaprograms	ECM/mesenchymal MP7		-0.682	Composite score
GSE206647 patient-level metaprograms	ECM/mesenchymal MP10		-0.679	Composite score

61 **Table S13d. Metaprogram-construction factorial sensitivity analysis.** For each of the 27 parameter settings (NMF rank range 3–8/4–9/5–10 × minimum 2/3/4 recurrent patients × clustering cut
62 height 0.85/0.90/0.95), the number of retained metaprograms, the proliferation metaprogram’s patient recovery, its Jaccard overlap with the reported MP5 signature, and its patient-level WHO-grade
63 Spearman rho, p and BH-FDR. The proliferation metaprogram was recovered in all 27 settings with an identical primary signature (Jaccard 1.00 versus the reported MP5); its patient-level grade
64 association was identical across all 27 settings (Spearman rho=0.68, reproducing the Table S10 value of 0.677) and survived Benjamini–Hochberg correction in all 27 settings. Each signature was
65 scored independently with a fixed seed, so the value does not depend on module ordering; the BH-FDR differs slightly from Table S10 (0.021 vs 0.009) only because it is corrected within each
66 setting’s own metaprogram set rather than the 12 canonical metaprograms. The complete table is reproduced below.

setting id	rank range	Minimum recurrent patients	Clustering cut height	Retained metaprograms	Proliferation recovery patients	Proliferation signature genes	Jaccard vs primary MP5	Grade Spearman rho	Grade p value	Grade BH-FDR	BH-FDR <0.05	Top genes
S01	3-8	2	0.85	22	6	50	1	0.68	0.00526	0.01929	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S02	3-8	3	0.85	13	6	50	1	0.68	0.00526	0.02279	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S03	3-8	4	0.85	5	6	50	1	0.68	0.00526	0.01315	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S04	3-8	2	0.9	16	6	50	1	0.68	0.00526	0.01608	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S05	3-8	3	0.9	13	6	50	1	0.68	0.00526	0.01568	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S06	3-8	4	0.9	8	6	50	1	0.68	0.00526	0.01403	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S07	3-8	2	0.95	7	6	50	1	0.68	0.00526	0.01227	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S08	3-8	3	0.95	7	6	50	1	0.68	0.00526	0.01227	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S09	3-8	4	0.95	5	6	50	1	0.68	0.00526	0.008767	TRUE	H2AFZ,HMGB2;NUS AP1;CKS1B;TOP2A; HMG2;SMC4;TUB A1B;UBE2C;STMN1
S10	4-9	2	0.85	24	6	50	1	0.68	0.00526	0.02104	TRUE	H2AFZ,HMGB2;NUS AP1;TOP2A;SMC4;T UBA1B;CKS1B;HM GN2;STMN1;UBE2C
S11	4-9	3	0.85	13	6	50	1	0.68	0.00526	0.03419	TRUE	H2AFZ,HMGB2;NUS AP1;TOP2A;SMC4;T UBA1B;CKS1B;HM GN2;STMN1;UBE2C
S12	4-9	4	0.85	6	6	50	1	0.68	0.00526	0.01578	TRUE	H2AFZ,HMGB2;NUS AP1;TOP2A;SMC4;T UBA1B;CKS1B;HM GN2;STMN1;UBE2C
S13	4-9	2	0.9	19	6	50	1	0.68	0.00526	0.01428	TRUE	H2AFZ,HMGB2;NUS AP1;TOP2A;SMC4;T UBA1B;CKS1B;HM GN2;STMN1;UBE2C
S14	4-9	3	0.9	12	6	50	1	0.68	0.00526	0.02104	TRUE	H2AFZ,HMGB2;NUS AP1;TOP2A;SMC4;T UBA1B;CKS1B;HM GN2;STMN1;UBE2C
S15	4-9	4	0.9	7	6	50	1	0.68	0.00526	0.01227	TRUE	H2AFZ,HMGB2;NUS AP1;TOP2A;SMC4;T UBA1B;CKS1B;HM GN2;STMN1;UBE2C
S16	4-9	2	0.95	7	6	50	1	0.68	0.00526	0.01315	TRUE	H2AFZ,HMGB2;NUS

setting id	rank range	Minimum recurrent patients	Clustering cut height	Retained metaprograms	Proliferation recovery patients	Proliferation signature genes	Jaccard vs primary MP5	Grade Spearman rho	Grade p value	Grade BH-FDR	BH-FDR <0.05	Top genes
S17	4-9	3	0.95	7	6	50	1	0.68	0.00526	0.01315	TRUE	API1;TOP2A;SMC4;TUBA1B;CKS1B;HMGN2;STMN1;UBE2C
S18	4-9	4	0.95	5	6	50	1	0.68	0.00526	0.009391	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;SMC4;TUBA1B;CKS1B;HMGN2;STMN1;UBE2C
S19	5-10	2	0.85	25	6	50	1	0.68	0.00526	0.02192	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S20	5-10	3	0.85	10	6	50	1	0.68	0.00526	0.01753	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S21	5-10	4	0.85	7	6	50	1	0.68	0.00526	0.01841	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S22	5-10	2	0.9	21	6	50	1	0.68	0.00526	0.01578	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S23	5-10	3	0.9	14	6	50	1	0.68	0.00526	0.01473	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S24	5-10	4	0.9	10	6	50	1	0.68	0.00526	0.0263	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S25	5-10	2	0.95	8	6	50	1	0.68	0.00526	0.01403	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S26	5-10	3	0.95	8	6	50	1	0.68	0.00526	0.01403	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C
S27	5-10	4	0.95	6	6	50	1	0.68	0.00526	0.01578	TRUE	H2AFZ;HMGB2;NUSAPI1;TOP2A;HMG2N2;TUBA1B;SMC4;STMN1;CKS1B;UBE2C

Supplementary Results: scoring and signature sensitivity. Restricting the program to the fixed 139-gene common-platform subset yielded retrospective recurrence AUCs of 0.962 in GSE16581 and 0.812 in the GSE74385 recurrence-only comparison; within-sample rank scoring yielded 0.966 and 0.818, respectively. In the signature benchmark, the program exceeded a size-matched random null in GSE16581 (AUC 0.96 vs null mean 0.49, empirical $p < 0.001$) and known-outcome GSE74385 (0.78 vs 0.54, $p = 0.009$), and exceeded a generic OXPHOS signature (0.82/0.63). Relative to a canonical proliferation signature, the program was higher in GSE16581 (0.96 vs 0.86) but slightly lower in GSE74385 (0.78 vs 0.81). These are retrospective outcome-group discrimination estimates, not clinical prediction performance.

Supplementary Methods and Results: Geneformer representation benchmark. Geneformer V2-104M was applied in zero-shot mode to a grade-balanced subsample of 1,800 GSE206647 tumor/tumor-like cells (600 per WHO grade) from 16 patients. All inference kept patient labels intact. In the primary patient-mean-embedding PCA, the best top-10 component was PC2 (rho with grade = -0.684; rho with patient program score = -0.665), with a 100,000-iteration patient-label permutation $p = 0.0516$. A complementary cell-PCA-then-patient-mean analysis yielded PC4 (rho with grade = -0.856; rho with program score = -0.688; $p = 0.00070$), demonstrating aggregation-order sensitivity. Repeated nested leave-one-patient-out discrimination was descriptively high for both Geneformer embeddings (mean AUC 0.977) and program-gene expression (0.992), but their paired difference was uncertain (classical minus Geneformer -0.016; patient-bootstrap 95% CI -0.094 to 0.000). The benchmark therefore does not establish Geneformer superiority or generalizability (Supplementary Fig. S4).

Supplementary Methods and Results: exploratory drug-signature reversal. The fixed program (73 symbol-resolved up genes and 95 symbol-resolved down genes after excluding unresolved Ensembl-only and antisense entries) was queried against the official L1000FWD drug-perturbation resource [26]. We retained the 50 opposing signatures and restricted translational review to marketed or clinically exposed compounds; L1000 scores were treated as hypothesis-generating because all returned profiles were generated in non-meningioma cell lines, and drug prioritization required convergence between present-signature reversal, plausible clinical status and independent meningioma experimental literature (no docking score was used). L1000FWD returned 50 opposing

signatures representing 49 perturbagens after treating the database missing-value code -666 as unresolved rather than a compound. The strongest identifiable clinically exposed hits were the topoisomerase-II poisons etoposide and amsacrine (score -0.120 ; one MCF7 signature each), not prioritized because their signal was confined to one non-meningioma cell line, likely reflects broad cytotoxic transcriptional effects, and meningioma cultures contain stem-like populations surviving etoposide exposure [28]. Retinoic acid produced a weaker opposing signature (rank 43/50; score -0.087 ; one MCF7 6-h profile) but had orthogonal meningioma-specific evidence, having reduced invasion and migration while increasing extracellular-matrix adhesion in cultured meningioma cells [29]; it was therefore nominated only as a literature-supported, experimentally testable hypothesis, not as an efficacy prediction. Itraconazole and perhexiline remained exploratory single-cell-line hits without direct meningioma validation; hormonal hits (estradiol benzoate, danazol, norethindrone, oxymetholone) and immunosuppressive cyclosporin were excluded on biological/safety grounds. None of the clinically better-supported meningioma agents reviewed separately (brigatinib, abemaciclib, panobinostat, mifepristone or verteporfin) appeared among the top 50 opposing perturbations, arguing against post-hoc promotion of these agents as program reversers (Table S4).

Supplementary Methods and Results: proliferation-adjusted enrichment. To test whether the higher-grade enrichment of oxidative-phosphorylation and ribosome-biogenesis transcripts is a cell-cycle artefact, the WHO II-versus-I contrast in GSE136661 was recomputed with a per-sample cell-cycle score as a covariate and gene-set enrichment re-run. The oxidative-phosphorylation, aerobic-respiration, electron-transport and ribosome-biogenesis enrichment persisted after adjustment (core-term mean normalized enrichment score $2.48 \rightarrow 2.67$; 14 of 16 core terms remained significant at Benjamini-Hochberg $FDR < 0.05$), indicating that the enrichment is not explained solely by proliferation; transcript-level enrichment nonetheless does not by itself indicate increased oxidative flux and is interpreted as a transcriptional program rather than a metabolic phenotype.

Supplementary Methods and Results: PI3 and PITX1 cross-cell-type distribution. Expression of the two nominated candidate transcripts across the six annotated GSE206647 cell types was computed from the raw 10x matrices and the per-cell annotation. *PI3* (elafin) transcripts were concentrated in the tumor/tumor-like compartment (89.6% of all *PI3* counts; highest mean log-normalized expression among cell types) but were detected in only 5.7% of tumor cells, so a contribution from ambient RNA or a minor secretory subpopulation cannot be excluded; *PITX1* was more broadly detected within tumor cells (96.5% of counts; 19.0% of cells). Both are presented as grade-associated candidate transcripts for orthogonal tissue validation.

Figure S1

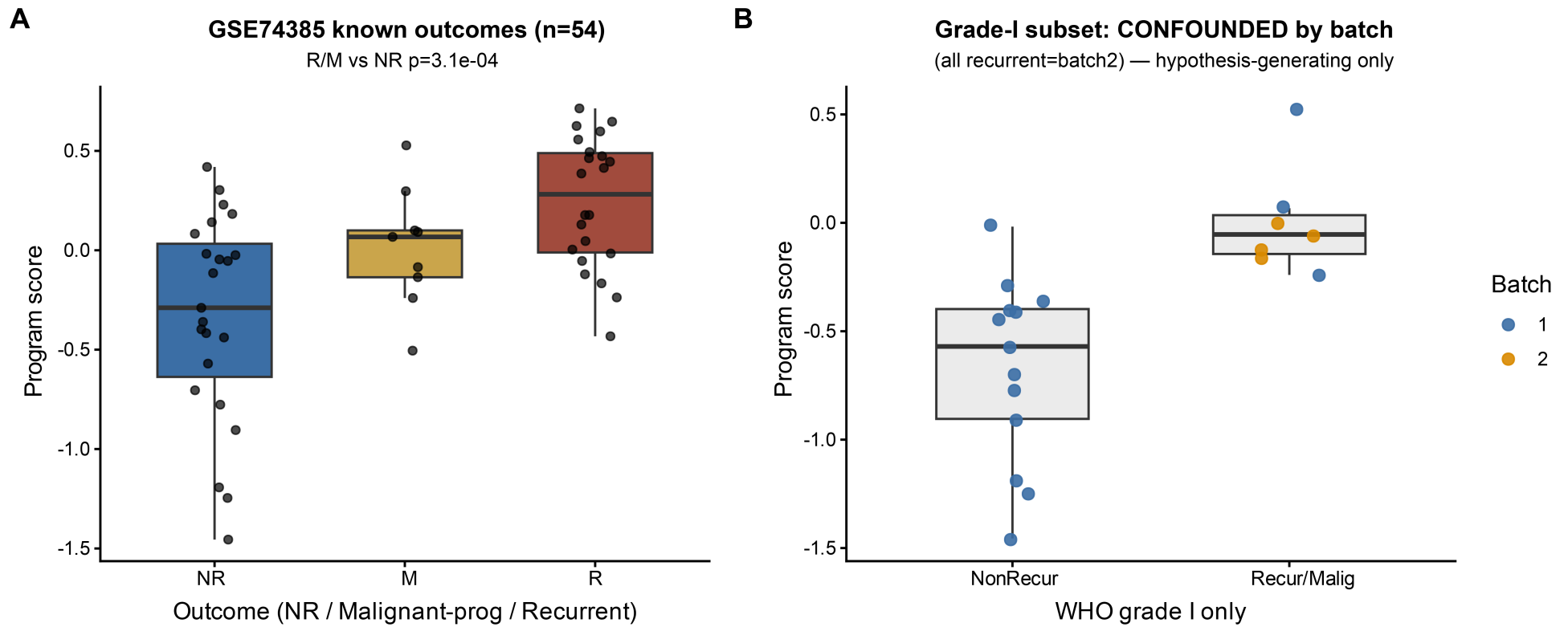


Figure S1. GSE74385 outcome and grade-I batch-confounding overview. (A) Program scores across non-recurrent, malignant-progression, and recurrent tumors with known outcome. (B) Within WHO grade I, recurrence status is fully confounded by processing batch; all grade-I recurrences are batch 2, whereas the malignant-progression cases in the Recur/Malig group are batch 1. This panel is descriptive and hypothesis-generating only.

Figure S2

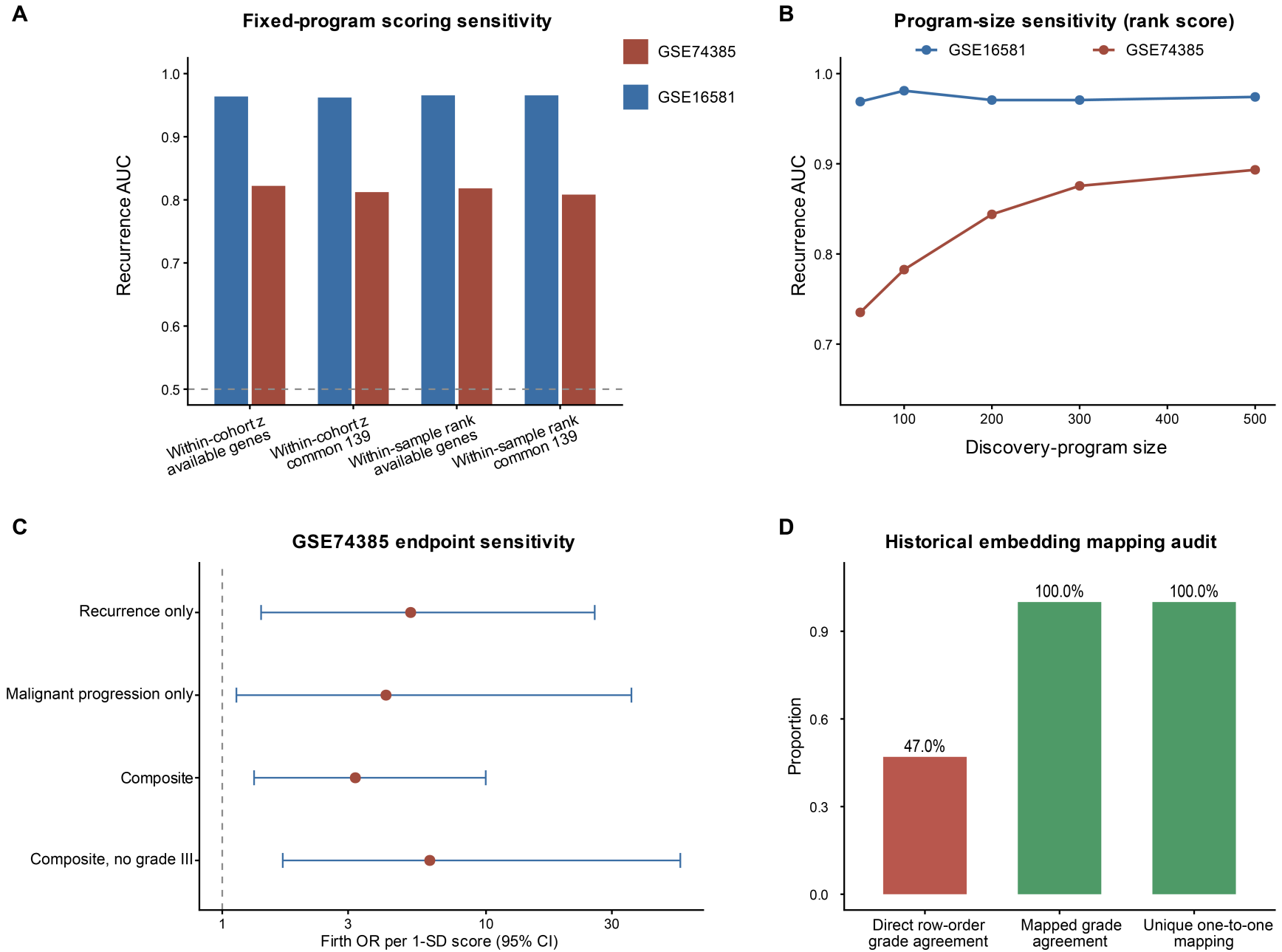


Figure S2. Scoring, program-size, endpoint, and historical-mapping sensitivity analyses. (A) Fixed-program scoring using cohort-available genes, the fixed 139-gene common-platform subset, and within-sample rank scoring. (B) Dependence of retrospective recurrence AUC on discovery-program size using the within-sample rank score. (C) GSE74385 endpoint sensitivity across recurrence-only, malignant-progression-only, composite, and grade-restricted specifications. (D) Audit of the historical embedding-to-patient mapping; this audit is provenance context and not independent biological validation.

Figure S3

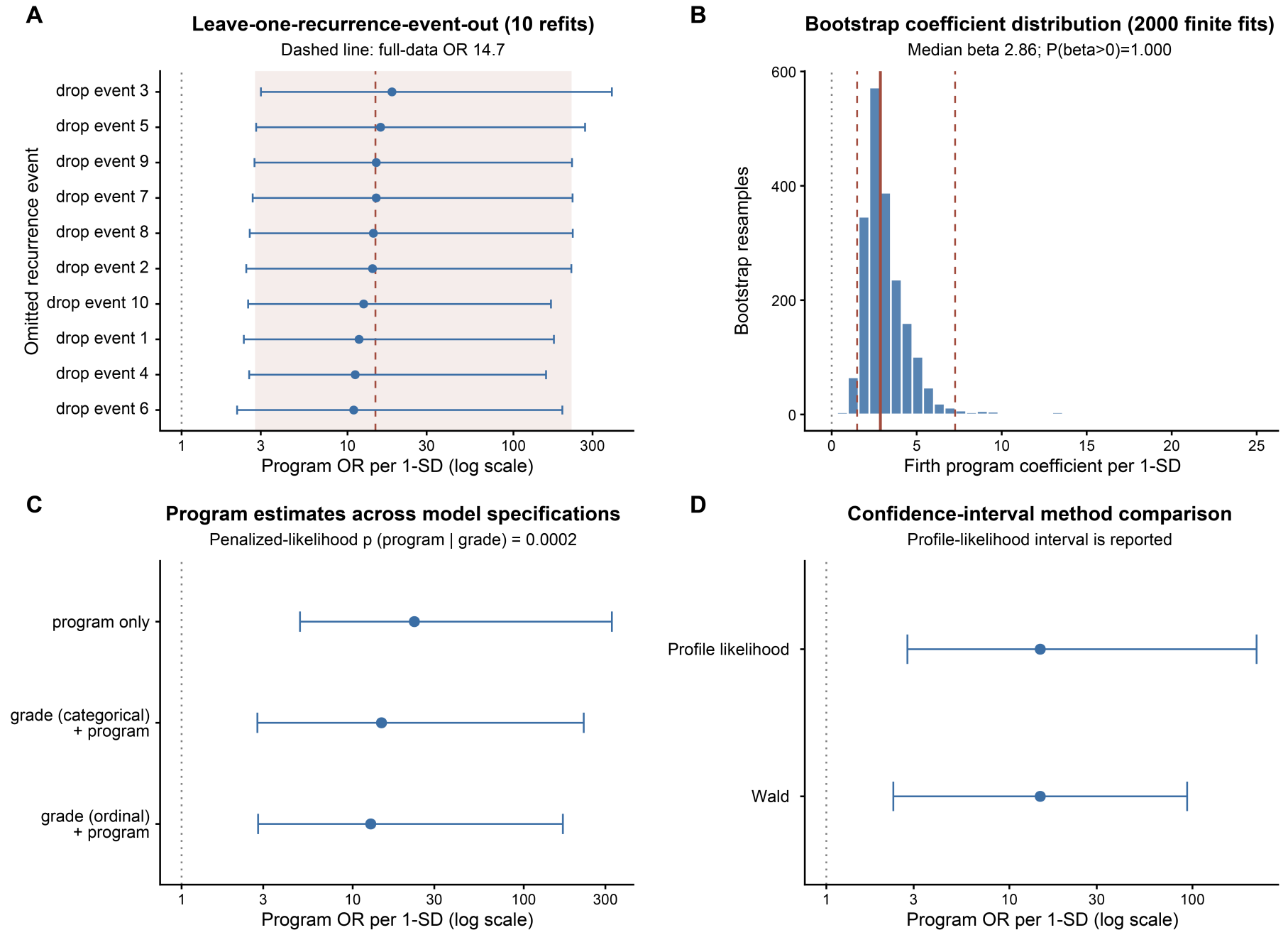


Figure S3. GSE16581 rare-event Firth stability analysis. (A) Leave-one-recurrence-event-out estimates. (B) Distribution of 2,000 bootstrap coefficients. (C) Program estimates across model specifications. (D) Profile-likelihood versus Wald confidence intervals. The resampling supports a consistently positive association direction but substantial uncertainty in effect magnitude.

Figure S4

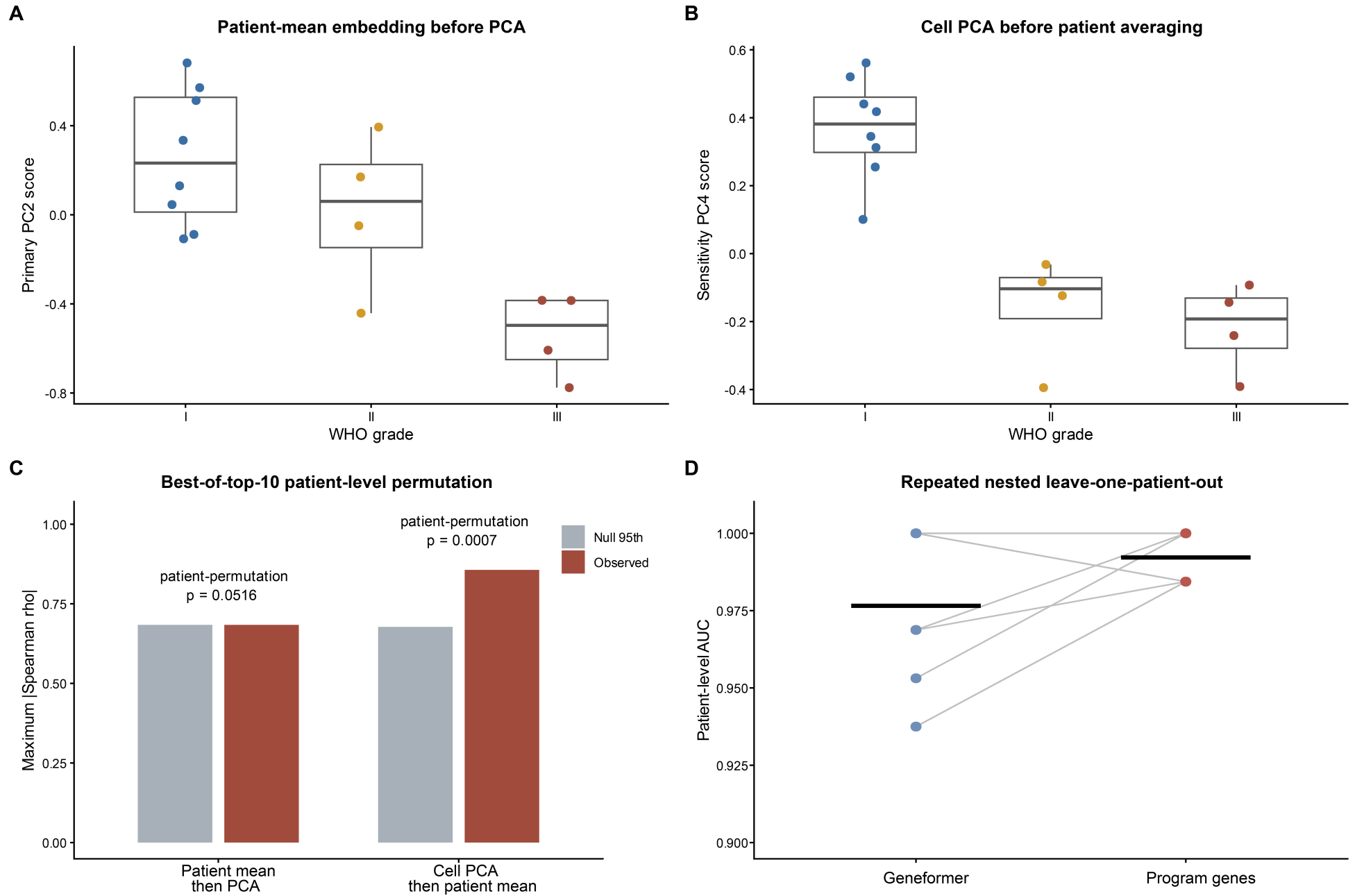


Figure S4. Secondary patient-level Geneformer representation benchmark. (A) Patient-mean embedding before principal-component analysis. (B) Cell-level principal-component analysis before patient averaging. (C) Patient-label permutation analysis for the best of the top 10 components under both aggregation orders. (D) Repeated nested leave-one-patient-out comparison of Geneformer and program-gene expression. The aggregation-order sensitivity and paired uncertainty do not establish Geneformer superiority or external generalizability.

Figure S5

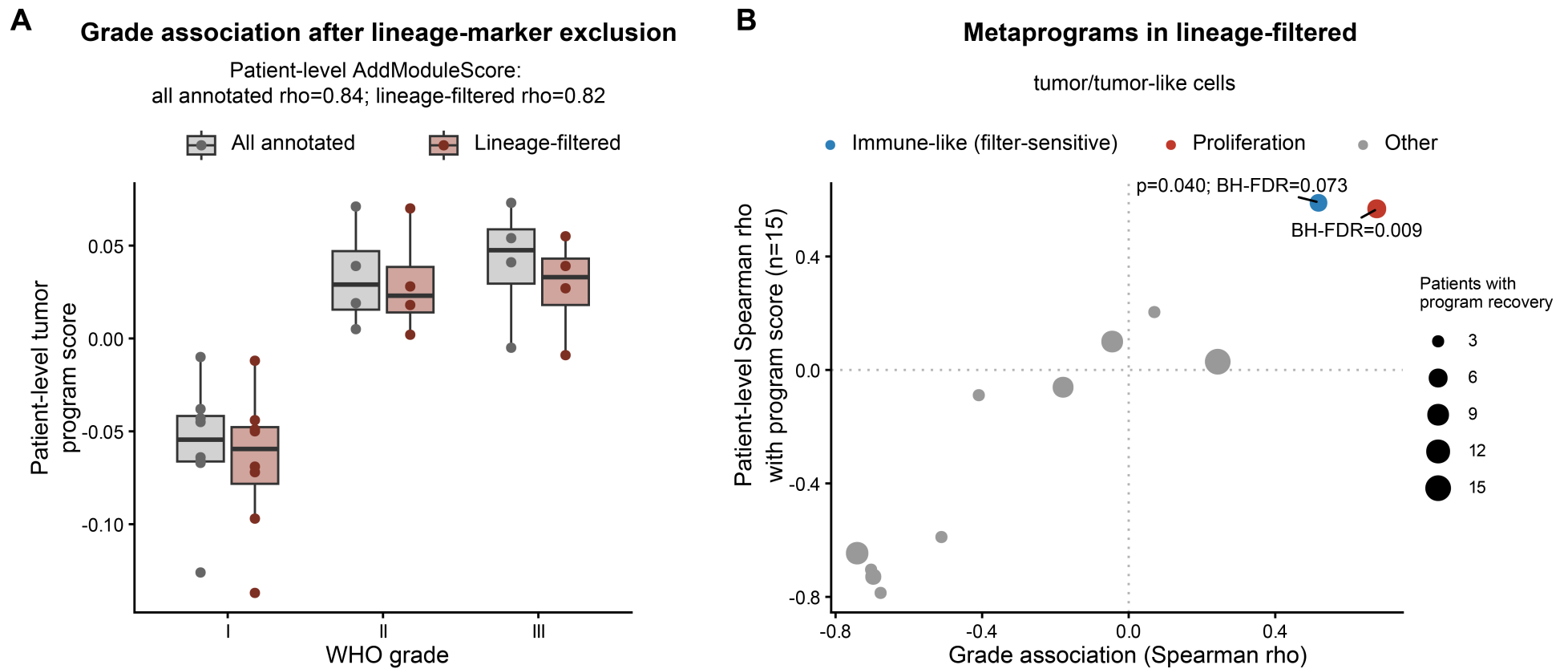


Figure S5. Lineage-marker exclusion sensitivity analysis and tumor-cell metaprograms (GSE206647). (A) Per-patient tumor-cell program score by WHO grade before and after excluding cells expressing canonical non-tumor lineage markers (21% of tumor-annotated cells removed; per-patient score by AddModuleScore); the grade association is preserved (Spearman rho 0.84→0.82, and the primary summed-count pseudobulk score changed from 0.87 to 0.83). (B) Reproducible cross-patient metaprograms of the lineage-filtered tumor/tumor-like cells, plotted by WHO-grade association (Spearman rho) versus patient-level correlation with the program score (Spearman rho over the 15 NMF-eligible patients). The cell-cycle metaprogram is the only positively grade-associated program surviving Benjamini–Hochberg correction (BH-FDR=0.009); a nominally positive immune-like program ($p=0.040$) did not survive correction (BH-FDR=0.073) and was sensitive to the exclusion rule. Present evidence cannot distinguish this immune-like signal from residual admixture, ambient RNA, or a tumor-intrinsic inflammatory state. Source files as in Table S10.