Supplementary Information

Published gastric cancer extracellular matrix prognostic signatures converge on a shared core-matrisome axis associated with molecular subtype

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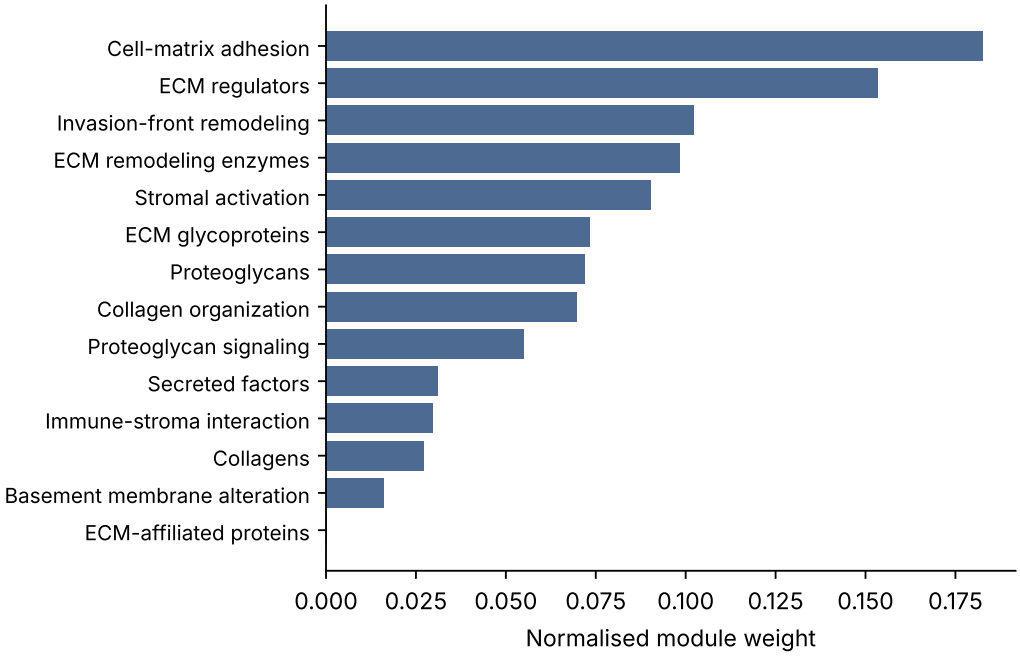
The following results use the construction panel of 995 genes measured in TCGA-STAD and GSE84437, on which the weights were estimated, or report diagnostics of the main models; they complement the common-panel results in the main text. On the construction panel the prior had concordance 0.563 in TCGA-STAD and 0.570 in GSE84437 (HR 1.269, 1.102–1.461), with a paired difference from the core average in GSE84437 of -0.0001 (-0.012–0.012). Internal validation gave mean test-fold concordances of 0.565 and 0.573 for patient and site-held-out splits, and the matched random-gene tail probabilities were 0.0010 in TCGA-STAD and 0.0030 in GSE84437.

Supplementary Table S1: Tumour–normal comparisons using a common gene-standardization reference within each dataset. TCGA Welch comparisons use 355 tumours and 36 normals from disjoint patient groups; paired sensitivity uses 32 matched patients. GSE26942 averages repeated inferred patient/tissue profiles before group testing. Paired p-values are unadjusted sensitivity results.

Module	STAD Δ	STAD q	Paired p	GSE Δ	GSE q
Basement membrane alteration	0.614	< 0.0001	0.0093	0.070	0.2982
Cell-matrix adhesion	0.902	< 0.0001	0.0011	0.488	0.0178
Collagen organization	0.682	< 0.0001	0.0009	0.205	0.0331
ECM remodeling enzymes	0.506	< 0.0001	< 0.0001	0.273	0.0015
Immune-stroma interaction	0.551	< 0.0001	< 0.0001	0.165	0.0622
Invasion-front remodeling	0.627	< 0.0001	< 0.0001	0.225	0.0070
Proteoglycan signaling	0.537	< 0.0001	0.0398	0.206	0.1160
Stromal activation	0.729	< 0.0001	0.0011	0.242	0.0622
Collagens	0.573	< 0.0001	0.0073	0.181	0.0622
ECM-affiliated proteins	0.279	< 0.0001	0.0011	0.129	0.0248
ECM glycoproteins	0.285	0.0022	0.1572	0.154	0.0752
ECM regulators	0.419	< 0.0001	< 0.0001	0.190	0.0012
Proteoglycans	0.306	0.0013	0.2810	0.201	0.0070
Secreted factors	0.232	< 0.0001	0.0111	0.227	0.0002

Supplementary Table S2: Frozen common-platform gene panel, evidence components and normalized weights. The eight process-oriented modules are heuristic gene-symbol groupings, not independently validated pathway measurements.

Module	Original	Panel	S_{diff}	S_{surv}	S_{prot}	Weight
Cell-matrix adhesion	10	10	0.991	0.748	0.800	0.183
ECM regulators	238	235	0.511	1.000	0.703	0.153
Invasion-front remodeling	91	90	0.858	0.455	0.728	0.102
ECM remodeling enzymes	115	113	0.669	0.590	0.697	0.098
Stromal activation	24	24	0.764	0.455	0.729	0.090
ECM glycoproteins	196	188	0.000	0.920	0.715	0.073
Proteoglycans	35	35	0.021	0.938	0.657	0.072
Collagen organization	61	60	0.616	0.453	0.725	0.070
Proteoglycan signaling	19	19	0.284	0.517	0.855	0.055
Secreted factors	343	334	0.057	0.708	0.630	0.031
Immune-stroma interaction	83	81	1.000	0.000	0.669	0.030
Collagens	44	43	0.357	0.430	0.692	0.027
Basement membrane alteration	24	24	0.372	0.294	0.781	0.016
ECM-affiliated proteins	170	160	0.128	0.423	0.721	0.000



Supplementary Fig. S1: Evidence weights of the fourteen modules after normalisation to sum to one.

Supplementary Table S3: Concordance of the frozen prior and prespecified literature comparators. A dash means that a required gene was absent; proxies and reconstructions are not exact reproductions of their source pipelines.

Score	STAD	GSE84437	GSE62254
Evidence prior	0.560	0.570	0.578
Equal modules	0.558	0.566	0.579
Differential + HPA	0.557	0.567	0.576
Matrisome average	0.561	0.545	0.560
Core average	0.567	0.570	0.593
Xu coefficient	0.587	0.502	0.592
Xu z-mean	0.602	0.569	0.602
Yang 2020 coefficient	0.598	–	–
Yang 2020 z-mean	0.584	–	–
Deng coefficient	0.578	0.586	0.689
Deng signed z-mean	0.563	0.556	0.682
Yuzhalin z-mean	0.531	0.576	0.561
Yang 2021 GSVA reconstruction	0.552	0.588	0.582

Supplementary Table S4: Dominant axis of the fourteen reduced-panel module activities. PCA used the survival-analysis sample and did not use outcomes to estimate the axis. PC1 was oriented to correlate positively with the core-matrisome average. Correlations are Spearman coefficients.

Cohort	n	PC1 variance	core–PC1	prior–PC1
STAD	387	0.844	0.964	0.989
GSE84437	431	0.773	0.912	0.956
GSE62254	300	0.699	0.935	0.969

Supplementary Table S5: Alignment of each frozen score with the core-matrisome average and its conditional prognostic information. ρ is the Spearman correlation with the core average in the survival-analysis sample; q is the Benjamini–Hochberg adjusted likelihood-ratio p for adding the score to an unpenalized Cox model that already contains the core average. A dagger marks a cohort used to develop or validate that score in its source publication; a dash marks an unavailable formula.

	STAD		GSE84437		GSE62254	
Score	ρ	q	ρ	q	ρ	q
Evidence prior	0.96	0.94	0.95	0.84	0.92	0.52
Equal modules	0.96	0.67	0.96	0.78	0.94	0.30
Differential + HPA	0.95	0.67	0.95	0.85	0.93	0.30
Matrisome average	0.96	0.60	0.90	0.099	0.87	0.21
Xu coefficient	0.85	0.022†	0.42	0.56	0.68	0.21
Xu z-mean	0.87	3.2e-04†	0.77	0.56	0.78	0.16
Yang 2020 coefficient	0.82	0.0052†	–	–	–	–
Yang 2020 z-mean	0.91	0.014†	–	–	–	–
Deng coefficient	0.54	0.22†	0.46	0.022	0.47	3.2e-10†
Deng signed z-mean	0.38	0.22†	0.33	0.21	0.37	2.1e-09†
Yuzhalin z-mean	0.68	0.84	0.54	0.22	0.64	0.78
Yang 2021 GSVA reconstruction	0.77	0.84	0.76	0.053	0.96	0.56

Supplementary Table S6: Conditional information beyond the core-matrisome average in the structured signature benchmark. Entries are passing pairs over evaluable signature–cohort pairs, with Wilson 95% intervals. Fisher tests are descriptive because pairs sharing a signature or cohort are dependent. The coefficient sensitivity uses only pairs in which every required gene was measured; the Benjamini–Hochberg family is the coefficient pairs.

Analysis	Source overlap	Source independent	Fisher p
Primary signed/unsigned z-mean	6/16 (0.18–0.61)	1/11 (0.02–0.38)	0.18
Clinical-covariate sensitivity	5/16 (0.14–0.56)	2/11 (0.05–0.48)	0.66
Published-coefficient sensitivity	7/11 (0.35–0.85)	2/7 (0.08–0.64)	0.33

Supplementary Table S7: Matched-signature null for the three external exceptions: the Deng coefficient score and Xu z-mean, which added information beyond the core average among the nearest literature comparators, and, marked †, the Wang 2023 signed z-mean, the only source-independent pair passing the structured benchmark. All three nulls were specified after the conditional results were observed. Each empirical tail probability compares the observed likelihood-ratio statistic with 1,000 outcome-blind matched gene replacements preserving signature size, formula, coefficient signs/weights, matrisome membership and expression mean/SD neighbourhood. This is a conditional sensitivity analysis, not a confirmatory test.

Cohort	Signature	Model	n/events	LRT statistic	asymptotic p	matched-null p
GSE84437	Deng coefficient	core	431/207	8.04	0.0046	0.058
GSE84437	Deng coefficient	clinical + core	431/207	8.33	0.0039	0.015
GSE62254	Xu z-mean	core	300/152	3.80	0.051	0.182
GSE62254	Xu z-mean	clinical + core	298/152	6.86	0.0088	0.049
GSE62254	Wang 2023 signed z-mean†	core	300/152	14.85	0.0001	0.019
GSE62254	Wang 2023 signed z-mean†	clinical + core	298/152	12.83	0.0003	0.021

Supplementary Table S8: STAD sensitivity to orthogonal DNA-based tumour purity and methylation-derived leukocyte fraction. All models retain the clinical covariates; intervals for ΔC use 1,000 fixed-risk patient bootstraps.

Score	Adjustment	n/events	HR (95% CI)	LRT p	ΔC	95% CI
Evidence prior	clinical	370/150	1.307 (1.106–1.545)	0.0017	0.012	-0.012–0.039
Evidence prior	clinical+purity	356/143	1.271 (1.059–1.526)	0.0099	0.007	-0.015–0.029
Evidence prior	clinical+purity+leukocyte fraction	356/143	1.264 (1.052–1.519)	0.012	0.004	-0.017–0.025
Core average	clinical	370/150	1.338 (1.134–1.579)	6.1e-04	0.018	-0.008–0.047
Core average	clinical+purity	356/143	1.307 (1.089–1.569)	0.0043	0.012	-0.011–0.037
Core average	clinical+purity+leukocyte fraction	356/143	1.290 (1.073–1.551)	0.0069	0.007	-0.015–0.028

Supplementary Table S9: Association after adjustment for molecular subtype. Subtypes are Pan-CanAtlas CIN, GS, EBV and hypermutated (MSI with POLE) in STAD, and ACRG MSS/TP53−, MSS/TP53+, MSI and EMT in GSE62254. Hazard ratios are per score SD; LRT compares models with and without the score on identical complete cases. ΔC is apparent, with 1,000 fixed-risk patient bootstraps. STAD rows are descriptive because the prior weights used STAD outcomes.

Cohort	Score	Model	n/events	HR (95% CI)	LRT p	ΔC (95% CI)
STAD	Evidence prior	clinical + subtype	343/136	1.281 (1.075–1.526)	0.0057	0.006 (-0.015–0.027)
STAD	Evidence prior	subtype only	358/146	1.299 (1.097–1.538)	0.0023	0.027 (-0.024–0.081)
STAD	Evidence prior	clinical + subtype, GS excluded	297/117	1.207 (1.004–1.452)	0.046	0.002 (-0.018–0.023)
STAD	Core average	clinical + subtype	343/136	1.283 (1.072–1.536)	0.0070	0.009 (-0.014–0.032)
STAD	Core average	subtype only	358/146	1.302 (1.097–1.545)	0.0027	0.029 (-0.025–0.077)
STAD	Core average	clinical + subtype, GS excluded	297/117	1.205 (1.000–1.452)	0.051	0.004 (-0.016–0.024)
GSE62254	Evidence prior	clinical + subtype	298/152	1.186 (0.977–1.439)	0.083	0.000 (-0.007–0.008)
GSE62254	Evidence prior	clinical + subtype + Lauren	298/152	1.198 (0.981–1.463)	0.076	0.002 (-0.006–0.010)
GSE62254	Evidence prior	subtype only	300/152	1.211 (1.008–1.456)	0.042	0.016 (-0.006–0.037)
GSE62254	Evidence prior	clinical + subtype, EMT excluded	252/119	1.155 (0.963–1.384)	0.12	0.003 (-0.006–0.012)
GSE62254	Core average	clinical + subtype	298/152	1.235 (0.997–1.531)	0.052	0.003 (-0.005–0.012)
GSE62254	Core average	clinical + subtype + Lauren	298/152	1.237 (0.992–1.542)	0.057	0.002 (-0.005–0.010)
GSE62254	Core average	subtype only	300/152	1.280 (1.042–1.571)	0.018	0.016 (-0.006–0.039)
GSE62254	Core average	clinical + subtype, EMT excluded	252/119	1.158 (0.963–1.392)	0.12	0.004 (-0.007–0.013)

Supplementary Table S10: Internal validation of the evidence-prior construction on the reduced panel. Each training fold recomputes gene scaling, differential and survival evidence, and weights. Test-patient normal samples are excluded from construction. Entries are unweighted means of within-test-fold concordances; the fold range describes heterogeneity, not a confidence interval.

Split	Folds	C_{prior}	Range	C_{clin}	C_{full}	ΔC
patient	15	0.562	0.479–0.668	0.620	0.626	0.006
site	5	0.572	0.497–0.657	0.630	0.633	0.004

Supplementary Table S11: Survival associations in TCGA-STAD (discovery, apparent estimates). C uses the prespecified higher-score/higher-risk direction. Cox HR is per analysis-sample score SD. *Coefficient application across platforms is a sensitivity analysis, not a complete replication of the original signature pipeline.

Score	n	HR (95% CI)	p	C (95% CI)
Evidence-weighted prior	387	1.31 (1.11–1.53)	0.0009	0.563 (0.517–0.611)
Equal module weights	387	1.29 (1.10–1.51)	0.0017	0.559 (0.513–0.608)
Differential + HPA (no survival)	387	1.28 (1.09–1.49)	0.0024	0.557 (0.512–0.607)
Survival evidence only	387	1.31 (1.12–1.53)	0.0009	0.563 (0.516–0.612)
HPA evidence only	387	1.29 (1.10–1.51)	0.0017	0.558 (0.512–0.607)
Full-matrisome average	387	1.32 (1.13–1.55)	0.0004	0.562 (0.515–0.610)
Core-matrisome average	387	1.31 (1.12–1.53)	0.0006	0.567 (0.520–0.616)
Six-category average	387	1.31 (1.12–1.54)	0.0006	0.562 (0.516–0.612)
Xu published coefficients*	387	1.39 (1.21–1.60)	< 0.0001	0.587 (0.543–0.634)
Xu six-gene z-mean*	387	1.49 (1.28–1.73)	< 0.0001	0.602 (0.558–0.649)

Supplementary Table S12: Apparent incremental association over age, sex and categorical stage in STAD. Both nested models are unpenalized and fitted on identical complete cases. These concordances are not out-of-sample estimates of a locked clinical prediction model.

Score	n	C_{clin}	C_{full}	ΔC	LRT p
Evidence-weighted prior	370	0.637	0.650	0.014	0.0012
Full-matrisome average	370	0.637	0.653	0.016	0.0006
Core-matrisome average	370	0.637	0.655	0.019	0.0006
Equal module weights	370	0.637	0.648	0.011	0.0020
Differential + HPA (no survival)	370	0.637	0.647	0.011	0.0031

Supplementary Table S13: Paired bootstrap of apparent incremental concordance, refitting both clinical models in each resample while holding molecular weights fixed. These intervals do not correct optimism. The number of successful fits is reported; all failures are retained in the machine-readable log.

Cohort	Successful / 200	ΔC	95% percentile interval
STAD	200	0.014	-0.0021–0.0399
GSE84437	200	0.008	-0.0005–0.0241

Supplementary Table S14: Rank-time Schoenfeld residual diagnostics for the full clinical-plus-prior models. These are exploratory per-term diagnostics; non-significance is not proof of proportional hazards.

Cohort	Term	PH test p
STAD	age	0.9600
STAD	male	0.6924
STAD	score	0.0558
STAD	stage_ord_2	0.4293
STAD	stage_ord_3	0.5254
STAD	stage_ord_4	0.8911
GSE84437	N_1	0.0383
GSE84437	N_2	0.0116
GSE84437	N_3	0.1394
GSE84437	T_2	0.7817
GSE84437	T_3	0.3997
GSE84437	T_4	0.2351
GSE84437	age	0.9865
GSE84437	male	0.2544
GSE84437	score	0.8815

Supplementary Table S15: Clinical-model sensitivity analyses. The N-stratified analysis was added after nominal PH diagnostic flags for N1 and N2; it is exploratory.

Cohort	Variant	n	HR (95% CI)	LRT p
STAD	ordinal	370	1.310 (1.108–1.550)	0.0016
STAD	categorical	370	1.320 (1.116–1.560)	0.0012
GSE84437	ordinal	431	1.227 (1.061–1.419)	0.0056
GSE84437	categorical	431	1.230 (1.063–1.423)	0.0053
GSE84437	N_stratified	431	1.231 (1.064–1.424)	0.0050

Supplementary Table S16: GSE84437 scored against the full 483-profile expression reference and against the 433 profiles that carry clinical data. The 50 excluded profiles form a separately deposited batch without follow-up. Concordance differences against the core average use 1,000 paired patient bootstraps.

Reference	Score	HR (95% CI)	C	adjusted HR (95% CI)	LRT p	C minus core (95% CI)
483 profiles	Evidence prior	1.266 (1.100–1.457)	0.570	1.230 (1.063–1.423)	0.0052	0.001 (-0.011–0.014)
483 profiles	Equal modules	1.247 (1.083–1.435)	0.566	1.219 (1.054–1.411)	0.0075	-0.003 (-0.015–0.009)
483 profiles	Core average	1.265 (1.104–1.450)	0.570	1.239 (1.075–1.428)	0.0031	–
433 profiles	Evidence prior	1.215 (1.052–1.403)	0.559	1.189 (1.026–1.378)	0.020	-0.001 (-0.012–0.010)
433 profiles	Equal modules	1.207 (1.045–1.395)	0.557	1.187 (1.024–1.377)	0.022	-0.002 (-0.013–0.009)
433 profiles	Core average	1.232 (1.071–1.417)	0.560	1.215 (1.051–1.403)	0.0083	–

Supplementary Table S17: Reduced-panel leave-one-module-out sensitivity. Frozen final module weights were renormalized after each omission. The narrow range does not imply module independence because memberships and activities overlap.

Cohort	n/events	minimum C	maximum C
STAD	387/160	0.558	0.562
GSE84437	431/207	0.562	0.573
GSE62254	300/152	0.576	0.582