

A population-level digital histologic biomarker for enhanced prognosis of invasive breast cancer

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Table S1 | Comparison of tumor characteristics between patient cohorts.

P-values correspond to the two-sided, one-way Chi-squared tests relative to CPS-II.

	CPS-II (N=1264)			CPS-3 (N=651)				PLCO (N=461)				TCGA (N=801)			
	Total	N	%	Total	N	%	P-val	Total	N	%	P-val	Total	N	%	P-val
Histologic subtype	1258							461				801			
Infiltrating Ductal		1065	84.7						360	78.1	0.068		583	72.8	9.85E-4 **
Infiltrating Lobular		166	13.2						63	13.7	0.889		147	18.4	0.128
Other		27	2.1						38	8.2	2.59E-5 **		71	8.9	3.56E-6 **
IHC/ISH markers	1264			651				461				801			
ER+		1066	84.3		550	84.5	0.967		317	68.8	1.83E-5 **		626	78.2	0.089
PR+		920	72.8		493	75.7	0.508		186	40.3	3.14E-13 **		539	67.3	0.217
Luminal-like (ER+/PR+,HER2-)		1013	80.1		471	72.4	0.051		296	64.2	6.49E-05 **		525	65.5	2.53E-4 **
HER2+		134	10.6		113	17.4	0.028 *		65	14.1	0.256		149	18.6	0.009 *
Triple-negative		117	9.3		67	10.3	0.721		100	21.7	1.78E-5 **		127	15.9	0.023 *
CK5/6+	1161	128	11.0	546	84	15.4	0.164								
EGFR+	1191	149	12.5	546	144	26.4	2.79E-5 **								
Nottingham grade	1247			626				443				517			
G1		358	28.7		138	22.0	0.141		91	20.5	0.071		48	9.3	1.76E-5 **
G2		528	42.3		292	46.6	0.384		187	42.2	0.979		205	39.7	0.586
G3		361	28.9		196	31.3	0.603		165	37.2	0.067		264	51.1	1.08E-6 **
Control groups	1247			626				443				517			
C1		313	25.1		127	20.3	0.267		56	12.6	0.004 *		45	8.7	1.56E-4 **
C2		562	45.1		326	52.1	0.159		165	37.2	0.116		224	43.3	0.726
C3		372	29.8		173	27.6	0.631		222	50.1	9.30E-6 **		248	48.0	7.36E-5 **
HiPS group	1264			651				461				801			
H1		417	33.0		172	26.4	0.162		57	12.4	1.15E-05 **		31	3.9	5.89E-10 **
H2		667	52.8		343	52.7	0.987		258	56.0	0.522		319	39.8	0.010 *
H3		180	14.2		136	20.9	0.057		146	31.7	6.11E-07 **		451	56.3	2.28E-33 **

Population-level signature for breast cancer prognosis

Table S2 | Comparison of clinical characteristics between patient cohorts.

P-values correspond to the two-sided, one-way Chi-squared tests relative to CPS-II. In the CPS datasets, we only have SEER stages, which we convert to TNM Stage I (localized) and Stages II-III (regional). We also do not have access to nodal status in CPS.

	CPS-II (N=1264)			CPS-3 (N=651)				PLCO (N=461)				TCGA (N=801)			
	Total	N	%	Total	N	%	P-val	Total	N	%	P-val	Total	N	%	P-val
Observed events	1264											801			
Breast cancer-specific deaths		117	9.3					134	56	41.8	3.04E-29 **				
Deaths		462	36.6					403	134	33.3	0.493		73	9.1	1.22E-8 **
Disease progression													72	9.0	
AJCC Stage	1264			648				461				789			
Stage 0		182	14.4						1	0.2	5.36E-5 **				
Stage 1		834	66.0		480	74.1	0.088		237	51.4	0.002 *		136	17.2	7.94E-25 **
Stage 2-3		248	19.6		168	25.9	0.112								
Stage 2									192	41.6			474	60.1	
Stage 3									31	6.7			179	22.7	
Tumor size (AJCC pT)	1179			631				456				801			
T1		857	72.7		424	67.2	0.218		300	65.8	0.122		205	25.6	4.10E-26 **
T2									132	28.9			474	59.2	
T2-3		322	27.3		207	32.8	0.218								
T3									14	3.1			97	12.1	
T4									8	1.8			25	3.1	
Nodal status (AJCC pN)								456				801			
N0									295	64.7			392	48.9	
N1									136	29.8			261	32.6	
N2									11	2.4			87	10.9	
N3									4	0.9			51	6.4	
Screening															
Cancer detected by screening	1230	860	69.9	627	402	64.1	0.206	458	279	60.9	0.050 *				
Mammogram <2 years prior	1222	1157	94.7	511	484	94.7	0.987								

Population-level signature for breast cancer prognosis

Table S3 | Comparison of demographic characteristics between patient cohorts.

P-values correspond to the two-sided, one-way Chi-squared tests relative to CPS-II. † P-value below precision limit.

	CPS-II (N=1264)			CPS-3 (N=651)				PLCO (N=461)				TCGA (N=801)			
	Total	N	%	Total	N	%	P-val	Total	N	%	P-val	Total	N	%	P-val
Age at diagnosis	1264							461				801			
>50 years		1263	99.9	651	488	75.0	0 † **		461	100.0	0.778		598	74.7	0 † **
>60 years		1218	96.4	651	195	30.0	1.93E-275 **		422	91.5	0.010 *		381	47.6	1.13E-149 **
Postmenopausal	1254	1226	97.8	544	298	54.8	4.16E-186 **	461	457	99.1	0.355	721	548	76.0	4.22E-49 **
BMI	1213			650				452							
>25		627	51.7		362	55.7	0.423		291	64.4	0.011 *				
>30		212	17.5		179	27.5	0.008 *		130	28.8	0.003 *				
Race: non-White	1260	27	2.1	650	48	7.4	2.95E-4 **	457	47	10.3	1.88E-8 **	712	168	23.6	1.18E-49 **

Table S4 | Comparison of continuous characteristics between patient cohorts.

P-values are two-sided and correspond to independent-sample t-tests relative to CPS-II.

	CPS-II (N=1264)			CPS-3 (N=651)				PLCO (N=461)				TCGA (N=801)			
	Total	Mean	Std	Total	Mean	Std	P-val	Total	Mean	Std	P-val	Total	Mean	Std	P-val
Age at diagnosis	1264	72.24	7.00	651	54.69	7.66	6.5E-289 **	461	68.52	6.65	6.73E-23 **	801	59.03	13.32	1.66E-115 **
BMI	1213	26.01	4.81	650	27.13	5.81	2.91E-5 **	452	27.67	5.58	3.15E-8 **				
Control score	1247	5.74	2.34	626	5.88	2.19	0.208	443	6.79	2.43	1.27E-14 **	517	6.82	2.16	6.74E-20 **
HiPS score	1264	4.36	1.61	651	4.74	1.62	1.19E-6 **	461	5.29	1.52	1.31E-26 **	801	6.31	1.56	2.14E-136 **

Table S5 | List of the histomic features and their meaning (Excel file).

This table is included as a separate Excel file. Themes and subthemes are provided for each feature. The most prognostic feature in each subtheme was included in HiPS, as measured using univariable BCSS Cox regression in CPS-II. This is the meaning of each column:

Column	Description
CamelCase name	Simple name of the histomic feature for easy interpretation.
Included in HiPS?	Whether this feature is included in the HiPS signature (i.e., is the most prognostic within its subtheme)
Theme.Subtheme	Biological theme and subtheme of the histomic feature.
Raw metric name	A more complex/technical name of the histomic feature that better captures how it was extracted.
Aggregation level 1 type	The first level of aggregating feature values. i.e., “Per 512uM ROI”, “Per WSI”, and “Per patient”.
Aggregation level 1 metric	How feature values were aggregated in the first level. Options include “Mean”, “Std” (standard deviation), or N/A.
Aggregation level 2 type	The second level of aggregating feature values. E.g., we may average the per-WSI values for multiple WSIs per patient.
Aggregation level 2 metric	How feature values were aggregated in the second level.
Aggregation level 3 type	The third level of aggregating feature values.
Aggregation level 3 metric	How feature values were aggregated in the third level.
Plain language	Relatively simple description of the feature meaning.
High value indicates?	What an increase in feature value indicates regarding tumor biology or known survival associations.
Metric type	Whether this feature captures tissue regions, cell nuclei, or both.

Table S6 | Multivariable BCSS Cox regression model for the HiPS score in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS score	0.248	0.055	0.140	0.356	1.281	1.150	1.428	7.29E-06
SEER stage: localized	0.547	0.523	-0.478	1.571	1.727	0.620	4.812	0.296
SEER stage: regional	1.155	0.535	0.107	2.203	3.173	1.113	9.052	0.031
Tumor size: 2+ cm	0.737	0.296	0.157	1.318	2.090	1.169	3.736	0.013
Tumor size: <2 cm	0.018	0.295	-0.561	0.596	1.018	0.571	1.814	0.953

Model fit statistics: N = 1179; Events = 114; Concordance index = 0.739; Partial AIC = 1471.86; Log-likelihood = -730.93; Baseline estimation: Breslow.

Table S7 | Multivariable BCSS Cox regression model for HiPS groups in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS group: H2	0.555	0.289	-0.012	1.122	1.742	0.988	3.071	0.055
HiPS group: H3	1.287	0.315	0.669	1.905	3.620	1.952	6.716	4.49E-5
SEER stage: localized	0.590	0.522	-0.433	1.612	1.804	0.649	5.015	0.258
SEER stage: regional	1.184	0.534	0.137	2.231	3.268	1.147	9.313	0.027
Tumor size: 2+ cm	0.749	0.297	0.168	1.331	2.116	1.183	3.785	0.012
Tumor size: <2 cm	0.011	0.297	-0.571	0.593	1.012	0.565	1.810	0.969

Model fit statistics: N = 1179; Events = 114; Concordance index = 0.734; Partial AIC = 1473.14; Log-likelihood = -730.57; Baseline estimation: Breslow.

Table S8 | Multivariable BCSS Cox regression model for the Control score in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in "Survival Analysis", 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control score	0.211	0.045	0.123	0.299	1.235	1.131	1.349	2.75E-6
SEER stage: localized	0.857	0.518	-0.158	1.873	2.357	0.854	6.508	0.098
SEER stage: regional	1.444	0.526	0.413	2.475	4.236	1.511	11.877	0.006
Tumor size: 2+ cm	0.951	0.313	0.337	1.565	2.588	1.401	4.781	0.002
Tumor size: <2 cm	0.241	0.312	-0.372	0.853	1.272	0.690	2.347	0.441

Model fit statistics: N = 1165; Events = 108; Concordance index = 0.749; Partial AIC = 1384.17; Log-likelihood = -687.08; Baseline estimation: Breslow.

Table S9 | Multivariable BCSS Cox regression model for the Control groups in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in "Survival Analysis", 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control group: C2	0.666	0.344	-0.007	1.340	1.947	0.993	3.818	0.052
Control group: C3	1.269	0.338	0.605	1.932	3.556	1.832	6.900	1.77E-4
SEER stage: localized	0.912	0.519	-0.105	1.929	2.490	0.901	6.882	0.079
SEER stage: regional	1.490	0.526	0.459	2.522	4.439	1.582	12.458	0.005
Tumor size: 2+ cm	0.939	0.315	0.322	1.556	2.557	1.380	4.740	0.003
Tumor size: <2 cm	0.236	0.313	-0.378	0.850	1.266	0.685	2.340	0.451

Model fit statistics: N = 1165; Events = 108; Concordance index = 0.743; Partial AIC = 1390.15; Log-likelihood = -689.08; Baseline estimation: Breslow.

Table S10 | Expanded multivariable BCSS Cox regression model for the HiPS score in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in "Survival Analysis", 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS score	0.342	0.094	0.158	0.526	1.407	1.171	1.692	2.75E-4
Age at diagnosis (years)	0.048	0.021	0.007	0.089	1.049	1.007	1.093	0.022
Body-mass index (kg/m2)	0.039	0.026	-0.013	0.090	1.040	0.987	1.095	0.140
Detected by screening	-0.366	0.274	-0.903	0.172	0.694	0.405	1.187	0.182
Treatment: chemotherapy	-0.342	0.323	-0.976	0.292	0.710	0.377	1.339	0.290
Treatment: radiation therapy	-0.403	0.260	-0.912	0.106	0.668	0.402	1.112	0.121
Treatment: targeted therapy	-0.684	0.443	-1.552	0.183	0.504	0.212	1.201	0.122
Race: Non-White	1.017	0.740	-0.434	2.468	2.765	0.648	11.800	0.170
SEER stage: localized	1.221	1.066	-0.868	3.309	3.389	0.420	27.370	0.252
SEER stage: regional	2.192	1.102	0.031	4.352	8.950	1.032	77.635	0.047
Tumor size: 2+ cm	1.100	0.490	0.138	2.061	3.003	1.149	7.854	0.025
Tumor size: <2 cm	0.423	0.480	-0.517	1.364	1.527	0.596	3.910	0.378
Pre- or peri-menopausal	1.251	0.752	-0.224	2.726	3.494	0.799	15.268	0.096
Never smoker	0.079	0.250	-0.412	0.570	1.082	0.663	1.768	0.752
Expression of EFGR or CK5/6	-0.465	0.368	-1.185	0.256	0.628	0.306	1.292	0.206

Model fit statistics: N = 720; Events = 68; Concordance index = 0.81; Partial AIC = 787.5; Log-likelihood = -378.75; Baseline estimation: Breslow.

Table S11 | Expanded multivariable BCSS Cox regression model for HiPS groups in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS group: H2	0.527	0.403	-0.264	1.317	1.694	0.768	3.733	0.191
HiPS group: H3	1.237	0.449	0.357	2.117	3.445	1.429	8.303	0.006
Age at diagnosis (years)	0.048	0.021	0.007	0.089	1.049	1.007	1.093	0.022
Body-mass index (kg/m2)	0.040	0.026	-0.010	0.091	1.041	0.990	1.095	0.116
Detected by screening	-0.410	0.273	-0.945	0.126	0.664	0.389	1.134	0.134
Treatment: chemotherapy	-0.285	0.327	-0.926	0.356	0.752	0.396	1.427	0.383
Treatment: radiation therapy	-0.369	0.259	-0.875	0.138	0.692	0.417	1.148	0.154
Treatment: targeted therapy	-0.729	0.438	-1.587	0.130	0.483	0.205	1.139	0.096
Race: Non-White	1.062	0.743	-0.393	2.517	2.893	0.675	12.397	0.153
SEER stage: localized	1.320	1.066	-0.770	3.410	3.744	0.463	30.274	0.216
SEER stage: regional	2.300	1.106	0.133	4.468	9.978	1.142	87.199	0.038
Tumor size: 2+ cm	1.183	0.491	0.221	2.145	3.265	1.247	8.545	0.016
Tumor size: <2 cm	0.534	0.476	-0.400	1.467	1.705	0.670	4.337	0.262
Pre- or peri-menopausal	1.263	0.768	-0.243	2.768	3.535	0.784	15.930	0.100
Never smoker	0.070	0.250	-0.420	0.559	1.072	0.657	1.749	0.781
Expression of EFGR or CK5/6	-0.372	0.358	-1.074	0.329	0.689	0.342	1.390	0.298

Model fit statistics: N = 720; Events = 68; Concordance index = 0.805; Partial AIC = 793.68; Log-likelihood = -380.84; Baseline estimation: Breslow.

Table S12 | Expanded multivariable BCSS Cox model for the Control score in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control score	0.285	0.074	0.140	0.430	1.330	1.151	1.537	1.12E-4
Age at diagnosis (years)	0.061	0.022	0.017	0.104	1.063	1.018	1.110	0.006
Body-mass index (kg/m2)	0.038	0.026	-0.013	0.088	1.038	0.987	1.092	0.143
Detected by screening	-0.449	0.278	-0.993	0.095	0.638	0.371	1.100	0.106
Treatment: chemotherapy	-0.316	0.341	-0.985	0.353	0.729	0.373	1.423	0.354
Treatment: radiation therapy	-0.323	0.262	-0.836	0.190	0.724	0.433	1.209	0.217
Treatment: targeted therapy	-0.618	0.450	-1.501	0.265	0.539	0.223	1.303	0.170
Race: Non-White	0.832	0.751	-0.640	2.304	2.299	0.527	10.018	0.268
SEER stage: localized	1.673	1.066	-0.416	3.762	5.329	0.660	43.046	0.116
SEER stage: regional	2.635	1.104	0.471	4.799	13.944	1.602	121.391	0.017
Tumor size: 2+ cm	1.360	0.520	0.341	2.379	3.896	1.406	10.794	0.009
Tumor size: <2 cm	0.761	0.506	-0.230	1.752	2.140	0.794	5.768	0.133
Pre- or peri-menopausal	1.133	0.761	-0.359	2.624	3.104	0.698	13.791	0.137
Never smoker	0.104	0.261	-0.406	0.615	1.110	0.666	1.850	0.689
Expression of EFGR or CK5/6	-0.421	0.372	-1.150	0.308	0.656	0.317	1.361	0.258

Model fit statistics: N = 712; Events = 65; Concordance index = 0.831; Partial AIC = 745.01; Log-likelihood = -357.51; Baseline estimation: Breslow.

Table S13 | Expanded multivariable BCSS Cox model for the Control groups in CPS-II. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in "Survival Analysis", 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control group: C2	0.295	0.444	-0.575	1.165	1.344	0.563	3.207	0.506
Control group: C3	1.270	0.433	0.421	2.120	3.561	1.523	8.328	0.003
Age at diagnosis (years)	0.059	0.022	0.016	0.102	1.061	1.016	1.108	0.008
Body-mass index (kg/m2)	0.042	0.025	-0.008	0.091	1.042	0.992	1.096	0.103
Detected by screening	-0.455	0.275	-0.995	0.085	0.635	0.370	1.089	0.099
Treatment: chemotherapy	-0.304	0.333	-0.957	0.349	0.738	0.384	1.418	0.361
Treatment: radiation therapy	-0.305	0.262	-0.818	0.208	0.737	0.441	1.231	0.243
Treatment: targeted therapy	-0.766	0.447	-1.641	0.109	0.465	0.194	1.116	0.086
Race: Non-White	0.963	0.750	-0.507	2.434	2.621	0.602	11.405	0.199
SEER stage: localized	1.845	1.079	-0.269	3.959	6.329	0.764	52.418	0.087
SEER stage: regional	2.778	1.118	0.587	4.969	16.083	1.798	143.853	0.013
Tumor size: 2+ cm	1.313	0.521	0.291	2.335	3.718	1.338	10.331	0.012
Tumor size: <2 cm	0.740	0.507	-0.254	1.733	2.096	0.776	5.659	0.144
Pre- or peri-menopausal	0.756	0.765	-0.743	2.255	2.130	0.475	9.539	0.323
Never smoker	0.097	0.260	-0.414	0.607	1.101	0.661	1.835	0.711
Expression of EFGR or CK5/6	-0.206	0.363	-0.919	0.506	0.814	0.399	1.659	0.570

Model fit statistics: N = 712; Events = 65; Concordance index = 0.833; Partial AIC = 748.46; Log-likelihood = -358.23; Baseline estimation: Breslow.

Table S14 | Multivariable OS Cox regression model for the HiPS score in PLCO. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS score	0.136	0.062	0.014	0.258	1.146	1.014	1.294	0.029
Age at diagnosis	0.082	0.014	0.056	0.109	1.086	1.058	1.115	1.11E-9
AJCC Stage III	-0.188	0.503	-1.173	0.798	0.829	0.309	2.222	0.709
AJCC pT2	0.383	0.199	-0.008	0.774	1.467	0.992	2.168	0.055
AJCC pT3+	1.606	0.508	0.611	2.602	4.984	1.841	13.488	0.002

Model fit statistics: N = 398; Events = 130; Concordance index = 0.691; Partial AIC = 1424.96; Log-likelihood = -707.48; Baseline estimation: Breslow.

Table S15 | Multivariable OS Cox regression model for the HiPS groups in PLCO. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS group: H2	0.188	0.328	-0.454	0.830	1.207	0.635	2.294	0.565
HiPS group: H3	0.575	0.345	-0.102	1.252	1.777	0.903	3.498	0.096
Age at diagnosis	0.084	0.014	0.057	0.110	1.087	1.059	1.116	6.83E-10
AJCC Stage III	-0.161	0.495	-1.131	0.810	0.852	0.323	2.247	0.745
AJCC pT2	0.402	0.197	0.016	0.789	1.495	1.016	2.200	0.041
AJCC pT3+	1.587	0.502	0.603	2.570	4.887	1.828	13.063	0.002

Model fit statistics: N = 398; Events = 130; Concordance index = 0.691; Partial AIC = 1426.85; Log-likelihood = -707.43; Baseline estimation: Breslow.

Table S16 | Multivariable OS Cox regression model for the Control score in PLCO. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control score	0.031	0.041	-0.049	0.111	1.032	0.952	1.118	0.449
Age at diagnosis	0.079	0.014	0.051	0.106	1.082	1.052	1.112	2.05E-8
AJCC Stage III	-0.249	0.505	-1.239	0.740	0.779	0.290	2.096	0.621
AJCC pT2	0.469	0.203	0.070	0.867	1.598	1.073	2.381	0.021
AJCC pT3+	1.717	0.497	0.744	2.691	5.570	2.104	14.747	0.001

Model fit statistics: N = 384; Events = 122; Concordance index = 0.68; Partial AIC = 1334.85; Log-likelihood = -662.43; Baseline estimation: Breslow.

Table S17 | Multivariable OS Cox regression model for the Control groups in PLCO. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control group: C2	0.133	0.329	-0.512	0.777	1.142	0.599	2.176	0.686
Control group: C3	0.180	0.323	-0.452	0.812	1.198	0.636	2.253	0.576
Age at diagnosis	0.079	0.014	0.051	0.106	1.082	1.052	1.112	2.04E-8
AJCC Stage III	-0.285	0.511	-1.286	0.716	0.752	0.276	2.046	0.577
AJCC pT2	0.479	0.203	0.082	0.877	1.615	1.086	2.403	0.018
AJCC pT3+	1.749	0.496	0.777	2.720	5.746	2.174	15.188	4.21E-4

Model fit statistics: N = 384; Events = 122; Concordance index = 0.679; Partial AIC = 1337.1; Log-likelihood = -662.55; Baseline estimation: Breslow.

Table S18 | Multivariable OS Cox regression model for the HiPS score in TCGA. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS score	0.200	0.077	0.049	0.351	1.222	1.051	1.421	0.009
AJCC Stage III	0.830	0.299	0.243	1.417	2.293	1.275	4.123	0.006
AJCC pT3+	0.299	0.346	-0.380	0.977	1.348	0.684	2.657	0.388

Model fit statistics: N = 789; Events = 72; Concordance index = 0.664; Partial AIC = 758.51; Log-likelihood = -376.25; Baseline estimation: Breslow.

Table S19 | Multivariable OS Cox regression model for the HiPS groups in TCGA. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
HiPS group: H2	0.430	0.753	-1.046	1.906	1.537	0.351	6.728	0.568
HiPS group: H3	1.052	0.742	-0.403	2.507	2.864	0.669	12.269	0.156
AJCC Stage III	0.833	0.301	0.244	1.422	2.300	1.276	4.147	0.006
AJCC pT3+	0.297	0.347	-0.383	0.978	1.346	0.682	2.659	0.392

Model fit statistics: N = 789; Events = 72; Concordance index = 0.663; Partial AIC = 759.97; Log-likelihood = -375.98; Baseline estimation: Breslow.

Table S20 | Multivariable OS Cox regression model for the Control score in TCGA. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in "Survival Analysis", 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control score	0.002	0.074	-0.142	0.147	1.002	0.868	1.158	0.974
AJCC Stage III	0.918	0.379	0.174	1.662	2.505	1.191	5.269	0.016
AJCC pT3+	0.351	0.477	-0.585	1.286	1.420	0.557	3.620	0.463

Model fit statistics: N = 507; Events = 44; Concordance index = 0.645; Partial AIC = 429.25; Log-likelihood = -211.63; Baseline estimation: Breslow.

Table S21 | Multivariable OS Cox regression model for the Control groups in TCGA. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in "Survival Analysis", 2nd Ed., p. 256.

	coef	se(coef)	coef lower 95%	coef upper 95%	exp(coef)	exp(coef) lower 95%	exp(coef) upper 95%	P-val
Control group: C2	0.309	0.634	-0.934	1.551	1.362	0.393	4.717	0.626
Control group: C3	0.036	0.627	-1.193	1.265	1.036	0.303	3.541	0.955
AJCC Stage III	0.939	0.384	0.188	1.691	2.558	1.206	5.424	0.014
AJCC pT3+	0.343	0.481	-0.600	1.287	1.409	0.549	3.621	0.476

Model fit statistics: N = 507; Events = 44; Concordance index = 0.653; Partial AIC = 430.48; Log-likelihood = -211.24; Baseline estimation: Breslow.

Table S22 | Feature coefficients and relative weights for the 30 features in HiPS.

Covariate	Theme.Subtheme	Coefficient	Normalized Coefficient
Is TNBC	ClinicalFeats.IHCMarker	4.05E-07	1.000
Is PR+	ClinicalFeats.IHCMarker	-2.65E-07	-0.655
Is ER+	ClinicalFeats.IHCMarker	-2.13E-07	-0.527
GlobalCAFDensity	Stroma.NonTILsCellularity	1.07E-07	0.263
StdOfChromatinClumpingOfEpithNuclei	Epithelium.NuclearPleomorphism	1.04E-07	0.257
PeriCAFMatrixHeteroin512uMROI	Stroma.StromalMatrixNonSpecific	-1.01E-07	-0.248
ChromatinClumpingOfEpithNuclei	Epithelium.NuclearAtypia	1.00E-07	0.248
GlobalCancerCellDensity	Epithelium.CancerCellularity	8.92E-08	0.220
TILsClusteringAroundEpithCell64uM	TILs.Clustering	8.15E-08	0.201
CAFClusteringAroundEpithCell64uM	Stroma.ClusteringOfCAFs	7.79E-08	0.192
ChromatinClumpingOfTILsNuclei	TILs.CellActivation	7.16E-08	0.177
CAFDensityWithin32uMOfEpithCell	Interactions.Epithelium-Stroma-Interaction	6.63E-08	0.164
AbundanceOfEpithCytoplasmPerNest	Epithelium.CytoplasmAmount	-6.52E-08	-0.161
EpithCellClustering64uM	Epithelium.NestFormation	-6.35E-08	-0.157
CircularityOfEpithNests	Epithelium.NestMorphology	-5.85E-08	-0.144
StdOfCircularityOfEpithNests	Epithelium.NestPleomorphism	-5.84E-08	-0.144
ComplexityOfCAFNuclBoundary	Stroma.ActivationOfCAFs	5.63E-08	0.139
StdOfChromatinClumpingOfTILsNuclei	TILs.CellPleomorphism	-5.41E-08	-0.134
Is HER2+	ClinicalFeats.IHCMarker	-4.31E-08	-0.106
StdOfEntropyOfCAFNuclStain	Stroma.PleomorphismOfCAFS	-4.16E-08	-0.103
NoOfStraightToAllCollagenEdges	Stroma.CollagenSeparation	-3.43E-08	-0.085
CAFDensityWithin16uMOfTILsCell	Interactions.TILs-Stroma-Interaction	3.08E-08	0.076
StdOfComplexityOfTILsClusterBoundary	TILs.ClusterPleomorphism	3.06E-08	0.075
TILsDensityWithin16uMOfEpithCell	Interactions.Epithelium-TILs-Interaction	-2.74E-08	-0.068
GlobalTILsDensity	TILs.Abundance	2.24E-08	0.055
EntropyOfCollagenOrientation	Stroma.CollagenOrientation	1.89E-08	0.047
ComplexityOfTILsClusterBoundary	TILs.ClusterMorphology	1.58E-08	0.039
StdOfStainingOfEpithCytoplasm	Epithelium.CytoplasmicPleomorphism	-7.82E-09	-0.019
StainingOfEpithCytoplasm	Epithelium.CytoplasmStaining	-3.09E-09	-0.008
StdOfNecrosisAmountAtEpithNestMargin	Necrosis.Abundance	-2.57E-09	-0.006

Table S23 | Univariable Cox regression for histomic features for CPS-II BCSS outcomes.

The covariate name is structured as “Theme.Subtheme.HistomicFeature”. The most prognostic feature in each subtheme, measured using the absolute value of the BCSS Cox regression coefficient, was admitted as one of the 30 features in the HiPS signature. P-values correspond to the two-sided, one-way Chi-squared test of the z-scored coefficients, as described by Klein and Moeschberger in “Survival Analysis”, 2nd Ed., p. 256.

Covariate	coef	se(coef)	p	c-index
Epithelium.CancerCellularity.EpithToStromaRegionRatio	0.161	0.064	0.0120	0.5797
Epithelium.CancerCellularity.GlobalCancerCellDensity	0.212	0.065	0.0010	0.5863
Epithelium.CancerCellularity.LocalCancerCellDensity32uM	0.088	0.085	0.3007	0.5278
Epithelium.CytoplasmAmount.AbundanceOfEpithCytoplasmPerNest	-0.186	0.085	0.0299	0.5664
Epithelium.CytoplasmicPleomorphism.StdOfRoughnessOfEpithCytoplasm	0.008	0.083	0.9281	0.4900
Epithelium.CytoplasmicPleomorphism.StdOfStainingOfEpithCytoplasm	-0.086	0.079	0.2761	0.5496
Epithelium.CytoplasmStaining.RoughnessOfEpithCytoplasm	-0.027	0.081	0.7444	0.5070
Epithelium.CytoplasmStaining.StainingOfEpithCytoplasm	-0.087	0.080	0.2755	0.5166
Epithelium.NestFormation.EpithCellClustering64uM	-0.200	0.083	0.0160	0.5752
Epithelium.NestFormation.EpithNuclOrientationEntropy	0.143	0.093	0.1259	0.5598
Epithelium.NestFormation.NoOfEpithNests	0.115	0.077	0.1319	0.5333
Epithelium.NestMorphology.CircularityOfEpithNests	-0.230	0.095	0.0155	0.5642
Epithelium.NestMorphology.ComplexityOfEpithNestBoundary	0.171	0.085	0.0454	0.5487
Epithelium.NestMorphology.EpithNestsHaveFewHoles	-0.076	0.032	0.0196	0.5978
Epithelium.NestMorphology.PerimeterOfEpithNests	0.098	0.033	0.0027	0.6189
Epithelium.NestMorphology.SizeOfEpithNests	0.106	0.038	0.0050	0.6081
Epithelium.NestPleomorphism.EpithNestsHaveVariableNoOfHoles	0.140	0.037	0.0002	0.6089
Epithelium.NestPleomorphism.StdOfCircularityOfEpithNests	-0.192	0.087	0.0277	0.5573
Epithelium.NestPleomorphism.StdOfComplexityOfEpithNestBoundary	0.136	0.091	0.1368	0.5394
Epithelium.NestPleomorphism.StdOfNoOfLowGradeNucleiPerEpithNest	-0.091	0.084	0.2752	0.5363
Epithelium.NestPleomorphism.StdOfPerimeterOfEpithNests	0.166	0.041	0.0000	0.6163
Epithelium.NestPleomorphism.StdOfSizeOfEpithNests	0.147	0.045	0.0010	0.6074
Epithelium.NuclearAtypia.ChromatinClumpingOfEpithNuclei	0.304	0.091	0.0008	0.6133
Epithelium.NuclearAtypia.ComplexityOfEpithNuclBoundary	0.097	0.093	0.2984	0.6007
Epithelium.NuclearAtypia.NoOfLowGradeNucleiPerEpithNest	0.014	0.083	0.8666	0.4718
Epithelium.NuclearAtypia.SizeOfEpithNuclei	0.160	0.094	0.0909	0.5882

Population-level signature for breast cancer prognosis

Epithelium.NuclearAtypia.StainingOfEpithNuclei	-0.084	0.076	0.2700	0.5681
Epithelium.NuclearPleomorphism.StdOfChromatinClumpingOfEpithNuclei	0.292	0.087	0.0008	0.6031
Epithelium.NuclearPleomorphism.StdOfComplexityOfEpithNuclBoundary	-0.033	0.081	0.6860	0.5877
Epithelium.NuclearPleomorphism.StdOfSizeOfEpithNuclei	0.171	0.089	0.0542	0.5711
Epithelium.NuclearPleomorphism.StdOfStainingOfEpithNuclei	0.105	0.090	0.2447	0.5562
Interactions.Epithelium-Stroma-Interaction.CAFDensityWithin16uMOfEpithCell	0.184	0.071	0.0091	0.5379
Interactions.Epithelium-Stroma-Interaction.CAFDensityWithin32uMOfEpithCell	0.197	0.071	0.0055	0.5456
Interactions.Epithelium-Stroma-Interaction.EpithCellDensityWithin16uMOfCAF	-0.132	0.090	0.1410	0.5389
Interactions.Epithelium-Stroma-Interaction.EpithCellDensityWithin32uMOfCAF	-0.083	0.087	0.3385	0.5263
Interactions.Epithelium-Stroma-Interaction.WhitespaceAtEpithNestMargin	-0.141	0.086	0.0999	0.5440
Interactions.Epithelium-TILs-Interaction.ActiveTILsDensityAtEpithNestMargin	0.020	0.048	0.6811	0.5054
Interactions.Epithelium-TILs-Interaction.EpithCellDensityWithin16uMOfTILsCell	0.030	0.061	0.6202	0.4892
Interactions.Epithelium-TILs-Interaction.EpithCellDensityWithin32uMOfTILsCell	0.017	0.065	0.7957	0.4678
Interactions.Epithelium-TILs-Interaction.TILsDensityAtEpithNestMargin	0.066	0.063	0.2923	0.5348
Interactions.Epithelium-TILs-Interaction.TILsDensityWithin16uMOfEpithCell	-0.092	0.088	0.2965	0.5368
Interactions.Epithelium-TILs-Interaction.TILsDensityWithin32uMOfEpithCell	-0.064	0.086	0.4605	0.5263
Interactions.TILs-Stroma-Interaction.CAFDensityWithin16uMOfTILsCell	0.123	0.062	0.0471	0.5670
Interactions.TILs-Stroma-Interaction.CAFDensityWithin32uMOfTILsCell	0.118	0.061	0.0520	0.5671
Interactions.TILs-Stroma-Interaction.TILsDensityWithin16uMOfCAF	0.049	0.083	0.5593	0.5162
Interactions.TILs-Stroma-Interaction.TILsDensityWithin32uMOfCAF	0.029	0.082	0.7274	0.5115
Necrosis.Abundance.NecrosisAmountAtEpithNestMargin	0.017	0.079	0.8331	0.5132
Necrosis.Abundance.StdOfNecrosisAmountAtEpithNestMargin	-0.064	0.089	0.4703	0.4919
Necrosis.Abundance.TotalNecrosisAmount	-0.013	0.084	0.8821	0.4936
Stroma.ActivationOfCAFs.ChromatinClumpingOfCAFNuclei	0.041	0.086	0.6292	0.5449
Stroma.ActivationOfCAFs.ComplexityOfCAFNuclBoundary	0.091	0.093	0.3257	0.5586
Stroma.ActivationOfCAFs.EntropyOfCAFNuclStain	-0.032	0.071	0.6556	0.4485
Stroma.ActivationOfCAFs.EpithelializationOfCAFs	0.057	0.082	0.4853	0.5505
Stroma.ActivationOfCAFs.RoundnessOfCAFs	-0.009	0.078	0.9102	0.4314
Stroma.ClusteringOfCAFs.CAFClustering32uM	-0.096	0.084	0.2512	0.5105
Stroma.ClusteringOfCAFs.CAFClustering64uM	-0.097	0.086	0.2605	0.5176
Stroma.ClusteringOfCAFs.CAFClusteringAroundEpithCell64uM	0.249	0.073	0.0007	0.5650

Population-level signature for breast cancer prognosis

Stroma.CollagenOrientation.AnantEntropyOfCollagenOrientation	0.025	0.089	0.7756	0.4928
Stroma.CollagenOrientation.EntropyOfCAFOrientation64uM	0.015	0.083	0.8614	0.5071
Stroma.CollagenOrientation.HistEntropyOfCollagenOrientation	-0.004	0.085	0.9592	0.5111
Stroma.CollagenOrientation.StdOfAnantEntropyOfCollagenOrientation	0.023	0.084	0.7886	0.5106
Stroma.CollagenSeparation.HistEntropyOfLengthOfCollagenEdges	-0.005	0.085	0.9548	0.4788
Stroma.CollagenSeparation.LengthOfCollagenEdges	-0.049	0.077	0.5262	0.5387
Stroma.CollagenSeparation.NoOfCollagenEdgesPer256uMROI	-0.036	0.082	0.6556	0.5203
Stroma.CollagenSeparation.NoOfStraightToAllCollagenEdges	-0.116	0.074	0.1162	0.5537
Stroma.CollagenSeparation.StdOfLengthOfCollagenEdges	-0.079	0.078	0.3147	0.5410
Stroma.NonTILsCellularity.AcellularStromaAtEpithNestMargin	-0.046	0.082	0.5722	0.5270
Stroma.NonTILsCellularity.AcellularStromaIn256uMROI	-0.084	0.079	0.2835	0.5399
Stroma.NonTILsCellularity.CAFDensityAtEpithNestMargin	0.202	0.076	0.0083	0.5594
Stroma.NonTILsCellularity.CAFDensityIn256uMROI	-0.006	0.084	0.9389	0.5070
Stroma.NonTILsCellularity.GlobalCAFDensity	0.299	0.072	0.0000	0.5774
Stroma.NonTILsCellularity.LocalCAFDensity32uM	0.001	0.082	0.9921	0.5046
Stroma.NonTILsCellularity.StdOfAcellularStromaIn256uMROI	-0.121	0.091	0.1832	0.5332
Stroma.NonTILsCellularity.StdOfCAFDensityIn256uMROI	-0.184	0.101	0.0687	0.5386
Stroma.NonTILsCellularity.StromalCAFDensity	-0.021	0.124	0.8679	0.5528
Stroma.PleomorphismOfCAFS.StdOfChromatinClumpOfCAFNUclei	-0.091	0.084	0.2759	0.4939
Stroma.PleomorphismOfCAFS.StdOfComplexityOfCAFNUclBoundary	-0.113	0.058	0.0523	0.5928
Stroma.PleomorphismOfCAFS.StdOfEntropyOfCAFNUclStain	-0.182	0.072	0.0109	0.5729
Stroma.PleomorphismOfCAFS.StdOfEpithelializationOfCAFs	0.002	0.082	0.9771	0.5253
Stroma.PleomorphismOfCAFS.StdOfRoundnessOfCAFs	-0.069	0.066	0.2987	0.5285
Stroma.StromalMatrixNonSpecific.EntropyOfStainOfStromMatrix256uMROI	-0.006	0.084	0.9409	0.5138
Stroma.StromalMatrixNonSpecific.PeriCAFMatrixHeteroIn512uMROI	-0.273	0.067	0.0000	0.6245
Stroma.StromalMatrixNonSpecific.PeriCAFMatrixHeteroPerCAF	-0.018	0.075	0.8086	0.4398
Stroma.StromalMatrixNonSpecific.StdOfStainOfStromaMatrix256uMROI	-0.080	0.083	0.3355	0.5384
TILs.Abundance.AreaOfTILsToStromaRegion256uMROI	-0.048	0.088	0.5841	0.5015
TILs.Abundance.GlobalTILsDensity	0.077	0.045	0.0882	0.5619
TILs.Abundance.LocalTILsDensity32uM	0.004	0.079	0.9562	0.4981
TILs.Abundance.NoOfTILsToNoOfCells	-0.051	0.087	0.5568	0.5287

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TILs.Abandance.NoOfTILsToNoOfStromalCells	-0.029	0.083	0.7230	0.5130
TILs.Abandance.NoOfTILsToStromaRegionArea512uMROI	-0.002	0.078	0.9844	0.4971
TILs.CellActivation.ActivationOfTILs	-0.147	0.100	0.1405	0.5455
TILs.CellActivation.ActivationOfTILsWithinCluster	0.005	0.080	0.9476	0.5211
TILs.CellActivation.ChromatinClumpingOfTILsNuclei	0.288	0.087	0.0010	0.5763
TILs.CellActivation.SizeOfTILsNuclei	-0.033	0.092	0.7168	0.4972
TILs.CellPleomorphism.StdOfActivationOfTILsWithinCluster	-0.148	0.093	0.1114	0.5452
TILs.CellPleomorphism.StdOfChromatinClumpingOfTILsNuclei	-0.150	0.091	0.0980	0.5434
TILs.CellPleomorphism.StdOfSizeOfTILsNuclei	-0.005	0.083	0.9509	0.5351
TILs.Clustering.NoOfTILsClusters	0.060	0.072	0.4051	0.5369
TILs.Clustering.TILsClustering32uM	0.159	0.062	0.0103	0.5499
TILs.Clustering.TILsClustering64uM	0.133	0.059	0.0230	0.5507
TILs.Clustering.TILsClusteringAroundEpithCell64uM	0.238	0.078	0.0023	0.5666
TILs.ClusterMorphology.CircularityOfTILsClusters	-0.028	0.084	0.7395	0.5088
TILs.ClusterMorphology.ComplexityOfTILsClusterBoundary	0.062	0.088	0.4792	0.5314
TILs.ClusterMorphology.PerimeterOfTILsClusters	0.062	0.050	0.2095	0.5431
TILs.ClusterMorphology.SizeOfTILsClusters	0.036	0.050	0.4717	0.5321
TILs.ClusterPleomorphism.StdOfCircularityOfTILsClusters	0.056	0.081	0.4882	0.5175
TILs.ClusterPleomorphism.StdOfComplexityOfTILsClusterBoundary	0.125	0.083	0.1346	0.5304
TILs.ClusterPleomorphism.StdOfPerimeterOfTILsClusters	0.065	0.042	0.1186	0.5507
TILs.ClusterPleomorphism.StdOfSizeOfTILsClusters	0.050	0.044	0.2561	0.5474

Table S24 | Association between histomic features, Nottingham grade, and survival outcomes (Excel).

This table is included as a separate Excel file. The meaning of each column is included below:

Heading	Column	Description
Feature		Name of histomic feature
Subtheme		Biological subtheme of histomic feature
Grade component		In TCGA, we have granular Nottingham grade components (eg. nuclear grade)
Histomic feature distribution within Nottingham grades	Grade1-N	No. of Nottingham grade 1 cases with available feature data
	Grade1-Median	Median feature value in Nottingham grade 1 cases
	Grade1-Q25	25th quantile of feature value in Nottingham grade 1 cases
	Grade1-Q75	75th quantile of feature value in Nottingham grade 1 cases
	Grade2-N	No. of Nottingham grade 2 cases with available feature data
	Grade2-Median	Median feature value in Nottingham grade 2 cases
	Grade2-Q25	25th quantile of feature value in Nottingham grade 2 cases
	Grade2-Q75	75th quantile of feature value in Nottingham grade 2 cases
	Grade3-N	No. of Nottingham grade 3 cases with available feature data
	Grade3-Median	Median feature value in Nottingham grade 3 cases
	Grade3-Q25	25th quantile of feature value in Nottingham grade 3 cases
	Grade3-Q75	75th quantile of feature value in Nottingham grade 3 cases
Ordinal regression (predicting Nottingham grade from histomic feature)	KruskalPValue	Kruskal–Wallis test p-value for difference in feature distributions
	coef	Coefficient of univariable ordinal regression model
	stderr	Standard error around the coefficient
	z	Z-value
	P> z	P-value
	coef_lowerbound_q0.025	Lower bound of the coefficient
	coef_lowerbound_q0.975	Upper bound of the coefficient
	AIC	Akaike information criterion
Cox regression for BCSS/PFI (predicting survival from histomic feature)	BIC	Bayesian information criterion
	coef	Coefficient of univariable Cox regression model
	exp(coef)	Exponent of the coefficient (i.e., Hazard ratio)
	se(coef)	Standard error around the coefficient
	coef lower 95%	Lower bound of the coefficient
	coef upper 95%	Upper bound of the coefficient
	exp(coef) lower 95%	Lower bound of the hazard ratio
	exp(coef) upper 95%	Upper bound of the hazard ratio
	z	Z-value
	p	P-value
	concordance_index	Harrell's Concordance index

Table S25 | Correlation between histomic features (Excel file).

This table is included as a separate Excel file. Pearson correlation coefficient for each of the histomic features against all other histomic features. Each sheet contains the correlations for one cohort. The off-diagonal correlations are stronger within the TCGA cohort, likely because it is mostly composed of advanced cases. Hence, there is less variation and distinctiveness of biological phenomena in TCGA. This higher variability of cases is why we chose CPS-II as our training cohort for the prognostic modeling.

Table S26 | Histomic feature distribution summaries for all datasets (Excel file).

This table is included as a separate Excel file. Mean and standard deviation value of each of the histomic features in the four datasets used. P-values are two-sided and represent the independent two-sample t-test compared to the CPS-II cohort.

Table S27 | Histomic feature values, HiPS scores, and other data for the TCGA cohort (Excel file).

This table is included as a separate Excel file. The excel sheets are described below:

Sheet	Description
TCGA_HiPSScores	HiPS scores, HiPS group, HiPS subscores, and HiPS sub-subscores (i.e. individual feature risk attribution)
TCGA_HistomicFeatures_Preprocessed	Preprocessed histomic feature values. These have been normalized and imputed using CPS-II data.
TCGA_HistomicFeatures_Raw	Raw histomic feature values for TCGA patients.
CPS-II_FeatureSummaryForZscoring	CPS-II histomic feature-wise mean and standard deviation values used for Z-scoring.
ClinicalFeatures	For convenience, we provide clinical data used for TCGA analysis (see online methods for data sources)
GenomicFeatures	For convenience, we provide genomic data used for TCGA analysis (see online methods for data sources).

Table S28 | Gene Set Enrichment Analysis (GSEA) for HiPS in TCGA (Excel file).

This table is included as a separate Excel file. All P-values shown are two-sided. While interpreting results, it is important to consider that the HiPS score is the result of a weighted combination of all its component features. Hence, the extent and directionality of gene set enrichment with regard to individual features may or may not be highly concordant with the enrichment results for the overall score. The excel sheets are described below:

Sheet	Description
HiPS_score_Hallmarks	GSEA results for the HiPS score using the <i>MSigDB_Hallmark_2020</i> gene set collection
GlobalCAFDensity_Hallmarks	GSEA results for the HiPS feature <i>GlobalCAFDensity</i> using <i>MSigDB_Hallmark_2020</i>
PeriCAFMatrixHet_Hallmarks	GSEA results for the HiPS feature <i>PeriCAFMatrixHeteroIn512uMROI</i> using <i>MSigDB_Hallmark_2020</i>
ChromatinClumpOfTILsNu_Hall	GSEA results for the HiPS feature <i>ChromatinClumpingOfTILsNuclei</i> using <i>MSigDB_Hallmark_2020</i>
ChromatinClumpOfTILsNuc_Azi	GSEA results for the HiPS feature <i>ChromatinClumpingOfTILsNuclei</i> using <i>Azimuth_Cell_Types_2021</i>
ComplexOfCAFNuclBou_Hall	GSEA results for the HiPS feature <i>ComplexityOfCAFNuclBoundary</i> using <i>MSigDB_Hallmark_2020</i>
ComplexCAFNuclBou_Azi	GSEA results for the HiPS feature <i>ComplexityOfCAFNuclBoundary</i> using <i>Azimuth_Cell_Types_2021</i>
HiPS_gene_correlations	Pearson correlation between the HiPS score and select HiPS features with gene expression

Table S29 | Summary of the datasets used in the development and validation of the HiPS signature.

Task	Dataset			
	CPS-II	TCGA	PLCO	CPS-3
Training the panoptic segmentation model	X	X		
Learning feature normalization values for z-scoring	X			
Histomic feature selection with univariable Cox regression	X			
Learning feature weights for the HiPS score with regularized Cox regression	X			
Learning cutoff values for the HiPS groups	X			
Demonstrating survival predictive value of HiPS	X	X	X	
Demonstrating HiPS associations with known survival risk clinical profiles	X	X	X	X
Demonstrating HiPS associations with gene expression data		X		

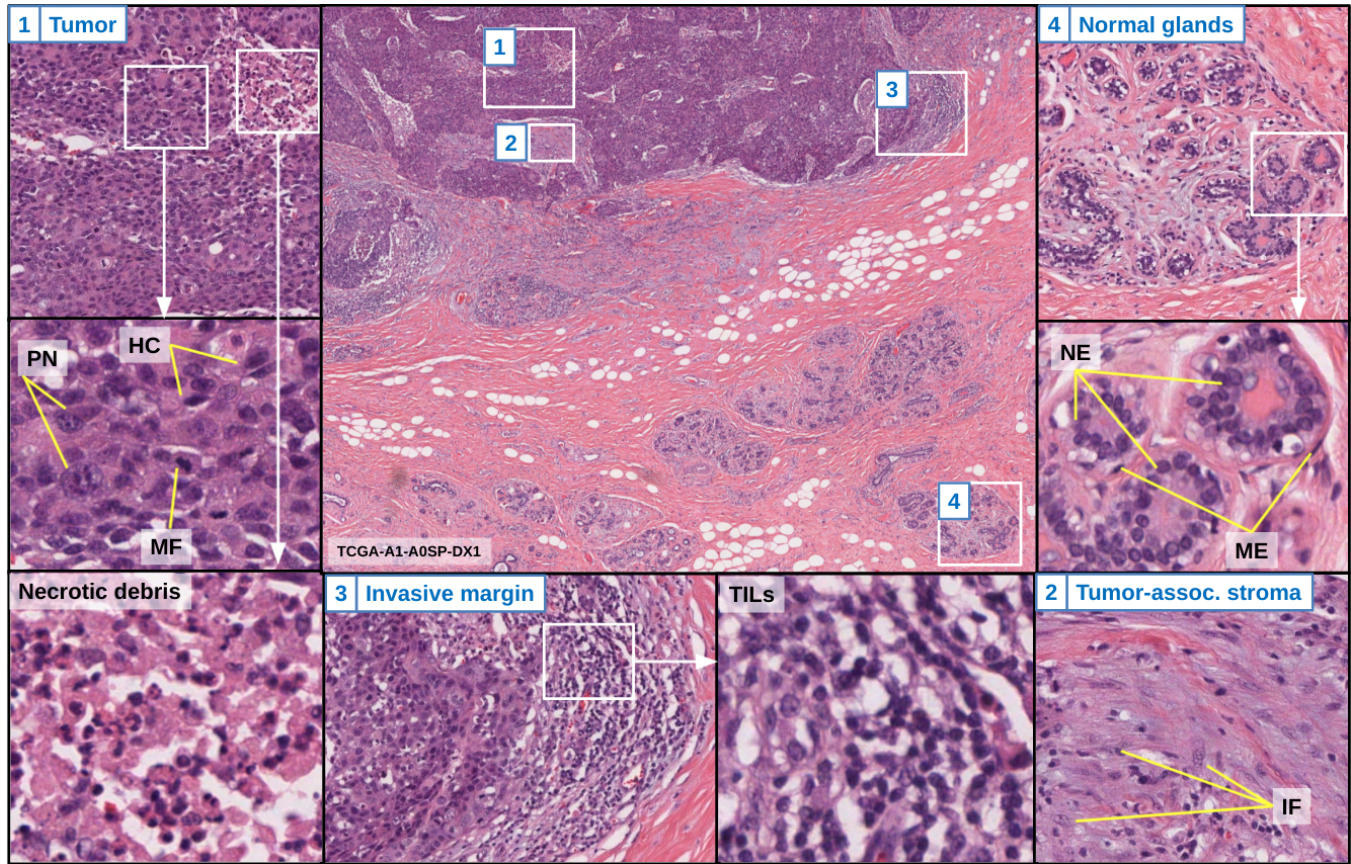


Fig. S1 | Histologic characteristics of the breast cancer tumor microenvironment (TME).

Most breast cancers are carcinomas arising from epithelial cells in ductal or lobular tissue. While the Nottingham grading criteria focus solely on epithelial (cancerous) tissue, the TME is heterogeneous and contains various other elements, including stromal cells, immune cells, acellular matrix, and necrotic debris. Breast cancers are complex to assess computationally, largely due to the morphologic variability of their composition. Note the differences between the tumor region in the upper corner and compare it to the central and lower portions of the field. Disturbed tissue architecture and poor differentiation are characteristic of high-grade tumors, which are, in turn, typically associated with poor patient survival outcomes. Region 1 shows a tumor region with evident architectural disruption, cell crowding, and cellular death (necrotic debris). Neoplastic nuclei show a significant degree of pleomorphism (note the variability in sizes in the left central box), hyperchromasia (HC), and prominent nucleoli (PN). A mitotic figure (MF) is also seen. Region 2 shows tumor-associated stroma with immature fibroblasts (IF), which are plumper and less dense than normal fibroblasts. Immature fibroblasts are increasingly being recognized as a prognostic indicator in some cancers. Region 3 shows the invasive margin of the tumor, with tumor-infiltrating lymphocytes (TILs). Region 4 shows a normal breast acinus. Note how orderly the glands are, showing diverse but uniform cellular elements, including normal epithelium (NE) and myoepithelium (ME). This WSI was obtained from the TCGA dataset.

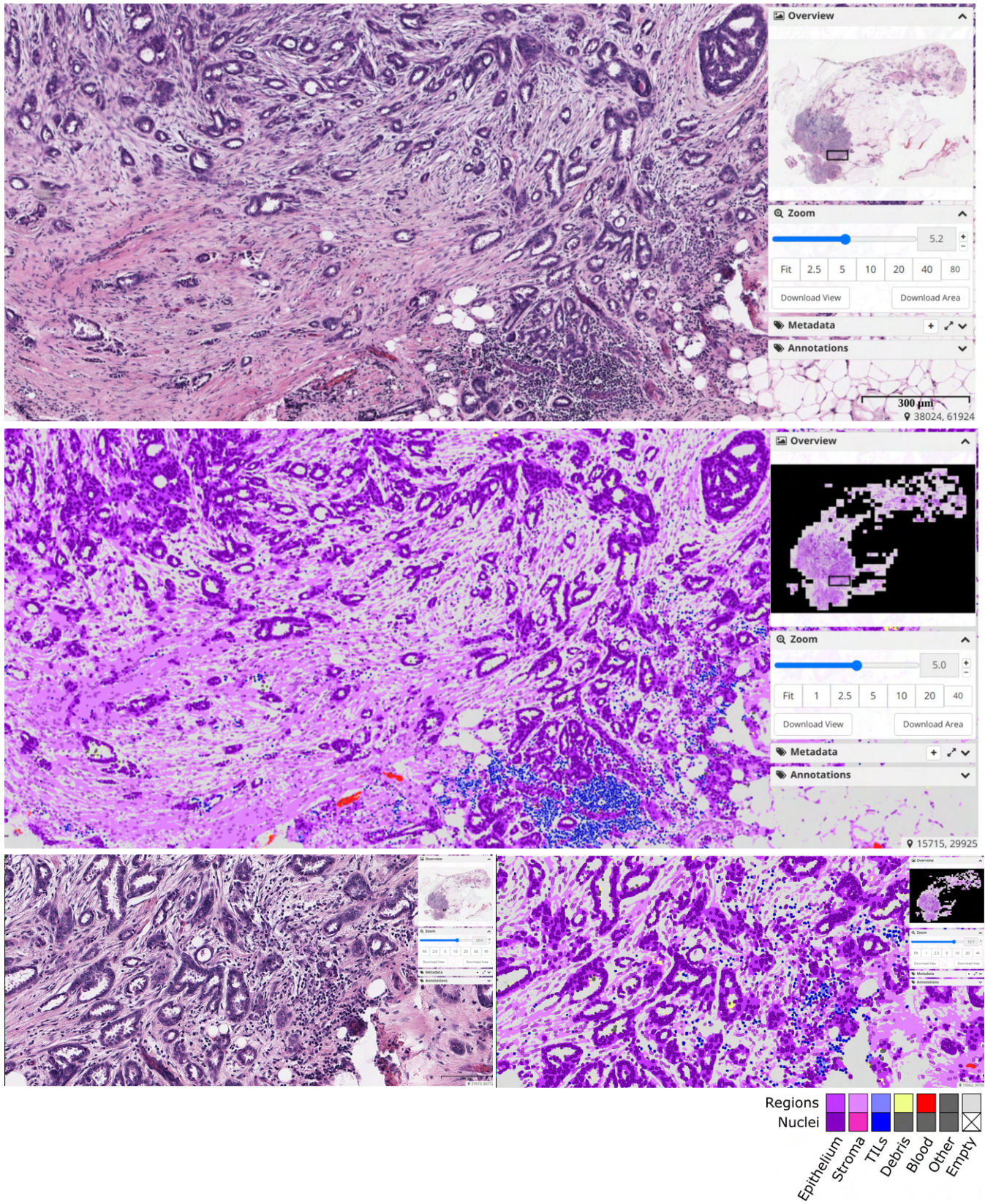


Fig. S2 | Sample panoptic segmentation results from the PLCO dataset (example 1).

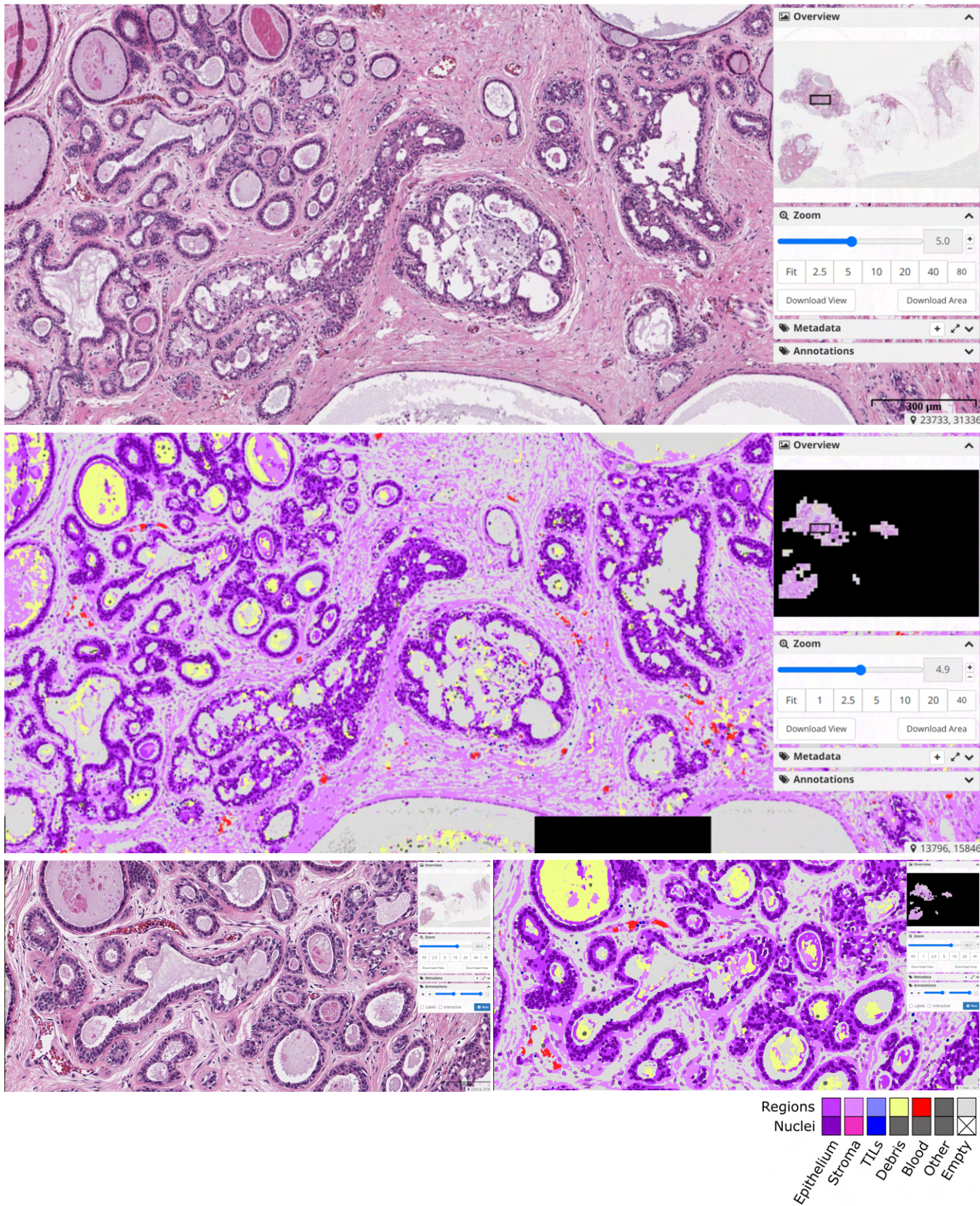


Fig. S3 | Sample panoptic segmentation results from the PLCO dataset (example 2).

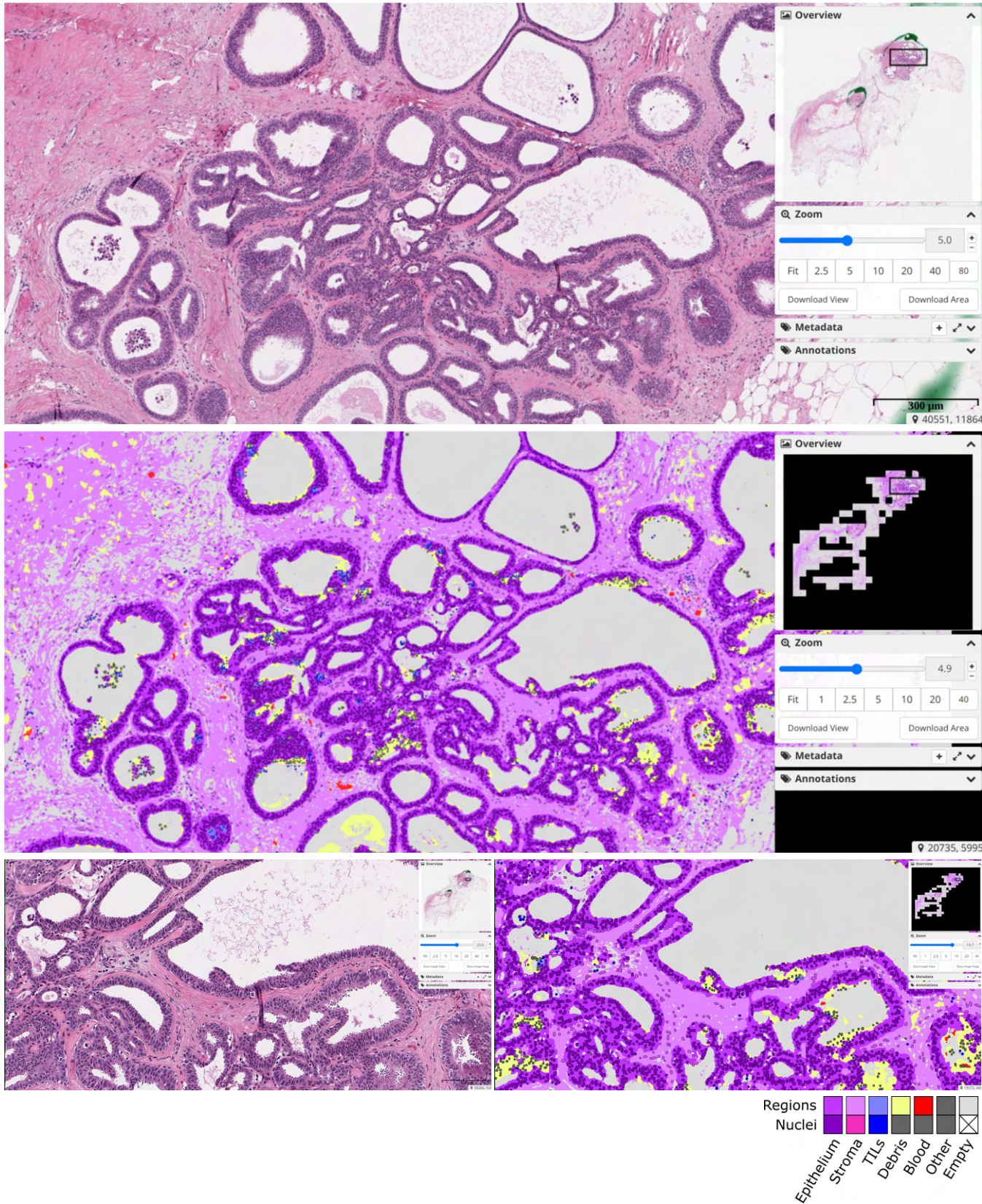


Fig. S4 | Sample panoptic segmentation results from the PLCO dataset (example 3).

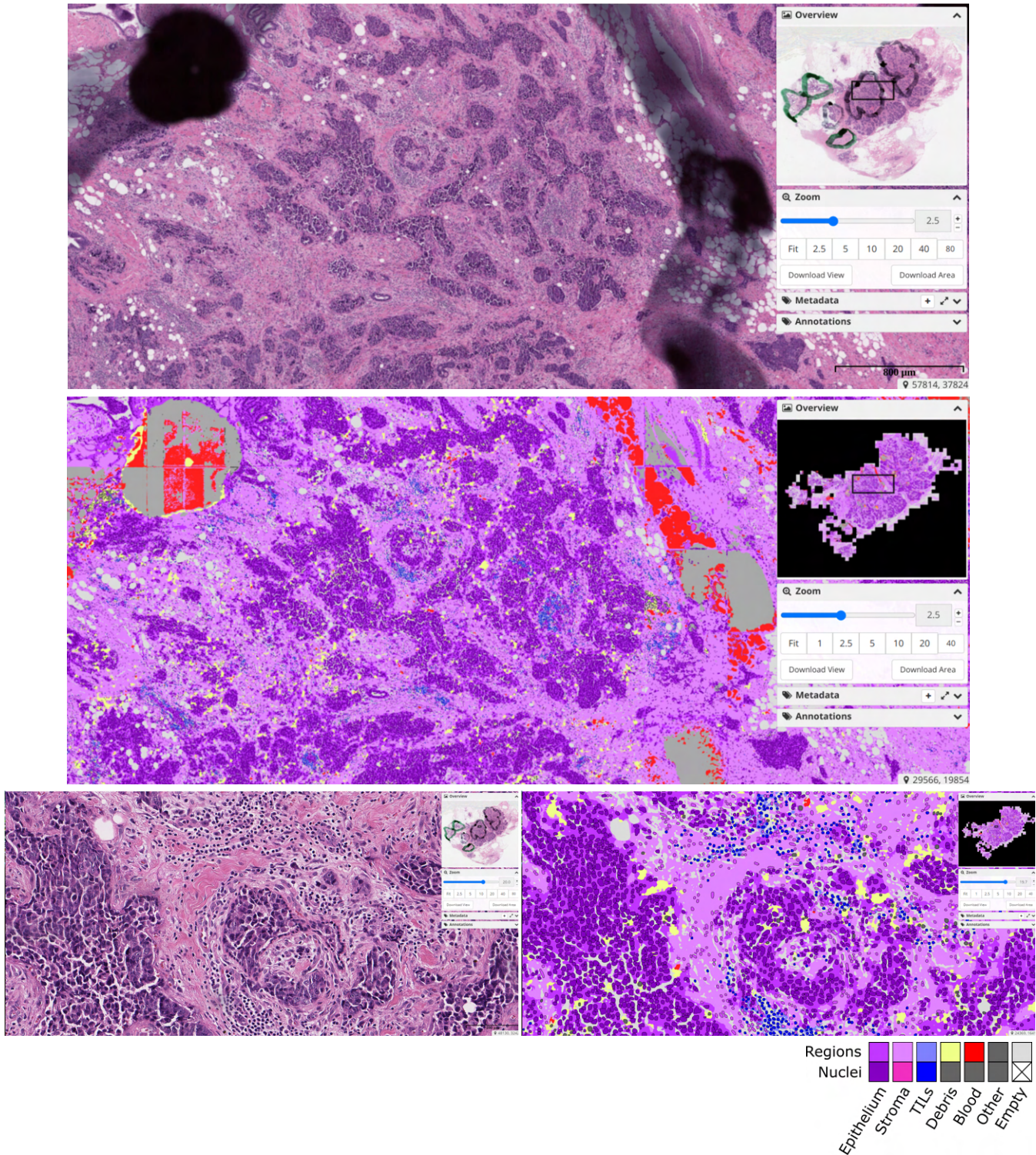


Fig. S5 | Effect of pen markings on panoptic segmentation results in the PLCO dataset.

Several slides had pen markings on them in the PLCO dataset. While the best way to handle this problem is to re-scan slides after wiping off the markings, we did not have that option for PLCO and TCGA. To mitigate this issue, we used color thresholding profiles to exclude red, green, and blue pen markings before WSI tiling. Black pen markings were tricky to exclude due to their inconspicuous color profile. However, the MuTILs model was generally able to handle these artifacts by assigning them to the “Other” or “Blood” classes which are irrelevant for feature extraction.

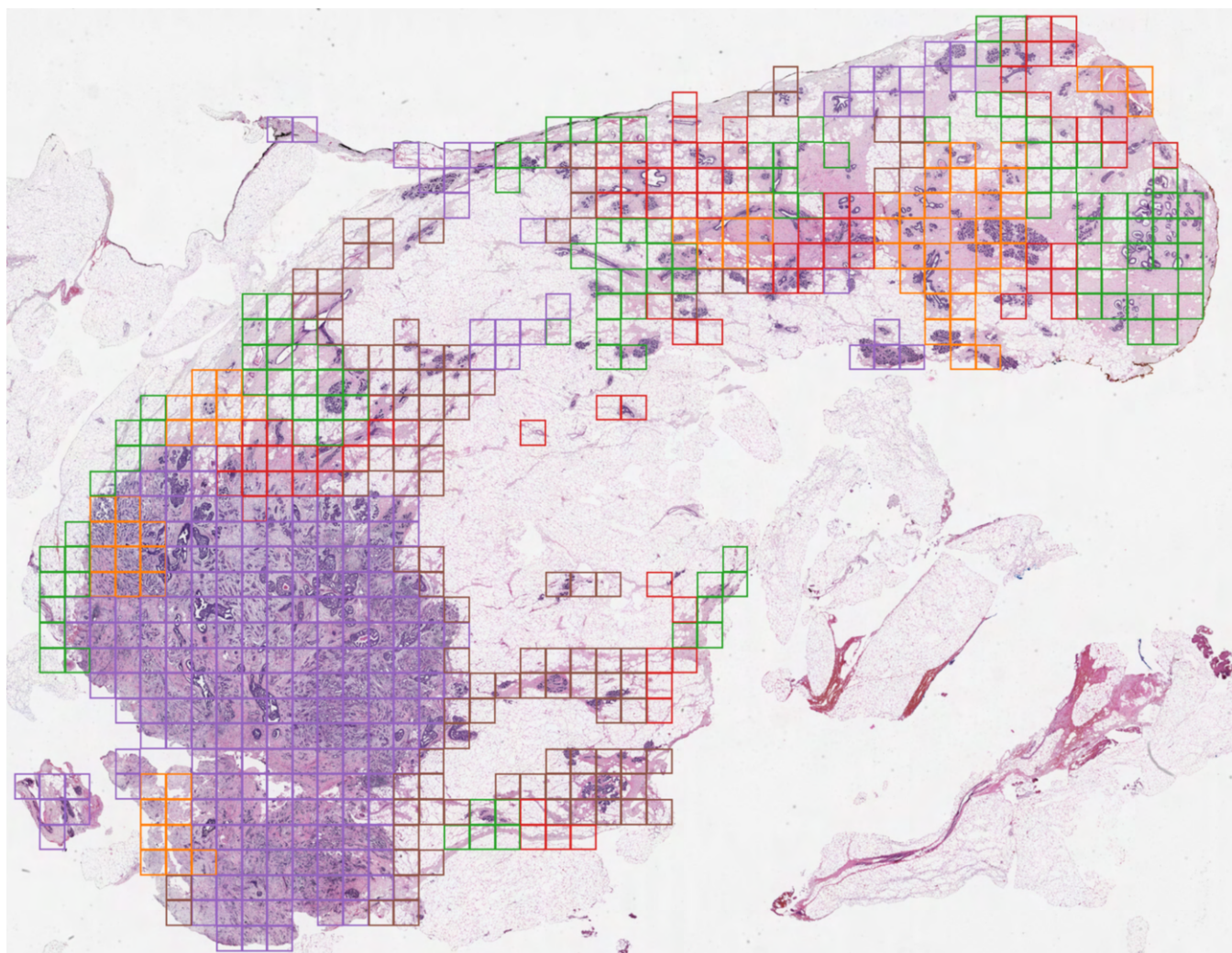


Fig. S6 | Region of interest assignment to different sets of MuTILs model weights.

After superpixel decomposition and region adjacency clustering at a 20 MPP resolution, the WSI was tiled into 512x512 μm ROIs, and each ROI was assigned to the superpixel cluster it maximally overlaps with. Each superpixel cluster was randomly assigned one of the five trained MuTILs models. Model weight assignment is color encoded here.

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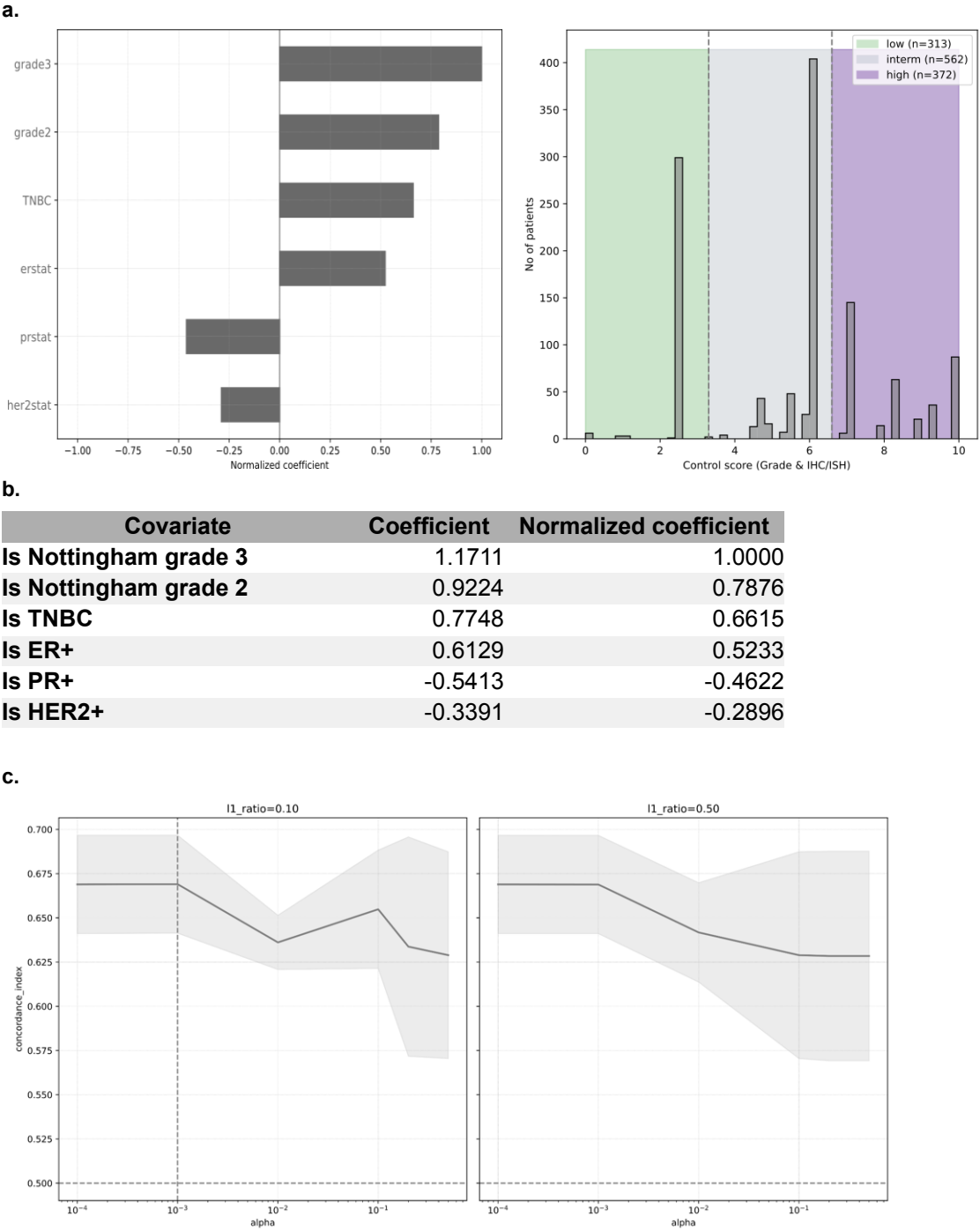
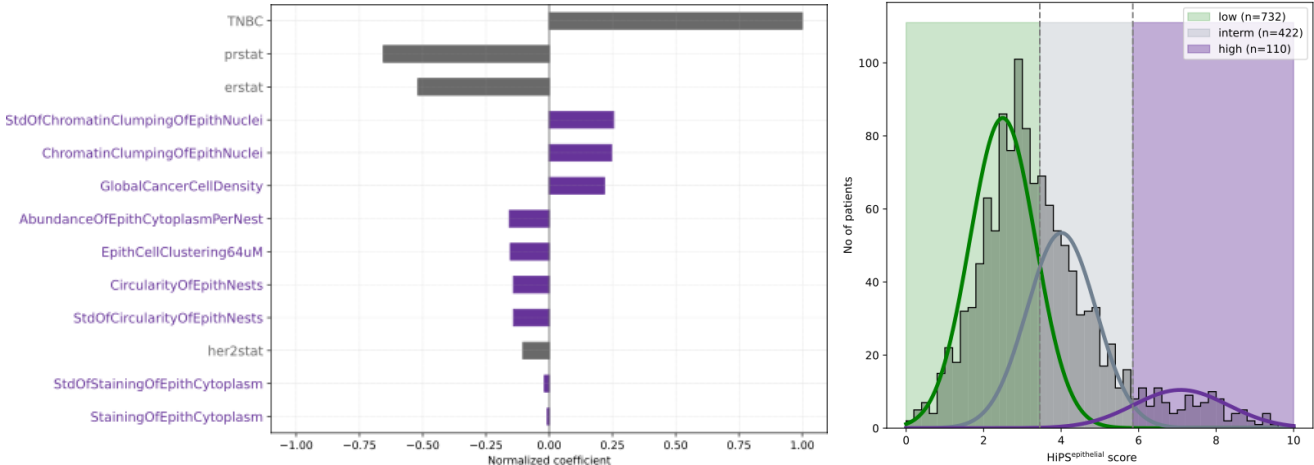


Fig. S7 | Feature weights and distribution of the Control scores in CPS-II.
a. Relative feature weights of the optimum model. Thresholds are at 3.3 and 6.6. **b.** Precise feature weights and normalized coefficients. **c.** Cross-validation fine-tuning of the Control model parameters. The plot shows the mean and error bands represent the standard deviation.

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a.



b.

Covariate	Coefficient	Normalized coefficient
Is TNBC	6.154E-07	1.0000
Is PR+	-4.034E-07	-0.6555
Is ER+	-3.192E-07	-0.5187
StdOfChromatinClumpingOfEpithNuclei	1.568E-07	0.2549
ChromatinClumpingOfEpithNuclei	1.511E-07	0.2456
GlobalCancerCellDensity	1.340E-07	0.2177
AbundanceOfEpithCytoplasmPerNest	-9.709E-08	-0.1578
EpithCellClustering64uM	-9.457E-08	-0.1537
CircularityOfEpithNests	-8.706E-08	-0.1415
StdOfCircularityOfEpithNests	-8.689E-08	-0.1412
Is HER2+	-6.375E-08	-0.1036
StdOfStainingOfEpithCytoplasm	-1.156E-08	-0.0188
StainingOfEpithCytoplasm	-4.573E-09	-0.0074

c.

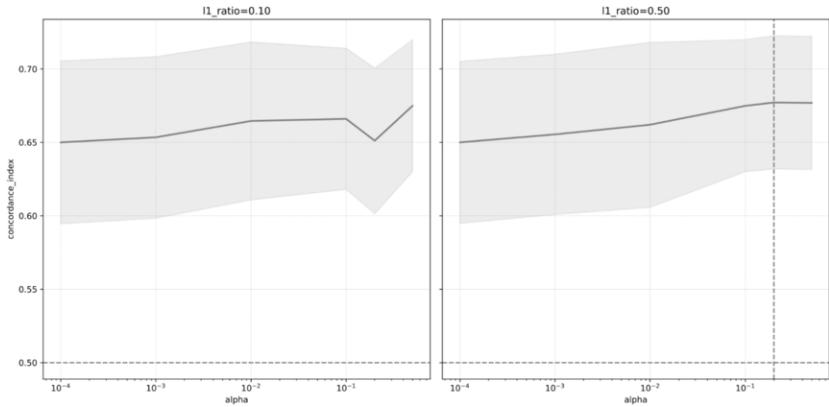


Fig. S8 | Feature weights and distribution of the HiPSepithelial scores in CPS-II.

a. Relative feature weights if the optimum model. Thresholds are at 3.45 and 5.85. **b.** Precise feature weights and normalized coefficients. **c.** Cross-validation fine-tuning of the HiPSepithelial model parameters. The plot shows the mean and error bands represent the standard deviation.

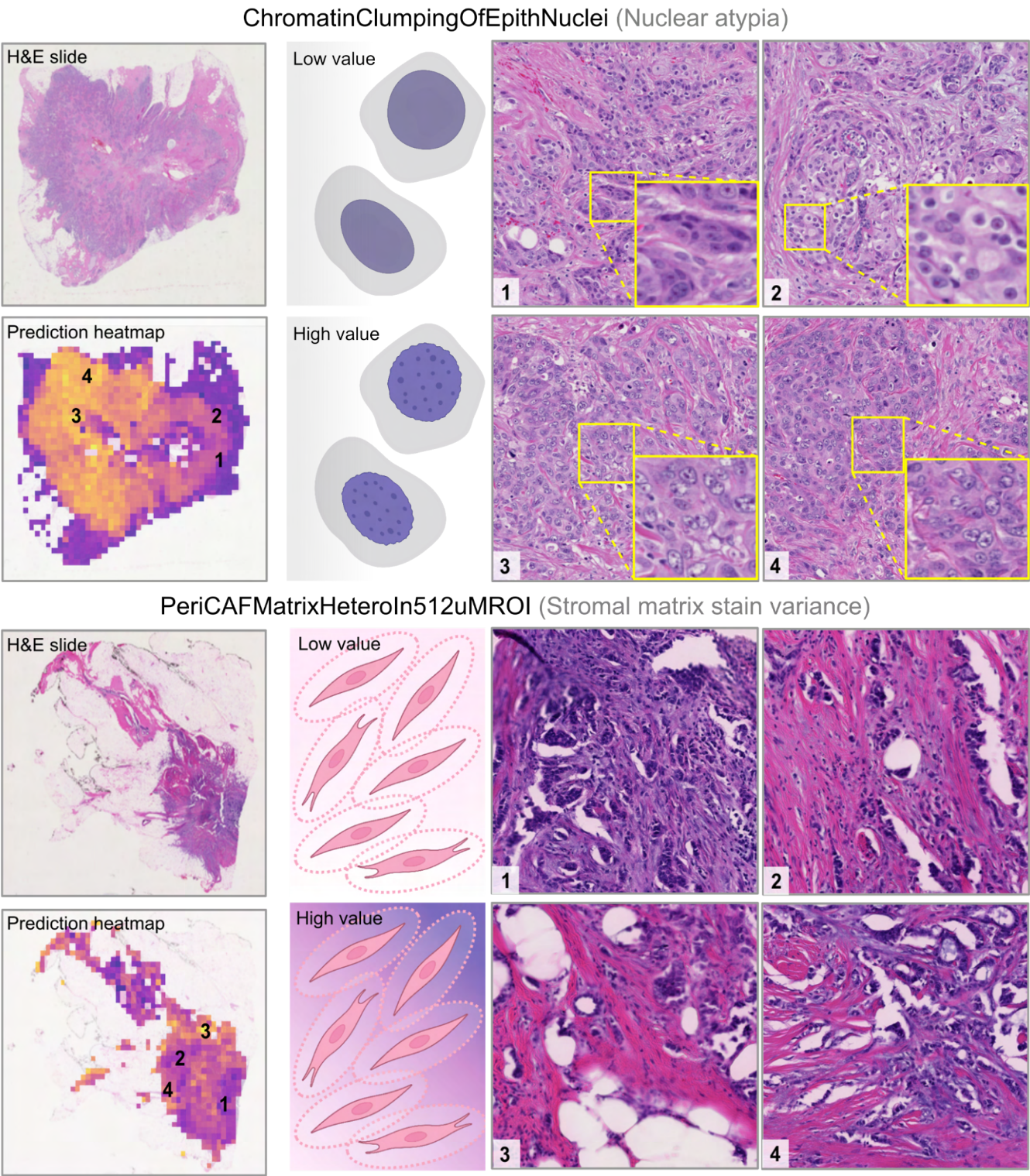


Fig. S9 | Visualization of the WSI spatial variation in two influential HiPS features.
The feature values were aggregated using weighted mean and variance to obtain a single value per patient. Created in part with BioRender.

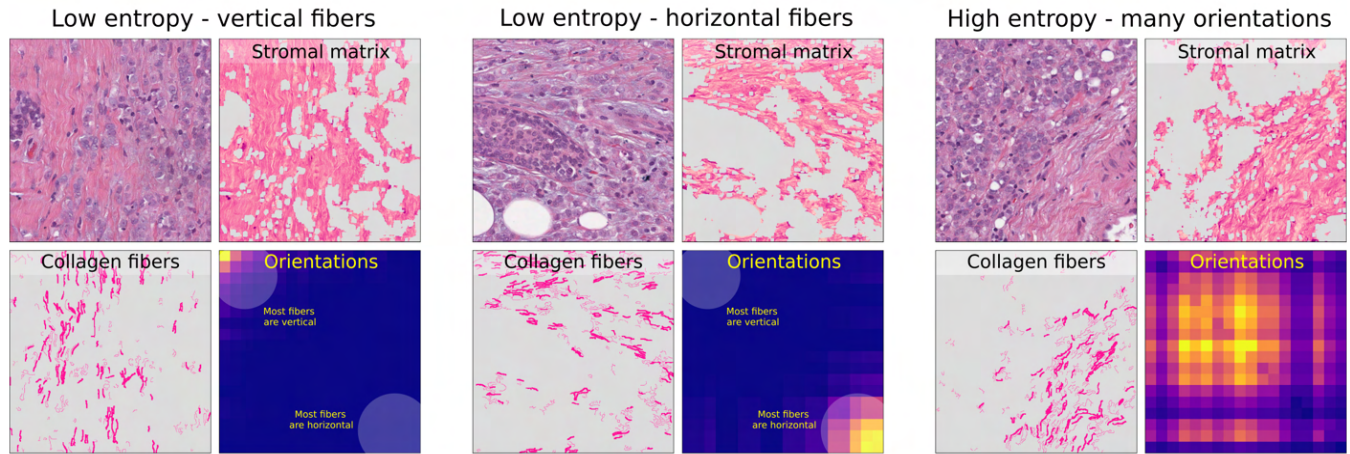


Fig. S10 | Calculating features for the acellular stromal matrix and collagen fibers.

The first step is removing all cellular material from the image, leaving only the acellular stroma. Various staining properties are extracted at this stage, including the highly prognostic PeriCAFMatrixHeteroIn512uMROI. Then we use an edge detection algorithm and other morphological operators to isolate the collagen fibers. Fibers with a low minor-to-major axis ratio were considered straight fibers (thickened here). Finally, we measured the entropy in the orientation of the straight collagen fibers. The orientations matrix shows the co-occurrence of fibers with various orientations. For example, if most fibers are vertical, this would be a low entropy field with co-occurrences in the top-left corner of the orientations matrix. We found the waviness of collagen fibers, but not their entropy, to influence the HiPS score.

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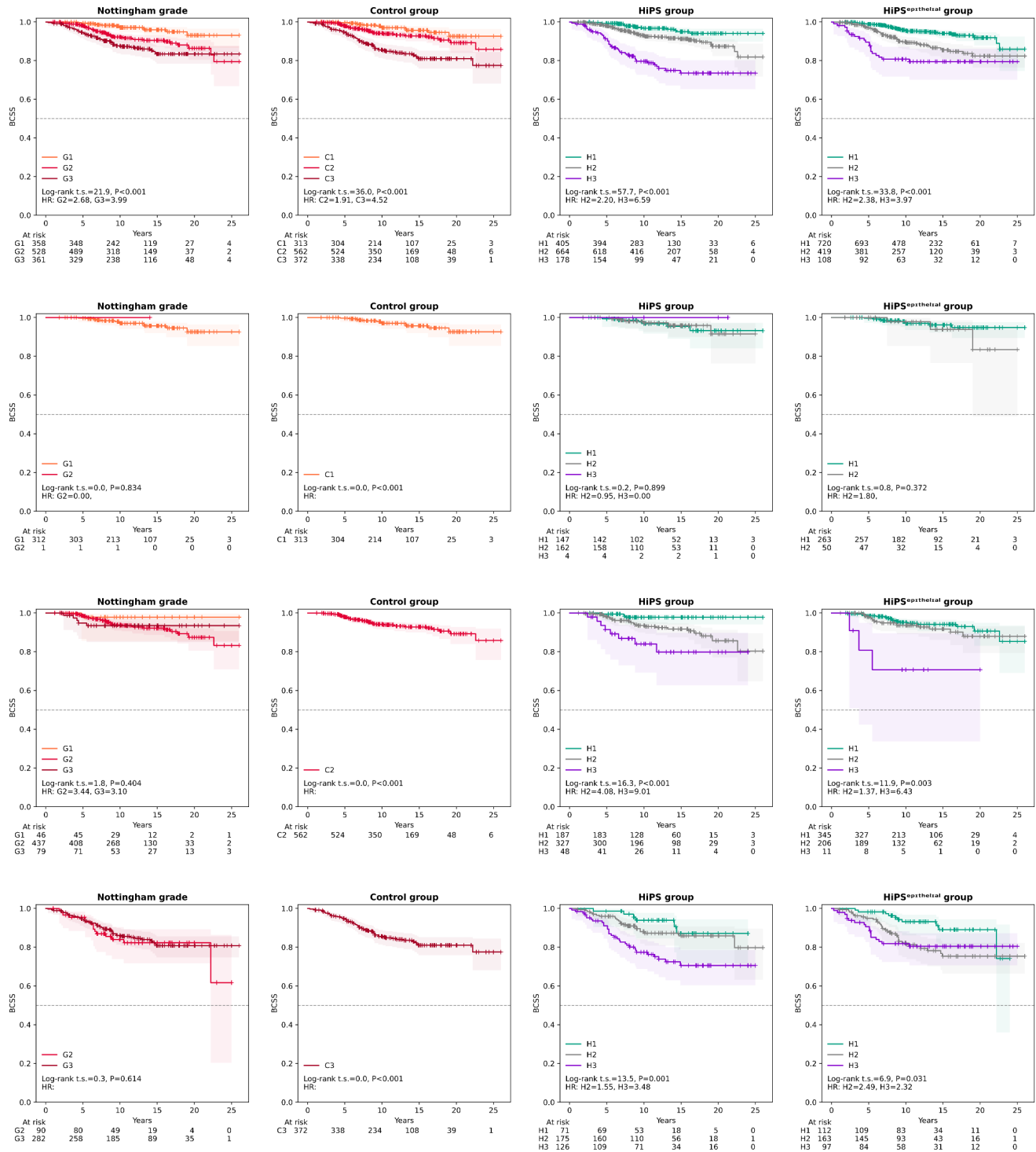


Fig. S11 | Kaplan-Meier curves for BCSS using grading vs. HiPS in the CPS-II cohort.
Top row: Comparison of stratification in the entire cohort. Second row onward: stratification within Control groups 1-3. Error bands represent the exponential Greenwood 95% confidence intervals.

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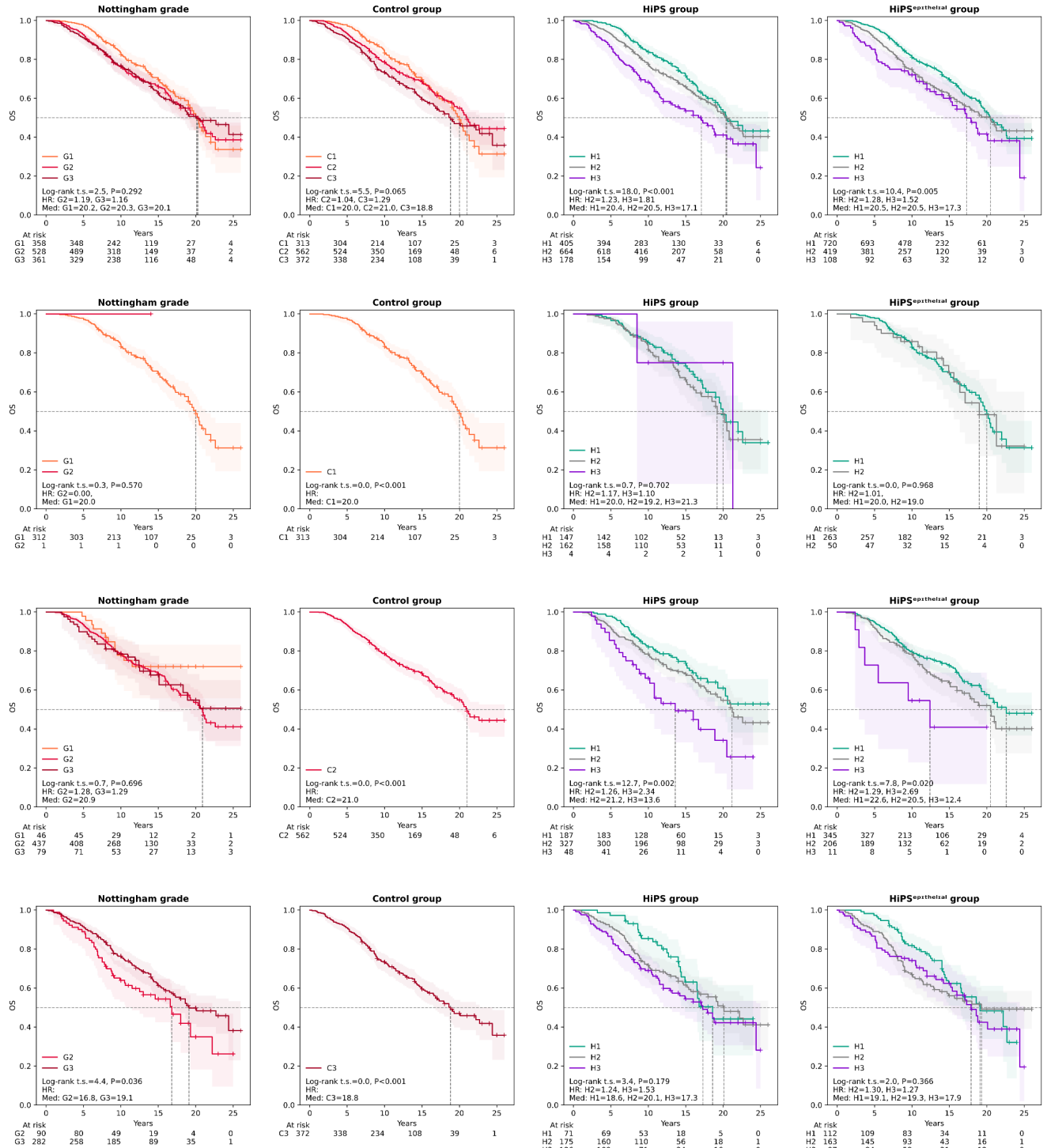


Fig. S12 | Kaplan-Meier curves for OS using grading vs. HiPS in the CPS-II cohort.

Top row: Comparison of stratification in the entire cohort. Second row onward: stratification within Control groups 1-3. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

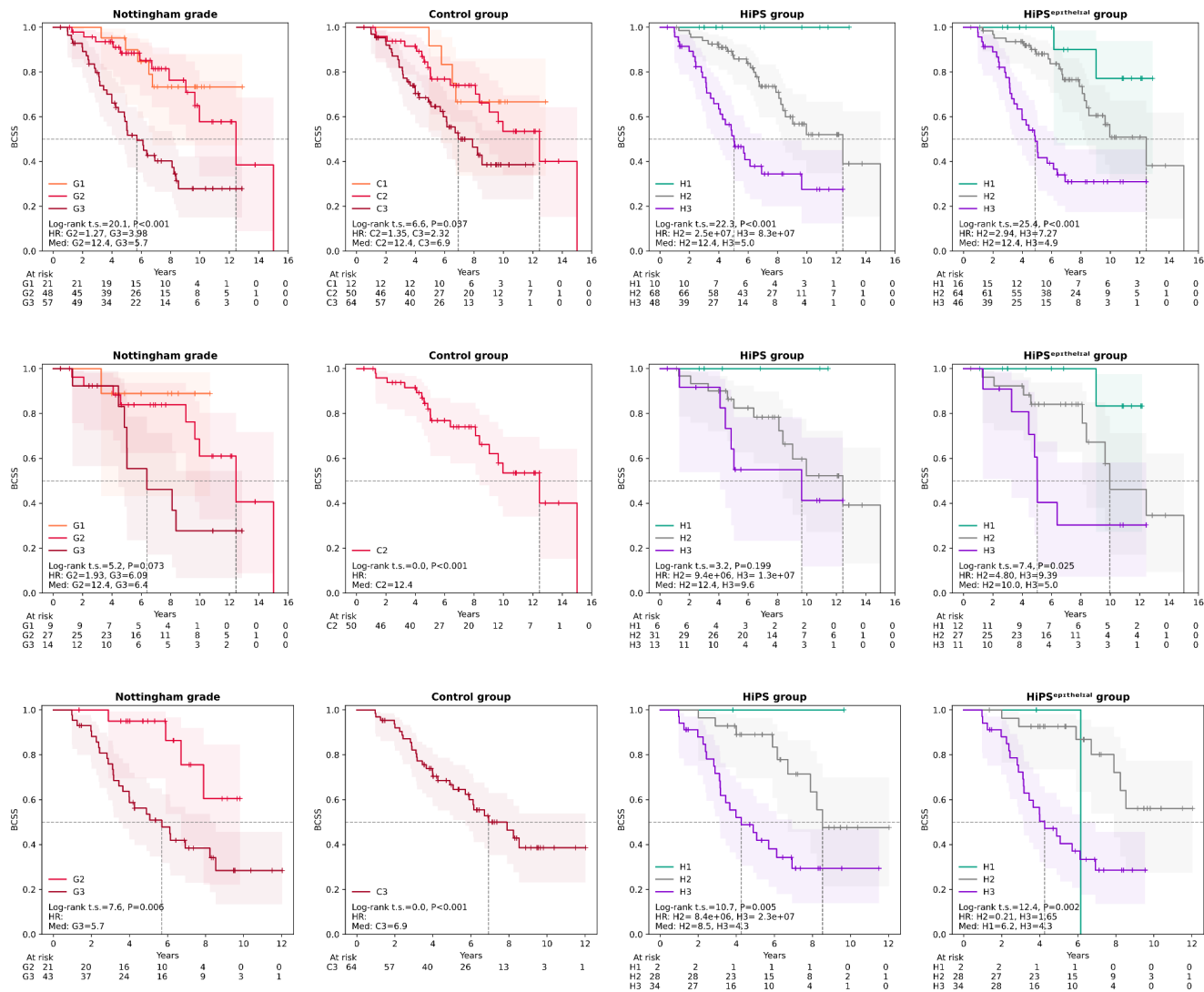


Fig. S13 | Kaplan-Meier curves for BCSS using grading vs. HiPS in the PLCO cohort.
Top row: Comparison of stratification in the entire cohort. Second row onward: stratification within Control groups 2-3. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

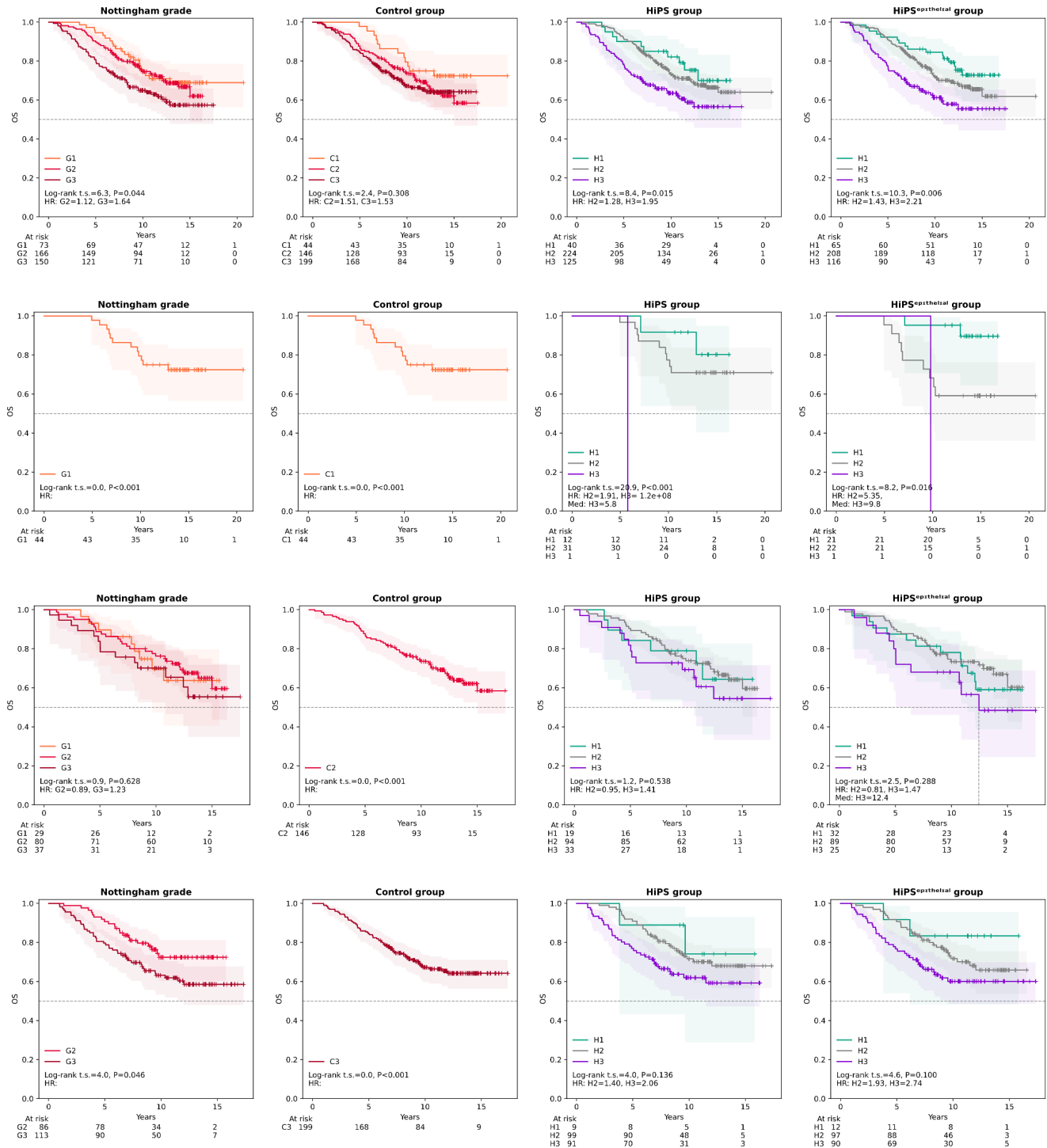


Fig. S14 | Kaplan-Meier curves for OS using grading vs. HiPS in the PLCO cohort.
Top row: Comparison of stratification in the entire cohort. Second row onward: stratification within Control groups 1-3. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

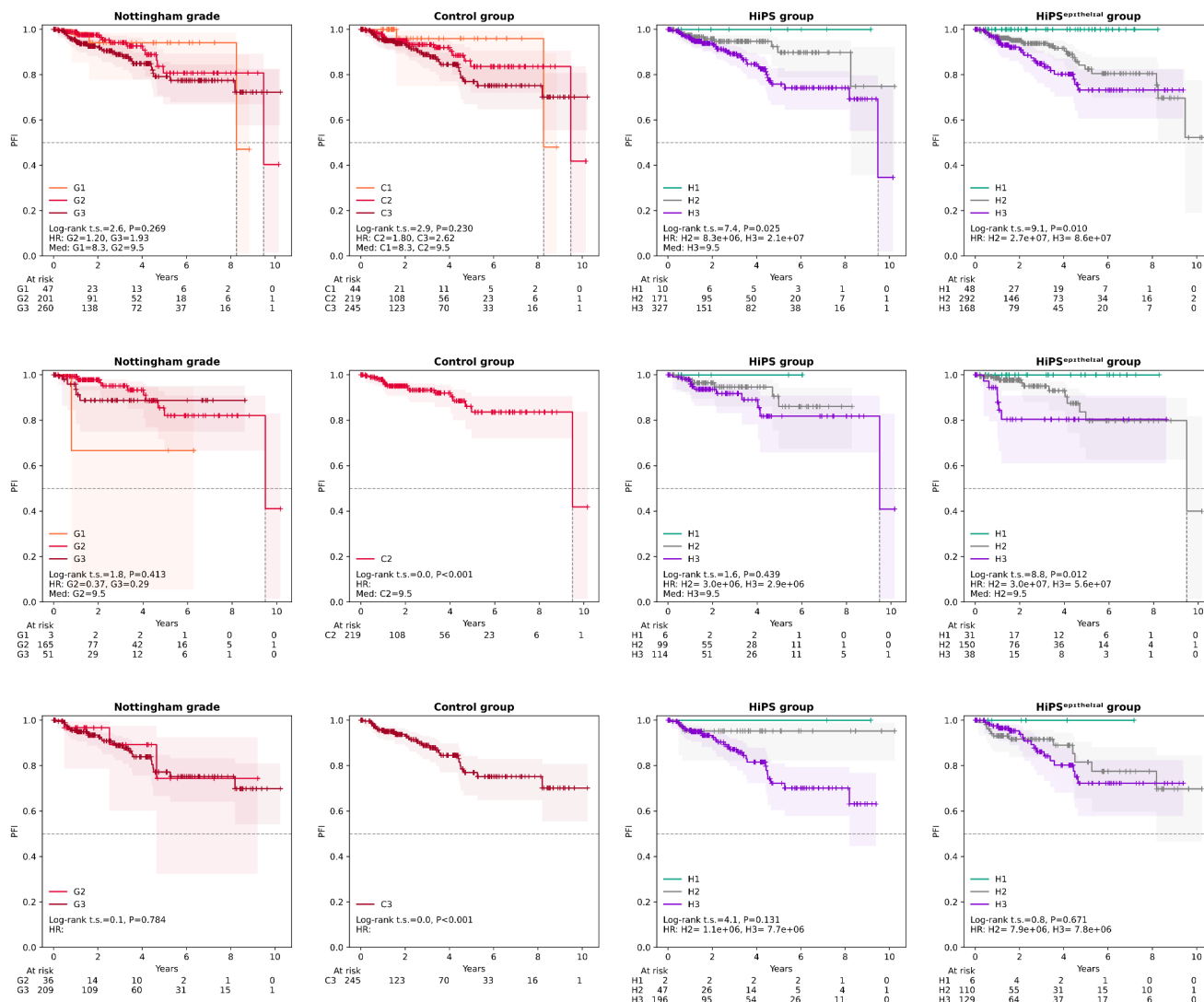


Fig. S15 | Kaplan-Meier curves for PFI using grading vs. HiPS in the TCGA cohort.

Top row: Comparison of stratification in the entire cohort. Second row onward: stratification within Control groups 2-3. Error bands represent the exponential Greenwood 95% confidence intervals.

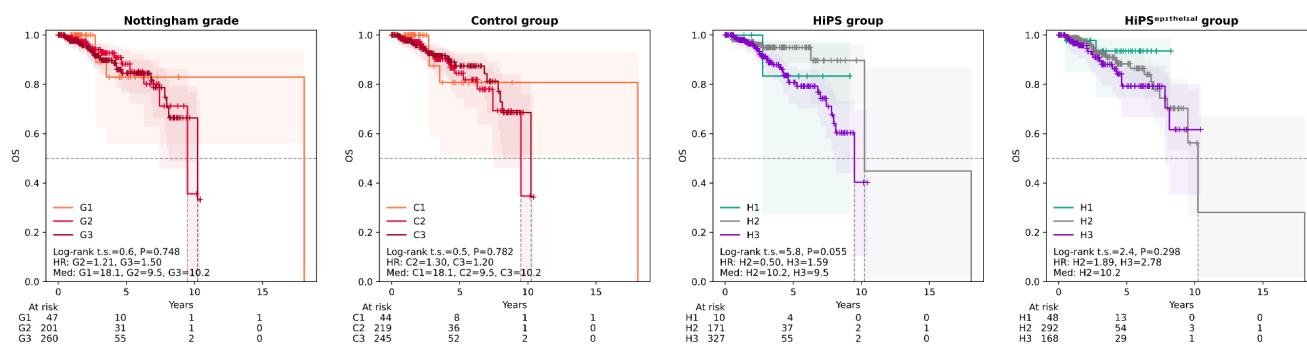


Fig. S16 | Kaplan-Meier curves for OS using grading vs. HiPS in the TCGA cohort. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

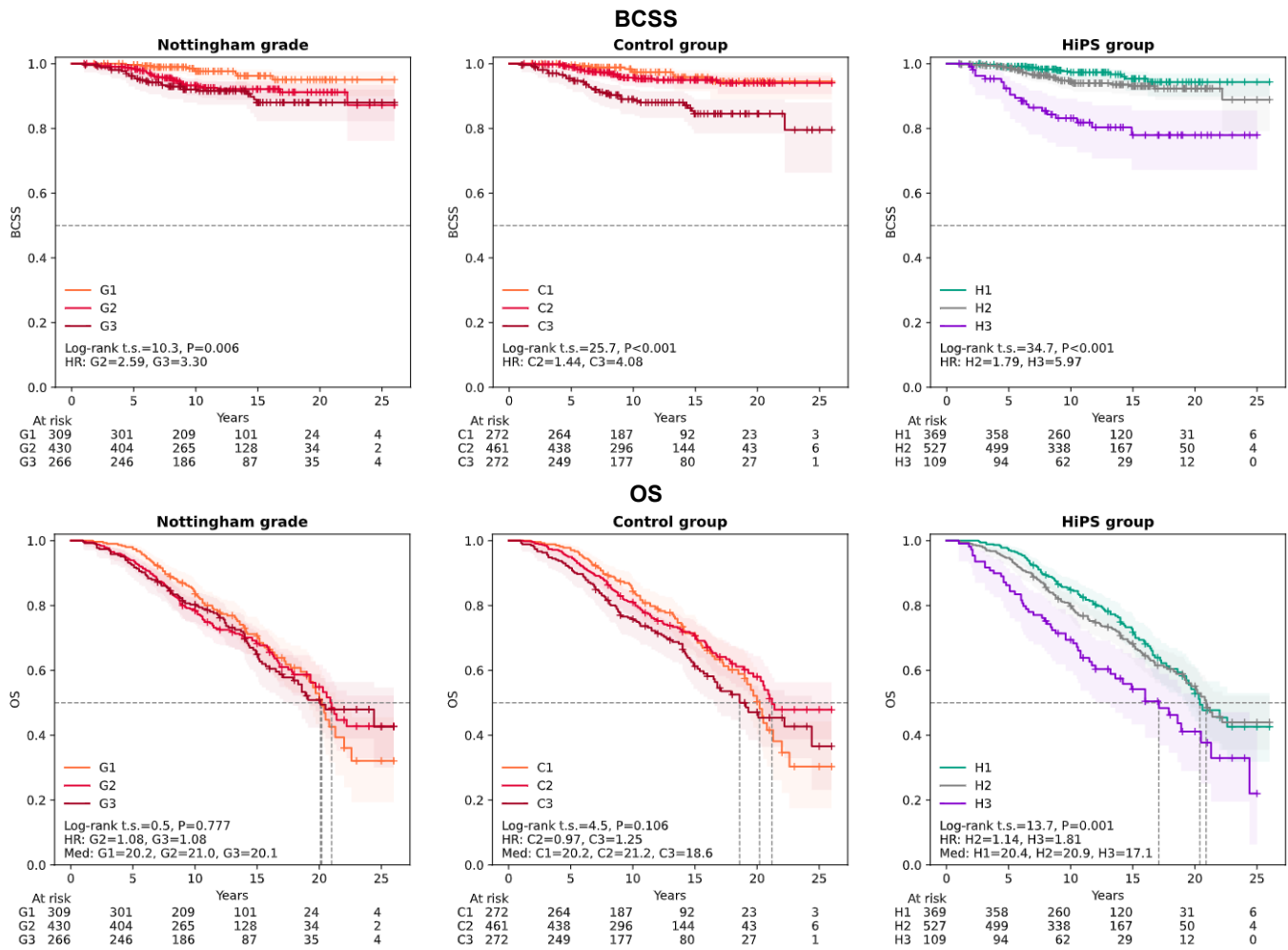


Fig. S17 | Kaplan-Meier curves for TNM stage I cases within the CPS-II cohort. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

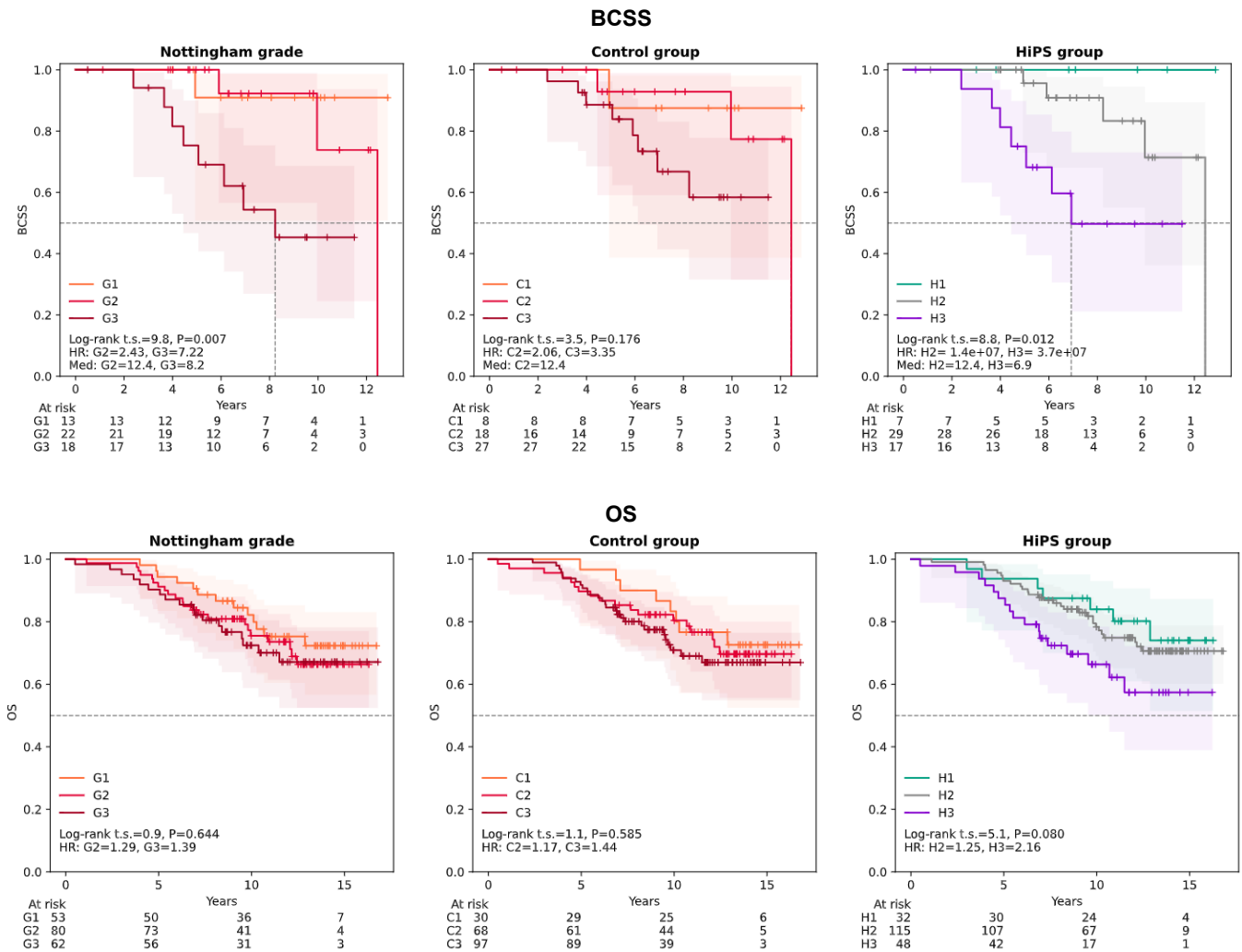


Fig. S18 | Kaplan-Meier curves for TNM stage I cases within the PLCO cohort. Error bands represent the exponential Greenwood 95% confidence intervals.

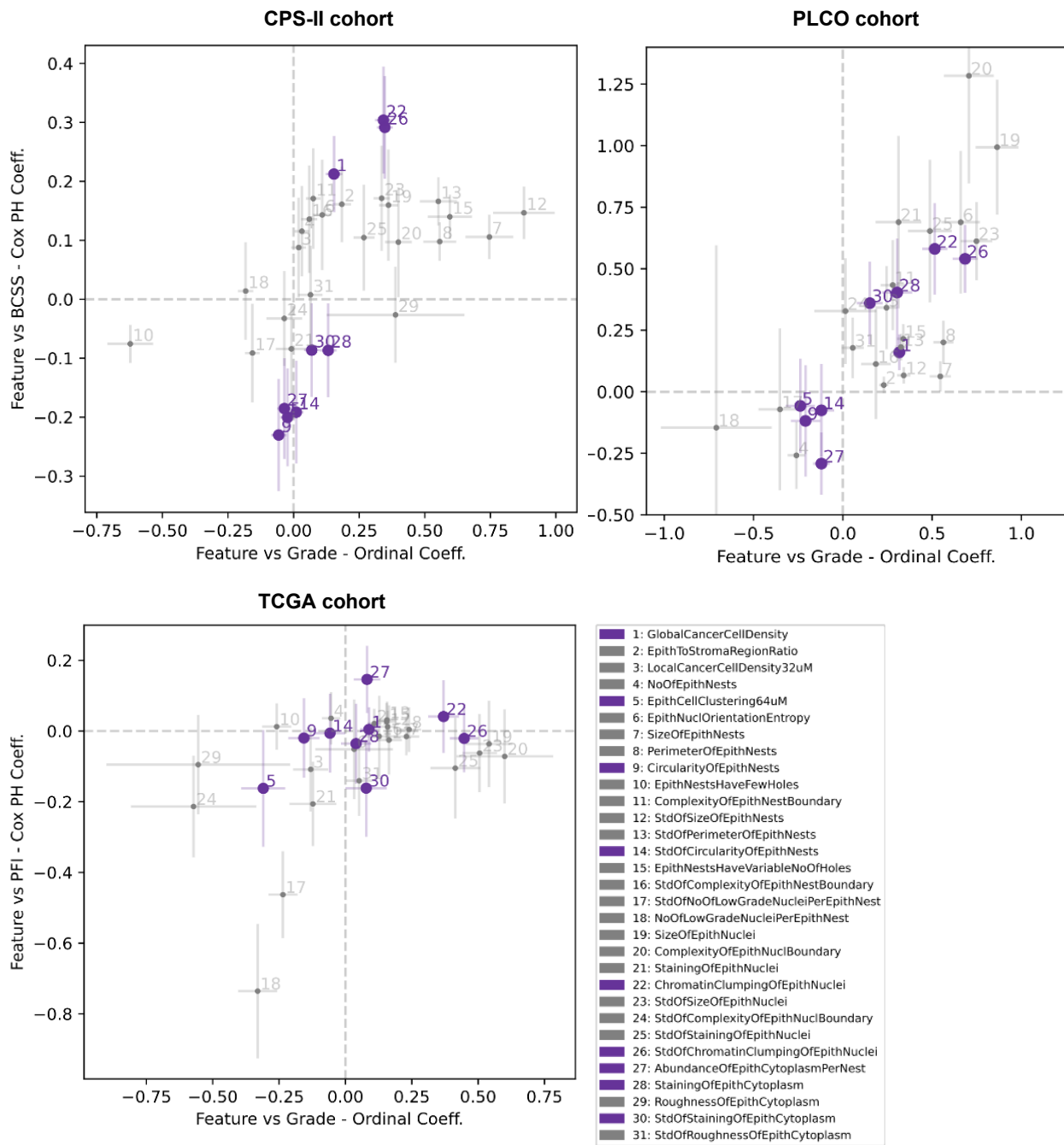


Fig. S19 | Association of epithelial features with grading versus association with survival. Features in purple were the most prognostic in CPS-II and were thus included in HiPS, and error bars represent the standard error. Many of our epithelial features provide objective measurements of the Nottingham grading criteria, including tubule formation (i.e., gland architectural disruption) and nuclear pleomorphism. While part of Nottingham grading, mitotic figure counting is not captured by our algorithms as we did not have reliable and sufficiently-specific algorithms for its detection. Nonetheless, we show that, at least in TCGA, mitotic grades 2-3 are very highly correlated with the tubule formation and nuclear pleomorphism grades of the Nottingham criteria. We determined the association between our epithelial histomic features and pathologist-determined Nottingham grades from the clinical records to answer two questions: 1. How strong is the association between histomic features and Nottingham grade?; 2. Are the most prognostic histomic features also those with the highest association with Nottingham grade? The latter question helps us empirically measure whether the Nottingham criteria itself is optimal. Univariable associations were measured using ordinal regression (grade) or Cox regression (survival) coefficients. The regression coefficient values are provided in the supplementary tables.

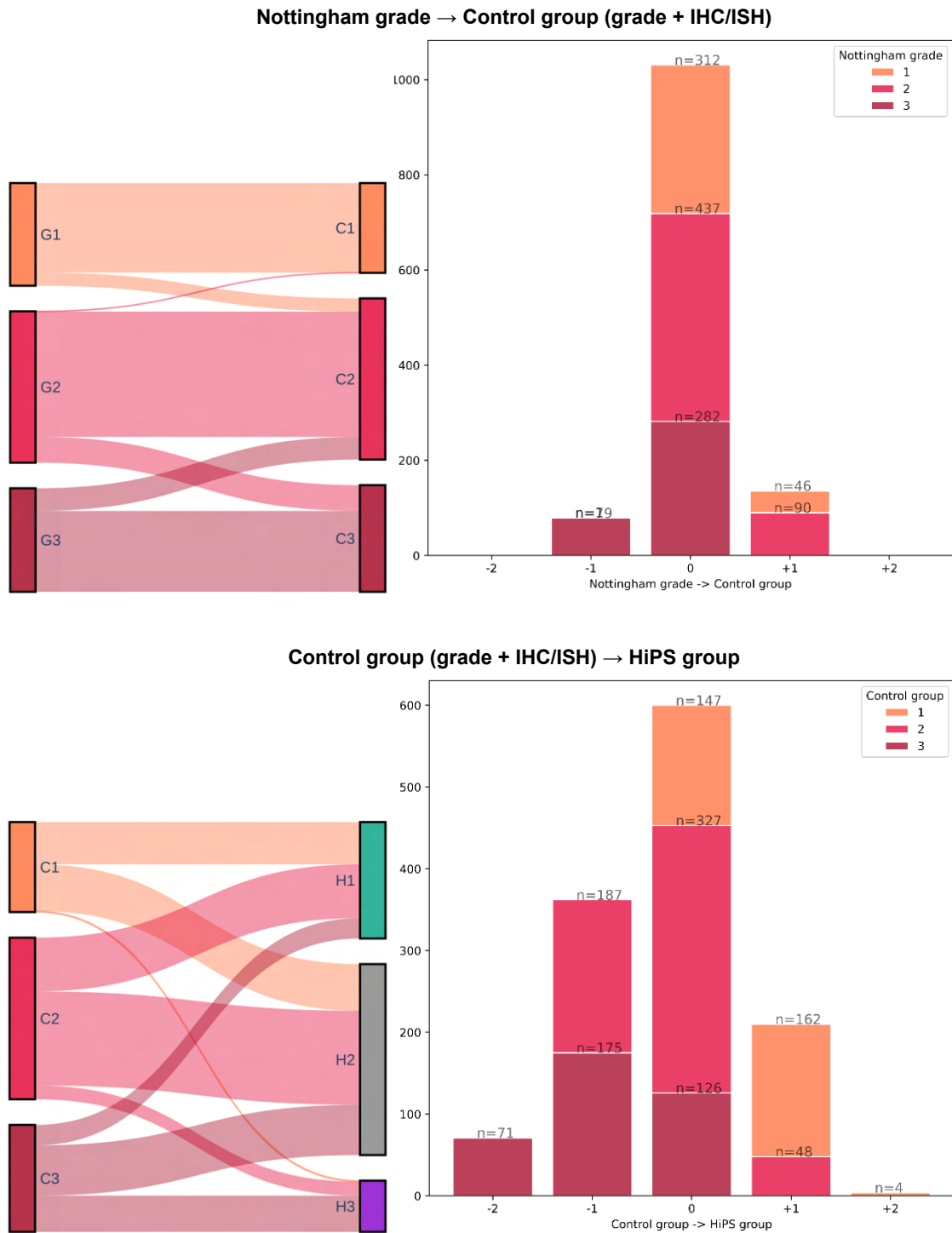


Fig. S20 | Change in risk categories with the Control model and HiPS in CPS-II.
Left: Sankey plots for the change in the risk category. Right: Stacked histogram of the change in risk categories, where colors represent the original category. The x-axis represents the group change; for example, in the top plot, 46 Nottingham grade 1 cases were upgraded by +1 to become Control group C2.

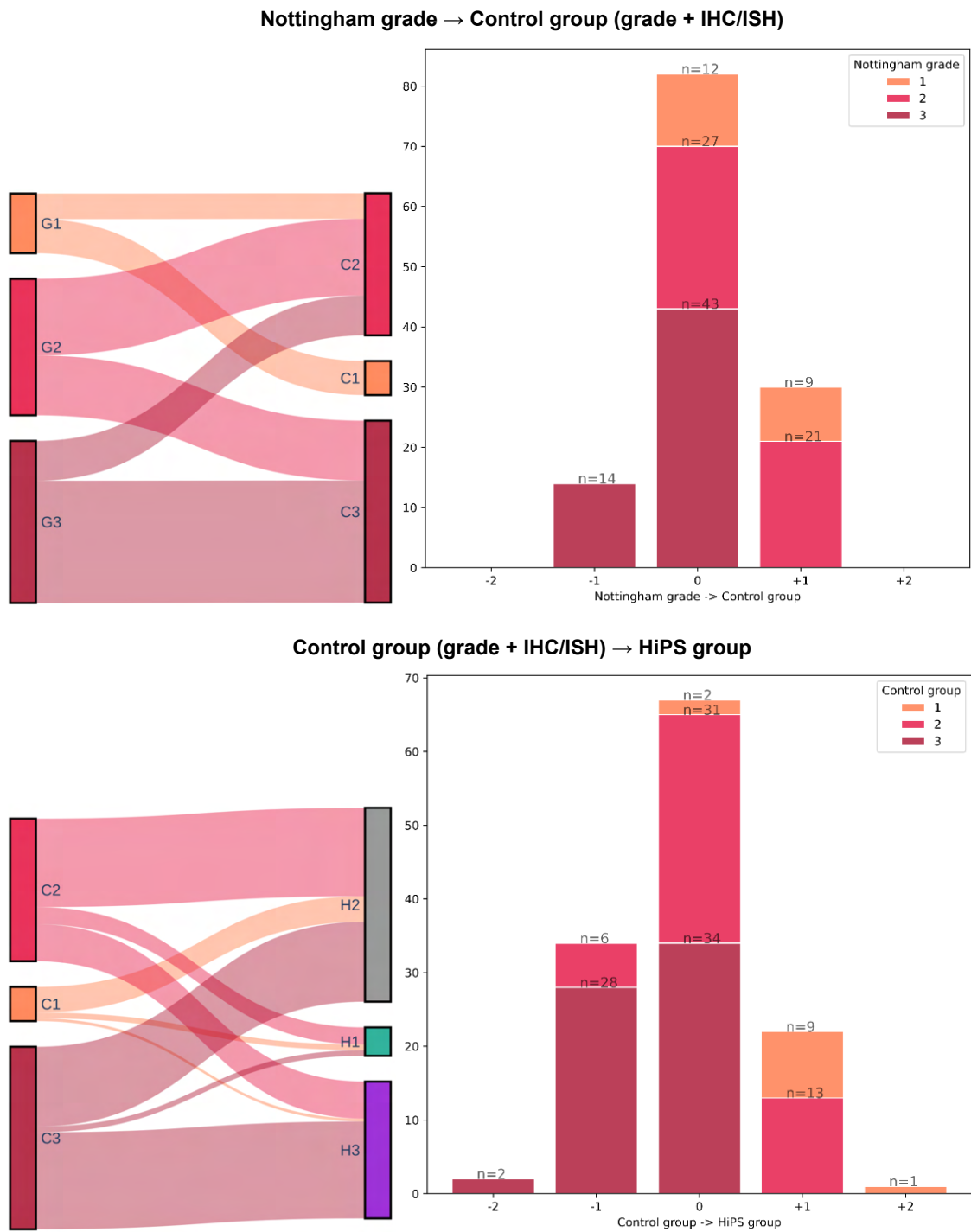


Fig. S21 | Change in risk categories with the Control model and HiPS in PLCO.
Left: Sankey plots for the change in the risk category. Right: Stacked histogram of the change in risk categories, where colors represent the original category. The x-axis represents the group change; for example, in the top plot, 9 Nottingham grade 1 cases were upgraded by +1 to become Control group C2.

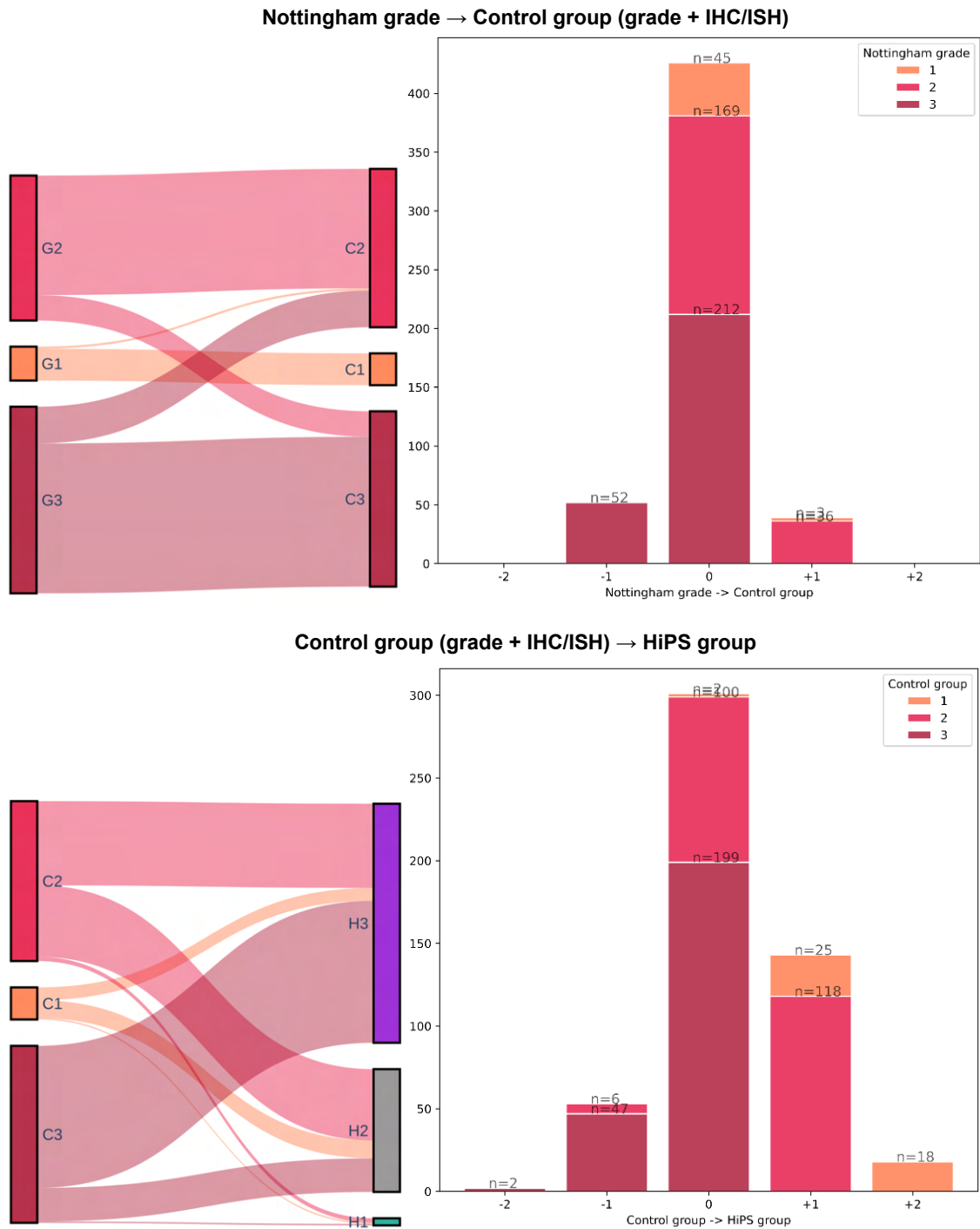


Fig. S22 | Change in risk categories with the Control model and HiPS in TCGA.
Left: Sankey plots for the change in the risk category. Right: Stacked histogram of the change in risk categories, where colors represent the original category. The x-axis represents the group change; for example, in the top plot, 52 Nottingham grade 3 cases were downgraded by -1 to become Control group C2.

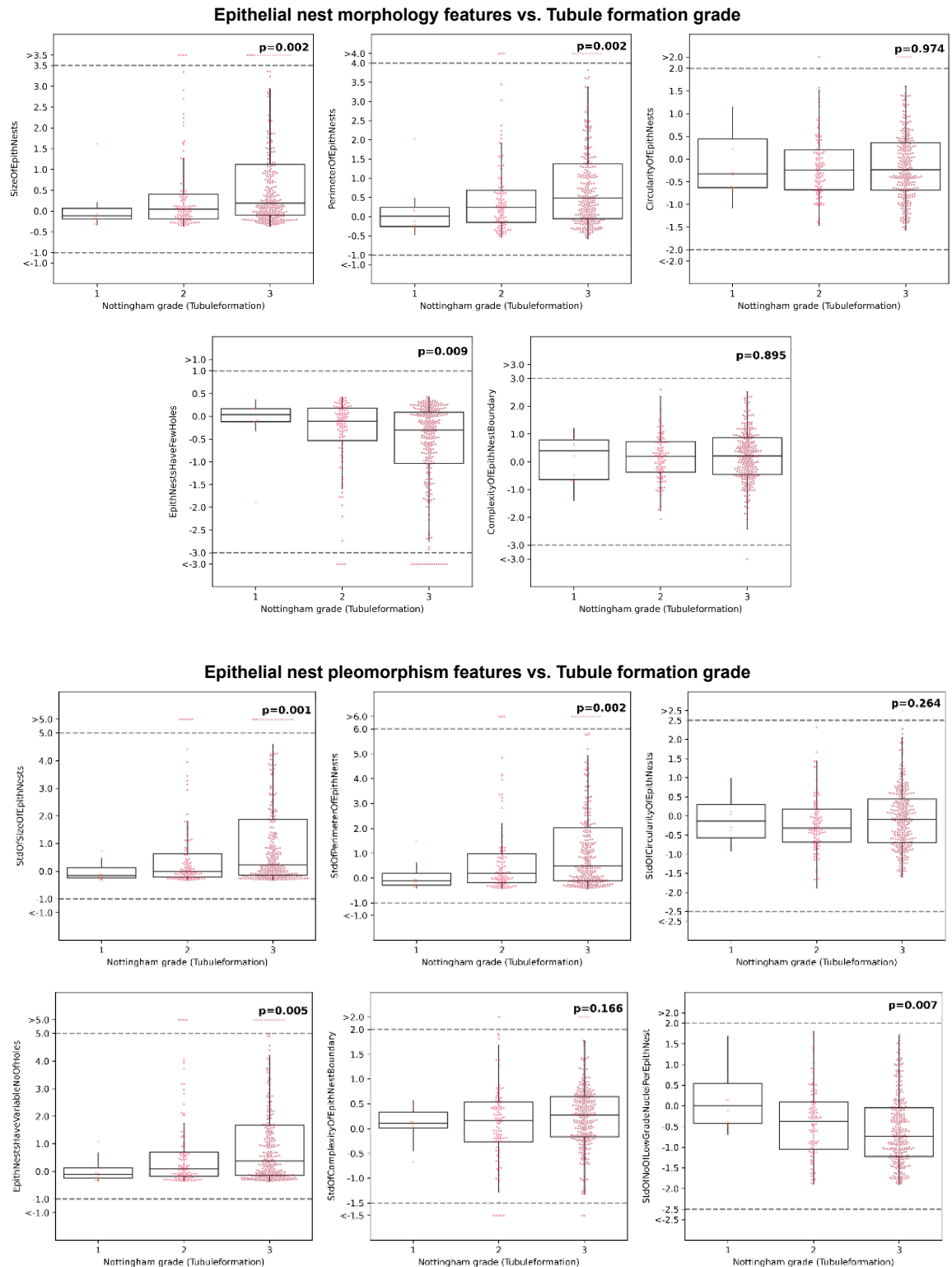


Fig. S23 | Association between architectural features and tubule formation grade in TCGA.
The raw values are provided in the supplementary tables. In all plots, each dot is a single patient, and n=10 (G1), 104 (G2), and 287 (G3) patients. Boxplot center line = median; box limits = upper and lower quartiles; whiskers = 1.5× interquartile range. All P-values are two-sided and represent the the Kruskal-Wallis test.

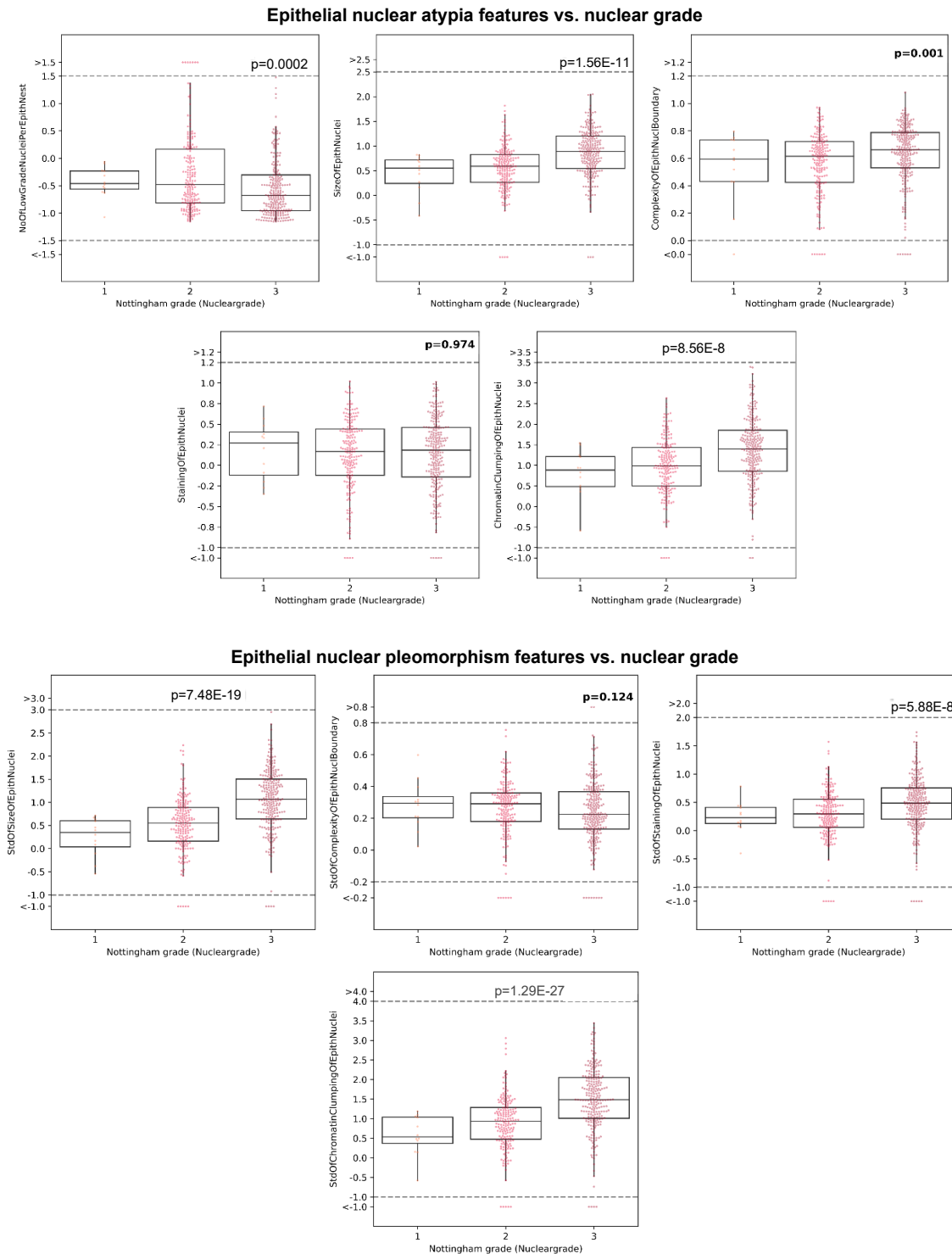


Fig. S24 | Association between nuclear epithelial features and nuclear grade in TCGA.
The raw values are provided in the supplementary tables. In all plots, each dot is a single patient, and n=12 (G1), 192 (G2), and 250 (G3) patients. Boxplot center line = median; box limits = upper and lower quartiles; whiskers = 1.5× interquartile range. All P-values are two-sided and represent the the Kruskal-Wallis test.

Population-level signature for breast cancer prognosis

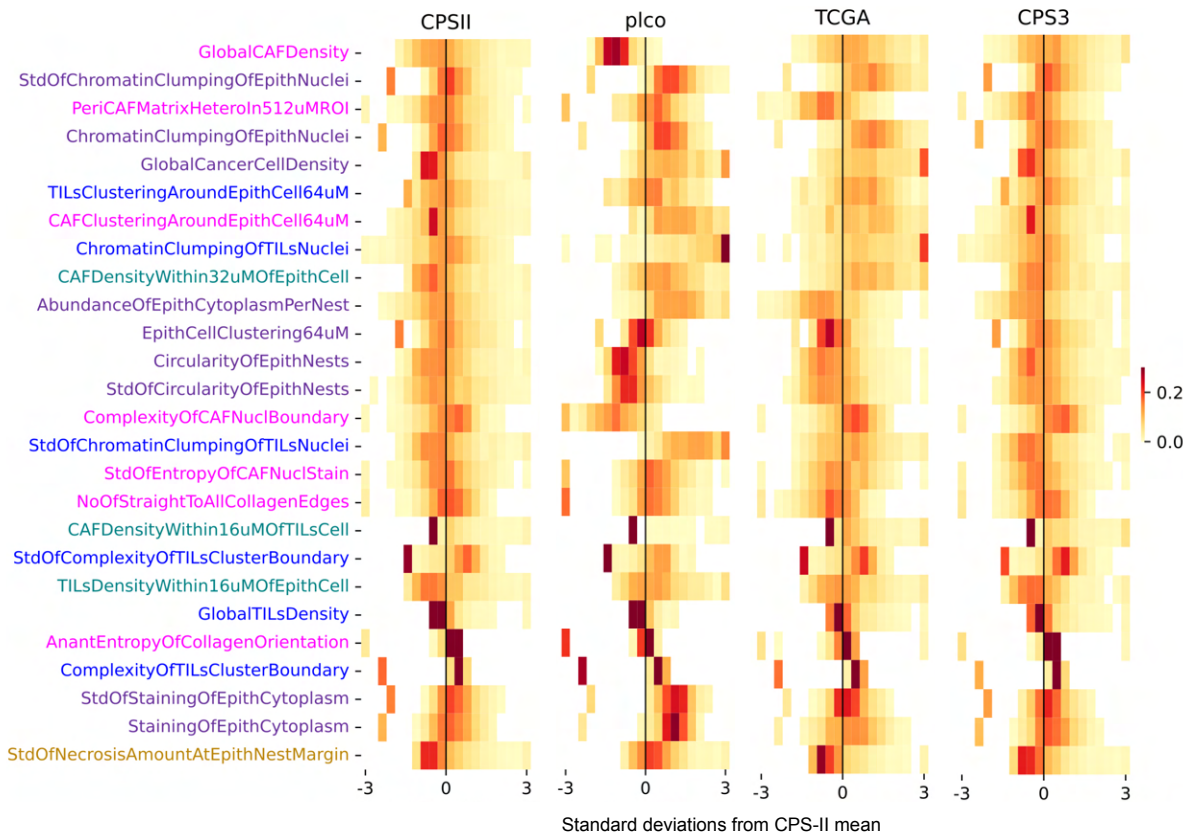


Fig. S25 | Heatmap of the distribution of HiPS features in the four datasets.

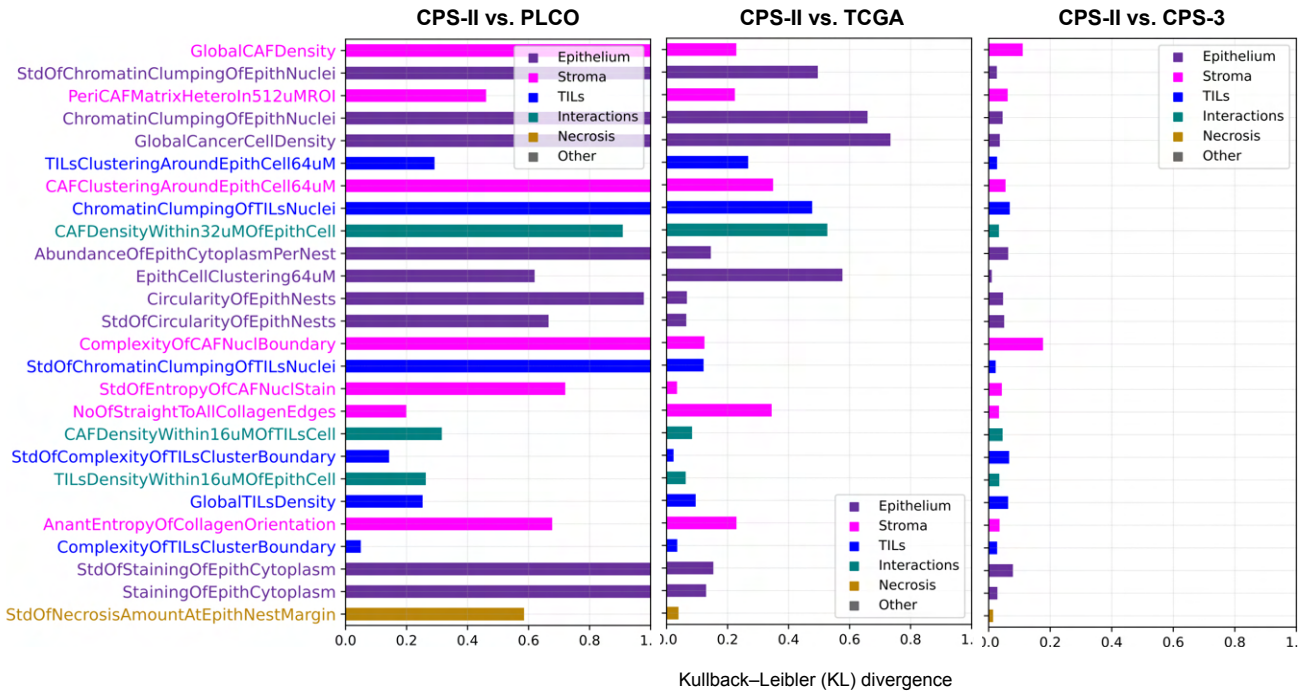


Fig. S26 | K-L divergence of HiPS features in the validation cohorts compared to CPS-II.

Population-level signature for breast cancer prognosis

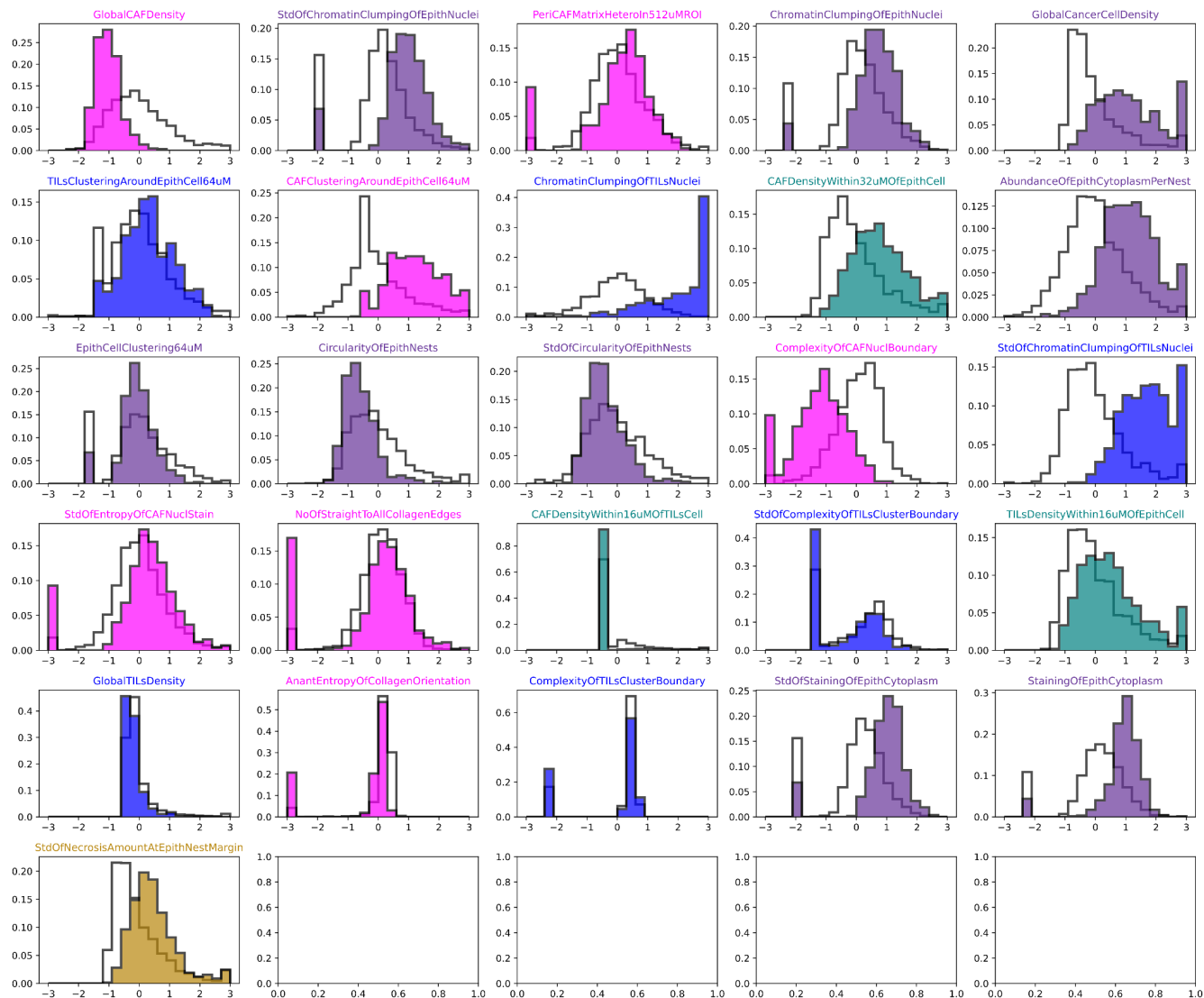


Fig. S27 | Histograms of HiPS feature distributions in the CPS-II cohort vs. PLCO.
Hollow histograms correspond to the CPS-II discovery cohort. Solid histograms correspond to the PLCO validation cohort. All feature values represent standard deviations from CPS-II mean. Y-axes represent the proportion of the patients in the cohort.

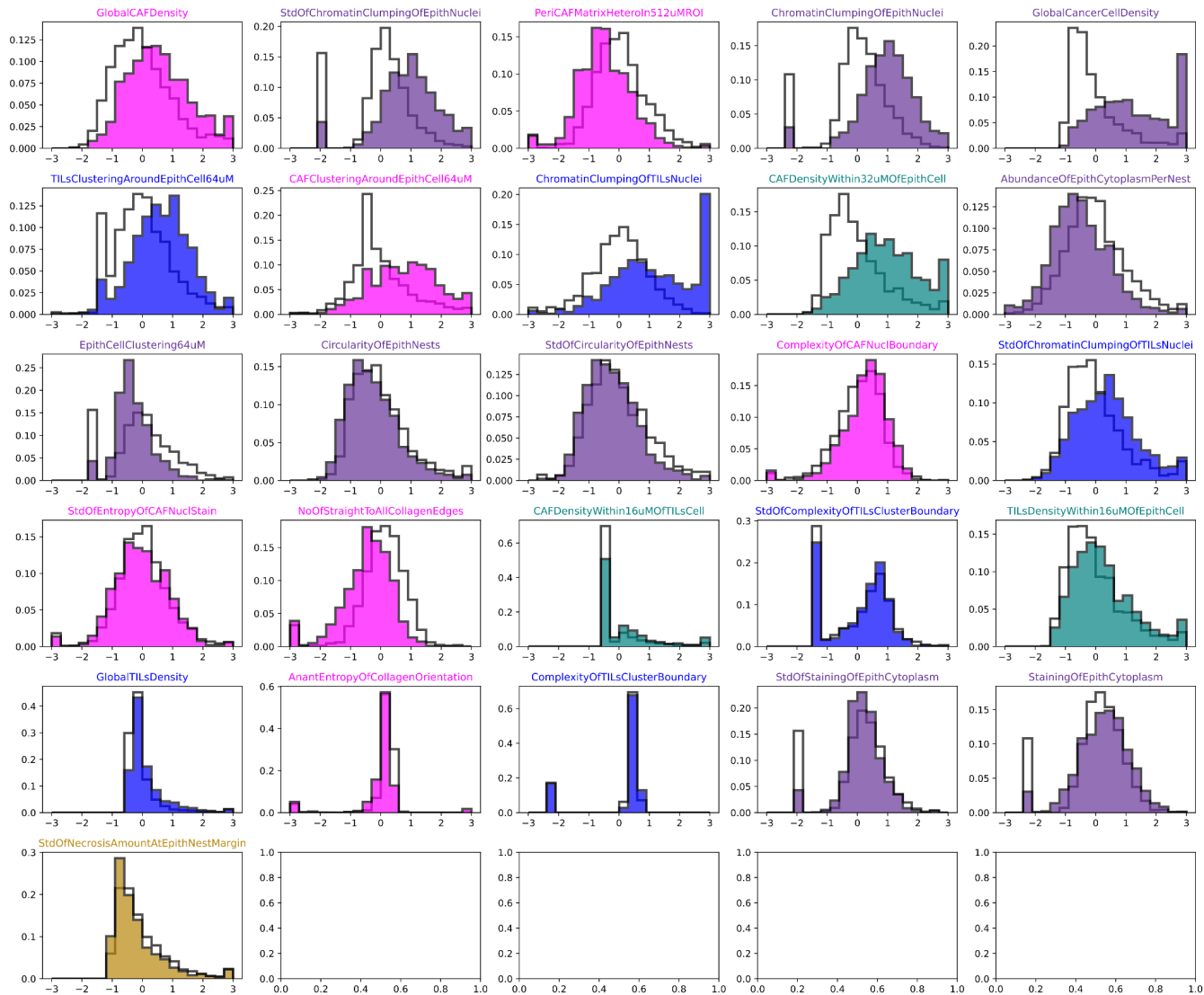


Fig. S28 | Histograms of HiPS feature distributions in the CPS-II cohort vs. TCGA.
Hollow histograms correspond to the CPS-II discovery cohort. Solid histograms correspond to the TCGA validation cohort. All feature values represent standard deviations from CPS-II mean. Y-axes represent the proportion of the patients in the cohort.

Population-level signature for breast cancer prognosis

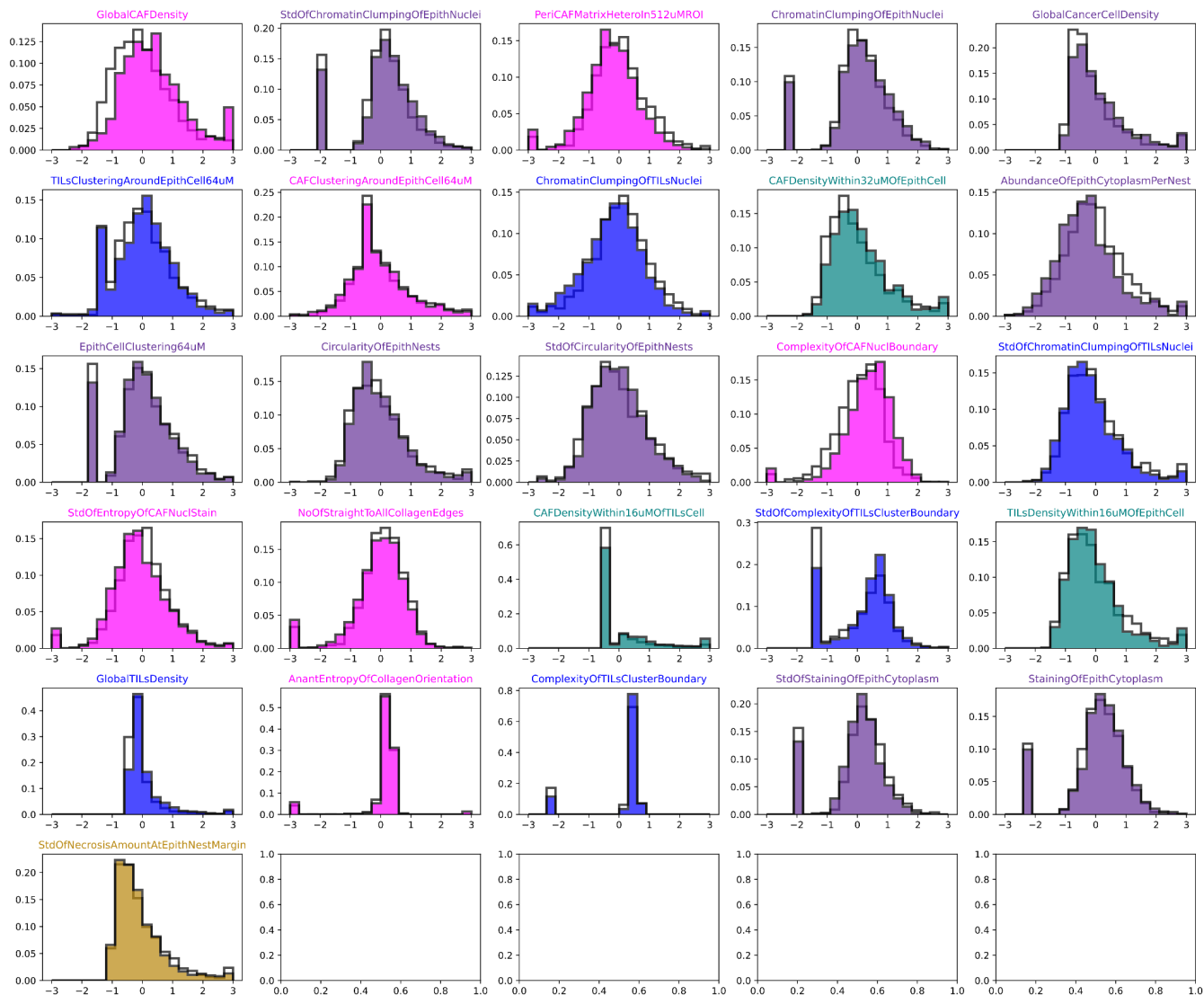


Fig. S29 | Histograms of HiPS feature distributions in the CPS-3 cohort vs. TCGA.
Hollow histograms correspond to the CPS-II discovery cohort. Solid histograms correspond to the CPS-3 validation cohort. All feature values represent standard deviations from CPS-II mean. Y-axes represent the proportion of the patients in the cohort.

Population-level signature for breast cancer prognosis

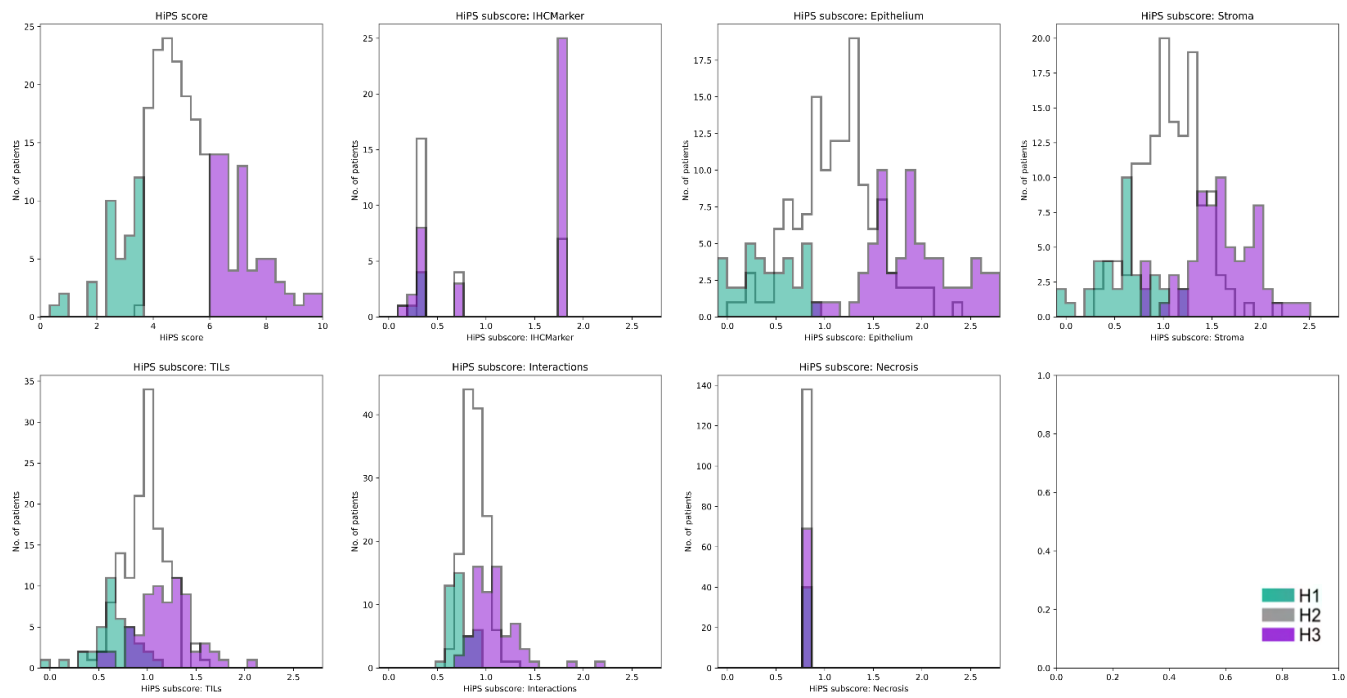


Fig. S30 | Distribution of HiPS scores and subscores in CPS-II Stage II-III patients.

Population-level signature for breast cancer prognosis

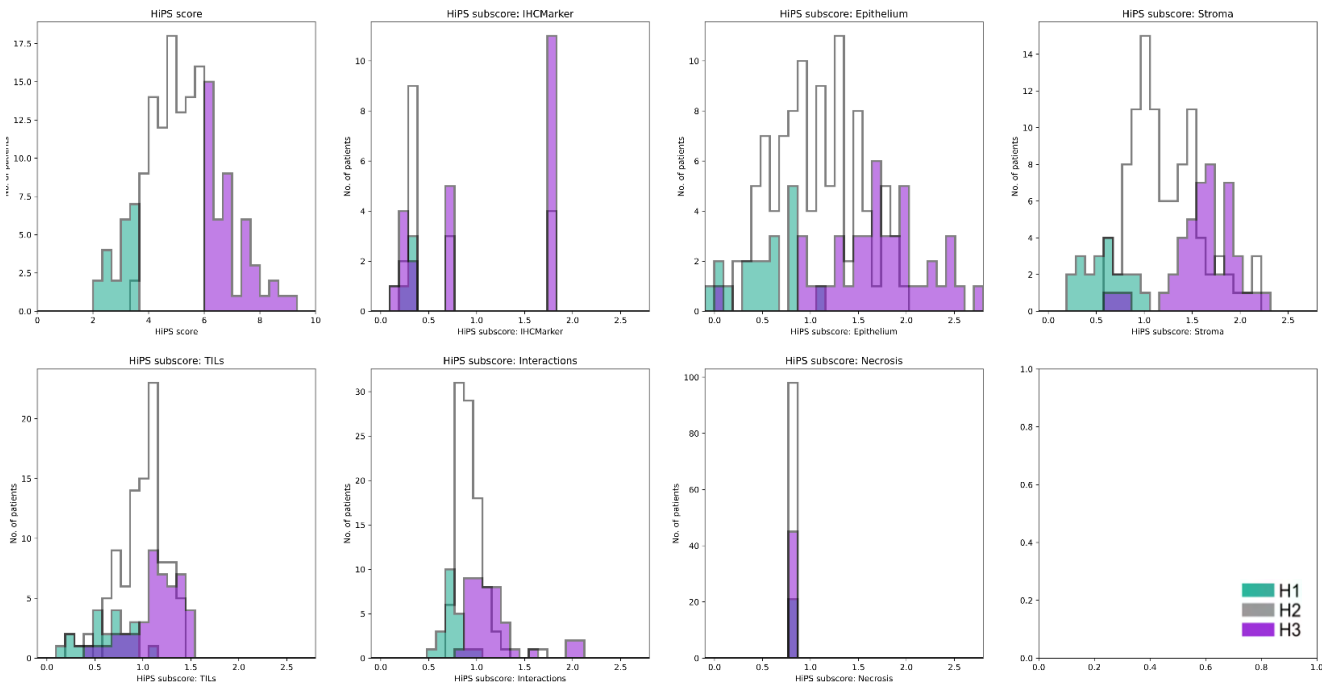


Fig. S31 | Distribution of HiPS scores and subscores in CPS-3 Stage II-III patients.

Population-level signature for breast cancer prognosis

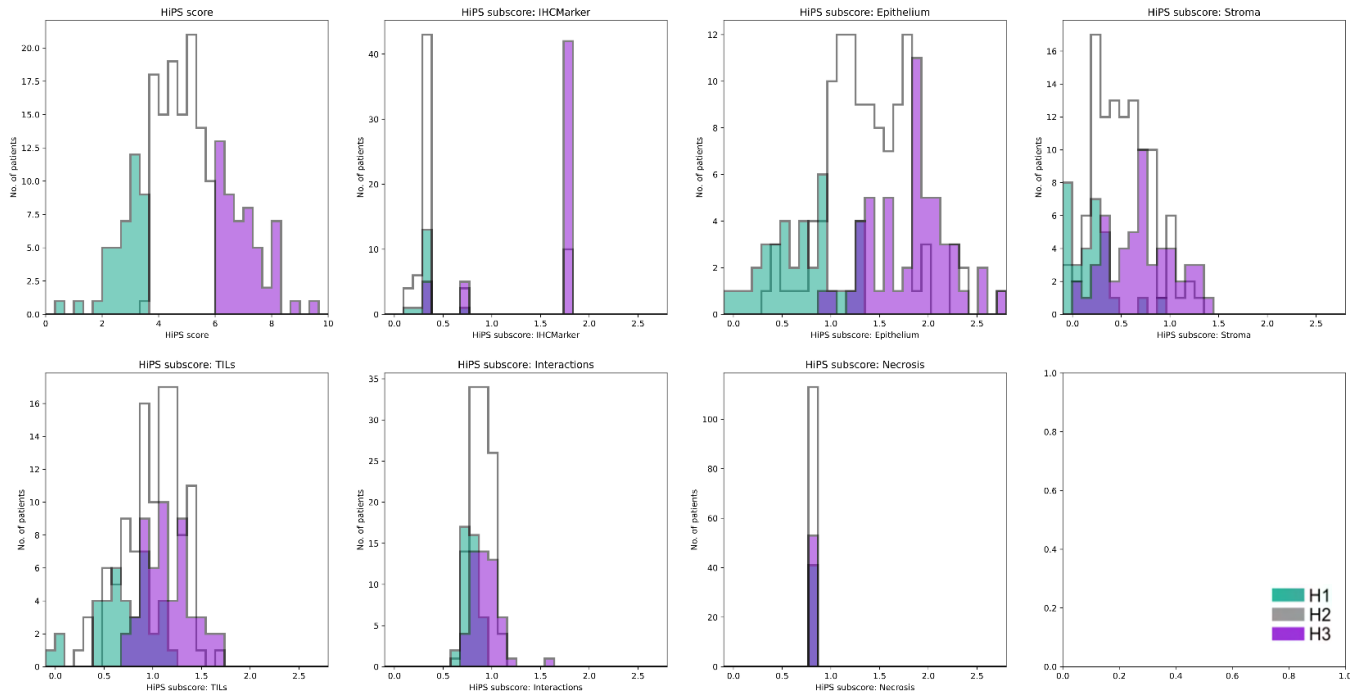


Fig. S32 | Distribution of HiPS scores and subscores in PLCO Stage I patients.

Population-level signature for breast cancer prognosis

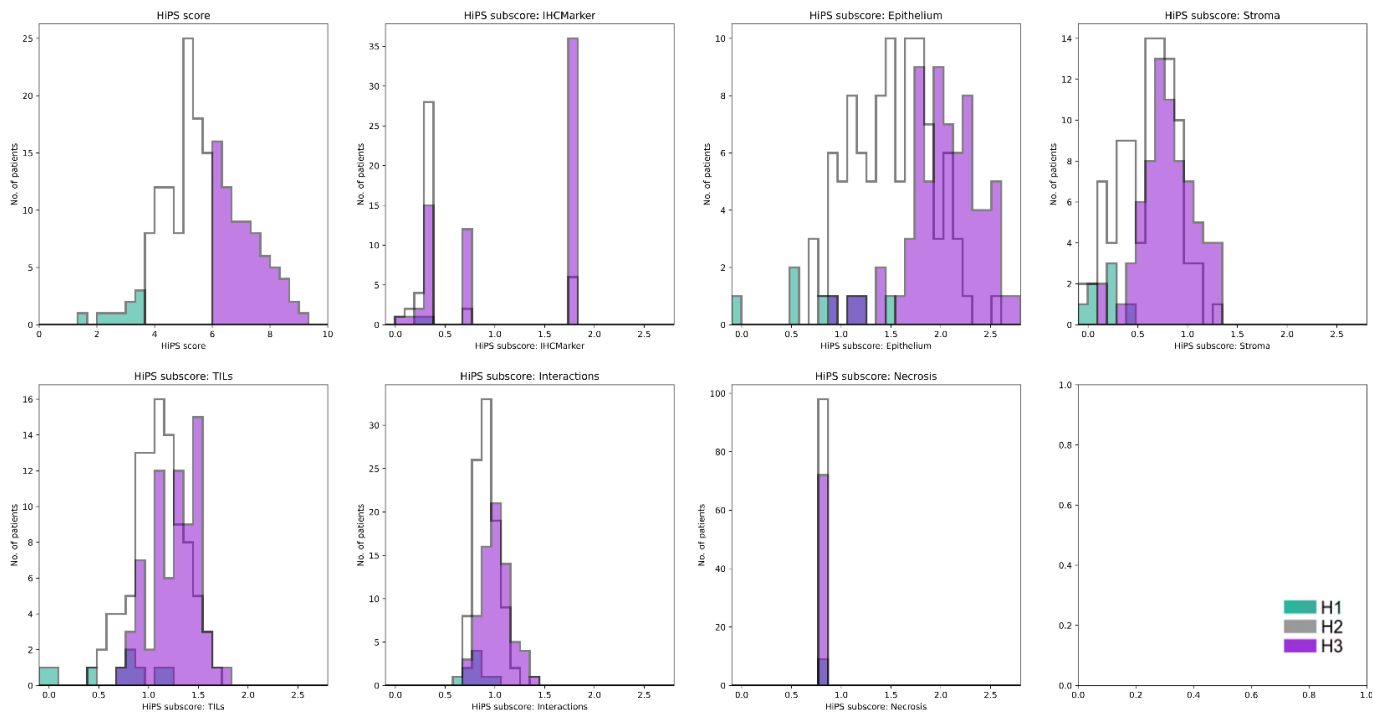


Fig. S33 | Distribution of HiPS scores and subscores in PLCO Stage II patients.

Population-level signature for breast cancer prognosis

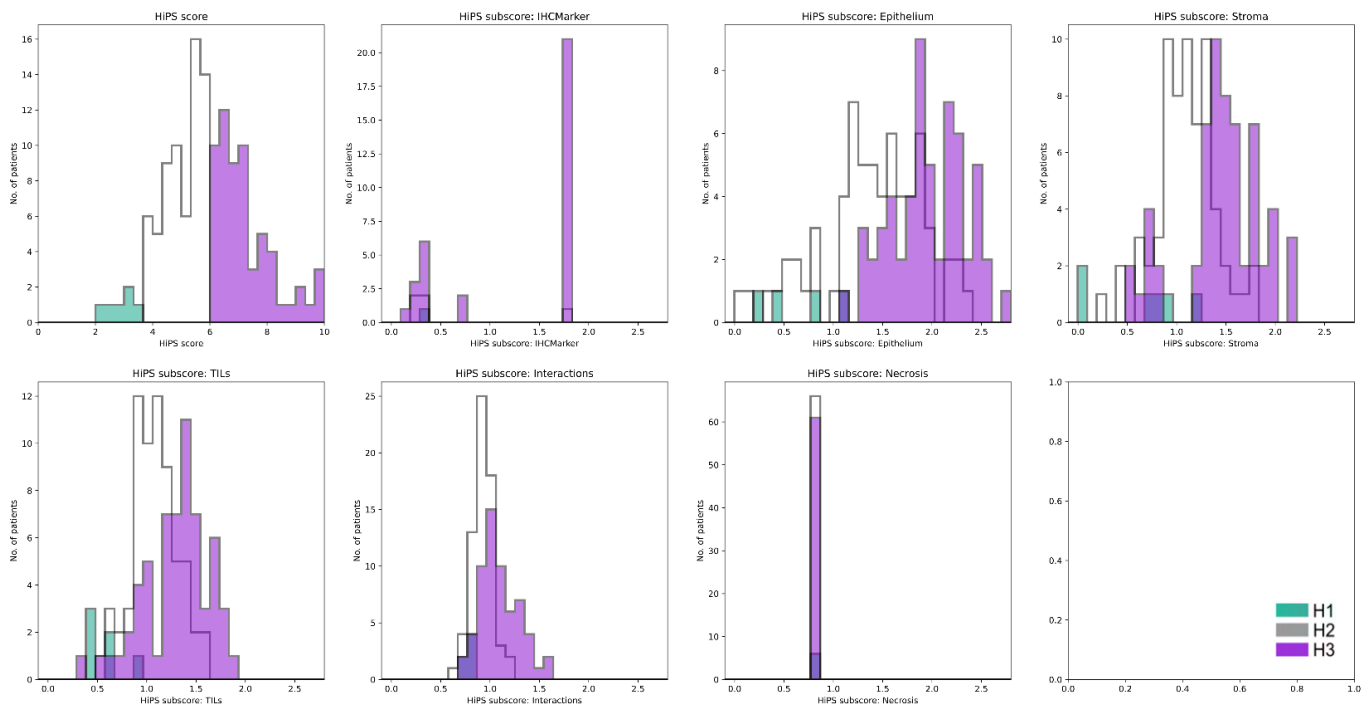


Fig. S34 | Distribution of HiPS scores and subscores in TCGA Stage I patients.

Population-level signature for breast cancer prognosis

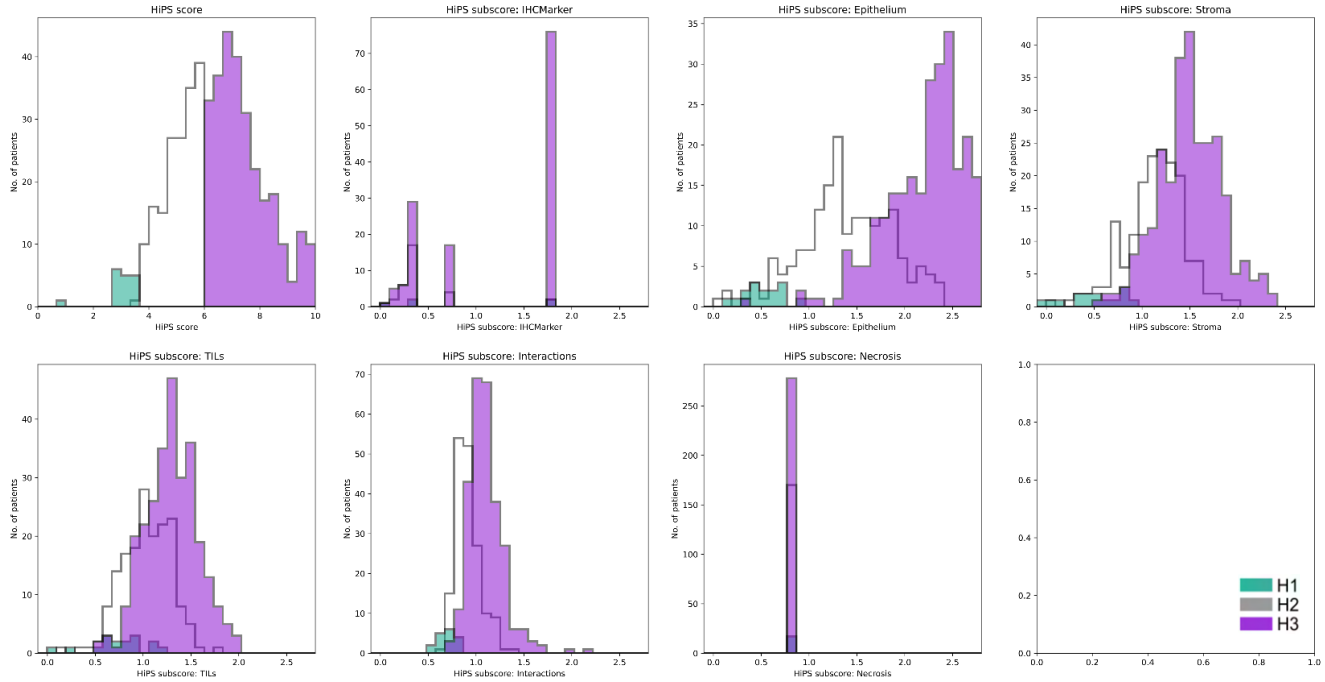


Fig. S35 | Distribution of HiPS scores and subscores in TCGA Stage II patients.

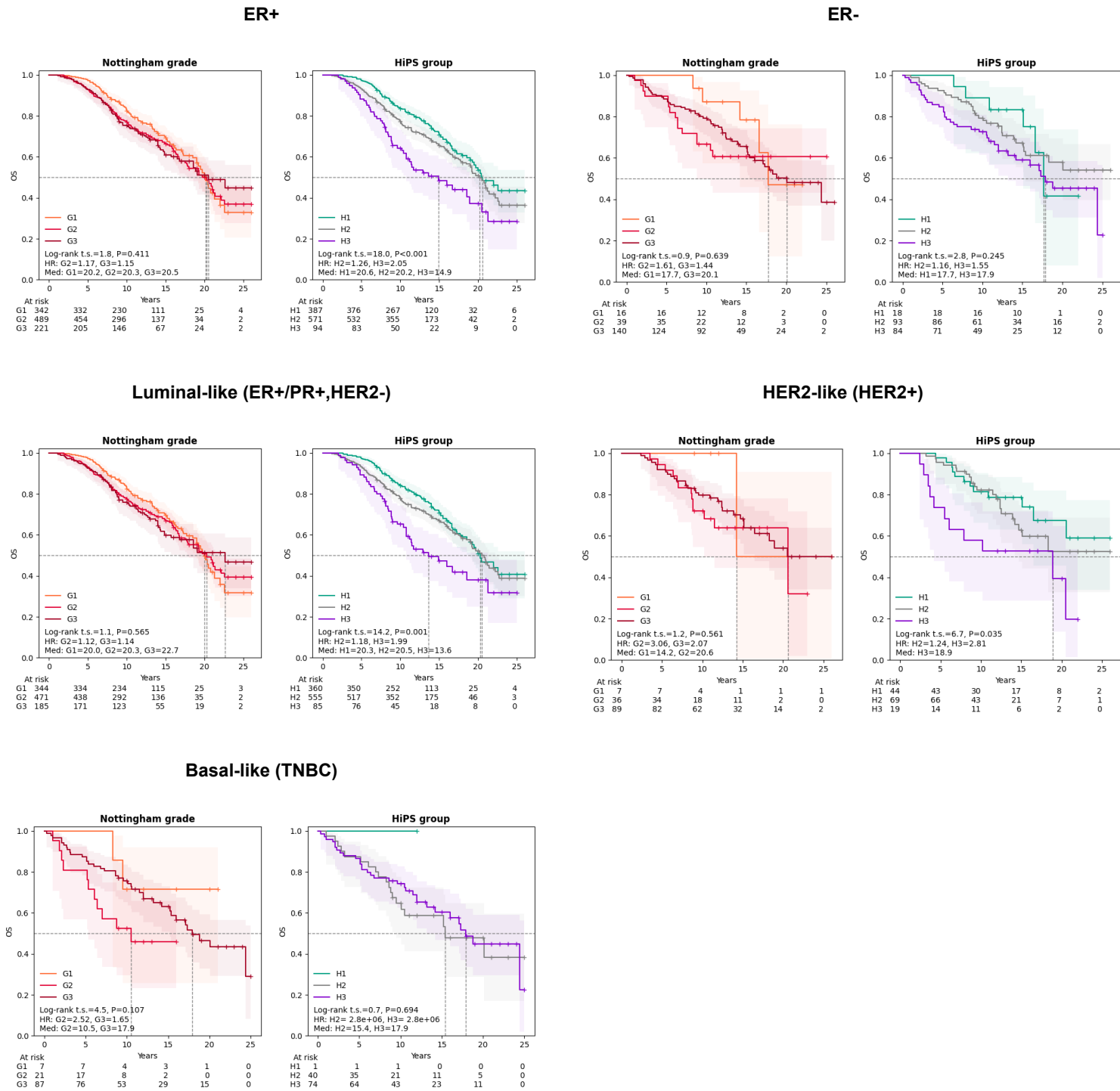


Fig. S36 | Kaplan-Meier curves for OS in CPS-II, stratified by IHC/ISH status. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

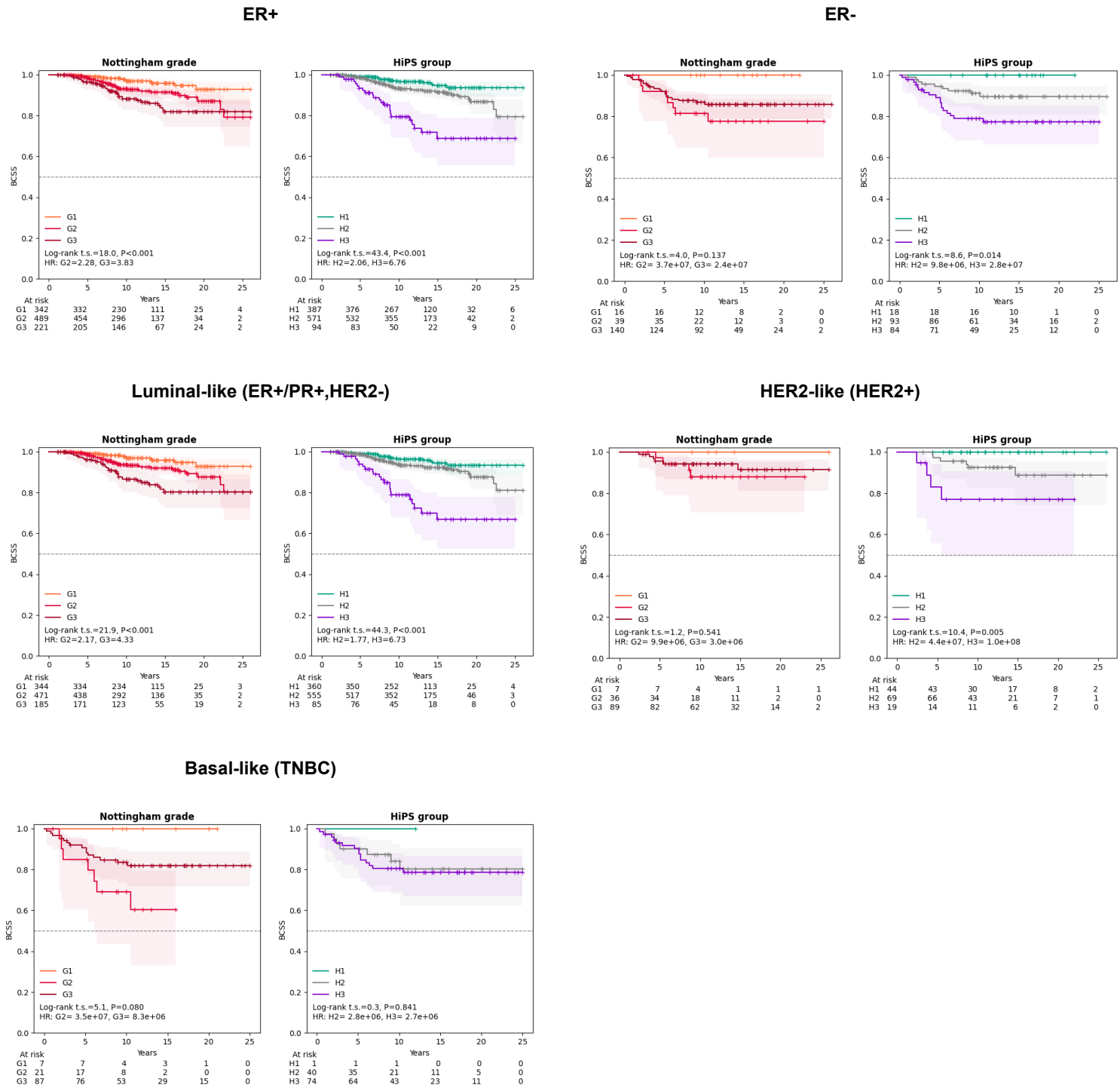


Fig. S37 | Kaplan-Meier curves for BCSS in CPS-II, stratified by IHC/ISH status. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

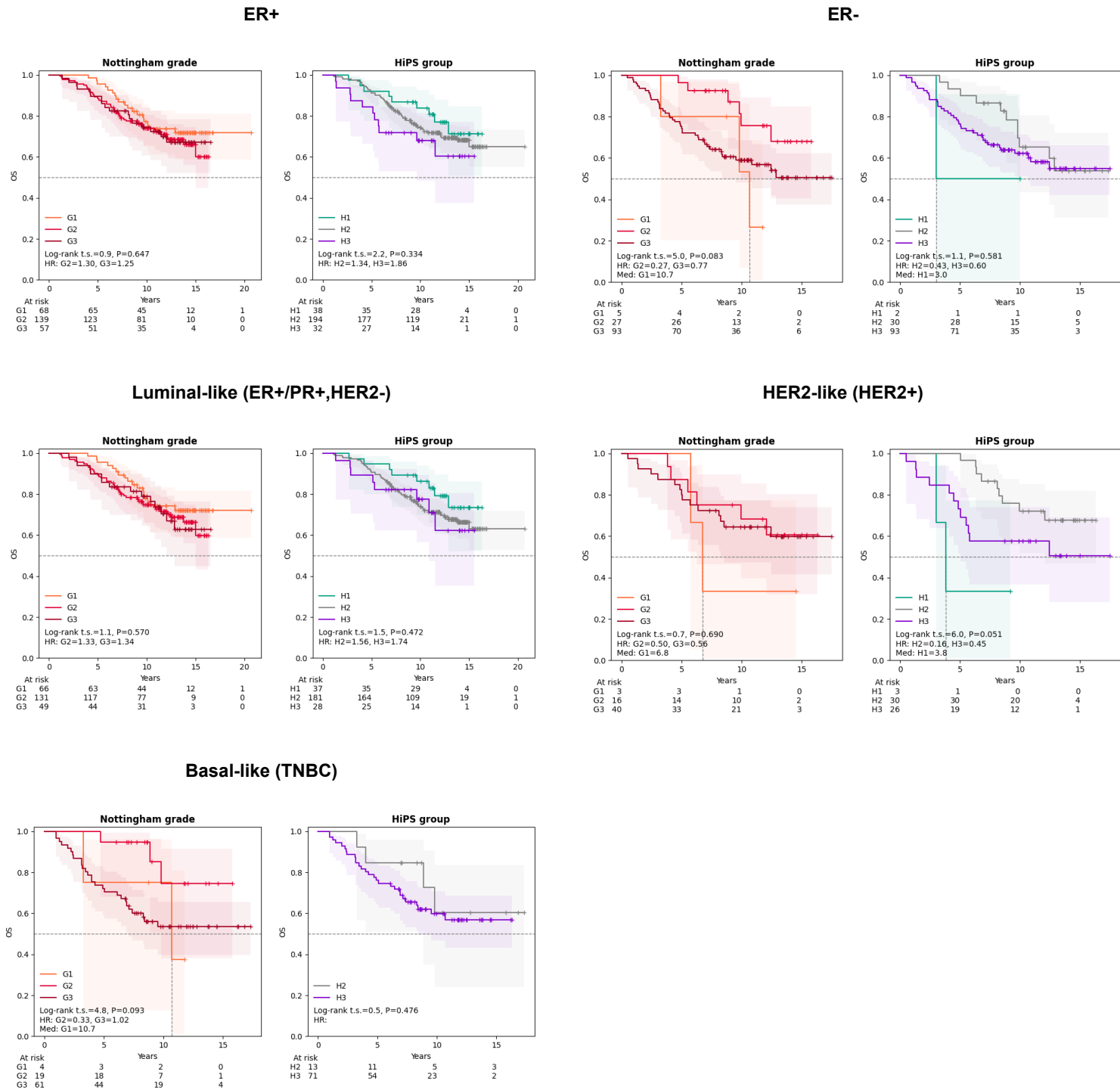


Fig. S38 | Kaplan-Meier curves for OS in PLCO, stratified by IHC/ISH status. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

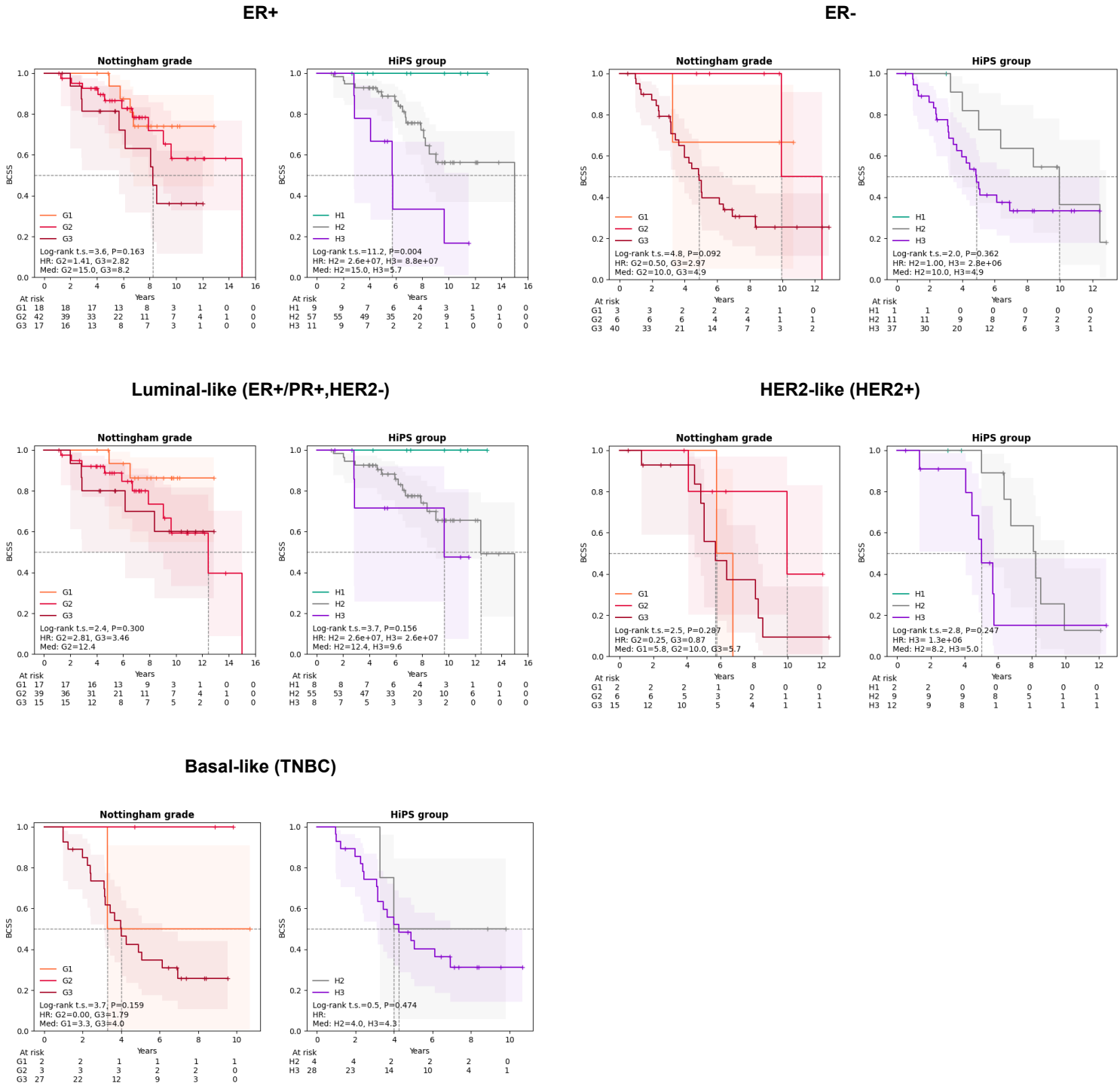


Fig. S39 | Kaplan-Meier curves for BCSS in PLCO, stratified by IHC/ISH status. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

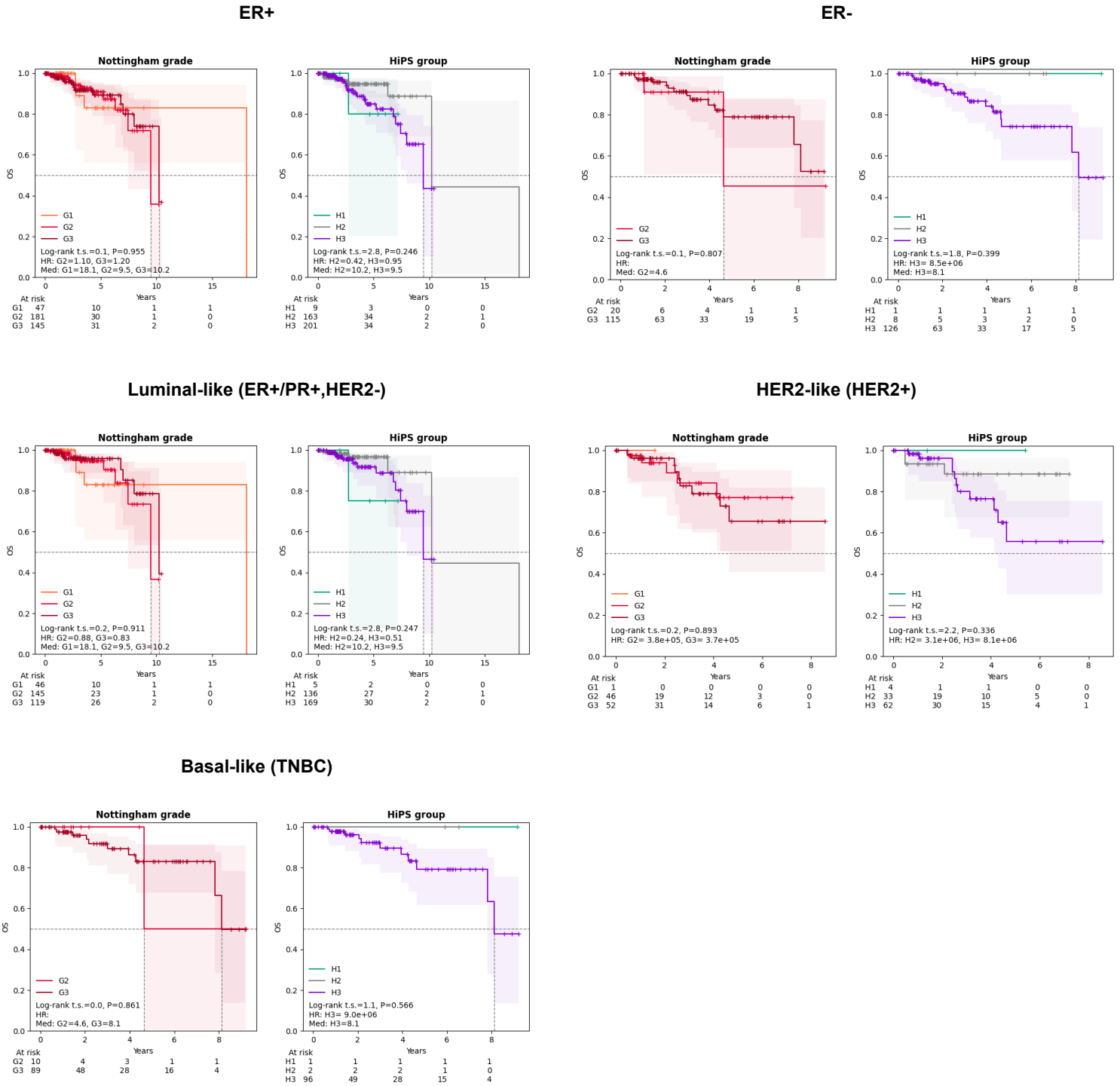


Fig. S40 | Kaplan-Meier curves for OS in TCGA, stratified by IHC/ISH status. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis

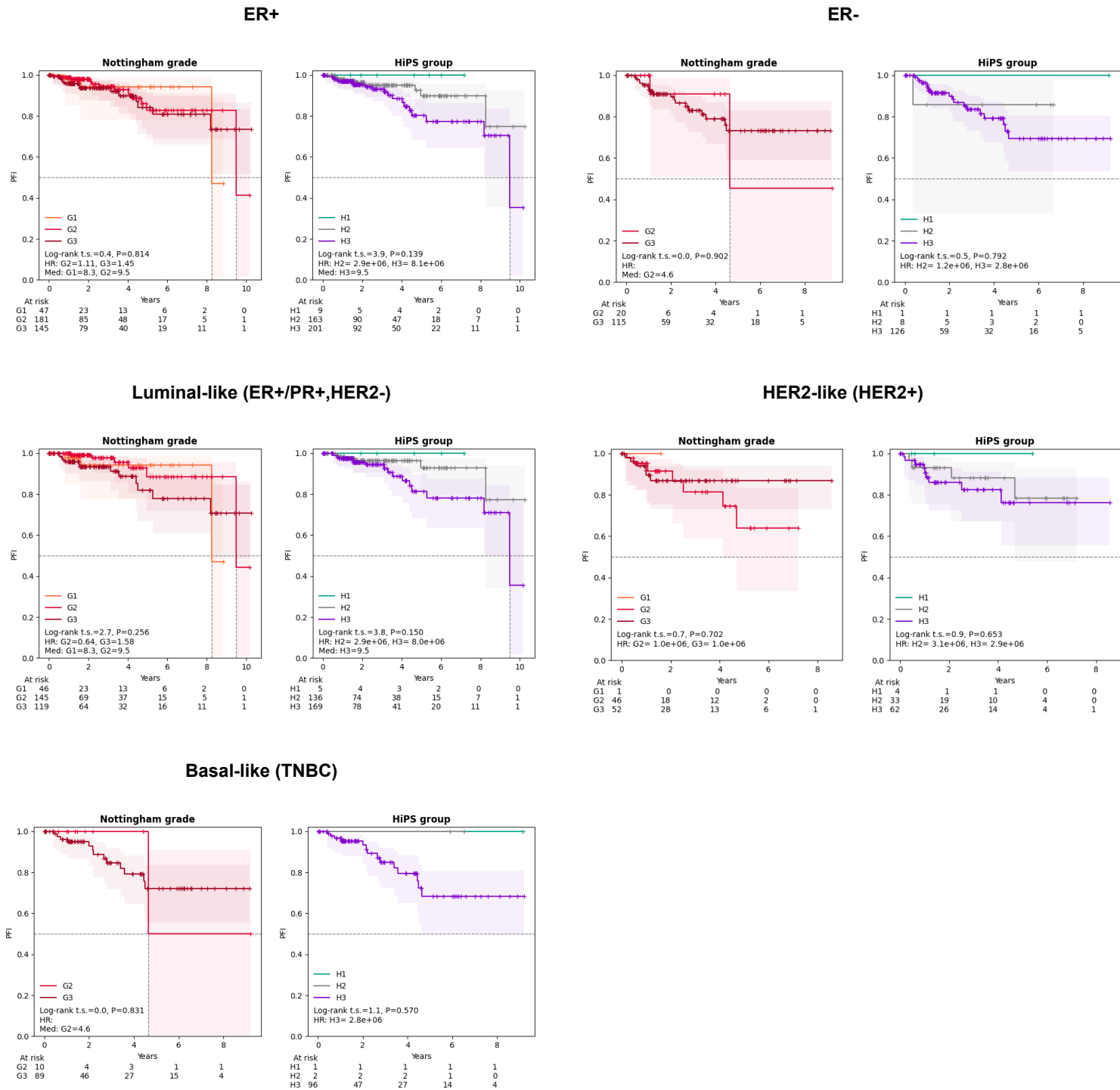
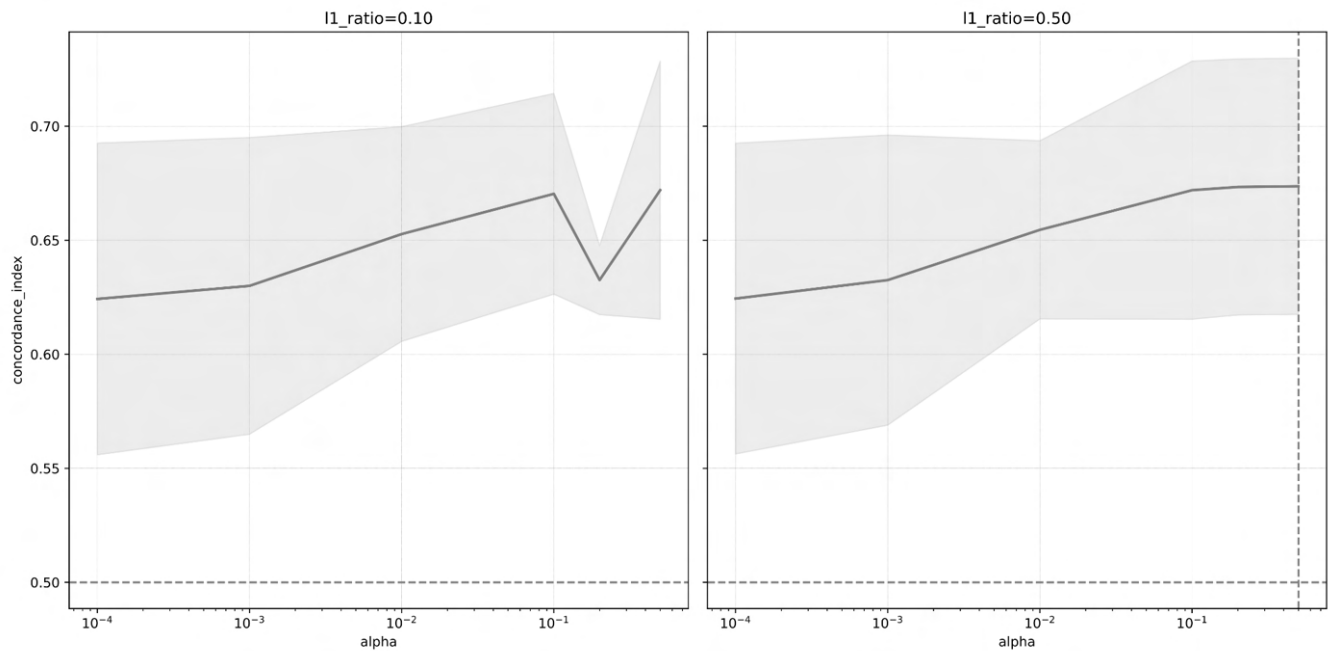


Fig. S41 | Kaplan-Meier curves for PFI in TCGA, stratified by IHC/ISH status. Error bands represent the exponential Greenwood 95% confidence intervals.

Population-level signature for breast cancer prognosis



model_rank	l1_ratio	alpha	Concordance index					
			Fold 1	Fold 2	Fold 3	Fold 4	Mean	Std
1	0.5	0.5	0.7534	0.6620	0.6213	0.6580	0.6737	0.0562
2	0.5	0.2	0.7528	0.6623	0.6206	0.6577	0.6734	0.0562
3	0.5	0.1	0.7512	0.6631	0.6170	0.6566	0.6720	0.0566
4	0.1	0.5	0.7512	0.6631	0.6170	0.6566	0.6720	0.0566
5	0.1	0.1	0.7304	0.6596	0.6248	0.6666	0.6704	0.0440
6	0.5	0.01	0.7127	0.6420	0.6309	0.6326	0.6546	0.0391
7	0.1	0.01	0.7232	0.6258	0.6336	0.6283	0.6527	0.0471
8	0.1	0.2	0.6311	0.6423	0.6117	0.6452	0.6326	0.0152
9	0.5	0.001	0.7221	0.5733	0.6263	0.6084	0.6325	0.0636
10	0.1	0.001	0.7219	0.5696	0.6216	0.6068	0.6300	0.0651
11	0.5	0.0001	0.7196	0.5590	0.6183	0.6008	0.6244	0.0682
12	0.1	0.0001	0.7197	0.5584	0.6175	0.6014	0.6243	0.0684

Fig. S42 | Cross-validation fine-tuning of the HiPS prognostic model parameters.
These parameters correspond to the ElasticNetCV class in the sklearn python library:
https://scikit-learn.org/stable/modules/generated/sklearn.linear_model.ElasticNetCV.html. Of note, “The parameter l1_ratio corresponds to alpha in the glmnet R package while alpha corresponds to the lambda parameter in glmnet.”.

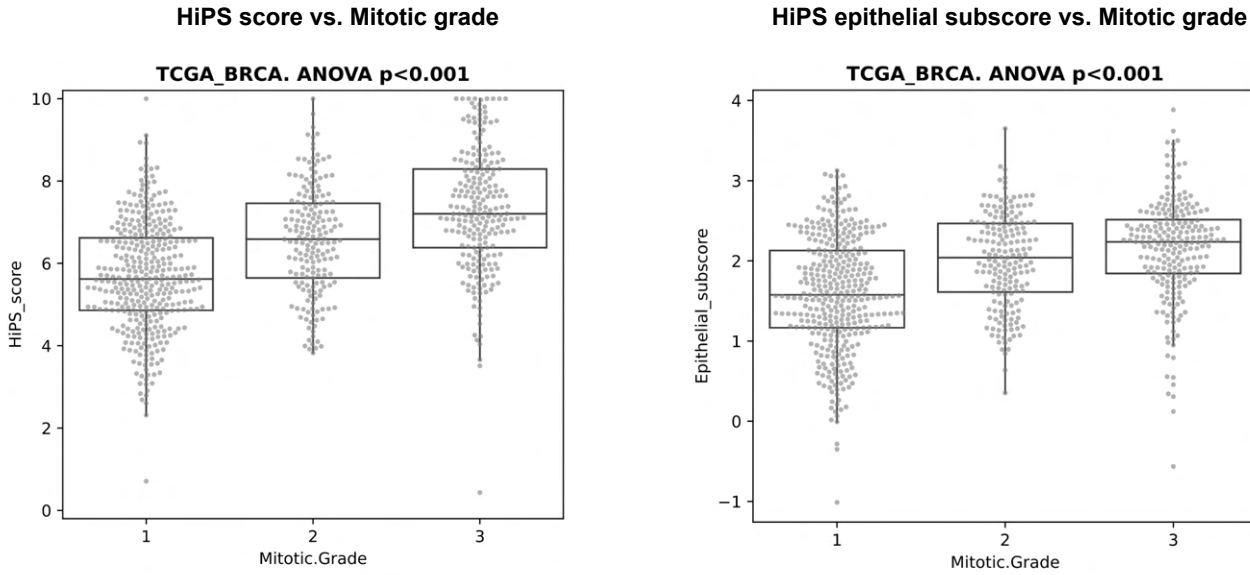


Fig. S43 | Association between the HiPS score, epithelial subscore, and the mitotic grade.
The HiPS score and epithelial subscore are significantly associated with the mitotic Nottingham grade. In all plots, each dot is a single patient, and n=365 (G1), 185 (G2), 225 (G3). Boxplot center line = median; box limits = upper and lower quartiles; whiskers = 1.5× interquartile range. P-values are two-sided and represent the one-way ANOVA

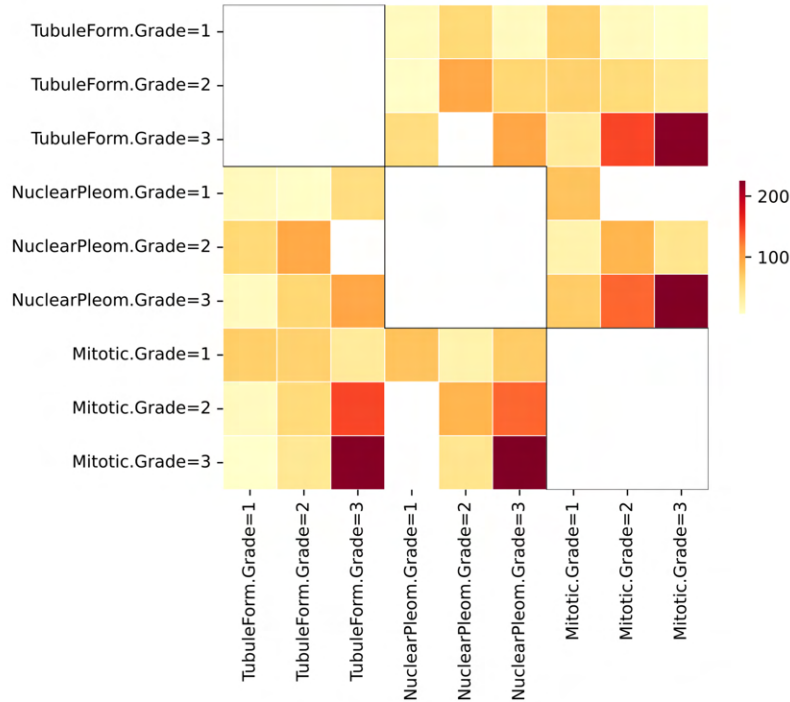


Fig. S44 | Mitotic grade is highly associated with tubule formation and nuclear pleomorphism grades.
The matrix shows patient counts in the TCGA dataset. Each patient's Nottingham grade is obtained by summing the tubule formation grade, nuclear pleomorphism grade, and mitotic grade. Higher mitotic grades (especially grade 3) are almost entirely explainable by the tubule formation and nuclear pleomorphism grades.

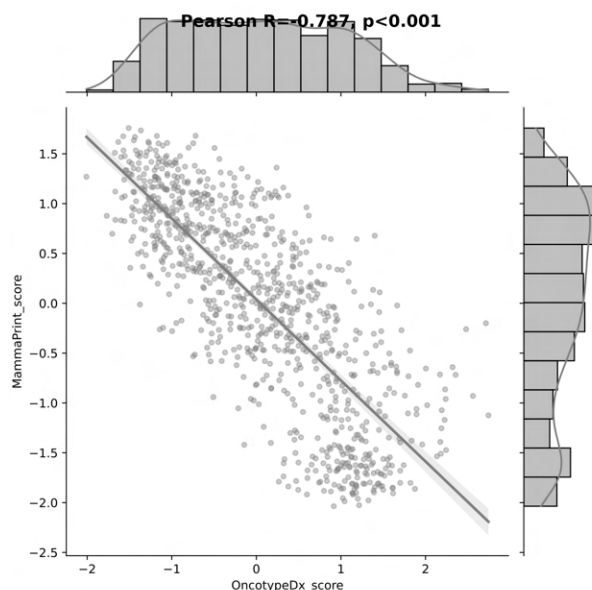


Fig. S45 | Oncotype DX and MammaPrint scores are strongly inversely correlated.

The P-value shown is two-sided. Research-only Oncotype DX recurrence score and MammaPrint metastasis risk scores for breast cancer for TCGA (obtained from *Howard et al, 2023*) are strongly and inversely correlated. Note that MammaPrint scores reflect the correlation between gene expression levels with the “average good prognosis profile”.

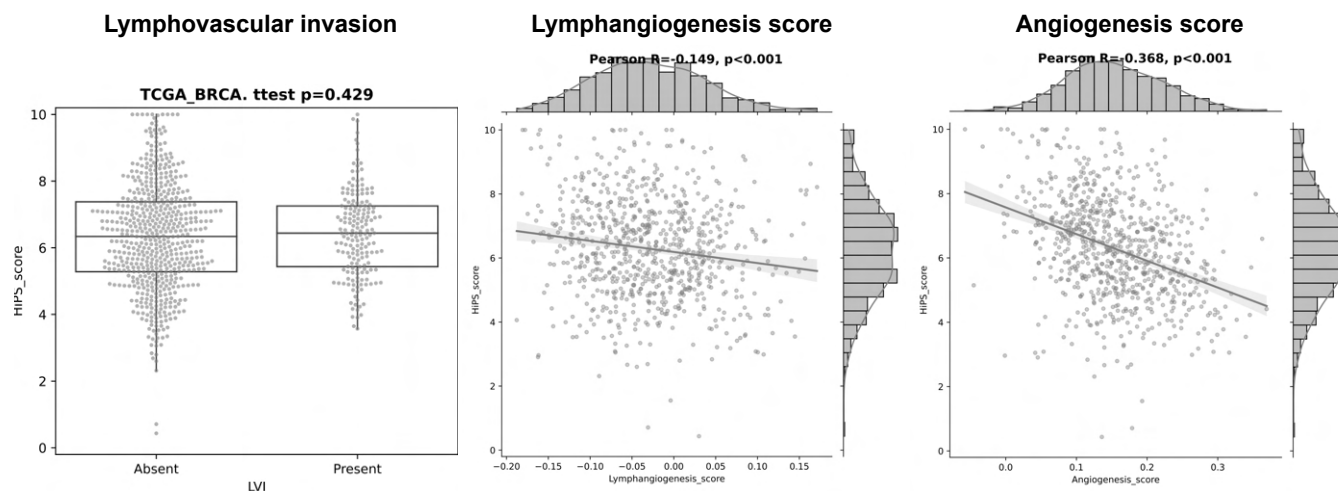


Fig. S46 | Association between HiPS, lymphovascular invasion and (lymph)angiogenesis scores in TCGA.

P-values are two-sided; for the boxplot they represent the independent two-sample t-test. In all plots, each dot is a single patient, and in the boxplot $n = 581$ (LVI absent) and 179 (LVI present). Boxplot center line = median; box limits = upper and lower quartiles; whiskers = $1.5 \times$ interquartile range. Pathologist-determined LVI status was obtained from pathology reports, compiled by *Thennavan et al., 2021*. Angiogenesis and lymphangiogenesis scores were obtained using mRNA expression from the PanImmune dataset by *Thorsson et al., 2018*. HiPS was not associated with lymphovascular invasion (LVI) and had a low, inverse association with lymphangiogenesis and angiogenesis scores. The lack of association with LVI may be due to either: 1. LVI not being captured by the morphologic features comprising HiPS, or 2. LVI plays a less important role in our cohort since we excluded metastatic patients. The weak inverse association with angiogenesis/lymphangiogenesis scores is possibly artifactual, as tumors with less architectural disruption may have more normal vessels which act as impurities in bulk gene expression analysis. Exact P-values are $2.83E-5$ and $1.75E-26$ for lymphangiogenesis and angiogenesis, respectively.

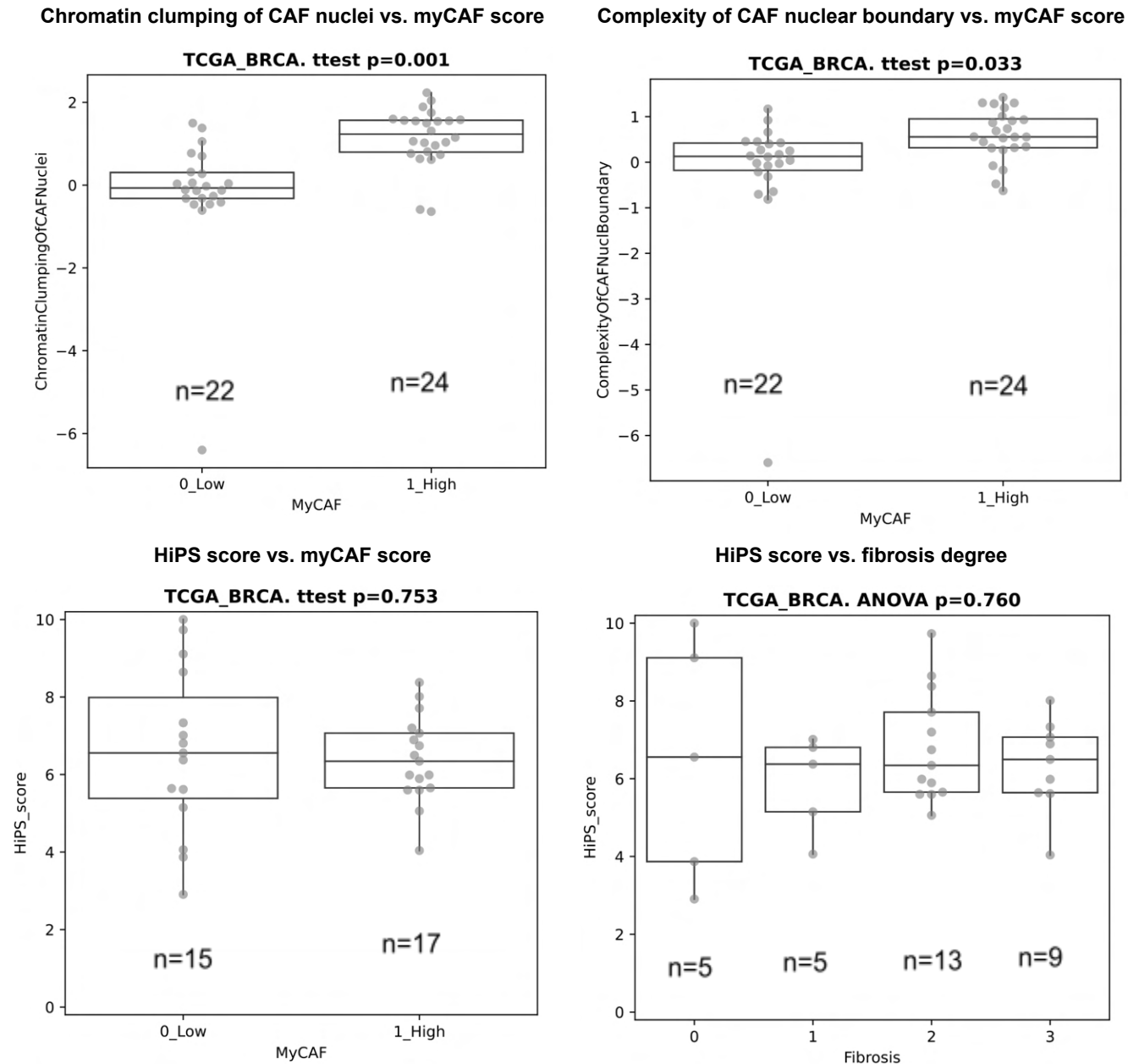


Fig. S47 | Association between HiPS and myoepithelial CAF abundance.

All P-values are two-sided; for the first three plots they represent the independent two-sample t-test, while the last panel P-value represents the one-way ANOVA. Each dot is a single patient, and the number of patients is included in each plot. Boxplot center line = median; box limits = upper and lower quartiles; whiskers = $1.5 \times$ interquartile range. CAF morphologic features were associated with myoepithelial CAF (myCAF) proportion, as determined by gene expression deconvolution by *Li et al., 2021*. Tumors with high myCAF composition relative to inflammatory CAFs (iCAF) had a high chromatin clumping and complexity of CAF nuclear boundary; the latter feature was more prognostic and included in the HiPS signature. However, the HiPS score was not associated with the abundance of myCAF or degree of pathologist-determined fibrosis on H&E slides, reflecting the aggregate nature of patient risk as determined by all morphologic features.

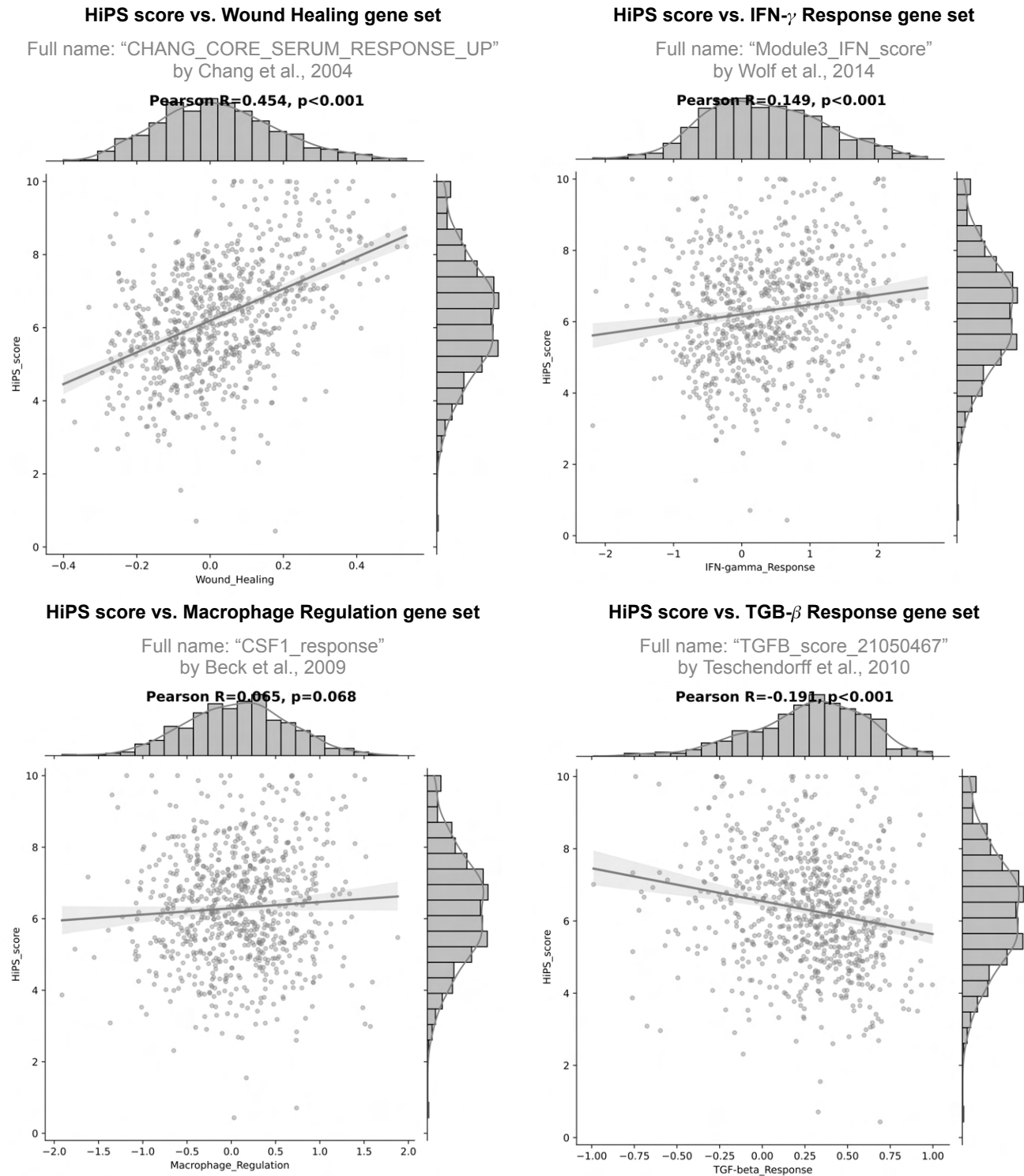
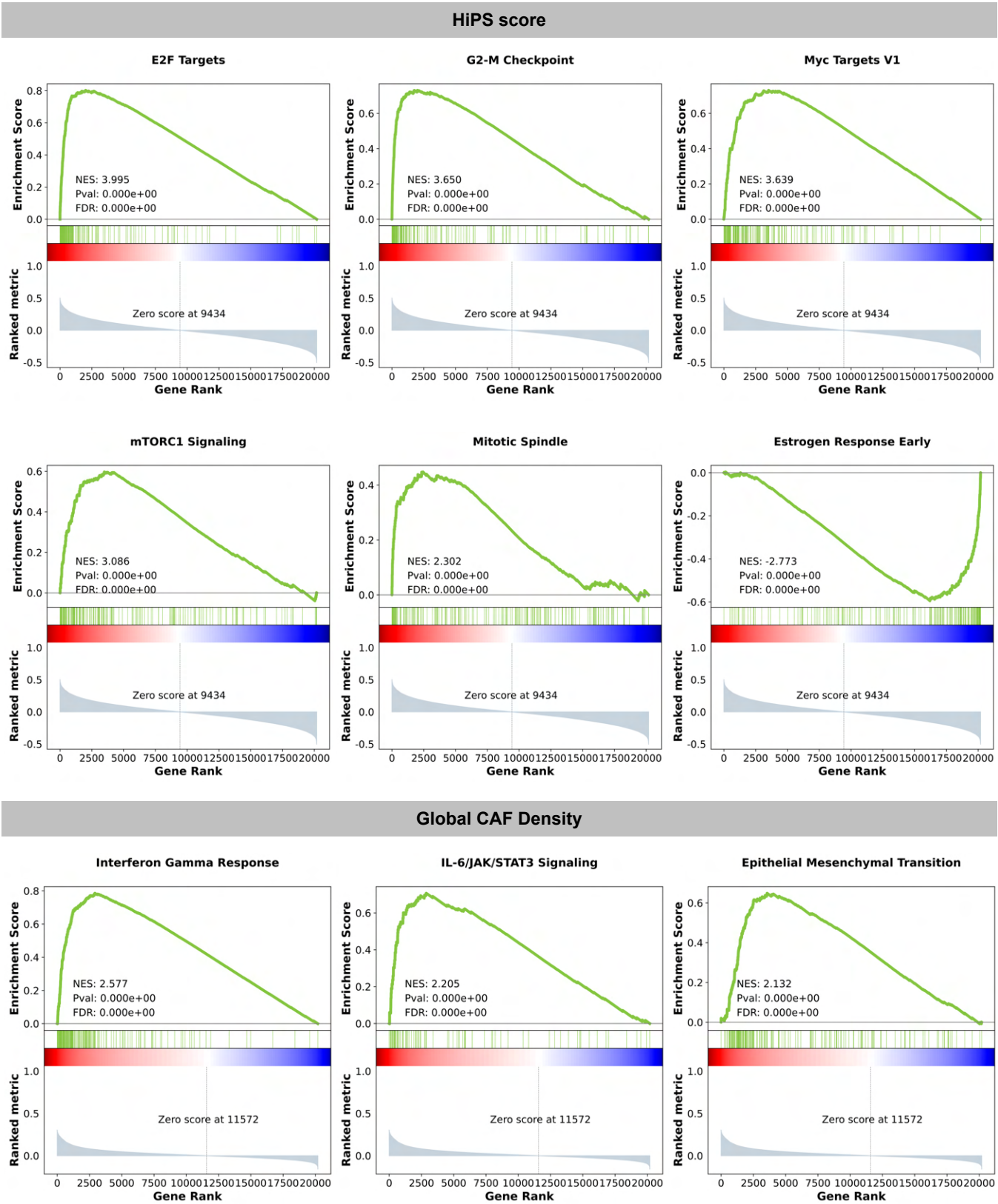


Fig. S48 | Association between HiPS and gene sets definitional of cancer immune subtypes.
The P-values shown is two-sided. HiPS scores had a moderate positive correlation with the wound healing gene signature, which is known to be high in the high-risk immune subtypes (IS) IS-C1 and IS-C2, and low in the low-risk subtype IS-C3, as defined by *Thorson et al, 2018*. From top-left to bottom-right, exact P-values are 1.61E-41, 2.63E-5, 0.068, and 6.15E-8.



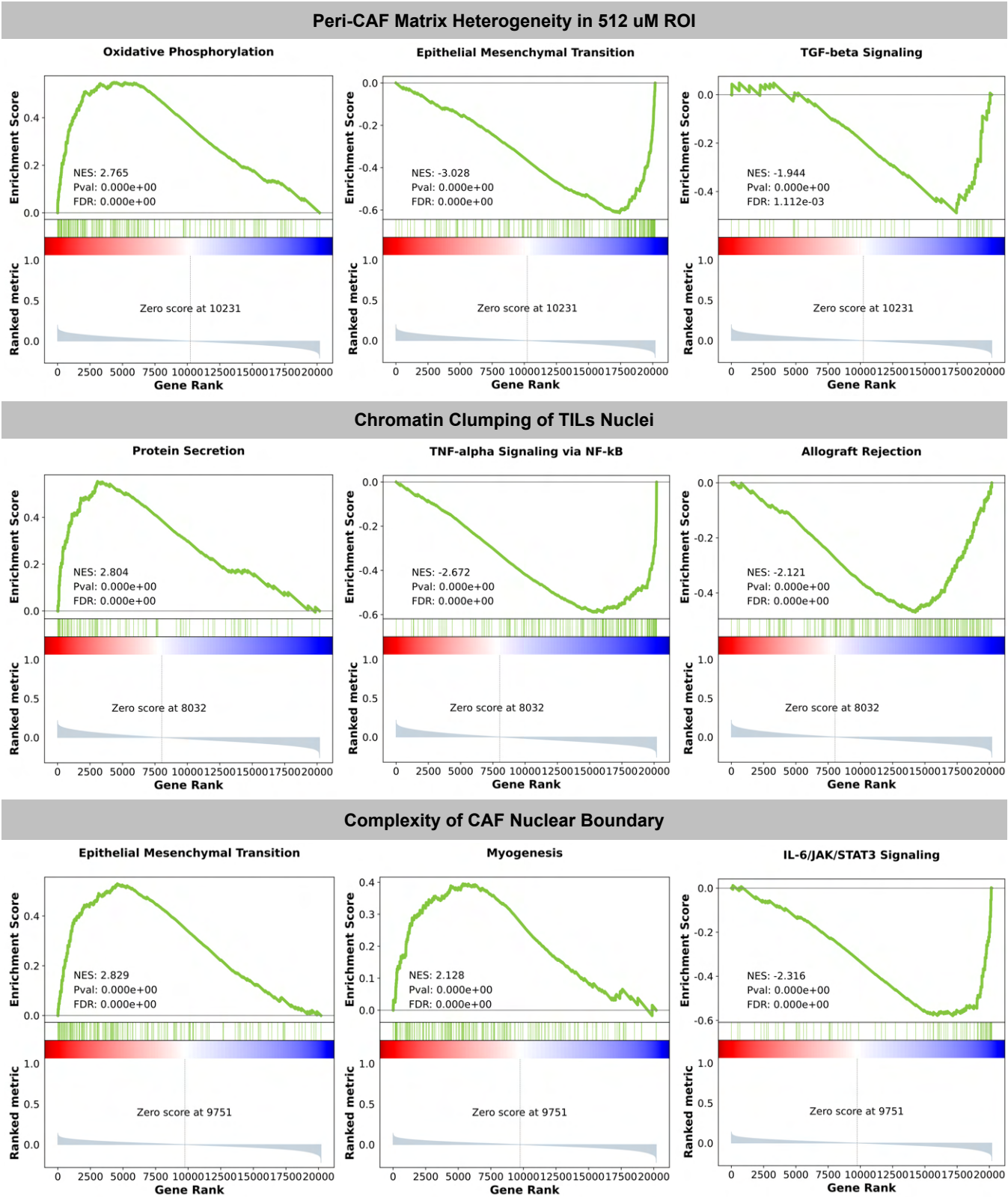


Fig. S49 | GSEA of HiPS score and features using the MSigDB_Hallmarks gene set collection.

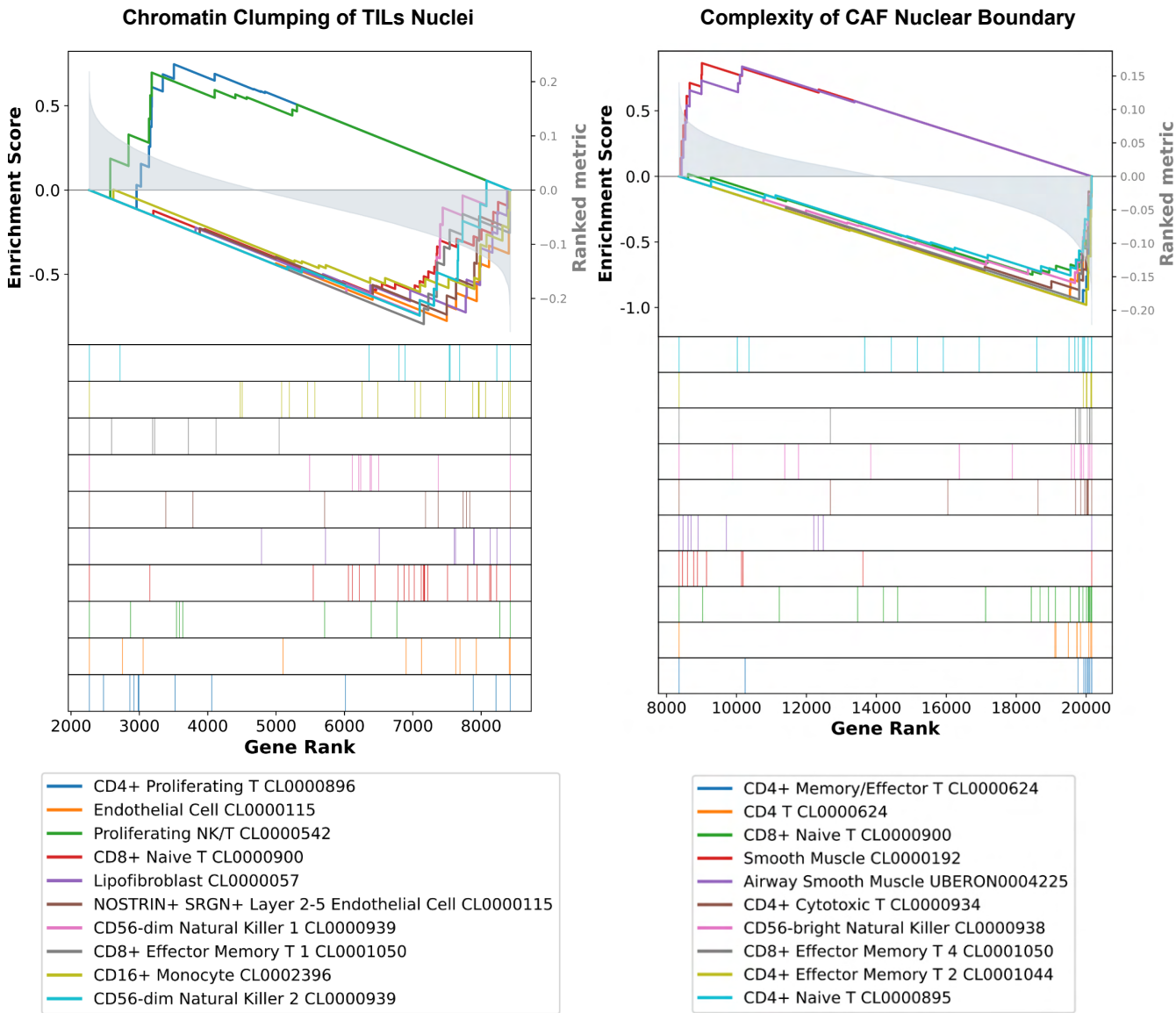


Fig. S50 | GSEA of CAF/TILs morphologic features in HiPS using the Azimuth_Cell_Types collection.

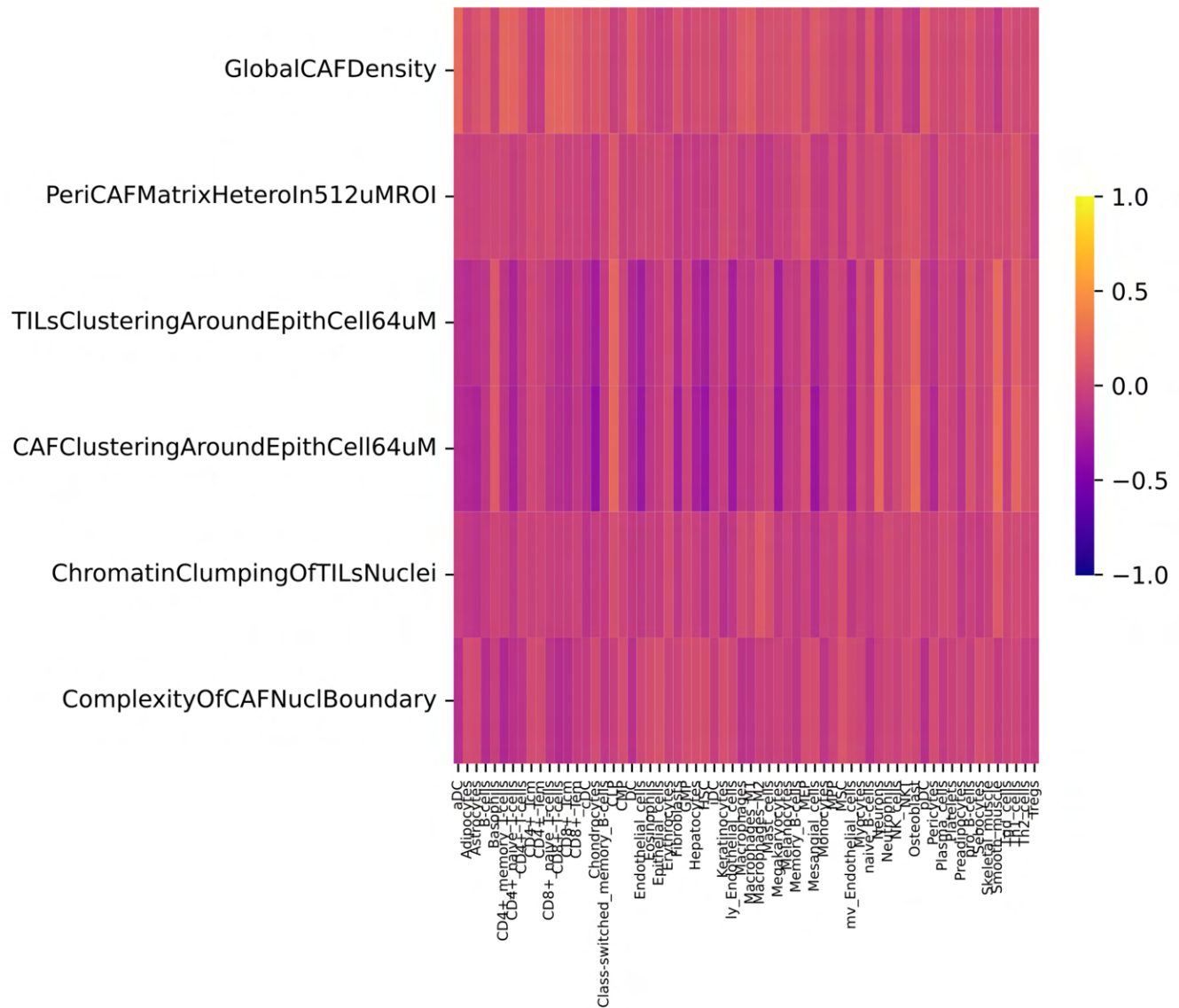


Fig. S51 | Correlation between top HiPS features and cell abundance by xCell deconvolution. Pearson correlation between select features in HiPS and the abundance of various cell types, as determined by the xCell genomic deconvolution assay. HiPS features did not correlate strongly with the abundance of any particular cell type, likely because: 1. Some of the morphological features are not associated with just one, but a mixture of related cell types; 2. Some features are associated with cell activation, clustering, or interactions, rather than abundance; 3. Correlation of the abundance of some cell populations with others, diffusing the specificity of the association between HiPS features and cell abundance.