

SUPPLEMENTARY MATERIAL

Relevance of spatial heterogeneity of immune infiltration for predicting risk of recurrence after endocrine therapy of ER+ breast cancer

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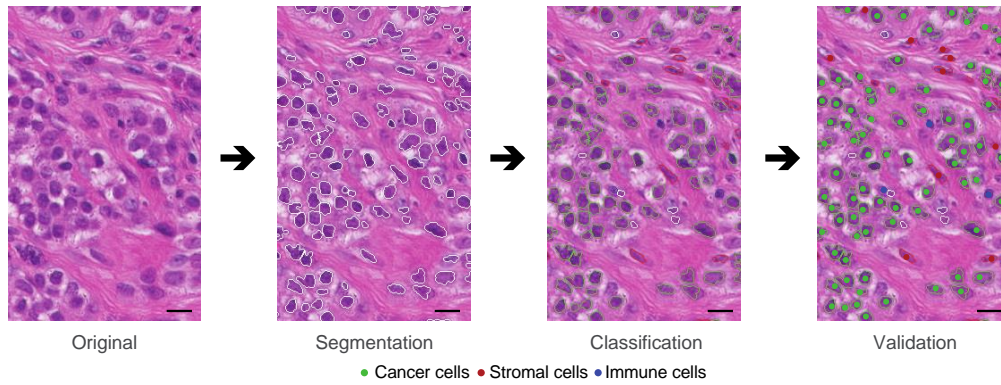
Supplementary Table 1. Baseline demographics and clinical characteristics for all patients included in analysis*

Demographics and characteristics	All patients, No. (%)	Training set, No. (%)	Validation set, No. (%)	HER2- subgroup, No. (%)
Total	1178 (100.0%)	589 (100.0%)	589 (100.0%)	1037 (100.0%)
Age, y [One of these categories below should be = as well. Please edit.]				
<65 years	671 (57.0%)	334 (56.7%)	337(57.2%)	590 (56.9%)
≥65 years	507 (43.0%)	255 (43.3%)	252 (42.8%)	447 (43.1%)
Nodal status				
Negative	883 (75.0%)	439 (74.5%)	445 (75.6%)	774 (74.6%)
Positive	295 (25.0%)	150 (25.5%)	144 (24.4%)	263 (25.4%)
Grade				
Well	262 (22.2%)	113 (19.2%)	149 (25.3%)	247 (24.0%)
Intermediate	715 (60.7%)	381 (64.7%)	334 (56.7%)	637 (61.6%)
Poor	201 (17.1%)	95 (16.1%)	106 (18.0%)	153 (14.9%)
Tumor size, cm				
<1	192 (16.3%)	86 (14.6%)	106 (18.0%)	169 (16.3%)
1-2	611 (51.9%)	310 (52.6%)	301 (51.1%)	546 (52.7%)
2-3	272 (23.1%)	136 (23.1%)	136 (23.1%)	230 (22.2%)
>3	103 (8.7%)	57 (9.7%)	46 (7.8%)	92 (8.8%)
HER2 (16 missing)				
HER2-negative	1037 (88.0%)	511 (86.8%)	526 (89.3%)	
HER2-positive	125 (10.6%)	70 (11.9%)	55 (9.3%)	
Treatment				
Anastrozole	587 (49.8%)	275 (46.7%)	311 (52.8%)	517 (49.9%)
Tamoxifen	591 (50.2%)	314 (53.3%)	278 (47.2%)	520 (50.1%)
All recurrence	224 (19.0%)	108 (18.3%)	116 (19.7%)	188 (18.1%)
Distant recurrence	168 (14.3%)	82 (13.9%)	86 (14.6%)	134 (12.9%)

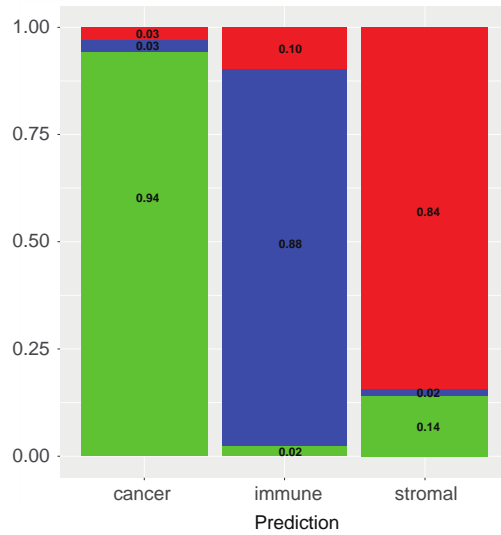
*There were no significant differences between training and validation sets in terms of demographics (Chi-square test for categorical variables. P-value two-sided ($P > 0.05$)). HER2- denotes the HER2- population within the entire cohort.

Supplementary Figure

A Cell classification and validation



B

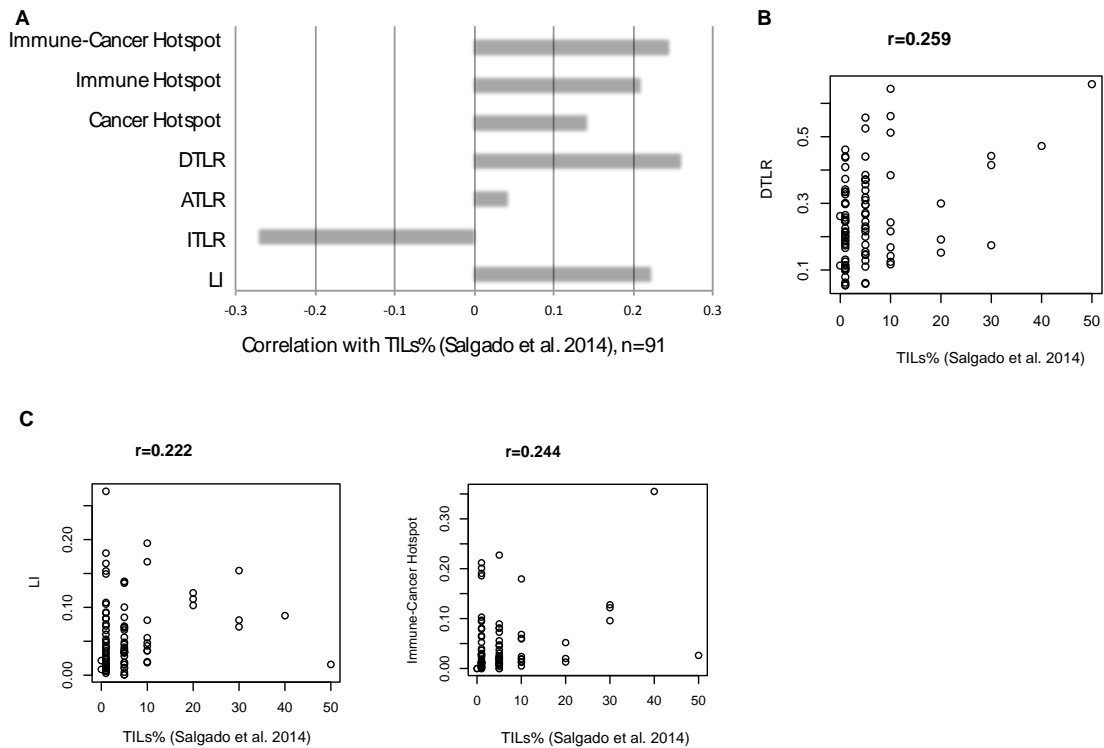


C

	Cancer	Immune	Stromal
Sensitivity	0.843	0.715	0.770
Specificity	0.885	0.963	0.982
Bal. Avg.	0.864	0.839	0.876

Supplementary Figure 1. Histology image analysis pipeline and validation. A) A small region of an hematoxylin & eosin slide image exemplifying the analysis pipeline leading to automated cell classification and validation using annotations given by a pathologist. Scale bar illustrates 10 μm . **B)** Proportions of cells accurately classified for each of the three cell classes. **C)** Sensitivity, specificity and their combined measure, balanced average for each of the three cell classes.

Supplementary Figure 2. Further details on how immune scores were calculated.



Supplementary Figure 3. Comparison of pathological TILs scoring and immune scores. A)

Correlation between pathological TILs scoring and immune scores based on image analysis.

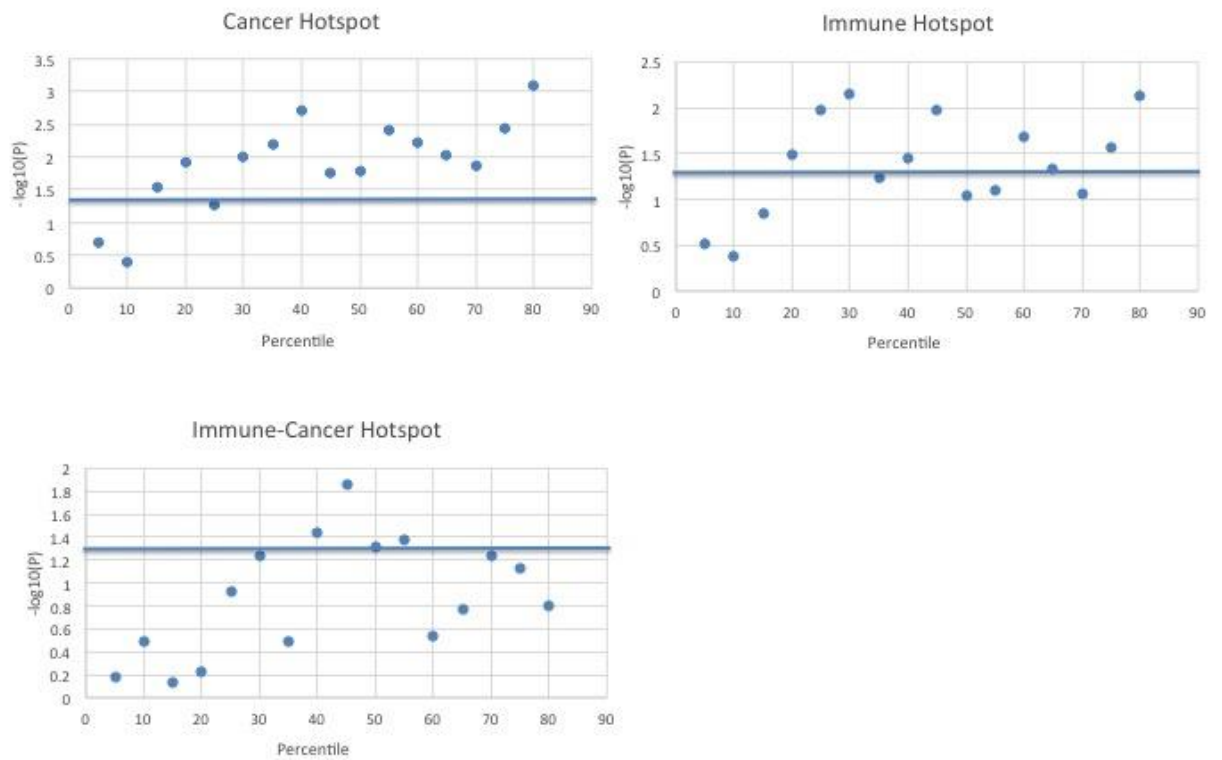
B) Scatter plot showing the correlation between TILs scoring and DTLR, found to be the

strongest among all immune scores. **C)** Scatter plots showing the correlations between TILs

scoring, LI and Immune-Cancer Hotspot. TILs: tumor infiltrating lymphocytes, LI: Lymphocytic

Infiltrate, ITLR: Intra-Tumor Lymphocyte Ratio, ATLR: Adjacent-Tumor Lymphocyte Ratio,

DTLR: Distal-Tumor Lymphocyte Ratio.



Supplementary Figure 4. The range of cutoff points for immune spatial scores in the discovery cohort of TransATAC. Y-axis is the $-\log_{10}$ p-values from survival analysis of 0-10 year and the horizontal line shows the statistical significance level of 0.05. Cox regression models were used to determine best P-value. P-value two-sided.