Cancers Special Issue TILs Figures and Tables

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This file produces the figures included in the manuscript titled "Protocol Development for Pathologists to Provide Machine Learning Validation Data of TILs in Breast Cancer" published in the Cancers Special Issue "Tumor Infiltrating Lymphocytes (TIL) in Solid Tumors: Emerging Insights."

This file uses the current `pilotHTT` data frame but can also be edited to load a copy of the `pilotHTT` data frame in this folder: `inst/extra/20220506-GarciaCancersPaper` to simplify reproducibility of the paper in case some data formatting changes to the current `pilotHTT` data frame.

Collected data totals

In the manuscript, we report the dataset size at the time of its preparation with 29 pathologists and 7,373 annotations. This count excludes the Expert Panel annotations.

```
Number of pathologists who participated in the Pilot Study as of today's
    date: 30
```

```
Number of annotations collected from the Pilot Study as of today's
    date: 7453
```

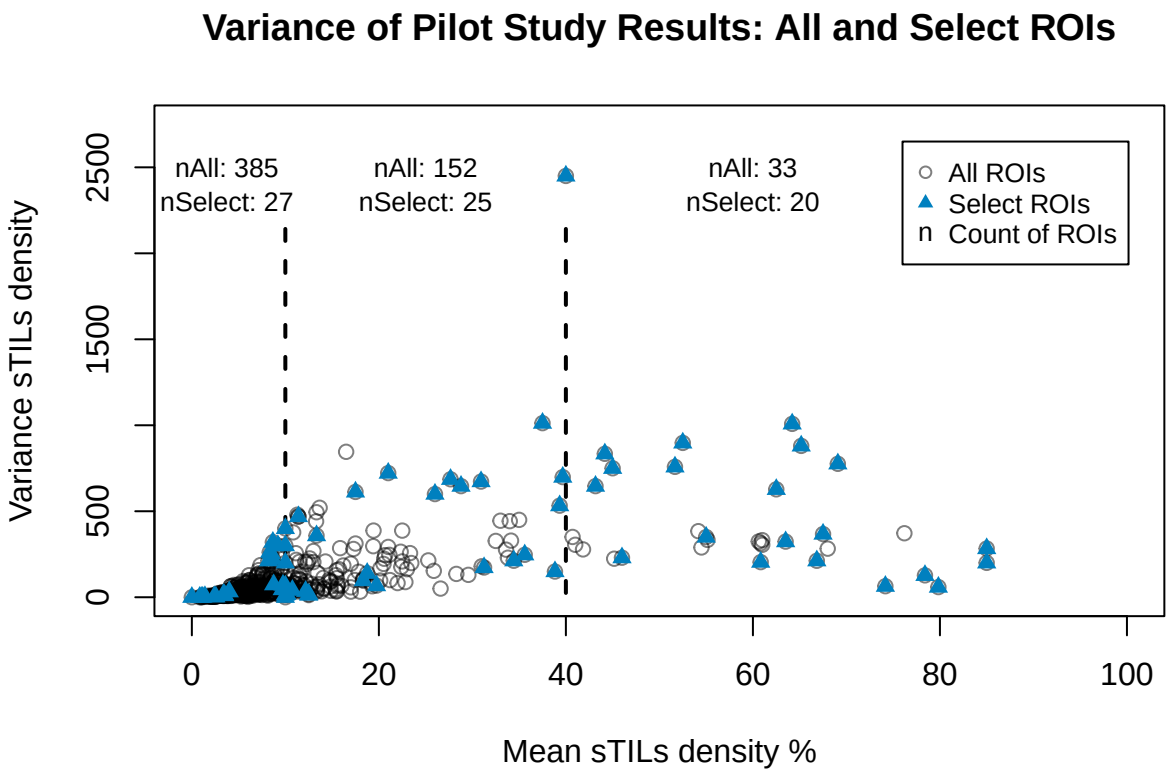
Variance of Pilot Study Results: All and Select ROIs
nAll: 385
nSelect: 27
nAll: 152
nSelect: 25
nAll: 33
nSelect: 20
All ROIs
Select ROIs
n Count of ROIs
Variance sTILs density
0
500
1500
2500
0
20
40
60
80
100
Mean sTILs density %

Table 1: Summary Statistics of example ROIs

Figure	Figure Description	Mean sTILs Density	Variance	Majority Label	Entropy
2A	High Variance LE10	10.00	400.00	Intra-Tumoral Stroma	1.01
2B	Low Variance LE10	0.00	0.00	Other Regions	0.64
2C	High Variance GT40	64.20	1008.20	Intra-Tumoral Stroma	0.45
2D	Low Variance GT40	79.83	58.97	Intra-Tumoral Stroma	0.64
3A	High Entropy LE10	3.50	9.67	Intra-Tumoral Stroma *AND* Invasive Margin *AND* Tumor with No Intervening Stroma	1.10
3B	Low Entropy LE10	9.75	70.79	Intra-Tumoral Stroma	0.00
3C	High Entropy GT40	69.08	775.90	Intra-Tumoral Stroma	0.86
3D	Low Entropy GT40	66.83	212.17	Intra-Tumoral Stroma	0.00

Table 2: Frequency of ROI Labels

Figure	Figure Description	Invasive Margin	Intra-Tumoral Stroma	Tumor with No Intervening Stroma	Other Regions
2A	High Variance LE10	1	3	2	0
2B	Low Variance LE10	0	2	0	4
2C	High Variance GT40	0	5	1	0
2D	Low Variance GT40	2	4	0	0
3A	High Entropy LE10	2	2	2	0
3B	Low Entropy LE10	0	8	0	0
3C	High Entropy GT40	2	10	3	0
3D	Low Entropy GT40	0	6	0	0

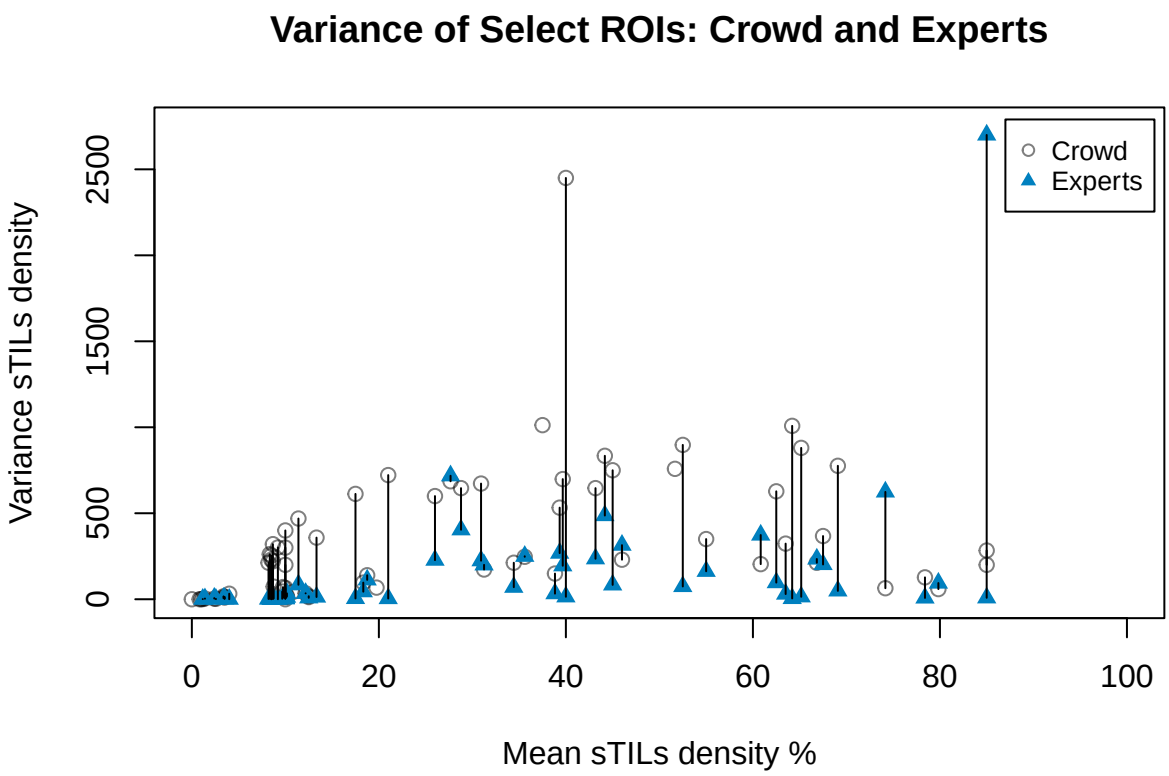
Variance of Select ROIs: Crowd and Experts
Variance sTILs density
0
500
1500
2500
0
20
40
60
80
100
Mean sTILs density %
Crowd
Experts

Table 3: Variance Summary Statistics Matched ROIs: Median [IQR]

	All Densities	$\leq 10\%$	$10\% < \% \leq 40\%$	$> 40\%$
Crowd - All	48.10 [20.58- 110.31]	30.70 [15.07- 59.50]	111.50 [56.30- 245.13]	324.55 [278.17- 627.50]
Crowd - Select	212.24 [39.33- 549.50]	44.67 [4.05- 225.28]	246.80 [67.58- 646.18]	358.75 [210.17- 762.73]
Experts	14.17 [4.23- 178.67]	3.07 [0.98- 4.32]	70.00 [14.17- 224.17]	96.67 [39.42- 275.03]

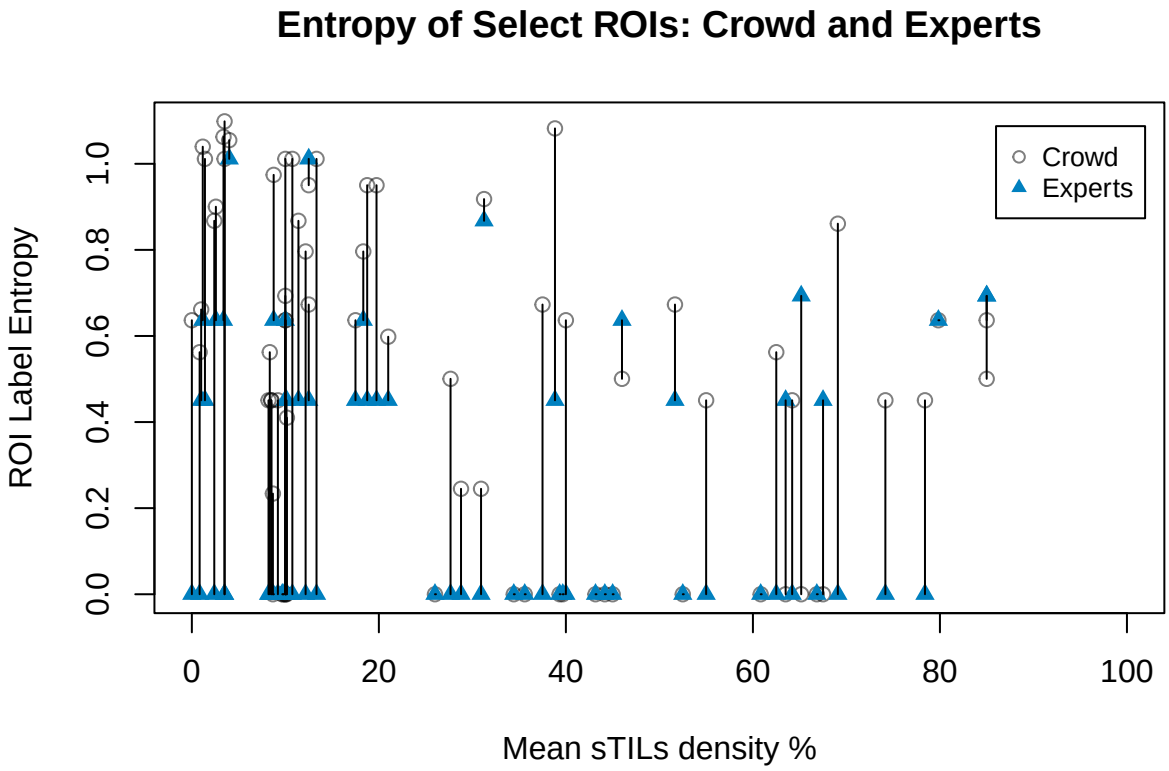
Entropy of Select ROIs: Crowd and Experts
ROI Label Entropy
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
Mean sTILs density %
Crowd
Experts

Table 4: Entropy Summary Statistics Matched ROIs: Median [IQR]
- excluded is.na(scoreVar) from All caMicro

	All Densities	$\leq 10\%$	$10\% < \% \leq 40\%$	$> 40\%$
Crowd - All	0.23 [0.00 - 0.45]	0.23 [0.00 - 0.41]	0.24 [0.00 - 0.50]	0.00 [0.00 - 0.45]
Crowd - Select	0.56 [0.00 - 0.86]	0.64 [0.45 - 0.99]	0.64 [0.24 - 0.92]	0.45 [0.00 - 0.52]
Experts	0.00 [0.00 - 0.45]	0.00 [0.00 - 0.45]	0.00 [0.00 - 0.45]	0.00 [0.00 - 0.50]

Table 5: ROI Label Frequency

Majority Label	Crowd - All	Crowd - Select	Experts
Intra-Tumoral Stroma	525 (82.03%)	54 (75%)	56 (77.78%)
Intra-Tumoral Stroma *AND* Invasive Margin	10 (1.56%)	1 (1.39%)	1 (1.39%)
Intra-Tumoral Stroma *AND* Invasive Margin *AND* Tumor with No Intervening Stroma	1 (0.16%)	1 (1.39%)	0 (0%)
Intra-Tumoral Stroma *AND* Other Regions	2 (0.31%)	0 (0%)	2 (2.78%)
Intra-Tumoral Stroma *AND* Tumor with No Intervening Stroma	4 (0.62%)	1 (1.39%)	0 (0%)
Invasive Margin	8 (1.25%)	2 (2.78%)	1 (1.39%)
Invasive Margin *AND* Other Regions	1 (0.16%)	1 (1.39%)	0 (0%)
Other Regions	80 (12.5%)	7 (9.72%)	12 (16.67%)
Tumor with No Intervening Stroma	9 (1.41%)	5 (6.94%)	0 (0%)

Table 6: Pitfall Summary Table

Pitfall Type	Pitfall Summary
Percent of Tumor-Associated Stroma	Exclude thick-walled vessels, benign glandular elements, adipocytes, carcinoma in situ, and necrosis from the area of tumor-associated stroma
	Calculate with respect to the entire ROI area
	Variations in tumor cell morphology can make it difficult to distinguish stroma from tumor
sTILs Density Score	Cells with small/pyknotic and/or perinuclear clearing can be difficult to categorize
	Non-lymphoid cells may be confused for lymphocytes
	Error in the percent tumor-associated stroma can affect the sTILs density
	Sparsely distributed tumor cells may be more challenging to quantitate