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Breast cancer intrinsic subtypes predict outcomes in primary and metastatic samples

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INTRODUCTION

- We retrospectively analyzed 7,021 de-identified breast cancer patients with known hormone receptor (HR) or HER2 status and a matched RNASeq sample.
- The prognostic and predictive value of the PAM50 intrinsic subtypes, namely Luminal A, Luminal B, Her2, and Basal-like subtypes, is well-studied in primary as well as metastatic breast cancer settings.
- Prosigna has emerged as a rapid PAM50 subtype predictor based on the NanoString nCounter assay.
- However, assay reproducibility across various RNASeq or qRT-PCR platforms can be challenging, especially when applying the predictor on metastatic breast cancer tumors.
- Here, we create an in-house subtype predictor that works on RNA sequencing data.
- We evaluate real-world outcomes for our intrinsic subtype predictions across various immunohistochemical (IHC) labels and metastatic tumor sites.

METHODS

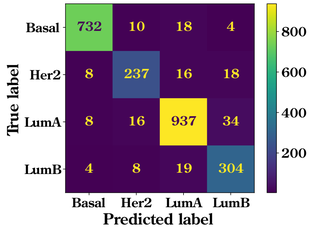
- The subtype predictor was trained on a cohort of 2,497 breast cancer patients using the PAM50 genes, profiled using Nanostring RNA nCounter assay (GSE148426)[1]. The reference dataset contained samples collected from various sites including breast (n=2440), liver (n=936), lymph node (n=577), lung (n=540), and bone (n=304).
- For subtype classification, we first batch-corrected the external dataset to the Tempus RNA-seq reference dataset using SpinAdapt[2], then trained a Support-Vector Classifier (SVC) on the corrected data. A 10-fold CV experiment was performed on the corrected dataset to analytically validate the intrinsic subtype predictions.
- The concordance between HR/HER2 status and PAM50 prediction was analyzed, and these patients were excluded from training.
- Real-world overall survival (rwOS) was evaluated from the time of first diagnosis. The outcomes across PAM50 subtypes were assessed according to tumor collection site and HR/HER2 IHC status.

KEY TAKEAWAYS

- Analyzing 7,021 patient samples finds a highly accurate PAM50 breast subtype predictor F1-score of 0.97 in a 10-fold CV experiment.
- The prognostic value of the basal subtype was significant for breast cancer patients across various sites of metastasis including lymph node, liver, lung, and bones.
- For patients in each of the HR+/HER2- and triple negative IHC groups, the PAM50 molecular subtypes provided an additional level of prognostic detail with statistical significance.

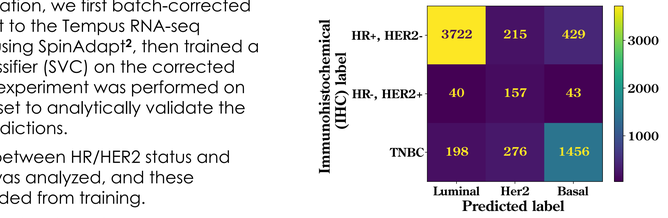
RESULTS

Figure 1. Confusion Matrix with Prosigna labels and model predictions



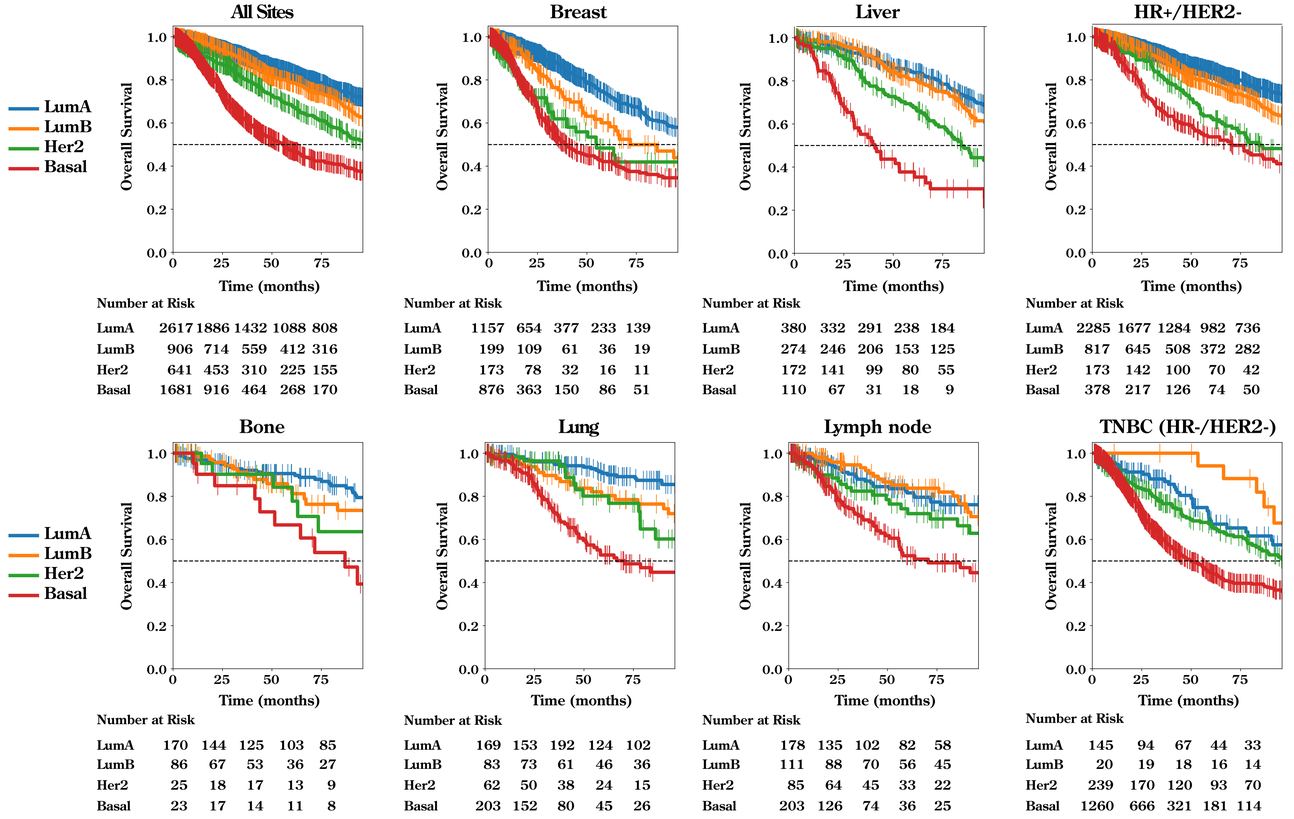
- The 10-fold CV experiment on the Tempus-adapted GSE148426 dataset achieved F-1 scores of 0.97, 0.86, 0.94, and 0.87 on Basal, HER2-like, Luminal A, and Luminal B PAM50 subtypes, respectively.

Figure 2. Confusion Matrix with IHC labels and model predictions



- Evaluating the PAM50 prediction model on Tempus Evaluation coohort, to compare the model predictions with immunohistochemical (IHC) labels.

Figure 3. Evaluation of Survival Outcomes by Cancer Type



Number at Risk

All Sites	0	25	50	75
LumA	2617	1886	1432	1088	808
LumB	906	714	559	412	316
Her2	641	453	310	225	155
Basal	1681	916	464	268	170

Breast	0	25	50	75
LumA	1157	654	377	233	139
LumB	199	109	61	36	19
Her2	173	78	32	16	11
Basal	876	363	150	86	51

Liver	0	25	50	75
LumA	380	332	291	238	184
LumB	274	246	206	153	125
Her2	172	141	99	80	55
Basal	110	67	31	18	9

HR+/HER2-	0	25	50	75
LumA	2285	1677	1284	982	736
LumB	817	645	508	372	282
Her2	173	142	100	70	42
Basal	378	217	126	74	50

Bone	0	25	50	75
LumA	170	144	125	103	85
LumB	86	67	53	36	27
Her2	25	18	17	13	9
Basal	23	17	14	11	8

Lung	0	25	50	75
LumA	169	153	192	124	102
LumB	83	73	61	46	36
Her2	62	50	38	24	15
Basal	203	152	80	45	26

Lymph node	0	25	50	75
LumA	178	135	102	82	58
LumB	111	88	70	56	45
Her2	85	64	45	33	22
Basal	203	126	74	36	25

TNBC (HR-/HER2-)	0	25	50	75
LumA	145	94	67	44	33
LumB	20	19	18	16	14
Her2	239	170	120	93	70
Basal	1260	666	321	181	114

- Basal rwOS was significantly shorter than non-basal patients (n=5,845, p< 2e-90) across all tumor sites.
- The predicted PAM50 basal rwOS remained significantly shorter than non-basal patients even when stratified by site of metastasis:
  - breast (n=2,405; p< 1e-27)
  - lymph node (n=577, p< 1e-7)
  - liver (n=936; p<1e-25)
  - lung (n=540, p< 1e-13)
  - bone (n=304, p< 1e-3).
- Among both HR+/HER2- (n=3,653) and HR-/HER2- (n=1,664) IHC cohorts with available outcomes data, the predicted PAM50 basal subtype could further stratify each of these IHC populations with basal-subtype showing significantly worse prognosis than the non-basal subtype (p< 1e-27 and p< 1e-7, respectively).

REFERENCES

1. Wallden, Brett, et al. "Development and verification of the PAM50-based Prosigna breast cancer gene signature assay." BMC medical genomics (2015).
2. Ahmed, Talal, et al. "Privacy preserving validation for multiomic prediction models." Briefings in Bioinformatics (2022).

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