A predictive test for neoadjuvant chemotherapy in breast cancer identifies a subset of triple negative patients with resistant disease and the poorest prognosis.

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P2-10-08

Summary

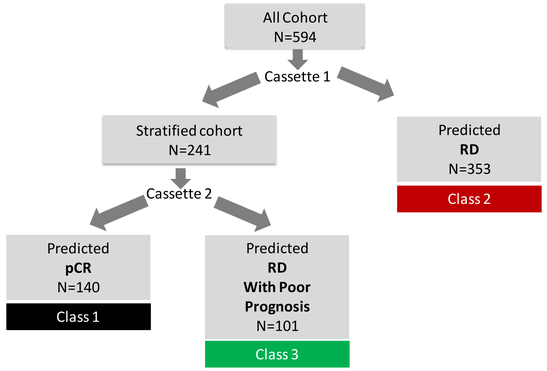
Prediction of pathological complete response (pCR) for neoadjuvant treatment is an unmet need, especially for triple negative breast cancer (TNBC)[1-3]. We developed a test to predict which patients are likely to achieve pCR or RD to the standard of care (taxane-based) neoadjuvant chemotherapy using gene expression profiling of 355 pre-selected biomarkers[4].

Three microarray datasets were used (GSE22226[1], GSE25055[5], and GSE25065[5]) including a total of 594 stage I-III breast cancer patients of which 125 (21%) achieved pCR, and 469 (79%) RD. ER+ tumors were present in 57% of the patients and 52% were PGR+. Almost 90% of the patients were HER2-. The cohort was divided into balanced populations with 80% of patients used for model development, while 20% of the patients were reserved as a test set for locked-down models. We developed gene cassettes with predictive and prognostic value by combining a "winnowing" process to remove genes with the least predictive power, and hundreds of thousands of step-wise runs, followed by ranking genes based on conditional probabilities. Models were generated by logistic regression methods. A total of 582 patients with subtype annotation were further analyzed. Of 203 TNBC, 66 (32.5%) achieved pCR, while 137 (67.5%) RD. Of 324 ER+HER- patients 33 (10.2%) achieved pCR while 291 (89.8%) had RD.

Taken together, we developed a predictive test (BA100) consisting of two gene cassettes that correctly identified 69.7% (85/122) of total pCR, and 88.9% (409/460) of total RD patients. BA100 also stratified TNBC patients with differential response to chemotherapy and survival rates so that novel approaches can be used without delay. Further validation will confirm the test utility.

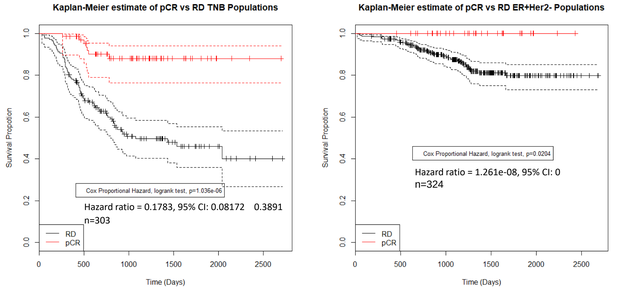
1. Esserman LJ, et al: J Clin Oncol 30:3242-9, 2012; 2. Masood S: Womens Health (Lond) 12:480-491, 2016; 3. Symmans WF, et al: J Clin Oncol 25:4414-22, 2007, 4. Fournier MV, et al: Cancer Res 2006; 66: (14). July 15, 2006; 5. Hatzis C, et al: JAMA 305:1873-81, 2011, 6. Cortazar et al: Lancet 384:164-72, 2014

BA100 Stratifies Patients in 3 Classes



pCR: Pathological Complete Response; RD Residual Disease

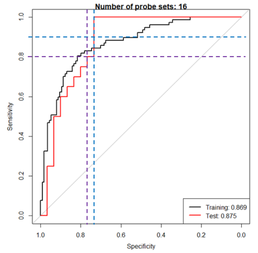
pCR Correlation with Outcomes

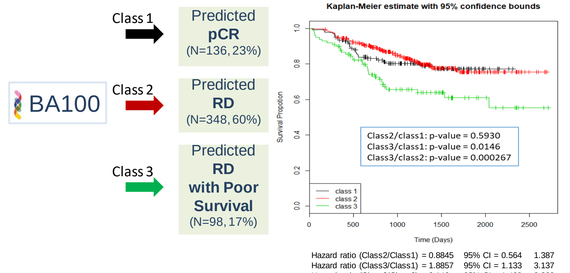


KM curves demonstrating significant Distant Recurrence-Free Survival (DRFS) benefit in patients who achieved pCR in TNBC and ER+/HER2- patients. The dashed lines represent a 95% confidence interval.

BA100 3 Classes Using Two Gene Cassettes

16 Gene Cassette 2 Training and Test ROC Curves

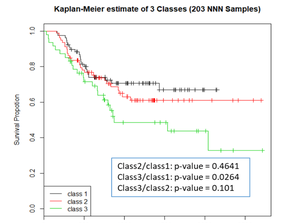




ALL patients (N=582)

Hazard ratio (Class2/Class1) = 0.8845 95% CI = 0.564 1.387
Hazard ratio (Class3/Class1) = 1.8857 95% CI = 1.133 3.137
Hazard ratio (Class3/Class2) = 2.146 95% CI = 1.409 3.269

TNBC (N=203)

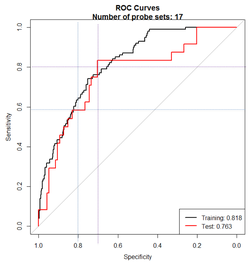


Hazard ratio (Class2/Class1) = 1.234 95% CI = 0.7027 2.168
Hazard ratio (Class3/Class1) = 1.942 95% CI = 1.0810 3.489
Hazard ratio (Class3/Class2) = 1.595 95% CI = 0.9136 2.786

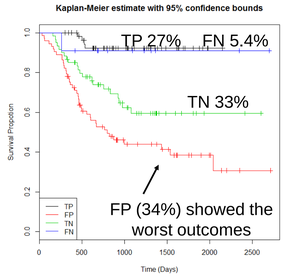
ROC curves for cassette 2 (16 gene model) applied to the training cohort (N=193) and locked-down test cohort (N=48). AUC values are 0.869 and 0.875 for training and test sets respectively. With a cut-off of 95% sensitivity and 73% specificity (PPV 0.7; NPV 0.95), applying Cassette 2 reduced the FP rates in the total population from 24% to 9%, while correctly predicting 88.9% of all RD. Class 3 patients showed significantly worse outcomes in ALL and TNBC populations. TNBC Class1 N=77 (37.9%), Class 2 N=79 (38.9%), Class 3 N=47 (23.2%).

Development of Cassette 1

17 Gene Cassette 1 Training and Locked-down Validation ROC Curves



KM of 8Y DRFS TNBC patients after Cassette 1 prediction



ROC curves for cassette 1 (17 gene model) applied to the training cohort (N=476) and locked-down test cohort (N=118). AUC values of 0.818 and 0.763 for training and test respectively. Cutoff 83% sensitivity and 68% specificity (PPV 0.4; NPV 0.94). True positive (TP), False positive (FP), True negative (TN), False Negative (FN). KM DRFS TP / TN (p=0.00453) or TP/ FP (p=2.09E-06).

BA100 Performance by Subtype

	Without BA100	BA100 Prediction				BA100 Discovery			
	pCR %	PPV %	NPV %	Sens. %	Spec. %	True Positive	False Positive	True Negative	False Negative
ER+/HER2-	10.2	45.2	95.0	57.6	92.1	19 (5.9%)	23 (7.1%)	268 (82.7%)	14 (4.3%)
TNBC	32.5	66.2	88.1	77.3	81.0	51 (21.5%)	26 (12.8%)	111 (54.7%)	15 (7.4%)
HER2+	47.2	84.6	73.9	64.7	89.5	11 (30.6%)	2 (5.6%)	17 (47.2%)	6 (16.7%)
PGR+ only	31.6	100.0	86.7	66.7	100.0	4 (21.1%)	0	13 (68.4%)	2 (10.5%)
Total (N=582)	21.0	62.5	91.7	69.7	88.9	85 (14.6%)	51 (8.8%)	409 (70.3%)	37 (6.4%)

pCR rates under the current paradigm for treatment are shown in the first column consistent with previously reported meta-analysis[6] For each sub-type, BA100 guidance increased pCR rates in the predicted positive populations while stratifying patients with RD with NPV 0.74-0.95.

BA100 Genes functions

17-Gene Cassette 1

pCR predictors

- EMT regulator
- Epigenetic factors
- Ubiquitination factors
- Antigen presentation
- miRNA synthesis
- Transcriptional repressor

RD predictors

- Adriamycin and tamoxifen resistance
- Marker of cancer invasion
- PI3 Kinase signaling
- Component of telomerase

16-Gene Cassette 2

pCR predictors

- EMT regulator
- Epigenetic factors
- DNA repair factor
- G-protein coupled receptor
- Antigen presentation
- Epithelial Transcription Factor

RD predictors

- Estrogen-independent proliferation in breast cancer
- EMT factor
- Ras activation factor
- G-protein coupled receptor

BA100 Guidance

BA100 proactively identifies breast cancer patients with resistant disease and the worst outcomes allowing informed decisions to pursue additional therapy or trials.

QR Code