Breast Cancer Treatment Outcomes Modeling from METABRIC Genomic Patient Data

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Abstract

The ability to more accurately predict outcomes of various cancer treatment regimes would be a transformative tool in risk-assessment for clinical therapeutic decision-making in response to cancer diagnosis. Our project aims to predictively model favorable outcomes in response to treatment in a dataset of Invasive Breast Carcinoma patients, where treatments post-surgery are any of a combination of chemotherapy, hormone therapy, and radiotherapy. We build separate random forest models for each therapeutic category in order to predict vital status and overall survival months (both represented as binary variables) in response to treatment. The dataset we are utilizing includes standard clinical diagnostic markers of breast cancer, as well as patient age and inferred menopausal state, which are useful attributes in a predictive model. However, the dataset also includes tumor genetic data, specifically SNP, copy number, and normalized gene expression for each patient. When we augment the clinical variables with genetic copy number and RNA-expression data for each patient, select top predictive variables, and evaluate model performance by multiple metrics, the comparative performance improves across the board. The greatest performance gain is achieved by incorporating gene expression data, although specific genes indicative of treatment response are not stable across treatment categories and do not exhibit over-representation of any particular biological process GO category. We therefore observe a useful contribution of genomic data in risk assessment modeling of breast cancer treatment regimes but not in terms of specific diagnostic gene targets.

Introduction

Since the publication of the first complete cancer genomes in 2009^{1,2}, it has become increasingly clear that cancer is not one single disease with a common cure. Not only do genetic differences of cancer cells exist between various types of cancer, but even a single cancer type is likely to exhibit a substantial amount of genetic variation³. Consequently, patients may require different therapies to treat the same disease – the idea behind "personalized medicine." Currently, Washington University's Genomics and Pathology Services provides testing for 42 gene mutations linked to cancer, which can help doctors tailor treatments⁴.

Breast cancer is a prime example of a complex disease in which patients with seemingly similar symptoms and clinical features respond quite differently to the same treatment therapies. The landmark 2012 METABRIC study⁵, from which we obtained our data, found breast cancer to exist as at least 10 distinct diseases, each with a different "molecular fingerprint." The researchers involved in the study were able to establish sub-categories by identifying key genetic variations responsible for turning on many cell processes associated with breast cancer (i.e. driver mutations) and mapping these variations to certain clinical features, such as high levels of the estrogen receptor. Our approach will focus on predicting favorable outcomes of breast cancer patients in response to treatment by integrating clinical and molecular data. The large size and completeness of the dataset will allow us to partition the patients based on treatment regimes to determine how genomic and expression data can supplement clinical data in predicting patient response to treatments.

Data Sources

This study utilizes the 2012 METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) dataset, consisting of 2509 cases of Invasive Breast Carcinoma. The dataset is made available through cbioPortal, which allows for easy access to all of the clinical phenotype data, as well as patients' genetic profiles. For this project, we limit our study of personalized genomic data to copy number variation (CNV)—notably, the first ever breast cancerspecific map of CNVs—and normalized mRNA gene expression. Clinical variables include age, cellularity, estrogen receptor (ER) status, progesterone receptor (PR) status, cancer grade, Nottingham Prognostic Index (NPI), inferred menopausal state, laterality, tumor size, and tumor stage, described in Table S1. Below, we explain how we determine the most important variables and variable types to include in our predictive models and evaluate response-prediction results. The dataset also contains binary variables for the type of treatment received—chemotherapy, radiotherapy, and hormone treatment, which we use to partition into treatment categories. We consider two response variables for classification of positive treatment outcome: vital status ("living" or "died of disease"), and overall

survival months. We define positive treatment response alternately as the vital status at the end of the study, and as overall survival months greater than average, in order to account for patients who may have died after the course of the study. Patients who died of other causes and patients with unknown vital status are discounted from predictive analysis and are removed from the data set, as are patients with incomplete data coverage, leaving 1375 usable patient cases.

Preliminary analysis of the dataset showed six treatment-regime subpopulations of reasonable size for classification (between 150 and 442 patients). For each of these, we move forward with training prediction models for both response metrics. Table S2 shows the number of patients in each subpopulation and the treatment outcomes by vital status and overall survival months greater than average. Figure 1 provides a graphic representation of the survival rates and size of each treatment group.

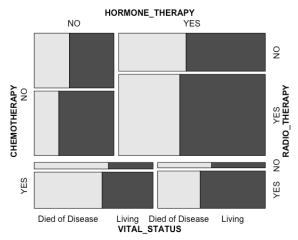


Figure 1: Plot of survival rates by vital status in each treatment subset of the data

Proposed Algorithm

We propose for each of the six sufficiently large treatment-segmented subsets of the data to build two sets of random forest classification models: one predicting favorable outcome defined by vital status at the end of the study, and one by overall survival months greater than average within that treatment regime. For each, we build a model using clinical variables alone, another using clinical variables supplemented by genomic copy number, one with clinical variables and gene expression data, and one using all three sets of variables together.

We perform feature ranking in five training/testing folds for these models by mutual information with the response variable, and average the mutual information for each feature across the five folds. We then heuristically determine the top N features in each configuration by increasing N until random forest out-of-bag-error increases due to over-fitting (see Figure 3 for an example). Finally, we evaluate which combined set of variables results in the most useful models across treatment regimes in terms of accuracy, positive predictive value, and negative predictive value under maximum likelihood classification, as well as area under the roc curve, all with five-fold cross-validation. We examine which features within these model sets were the most relevant for treatment efficacy prediction. The overall flow of the algorithm is described in Figure 2.

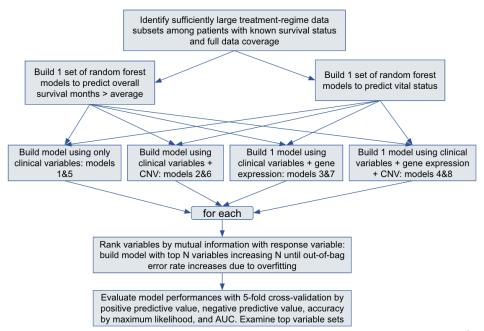


Figure 2. Algorithm flow chart, describing a total of 8 random forest models trained for each treatment regime subset. Models 1 and 5 rely only on clinical variables to predict vital status and overall survival months greater than average, respectively. Models 2 and 6 use clinical variables and CNV. Models 3 and 7 use clinical variables with gene expression data. Models 4 and 8 use all variables.

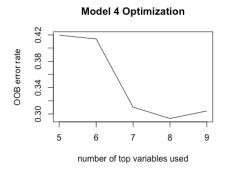


Figure 3. A plot of out-of-bag-error rate for the random forest model 4 trained in the (chemo, no hormone, radio) therapy set. Out-of-bag-error continuously decreases when incorporating the first 8 features by mutual information into the model, and then increases when the 9th feature is added. Therefore the training stops at 8 top features, used for further performance evaluation.

Results

We build models on each of the six identified treatment subsets, using clinical data and varying levels of genomic information to predict treatment outcome defined by two binary classification metrics, vital status and overall survival months greater than average. We see an improvement across the board in mean model performance when incorporating copy number and gene expression data in addition to the clinical data baseline (Figure 4). This improvement is seen by all metrics, including accuracy and area under the roc curve as a general measure of overall model performance, as well as the more targeted positive predictive value, which indicates the degree to which the model accurately predicts positive response to treatment, and negative predictive value, which indicates the degree to which the model accurately predicts negative response to treatment. Best improvement relative to clinical variable baseline is seen for the models incorporating gene expression data, and although positive predictive value is higher than negative predictive value, there is no compromising drop in negative predictive value. Overall area under the

curve (AUC) is comparatively high in the gene expression models at around 0.75, relative to baseline around 0.65, with statistical significance in some comparisons (Table 1).

When examining the top variables for these models, we note that the top variables selected for model 3 and model 4 are universally identical or near-identical, as are the top variables selected for model 7 and model 8 (Table 2). This indicates that the most useful added information for predicting treatment response was present in the gene expression data and not the CNV data. Furthermore, these top-performing variable sets often do not include many clinical variables or any at all. The most commonly recurring clinical variables, and therefore likely the most informative, are the Nottingham Prognostic Index (NPI) and tumor size, but even these are routinely outperformed by gene expression features.

Although gene expression produces an improved model performance, and individual genes selected as top features may have been implicated in cancer progression in prior studies, the top gene expression variables are divergent across treatment regimes. Even within the same treatment regime the top genes selected are almost entirely divergent between models trained on the two different response variables (Table 2). Furthermore, there is no trend of over-represented PANTHER biological processes⁶ in these top gene lists, so there is no specific gene target to probe as a link to cancer treatment response and no set of biological processes that are especially implicated as treatment response drivers (Figure 5).

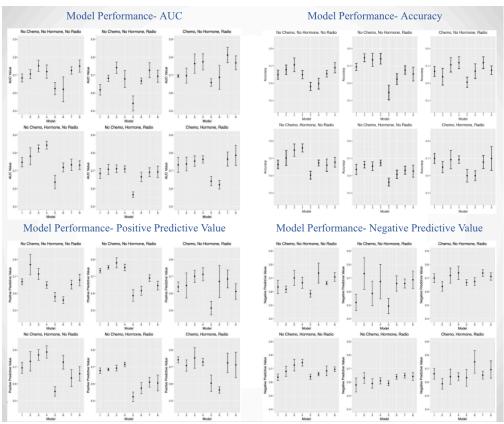


Figure 4. The mean performance with standard error across five folds for each model trained within each treatment set. The upper left plots show area under the roc curve, the upper right show accuracy by maximum likelihood classification, the bottom left show positive predictive value, and the bottom right show negative predictive value. Positive predictive value is higher than negative predictive value, and there is more improvement for PPV in performance of the personalized genetic models relative to baseline (2,3,4 vs 1 and 6,7,8 vs 5), but the greatest improvement is in AUC for models 7 and 8 vs model 5, predicting overall survival months with gene expression data vs without. P-values for the improvements are listed in Table 1.

Accuracy T-	-tests		Positive Predic	ctive T-tests	Negative Predictive T-tests		AUC T-tests	
No Chemo, No Hormone, No Radio			No Chemo, No Hormone, No Radio		No Chemo, No Hor	mone, No Radio	No Chemo, No	o Hormone, No Radio
Models	💌	P-Value	Models 🔽	P-Value	Models	P-Value	Models	P-Value
M1 vs M2		0.478513	M1 vs M2	0.1673389	M1 vs M2	0.7673451	M1 vs M2	0.5338549
M1 vs M3		0.2741938	M1 vs M3	0.2557431	M1 vs M3	0.3988461	M1 vs M3	0.1186961
M1 vs M4		0.9899183	M1 vs M4	0.4927239	M1 vs M4	0.6438287	M1 vs M4	0.445543
M5 vs M6		0.6793166	M5 vs M6	0.5661934	M5 vs M6	0.1088352	M5 vs M6	0.9650166
M5 vs M7		0.04448803	M5 vs M7	0.08673818	M5 vs M7	0.03748736	M5 vs M7	0.04007806
M5 vs M8		0.02406805	M5 vs M8	0.05418413	M5 vs M8	0.01755876	M5 vs M8	0.03070078
	No Chemo, Hormone,			emo, Hormone, No Radio	No Chemo, Horm			Hormone, No Radio
Models	<u> </u>	P-Value		P-Value 💌		P-Value		P-Value 🔽
M1 vs M2		0.4894488	M1 vs M2	0.5809613	M1 vs M2	0.362713	M1 vs M2	0.5566943
M1 vs M3		0.09879367	M1 vs M3	0.135601	M1 vs M3	0.1178536	M1 vs M3	0.05142955
M1 vs M4		0.02446095	M1 vs M4	0.09068075	M1 vs M4	0.01445173	M1 vs M4	0.02426606
M5 vs M6		0.03956691	M5 vs M6	0.009985125	M5 vs M6	0.4309919	M5 vs M6	0.1085977
M5 vs M7		0.2174603	M5 vs M7	0.2148639	M5 vs M7	0.3289958	M5 vs M7	0.08276847
M5 vs M8		0.07499059	M5 vs M8	0.07855994	M5 vs M8	0.06875703	M5 vs M8	0.07208823
	No Chemo, No Hormo			emo, No Hormone, Radio	No Chemo, No Ho			No Hormone, Radio
Models		P-Value 💌		P-Value 💌		P-Value		P-Value 🔽
M1 vs M2		0.1294978	M1 vs M2	0.2809974	M1 vs M2	0.1576195	M1 vs M2	0.1062091
M1 vs M3		0.3742491	M1 vs M3	0.2077093	M1 vs M3	0.5561789	M1 vs M3	0.02197213
M1 vs M4		0.2487952	M1 vs M4	0.452376	M1 vs M4	0.3170737	M1 vs M4	0.3153895
M5 vs M6		0.1870807	M5 vs M6	0.5302726	M5 vs M6	0.07297795	M5 vs M6	0.03679609
M5 vs M7		0.0375687	M5 vs M7	0.03992262	M5 vs M7	0.04244762	M5 vs M7	0.01369019
M5 vs M8		0.1058182	M5 vs M8	0.2118689	M5 vs M8	0.05482166	M5 vs M8	0.02329823
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Models		e, Radio P-Value	No (Chemo, Hormone, Radio P-Value	No Chemo, Hor Models	none, Radio P-Value	No Chemo Models	, Hormone, Radio P-Value
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M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6	Chemo, No Hormon	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.222088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Che Models M1 vs M3 M1 vs M4 M1 vs M4 M5 vs M6	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1169098 0.2678359 0.06452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158	No Chemo, Hor Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6	mone, Radio P-Value 0.4493746 0.8623454 0.612334 0.106554 0.06639298 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.8356422	No Chemo Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N Models M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M8	Normone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 Derrome, Radio P-Value 0.9793804 0.2719921 0.1573064 0.6957178
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M8	Chemo, No Hormon	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chet Models M1 vs M3 M1 vs M4 M5 vs M8	Chemo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.26783599 0.06452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03488473 0.1500748	No Chemo, Hor Models M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M1 vs M8 M1 vs M8 M5 vs M7 M1 vs M8 M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M8 M1 vs M4 M5 vs M6 M5 vs M8	mone, Radio P-Value 0.4493746 0.8623454 0.106554 0.06633298 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.3356422 0.06551687 0.2270437	No Chemo Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 0 Hormone, Radio P-Value 0.9793804 0.2719921 0.1573064 0.6957178 0.01934901 0.04586046
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M8 M1 vs M2 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M6	Chemo, No Hormone,	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795	Models	Chemo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.2678359 0.06452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03488473 0.1500748	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor Models M1 vs M3 M1 vs M4 M5 vs M6 Chemo, No Hor M5 vs M6 Chemo, Hormo, Hormo, Hormo, Hormo, Hormo, Hormo	none, Radio P-Value 0.4493746 0.6623454 0.106554 0.06639298 0.2002502 none, Radio P-Value 0.233688 0.7738357 0.530582 0.8356422 0.05551687 0.2270437	No Chemo, Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N Models M1 vs M2 M1 vs M4 M5 vs M6 M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M6 Chemo, N M5 vs M6 M6 vs M7 M5 vs M6 M6 vs M7 M6 vs M8	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 0 Hormone, Radio P-Value 0.7973804 0.27719921 0.1573064 0.6957178 0.01934901 0.04586046
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M6	Chemo, No Hormone,	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795 Radio P-Value	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M8 M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.2678359 0.06452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03489473 0.1500748 emo, Hormone, Radio P-Value	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor Models M1 vs M2 M1 vs M4 M5 vs M8 Chemo, No Hor Models M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	mone, Radio P-Value 0.4493746 0.6823454 0.106554 0.06639298 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.38356422 0.06551687 0.2270437 one, Radio	No Chemo, Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N M5 vs M8 M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 0 Hormone, Radio P-Value 0.9793804 0.2719921 0.1573064 0.6957178 0.01934901 0.04586046 Hormone, Radio
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M2 M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	Chemo, No Hormone,	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795 Radio P-Value	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Che Models M1 vs M4 M5 vs M8	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.26783599 0.046452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03489473 0.1500748 emo, Hormone, Radio P-Value 0.4060488	No Chemo, Hor Models M1 vs M2 W1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M1 vs M8 W1 vs M8 W1 vs M8 W1 vs M8 W1 vs M9 W1 vs M1 vs M1 vs M4 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, Horm Models W1 vs M8 W1 vs W1	mone, Radio P-Value 0.4493746 0.8623454 0.612334 0.106554 0.06633298 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.06551687 0.2270437 one, Radio P-Value 0.2230425	No Chemo, Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N, Models M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N, Models M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 0 Hormone, Radio P-Value 0.3793804 0.2719921 0.1573064 0.6957178 0.01934901 0.04586046 Hormone, Radio P-Value
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M1 vs M8 M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8	Chemo, No Hormone,	e, Radio P-Value 0.4353787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795 Radio P-Value 0.275535 0.9075649	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Che Models M1 vs M4 M5 vs M6 M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M8	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1166998 0.2678359 0.06452643 0.1814283 me, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03484943 0.1500748 emo, Hormone, Radio P-Value 0.4060488 0.8703398	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor Models M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor M5 vs M6 M5 vs M7 M5 vs M8	mone, Radio P-Value 0.4493746 0.6612334 0.106554 0.06639298 0.2002502 mone, Radio P-Value 0.233688 0.7738357 0.530582 0.8356422 0.065551687 0.2270437 one, Radio P-Value 0.223628	No Chemo, No Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N Models M1 vs M4 M5 vs M6 M5 vs M6 M1 vs M4 M5 vs M6 M1 vs M8 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 0 Hormone, Radio P-Value 0.773924 0.1573064 0.6957178 0.01934901 0.04586046 P-Value 0.9310573 0.6890556
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M4 M1 vs M4 M5 vs M8 M1 vs M8 M5 vs M7 M5 vs M8 M5 vs M7 M5 vs M8 M1 vs M4 M5 vs M8 M1 vs M4 M5 vs M8	Chemo, No Hormone,	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795 Radio P-Value	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M3 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M8	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.2678359 0.06452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03489473 0.1500748 emo, Hormone, Radio P-Value 0.4060488 0.8703398 0.8703398 0.8703398	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor Models M1 vs M2 M1 vs M4 M5 vs M6 M1 vs M8 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M7 M6 vs M8 Chemo, Horm Models M1 vs M2 M1 vs M3 M1 vs M4 M1 vs M3 M1 vs M4	mone, Radio P-Value 0.4493746 0.6823454 0.106554 0.06639298 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.3856422 0.06551687 0.2270437 one, Radio P-Value 0.2230425 0.6555847 0.2270437	No Chemo, Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N Models M1 vs M3 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M3	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 b Hormone, Radio P-Value 0.7739804 0.2719921 0.1573064 0.6957178 0.01934901 0.04586046 Hormone, Radio P-Value 0.3310573 0.6890556 0.5379708
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M0dels M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M6 M1 vs M4 M5 vs M6 M1 vs M4 M5 vs M8	Chemo, No Hormone,	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795 Radio P-Value 0.275335 0.9075649 0.8457223	Models M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M6 M6 M5 vs M6 M6 M5 vs M6 M6 M5 vs M6	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.2678359 0.046452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03488473 0.1500748 emo, Hormone, Radio P-Value 0.4060488 0.8703398 0.6518544 0.4752915	No Chemo, Horn Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M6 vs M7 M6 vs M7 M7 vs M8 M1 vs M3 M1 vs M4 M1 vs M4 M1 vs M6 M1 vs M6 M1 vs M6 M1 vs M7 M6 vs M6 M1 vs M8 M1 vs M9 M1 vs M6 M5 vs M6 M6 M8 M1 vs M6 M5 vs M6 M8 M1 vs M6 M8 M1 vs M6 M8 M1 vs M6 M8 M8 M8 M8 M8 M8 M8	mone, Radio P-Value 0.4493746 0.8623454 0.612334 0.10655328 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.8356422 0.06551687 0.2270437 one, Radio P-Value 2.230425 0.7652534 0.7652534 0.7652534 0.6851914 0.2941189	No Chemo, Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N Models M1 vs M2 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N M1 vs M2 M1 vs M4 M5 vs M8 Chemo, N M5 vs M8	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 0 Hormone, Radio P-Value 0.9793804 0.2719921 0.1573064 0.0595178 0.01934901 0.04586046 Hormone, Radio P-Value 0.99310573 0.6890556 0.5379708 0.5835549
M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M4 M1 vs M4 M5 vs M8 M1 vs M8 M5 vs M7 M5 vs M8 M5 vs M7 M5 vs M8 M1 vs M4 M5 vs M8 M1 vs M4 M5 vs M8	Chemo, No Hormone,	e, Radio P-Value 0.4535787 0.6439052 0.3057495 0.2220088 0.07021734 0.1710669 e, Radio P-Value 0.5957921 0.4820906 0.2981639 0.2514875 0.03724758 0.1106795 Radio P-Value 0.775535 0.9075649 0.8457223	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M3 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M8	Demo, Hormone, Radio P-Value 0.6981967 0.5348362 0.1160908 0.2678359 0.06452643 0.1814283 mo, No Hormone, Radio P-Value 0.9205452 0.2110895 0.1639234 0.1854158 0.03489473 0.1500748 emo, Hormone, Radio P-Value 0.4060488 0.8703398 0.8703398 0.8703398	Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, No Hor Models M1 vs M2 M1 vs M4 M5 vs M6 M1 vs M8 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M6 M5 vs M7 M6 vs M8 Chemo, Horm Models M1 vs M2 M1 vs M3 M1 vs M4 M1 vs M3 M1 vs M4	mone, Radio P-Value 0.4493746 0.6823454 0.106554 0.06639298 0.2002502 mone, Radio P-Value 0.2336788 0.7738357 0.530582 0.3856422 0.06551687 0.2270437 one, Radio P-Value 0.2230425 0.6555847 0.2270437	No Chemo, Models M1 vs M2 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 Chemo, N Models M1 vs M3 M1 vs M3 M1 vs M3 M1 vs M4 M5 vs M6 M5 vs M7 M5 vs M8 M1 vs M3	, Hormone, Radio P-Value 0.575567 0.4721013 0.468723 0.01662181 0.004311021 0.01238407 b Hormone, Radio P-Value 0.7739804 0.2719921 0.1573064 0.6957178 0.01934901 0.04586046 Hormone, Radio P-Value 0.3310573 0.6890556 0.5379708

Table 1. This table shows p-values for the model 1,2,3 vs 4 and 6,7,8 vs 5 performance comparisons in Figure 4. P-values are derived by 2-sample t-test, since performances across the five folds are normally distributed around the mean. Significant p-values (p<0.05) are highlighted in yellow. Significant improvement of experimental model vs clinical baseline is seen most often for the AUC of models 7 and 8 compared to model 5, predicting overall survival months with gene expression data vs without.

Model 1	Model 2	•			Model 4			Model 7		lodel 8	
TUMOR_SIZE	CORT		CD1C	- 0	CORT	NPI	NPI	RAMP3	R/	AMP3	
NPI	DFFA		KIF14	- 1	DFFA	TUMOR_SIZE	CYP4F3	ABCB1	A	BCB1	
AGE_AT_DIAGNOSIS	PGD		MKI67		PGD	AGE_AT_DIAGNOSIS	CYP4F8	CD1C	CI	D1C	
GRADE	UBE4B		HOXC10	- 1	UBE4B	GRADE	DNAJB1	LAT2	LA	AT2	
HISTOLOGICAL_SUBTYPE	NOV		AURKA		NOV	ER STATUS	NDUFB7	KLK1		LK1	
PR_STATUS	PIK3CD		PPP1CB		PIK3CD		PKN1	NPI	N	PI	
R STATUS	ENPP2		EZR	Т,				INHBA		IHBA	
BREAST_SURGERY	MTOR			\rightarrow				GNRH1	_	NRH1	
NEAD1_SONGEN1	EXOSC10			_				CITILITY		1411112	
	EXOSCIO				No.	Chemo, Hormone, No Radio					
Model 1	Model 2	-	Model 3	₩.	Model 4		Model 6	Model 7	■ M	lodel 8	
IPI	NPI		NPI		NPI	AGE AT DIAGNOSIS	AGE AT DIAGNOSIS			GE AT DIAGN	OSI
UMOR_SIZE	TUMOR_SIZE					INFERRED MENOPAUSAL STATE		BIRC2		IRC2	U3
			CDK3		CDK3	NPI	ZNF217	UBE2L3		BE2L3	
GE_AT_DIAGNOSIS	CCNB1										
RADE	FADD		EZR		EZR		PDGFA	OLFM4		LFM4	
ATERALITY	CDK7		RECQL5		RECQL5	CELLULARITY	NUDT1	CSH2		SH2	
REAST_SURGERY	FLI1		HMBS		HMBS	PR_STATUS	GPER1	MYBPC1		RKAR1B	
								ZNF185	ZI	VF217	
								ROBO2			
								STK25			
					No (hemo, No Hormone, Radio					
Model 1	Model 2	▼	Model 3	\blacksquare	Model 4		Model 6	Model 7	▼ M	lodel 8	
REAST_SURGERY	CPT2		PDHA1		CPT2	LATERALITY	MEF2A	SORBS1	_	ORBS1	
GE_AT_DIAGNOSIS	MAGOH		GADD45A	_	MAGOH	NPI	HSP90B2P	PDIA4	_	1EF2A	
UMOR SIZE	LRP8		PTGER3		LRP8	GRADE	NR2F2	STIP1		SP90B2P	
R_STATUS	C8B		ASAH1		C8B	PR_STATUS	GPR37	LRP2		R2F2	
K_STATUS IPI	C8A		TLR3	_	C8A	TUMOR SIZE	IGF1R	CCDC6	_	DIA4	
HEEDDED MENODALICAL C											
NFERRED_MENOPAUSAL_S	TATE CYP2J2		SRSF4	- (CYP2J2	AGE_AT_DIAGNOSIS	ABHD2	AMHR2	_	ΓIP1	
GRADE	TATE CYP2J2		SRSF4				ABHD2	AMHR2	_	PR37	
GRADE HISTOLOGICAL_SUBTYPE Model 1	Model 2				No	Chemo, Hormone, Radio	Model 6	Model 7	G N	PR37	105
GRADE HISTOLOGICAL_SUBTYPE Model 1	▼ Model 2		Model 3		Nodel 4	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS	Model 6 AGE_AT_DIAGNOSIS	Model 7 AGE_AT_DIAGNOSIS	G M	PR37 Model 8 GE_AT_DIAGN	109
GRADE HISTOLOGICAL_SUBTYPE Model 1 HPI UMOR_SIZE	Model 2 NPI TUMOR_SIZE		Model 3 NPI FOXM1		Model 4 VNPI	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE	Model 6 AGE_AT_DIAGNOSIS SYT4	Model 7 AGE_AT_DIAGNOSIS AGFG1	G M A A	PR37 fodel 8 GE_AT_DIAGN GFG1	105
RADE IISTOLOGICAL_SUBTYPE Aodel 1 IPI UMOR_SIZE GGE_AT_DIAGNOSIS	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO		Model 3 NPI FOXM1 E2F2		Model 4 NPI FOXM1 E2F2	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P	G M A A A	PR37 Model 8 GE_AT_DIAGN GFG1 IR7E14P	105
GRADE IISTOLOGICAL_SUBTYPE Model 1 IIPI UMOR_SIZE IGE_AT_DIAGNOSIS IREAST_SURGERY	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2	OSIS	Model 3 NPI FOXM1 E2F2 AURKB		Model 4 NPI FOXM1 E2F2 AURKB	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44	G M A A O SI	PR37 Model 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44	108
GRADE HISTOLOGICAL_SUBTYPE Model 1 HPI TUMOR_SIZE HGE_AT_DIAGNOSIS HREAST_SURGERY GRADE	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER	OSIS	Model 3 NPI FOXM1 E2F2 AURKB KIFC1		Model 4 NPI FOXM1 E2F2 AURKB KIFC1	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214	A A O SI	PR37 fodel 8 GE_AT_DIAGN GFG1 PR7E14P LC25A44 NF214	108
GRADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE IGE_AT_DIAGNOSIS IREAST_SURGERY SIRADE NFERRED_MENOPAUSAL_S	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1	OSIS	Model 3 NPI FOXM1 E2F2 AURKB KIFC1		Model 4 NPI FOXM1 E2F2 AURKB KIFC1	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44	A A O SI	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NF214 D68	105
GRADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE IGE_AT_DIAGNOSIS IREAST_SURGERY SIRADE NFERRED_MENOPAUSAL_S	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4	OSIS	Model 3 NPI FOXM1 E2F2 AURKB KIFC1		Model 4 NPI FOXM1 E2F2 AURKB KIFC1	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214	A A O SI	PR37 fodel 8 GE_AT_DIAGN GFG1 PR7E14P LC25A44 NF214	105
RADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY IRADE NFERRED_MENOPAUSAL_S	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1	OSIS	Model 3 NPI FOXM1 E2F2 AURKB KIFC1		Nodel 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214	A A O SI	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NF214 D68	105
RADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY IRADE NFERRED_MENOPAUSAL_S R_STATUS	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7	DSIS XY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZ	Z I	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMON_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio	Model 6 AGE_AT_DIAGNOSIS SY14 RIT2 SLC14A1 ZNF24 PSTPIP2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68	A A A O SI	PR37 fodel 8 GE_AT_DIAGN GFG1 R7F214P LC25A44 NF214 D68 YT4	105
INADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY INADE VFERRED_MENOPAUSAL_S R_STATUS	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2	DSIS XY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZ	ZZE T	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7	A A A A C C C C S Y	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NNF214 D68 YT4	105
MADE ISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY RADE REFERRED_MENOPAUSAL_SI R_STATUS Model 1 REAST_SURGERY	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1	DSIS XY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZ	ZE T	Model 4 V NO Model 4 V FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 V AQP4	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17	A A A A A A A A A A A A A A A A A A A	PR37 fodel 8 GE_AT_DIAGN GFG1 PR7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17	105
ANDE	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI Model 3 AQP4 PRKCZ	ZZE T	Model 4 FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 AQP4 PRKCZ	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1	A A A A A A A A A A A A A A A A A A A	PR37 fodel 8 GE_AT_DIAGN GFG1 R7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2	105
RADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY IRADE NFERRED_MENOPAUSAL_S R_STATUS Model 1 REAST_SURGERY UMOR_SIZE	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZ Model 3 AQP4 PRKCZ SEPW1	ZZE :	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Model 4 AQP4 PRKCZ SEPW1	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMON_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMON_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE	Model 6 AGE_AT_DIAGNOSIS SY14 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2	G N A A A A A A A A A A A A A A A A A A	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CNH1	105
RADE IISTOLOGICAL_SUBTYPE Aodel 1 IIPI UMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY SRADE INFERRED_MENOPAUSAL_S R_STATUS Aodel 1 REAST_SURGERY UMOR_SIZE IIPI IREAST_SURGERY UMOR_SIZE IIPI IREADE	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI: Model 3 AQP4 PRKCZ SEPW1 CIRBP	ZE T	Model 4 No NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZD14 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA	A A A A A A A A A A A A A A A A A A A	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NNF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1	109
Ande 1 INTERPRETATION OF THE PROPERTY OF THE P	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2	ZZE T	Model 4 V FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 V AQP4 PRKCZ SEPW1 CIRBP NEURL1	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3	A A A A A A A A A A A A A A A A A A A	PR37 fodel 8 GE_AT_DIAGN GFG1 PR7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CCNH1 LRB1 LRB4	109
Ande 1 INTERPRETATION OF THE PROPERTY OF THE P	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI: Model 3 AQP4 PRKCZ SEPW1 CIRBP	ZZE T	Model 4 No NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZD14 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA	A A A A A A A A A A A A A A A A A A A	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NNF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1	109
Ande 1 INTERPRETATION OF THE PROPERTY OF THE P	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2	ZZE T	Model 4 V FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 V AQP4 PRKCZ SEPW1 CIRBP NEURL1	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3	G G G G G G G G G G G G G G G G G G G	PR37 fodel 8 GE_AT_DIAGN GFG1 PR7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CCNH1 LRB1 LRB4	105
Ande 1 INTERPRETATION OF THE PROPERTY OF THE P	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2 CHST4	ZZE T	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 PRKCZ SEPW1 CIRBP NEURL1 PCGF2	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3	G G G G G G G G G G G G G G G G G G G	PR37 fodel 8 GE_AT_DIAGN GFG1 R7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1 LLRB4 PAST	10:
INADE IISTOLOGICAL_SUBTYPE IMMOR_SIZE GE_AT_DIAGNOSIS REAST_SURGERY INFERRED_MENOPAUSAL_SI R_STATUS IMMOR_SIZE IMMOR_SI	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZ Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2 CHST4 GPX4	ZZE T	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Model 4 AQP4 PRKCZ SEPW1 CIRBP NEURL1 PCGF2 CHST4	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3	G G G G G G G G G G G G G G G G G G G	PR37 fodel 8 GE_AT_DIAGN GFG1 R7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1 LLRB4 PAST	
Ande 1 INTERPRETATION OF THE PROPERTY OF THE P	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3	DOSIS NY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZ Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2 CHST4 GPX4 PALM	ZZE T	Model 4 Note N	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS ER_STATUS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3	G G G G G G G G G G G G G G G G G G G	PR37 fodel 8 GE_AT_DIAGN GFG1 R7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1 LLRB4 PAST	105
GRADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE IGE_AT_DIAGNOSIS IREAST_SURGERY IREAST_SURGERY IREAST_SURGERY Model 1 IREAST_SURGERY UMOR_SIZE IPI IREAST_SURGERY UMOR_SIZE IPI IREAST_SURGERY IREAST_SURGERY UMOR_SIZE IPI IREAST_SURGERY IREAST_SURGERY UMOR_SIZE IPI IREAST_SURGERY IREAST_SURGERY UMOR_SIZE IPI IREAST_SURGERY IREAST_SURGER	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3 MEFV	DSIS RY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2 CHST4 GPX4 PALM KCNH1	ZZE T	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 PRKCZ SEPW1 CIRBP NEURL1 PCGF2 CHST4 GPX4	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMOR_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMOR_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS ER_STATUS	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2 LILRA1	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3 MSX2	G G G E E K K L L L L L L L L L L L L L L L L	PR37 fodel 8 GE_AT_DIAGN GFG1 R7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1 LLRB4 PAST AIR2	105
IRADE IISTOLOGICAL_SUBTYPE Model 1 IPI UMOR_SIZE GE_AT_DIAGNOSIS IREAST_SURGERY IRADE INFERRED_MENOPAUSAL_S R_STATUS Model 1 IREAST_SURGERY UMOR_SIZE IPI IRADE R_STATUS Model 1 IRADE R_STATUS	Model 2 NPI TUMOR_SIZE AGE_AT_DIAGNO BCL2 BREAST_SURGER TATE DSG1 LDLRAD4 CDH7 Model 2 NEURL1 SH3PXD2A CREBBP IGFBP1 IGFBP3 MEFV Model 2	DSIS RY	Model 3 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SI Model 3 AQP4 PRKCZ SEPW1 CIRBP PCGF2 CHST4 GPX4 PALM KCNH1 Model 3	ZZE :	Model 4 NPI FOXM1 E2F2 AURKB KIFC1 TUMOR_SIZE Ch Model 4 AQP4 PPRKCZ SEPW1 CIRBP NEURL1 PCGF2 CHST4 GPX4	Chemo, Hormone, Radio Model 5 AGE_AT_DIAGNOSIS TUMON_SIZE INFERRED_MENOPAUSAL_STATE PR_STATUS NPI BREAST_SURGERY emo, No Hormone, Radio Model 5 TUMON_SIZE BREAST_SURGERY INFERRED_MENOPAUSAL_STATE GRADE AGE_AT_DIAGNOSIS ER_STATUS hemo, Hormone, Radio Model 5	Model 6 AGE_AT_DIAGNOSIS SYT4 RIT2 SLC14A1 ZNF24 PSTPIP2 Model 6 EYA2 LILRB1 LILRB4 SPAST LAIR2 LILRA1 Model 6	Model 7 AGE_AT_DIAGNOSIS AGFG1 OR7E14P SLC25A44 ZNF214 CD68 Model 7 GPR17 KCNH1 MAPKAPK2 INPPSA EPHB3 MSX2 Model 7	G G G S S S S S S S S S S S S S S S S S	PR37 fodel 8 GE_AT_DIAGN GFG1 IR7E14P LC25A44 NF214 D68 YT4 fodel 8 PR17 YA2 CNH1 LRB1 LRB4 PAST AIR2	
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Table 2. Top variables used for best-performing models in each treatment subset, as selected by the method shown in Figure 3. Between 6 and 9 top variables are used in each model, making them comparable by number of variables. Model performances in five-fold cross-validation can be seen in Figure 4.

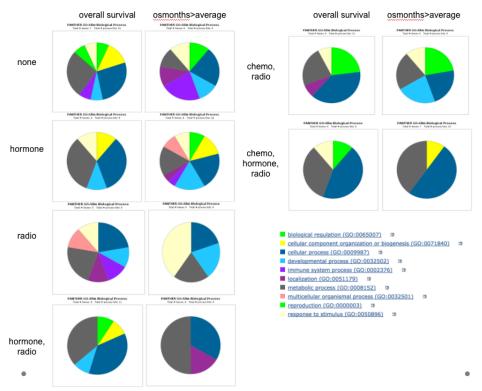


Figure 5. PANTHER biological process categories associated with the top genes selected in training model 3 and model 7 (Table 2). There are a lot of genes associated with metabolic processes (grey), and cellular processes (blue), but these are not over-represented with statistical significance.

Conclusion

The goal of this project was to take advantage of the 2012 METABRIC Breast Cancer genomic phenotyping study in order to predict breast cancer treatment responses by integrating several types of personalized genetic data. Ultimately, tumor genetic data combined with clinical history and demographic information should be able to help practitioners make better-informed decisions about an appropriate and effective treatment regime for a particular patient, as improvement in predictive model performance was seen across the board when incorporating genetic data as a supplement to clinical data. mRNA gene expression data has shown to be more useful in this regard than CNV, capturing all of the most informative features in the top models even when used in conjunction with CNV. The better performance improvement when predicting overall survival months vs vital status is also encouraging, as overall survival months seems like a more informative response variable in this study, where patients may have died following data collection or been diagnosed at different initial time points. Unfortunately, the top gene expression variable set used in the models (Table 2) is difficult to biologically validate and not very interpretable in terms of novel gene targets for clinical tracking of cancer progression. The gene expression data overall still provided a valuable improvement in model performance, which may translate to a potential for better-informed clinical decision-making in the course of genetically personalized breast cancer treatment.

Since we were unable to select an informative gene set as is, future work might further improve model performance with clinical and gene expression data by performing Principal Component Analysis to transform the feature set. This will obscure the driving features from the original untransformed data, but those are already unstable, so the reduced auto-correlation of variables may be a worthwhile tradeoff. We may also modify the core classification algorithm to a regularized logistic regression or other alternative, simply to further confirm the observations from this set of experiments. If given additional time to explore the dataset, we might take advantage of the cancer phenotypes derived in the 2012 METABRIC paper⁵ as a potential feature set, but these would need to be re-derived using only secondary genomic features to avoid incorporating treatment-regime information in the phenotype features, as was done by Curtis et al. This is also less desirable for our treatment response task, since it requires incorporation of every level of genomic information from the study—CNV, gene expression, and SNP—which is more expensive diagnostically than any one of those alone.

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Treatment Variables					
Chemotherapy	Binary: 1094 NO, 398 YES				
Radiotherapy	Binary: 549 NO, 934 YES				
Hormone Treatment	Binary: 595 NO, 888 YES				
Clinical Variables					
Age at diagnosis	Min. 1st Qu. Median Mean 3rd Qu. Max.				
	21.93 49.22 58.56 58.23 67.61 96.29				
Breast surgery type	623 breast conserving, 842 mastectomy				
cellularity	726 high, 160 low, 548 moderate				
ER status	406 negative, 1077 positive				
PR status	746 negative, 737 positive				
Cancer grade	118 one, 558 two, 758 three				
NPI- Nottingham Prognostic Index	Min. 1st Qu. Median Mean 3rd Qu. Max.				
	1.000 3.050 4.044 4.103 5.050 6.360				
Inferred menopausal state	1080 post, 403 pre				
Laterality	722 L, 679 R				
Tumor size	Min. 1st Qu. Median Mean 3rd Qu. Max.				
	0.00 17.00 22.00 26.25 30.00 182.00				
Tumor stage	10 zero, 386 one, 625 two, 99 three, 10 four				
mRNA expression variables	z-scores available at gene level for 7,281 genes				
CNV state variables	Inferred copy number count available at gene level for 7,782 genes				
Response Variables					
Overall Survival Months	Min. 1st Qu. Median Mean 3rd Qu. Max.				
	0.00 55.68 113.70 123.60 185.50 337.00				
Vital Status	Binary: 837 Living, 646 Died of Disease				

Table S1: Experimental variables extracted from the Data Set for patients with known vital status (excluding "NA" and "Died of other Causes")

Treatment Regime	Number of patients	patients with vital status == "Living"	patients with overall survival months > average
hormone, chemo, radiation	150	86	79
hormone, chemo, no radiation	27	10	11
hormone, no chemo, radiation	442	259	279
hormone, no chemo, no radiation	269	144	185
no hormone, chemo, radiation	173	76	67
no hormone, chemo, no radiation	46	17	17
no hormone, no chemo, radiation	166	123	124
no hormone, no chemo, no radiation	207	122	155

Table S2: This table shows the number of patients in each treatment category defined on the dataset, including only patients where treatment labels are known and vital status is either "Living" or "Died of Disease". It also shows the number of patients positively responding to treatment according to both metrics described above. The sizes of most treatment regime sets and positive response rates within them are large enough to perform practical classification model training and testing, and so we move forward with the project on all treatment categories except (hormone, chemo, no radiation) and (no hormone, chemo, no radiation).