

Table S1. Characteristics of the studied gene signatures and the breast cancer cohorts they were developed from and validated on.

| <i>Signature</i> | <i>Predicted phenotype/endpoint</i> | <i>Training Cohort</i> | <i>Validation Cohort</i> |
|------------------|---|--|--|
| Intrinsic | Subtypes | Locally advanced BC [1] | Consecutive BC ^a [2, 3] |
| PAM50 | Subtypes 5-year relapse | Consecutive BC [9] Node- [9] | Consecutive BC [9, 61] Node- & + [9, 61] |
| 70gene | 5 year distant metastasis | Node- [4] | Node- & + [5, 22-24] |
| 76gene | 5 year distant metastasis | Node- [6] | Node- [25, 26] |
| GG1 | HG1- or HG3-like in HG2 | ER+ [7] | Consecutive BC [17, 27] |
| WR | Active or Quiescent CSR Population based prognosis | Representative BC ^b [28] | Representative BC [15, 29] Consecutive BC |
| Hypoxia | Hypoxic or Non-hypoxic | Representative BC [30] | Representative BC [15, 30] |
| RS | 10 year distant metastasis | Tamoxifen-treated/ER+;Node-[12] | Tamoxifen-treated/ER+;Node-,+[12, 31] |
| EP | 10 year distant metastasis | ER+, HER2-, treat by adjuvant hormonal therapy | ER+, HER2-, treat by adjuvant hormonal therapy |

^a *Consecutive BC*: heterogeneous breast cancer cohort with consecutive clinical parameter distribution as reflected in the whole population of this disease.

^b *Representative BC*: breast cancer dataset at hand carries representative features that are associated with a certain breast cancer subpopulation.

Table S2. Summary of the studied cohort (n=947). (A) Sample sizes for available clinical endpoints of the included studies. Summary was calculated using samples with both survival time and status available. Distant Metastasis Free Survival (DMFS) was selected as endpoint due to its clinical and biological implications. Being able to metastasize to distant organs makes cancer a deadly disease. DMFS is an endpoint that impacts treatment decisions. In addition, information for DMFS is available across all included studies. **(B)** Clinicopathological characteristics of the studied cohort for Distant Metastasis Free Survival.

(A)

| Dataset | n | DMFS | | BCSS | | RFS | | OS | | | | | |
|--------------|-----|--------------------|------------------|--------------------|------------------|--------------------|------------------|--------------------|------------------|------|-----|-------|------|
| | | n _{event} | t _{med} | n _{event} | t _{med} | n _{event} | t _{med} | n _{event} | t _{med} | | | | |
| Desmedt [26] | 147 | √ | 48 | 130·7 | - | - | √ | 72 | 103·8 | √ | 43 | 139·6 | |
| Miller [34] | 247 | √ | 69 | 78·0 | √ | 54 | 124·0 | √ | 92 | 75·0 | - | - | |
| Minn [36] | 96 | √ | 26 | 65·4 | - | - | - | - | - | - | - | - | |
| Pawitan [35] | 156 | √ ^a | 46 | 81·5 | √ | 29 | 84·7 | √ | 40 | 85·6 | √ | 40 | 84·7 |
| Loi [27] | 178 | √ | 36 | 72·1 | - | - | √ | 59 | 66·6 | - | - | - | |
| Chin [37] | 123 | √ | 25 | 67·6 | √ | 28 | 72·8 | √ | 37 | 67·6 | √ | 41 | 72·8 |
| <i>n</i> | 947 | 912 | 250 | 80·8 | 525 | 111 | 92·8 | 842 | 300 | 78 | 425 | 124 | 91·1 |

(B)

| Characteristics | n | % ^b |
|--|-----|----------------|
| All | 912 | |
| Estrogen receptor (IHC) | | |
| Positive | 687 | 76·1 |
| Negative | 216 | 23·9 |
| Missing | 9 | |
| Estrogen receptor (IHC + gene expression) | | |
| Positive | 692 | 75·9 |
| Negative | 220 | 24·1 |
| Missing | 0 | |
| Human Epidermal Growth Factor Receptor 2 (IHC) | | |
| Positive | 16 | 15·4 |
| Negative | 88 | 84·6 |
| Missing | 808 | |
| Human Epidermal Growth Factor Receptor 2 (IHC + gene expression) | | |
| Positive | 114 | 12·5 |
| Negative | 798 | 87·5 |
| Missing | 0 | |
| Progesterone receptor (IHC) | | |
| Positive | 291 | 65·1 |
| Negative | 156 | 34·9 |
| Missing | 465 | |
| Histological Grade | | |
| I | 155 | 19·8 |
| II | 354 | 45·3 |
| III | 272 | 34·8 |
| Missing | 131 | |
| Tumor status | | |
| pT1 (≤ 2cm) | 431 | 47·6 |
| pT2 (> 2 ≤ 5cm) | 441 | 48·7 |
| pT3-4 (> 5cm) | 33 | 3·6 |
| missing | 7 | |
| Nodal status | | |
| Positive | 291 | 32·6 |
| Negative | 602 | 67·4 |
| Missing | 19 | |

| | | | |
|--------------------------|----------------------|------|------|
| Systemic Treatment | Yes | 436 | 52·5 |
| | No | 395 | 47·5 |
| | Unknown ^c | 81 | |
| Event | Yes | 250 | 27·4 |
| | Censored | 662 | 72·6 |
| Median follow-up (month) | | 80·8 | |

Abbreviations:

DMFS: Distant Metastasis Free Survival

BCSS: Breast Cancer Specific overall Survival

RFS: Relapse Free Survival

OS: Overall Survival

n_{event} : number of events

t_{med} : median follow-up time in month

^a In Pawitan set, a modified DMFS was used as an event was defined as distant metastasis or death.

^b For all parameters, numbers are calculated excluding missing data.

^c Treatment information was not provided for the Minn dataset.[36]

Table S3. The pairwise Pearson correlations matrix of the predicted risk scores on continuous scale identified by individual gene signatures.

| | Intrinsic-RORs | PAM50-RORs | 70-gene | 76-gene | GGI | WR | Hypoxia | RS | EP |
|----------------|----------------|------------|---------|---------|-------|-------|---------|-------|-------|
| Intrinsic-RORs | 1 | 0.611 | 0.627 | 0.228 | 0.602 | 0.566 | 0.223 | 0.809 | 0.724 |
| PAM50-RORs | 0.611 | 1 | 0.677 | 0.626 | 0.903 | 0.777 | 0.051 | 0.777 | 0.814 |
| 70-gene | 0.627 | 0.677 | 1 | 0.403 | 0.662 | 0.529 | 0.093 | 0.649 | 0.679 |
| 76-gene | 0.228 | 0.626 | 0.403 | 1 | 0.671 | 0.634 | -0.024 | 0.436 | 0.525 |
| GGI | 0.602 | 0.903 | 0.662 | 0.671 | 1 | 0.868 | 0.006 | 0.786 | 0.827 |
| WR | 0.566 | 0.777 | 0.529 | 0.634 | 0.868 | 1 | 0.009 | 0.692 | 0.696 |
| Hypoxia | 0.223 | 0.051 | 0.093 | -0.024 | 0.006 | 0.009 | 1 | 0.098 | 0.041 |
| RS | 0.809 | 0.777 | 0.649 | 0.436 | 0.786 | 0.692 | 0.098 | 1 | 0.823 |
| EP | 0.724 | 0.814 | 0.679 | 0.525 | 0.827 | 0.696 | 0.041 | 0.823 | 1 |

Table S4. Multivariate analysis on gene signatures with known prognostic factors.

(A) In ER-positive samples. Using multivariate Cox model, prognosis of individual signature was adjusted by clinical parameters. The following Cox models were fitted: **(Model 1)** $Risk = Node + Grade + Tumor\ size + Signature$; **(Model 2)** $Risk = Tumor\ size + Signature$; **(Model 3)** $Risk = Grade + Signature$. Results from univariate models are presented for comparison: **(Univariate)** $Risk = Signature$ as well as similar univariate models for each of the clinical parameters. Models were fitted on the complete data set with available information for endpoint and included clinical parameters (n=586) and on the entire follow-up time. For each Cox model, parameters were added sequentially into the model in the order specified in the table, and the added (type I) effect of each subsequent covariate is reported under *Analysis of deviance* as the reduction in the residual deviance χ^2 with its corresponding p value. Time trend associated with individual gene signature covariate was assessed by testing for violation of proportional hazard (PH) assumption in the corresponding Cox model (“*Time trend for signature*”). Violation of the PH assumption (significant p value for correlation ρ) indicates significant time dependency of individual signatures on prognosis.

| Deviance (type I) | Univariate | | Model 1 | | Model 2 | | Model 3 | |
|---------------------------------|--------------------------|----------|--------------------------|----------|--------------------------|----------|--------------------------|----------|
| | χ^2 | p | χ^2 | p | χ^2 | p | χ^2 | p |
| <i>Clinical variables:</i> | | | | | | | | |
| Node (df=1) | 21.5 | <0.0001 | 21.5 | <0.0001 | - | - | - | - |
| Tumor size (df=2) | 36.4 | <0.0001 | 22 | <0.0001 | 36.4 | <0.0001 | - | - |
| Histological grade (df=2) | 16.3 | 0.0003 | 12.6 | 0.0018 | - | - | 16.3 | 0.0003 |
| <i>Gene signature (df=1):</i> | | | | | | | | |
| Intrinsic-RORs | 11.8 | 0.0006 | 4.2 | 0.0397 | 9.7 | 0.0018 | 5.1 | 0.0242 |
| PAM50-RORs | 53.2 | <0.0001 | 31.9 | <0.0001 | 44.3 | <0.0001 | 38.1 | <0.0001 |
| 70-gene | 36.0 | <0.0001 | 21.5 | <0.0001 | 32.8 | <0.0001 | 24.9 | <0.0001 |
| 76-gene | 40.6 | <0.0001 | 18.8 | <0.0001 | 30.6 | <0.0001 | 27.1 | <0.0001 |
| GGI | 55.0 | <0.0001 | 36.1 | <0.0001 | 46.6 | <0.0001 | 40.6 | <0.0001 |
| WR | 45.3 | <0.0001 | 25.4 | <0.0001 | 34.1 | <0.0001 | 31.6 | <0.0001 |
| Hypoxia | 0.01 | 0.9275 | 0.1 | 0.7351 | 0.2 | 0.6501 | 0.1 | 0.7317 |
| RS | 43.6 | <0.0001 | 23.1 | <0.0001 | 34.3 | <0.0001 | 30.2 | <0.0001 |
| EP | 53.6 | <0.0001 | 31.4 | <0.0001 | 43.8 | <0.0001 | 38.8 | <0.0001 |
| Time trend for signature | ρ | p | ρ | p | ρ | p | ρ | p |
| Intrinsic-RORs | -0.233 | 0.0032 | -0.160 | 0.0584 | -0.042 | 0.6121 | -0.209 | 0.0109 |
| PAM50-RORs | -0.269 | 0.0005 | -0.154 | 0.0698 | 0.008 | 0.9211 | -0.183 | 0.0226 |
| 70-gene | -0.180 | 0.0232 | -0.156 | 0.0658 | -0.044 | 0.591 | -0.211 | 0.0102 |
| 76-gene | -0.202 | 0.0092 | -0.160 | 0.0514 | -0.022 | 0.7835 | -0.205 | 0.0100 |
| GGI | -0.324 | <0.0001 | -0.145 | 0.0888 | 0.009 | 0.9108 | -0.186 | 0.0224 |
| WR | -0.283 | 0.0001 | -0.146 | 0.0879 | 0.017 | 0.8391 | -0.192 | 0.0189 |
| Hypoxia | -0.020 | 0.7717 | -0.161 | 0.0576 | -0.067 | 0.418 | -0.219 | 0.0073 |
| RS | -0.250 | 0.0019 | -0.146 | 0.0866 | -0.006 | 0.9446 | -0.193 | 0.0185 |
| EP | -0.274 | 0.0004 | -0.148 | 0.0831 | 0.004 | 0.9642 | -0.189 | 0.0195 |

(B) In ER-negative samples. The following Cox models were fitted: **(Model 1)** $Risk = Node + Signature$; **(Model 2)** $Risk = Tumor\ size + Signature$ and **(Model 3)** $Risk = Grade + Signature$ and **(Model 4)** $Risk = Node + Tumor\ size + Grade + Signature$. Results from univariate models are presented for comparison: **(Univariate)** $Risk = Signature$ as well as similar univariate models for each of the clinical parameters. Models were fitted on the complete data set with available information for endpoint and included clinical parameters (n=174) and on the entire follow-up time.

| Deviance (type I) | Univariate | | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---------------------------------|--------------------------|----------|--------------------------|----------|--------------------------|----------|--------------------------|----------|--------------------------|----------|
| | χ^2 | P | χ^2 | P | χ^2 | P | χ^2 | P | χ^2 | P |
| <i>Clinical variables:</i> | | | | | | | | | | |
| Node (df=1) | 1.9 | 0.1659 | 1.9 | 0.1659 | - | - | - | - | 1.9 | 0.1659 |
| Tumor size (df=2) | 0.6 | 0.7342 | - | - | 0.6 | 0.7342 | - | - | 0.4 | 0.8391 |
| Histological grade (df=2) | 1.3 | 0.5248 | - | - | - | - | 1.3 | 0.5248 | 1.3 | 0.5311 |
| <i>Gene signature (df=1):</i> | | | | | | | | | | |
| Intrinsic-RORs | 0.7 | 0.408 | 0.6 | 0.4219 | 0.8 | 0.3814 | 1.3 | 0.251 | 1.3 | 0.2551 |
| PAM50-RORs | 0.2 | 0.6827 | 0.2 | 0.6785 | 0.2 | 0.6853 | 0.5 | 0.4726 | 0.4 | 0.5431 |
| 70-gene | 0.6 | 0.4381 | 0.6 | 0.4355 | 0.5 | 0.4589 | 0.3 | 0.5989 | 0.3 | 0.5941 |
| 76-gene | 4.1 | 0.0427 | 4.6 | 0.0311 | 4.3 | 0.0379 | 4.2 | 0.0396 | 5 | 0.0241 |
| GGI | 0 | 0.9934 | 0 | 0.975 | 0 | 0.9805 | 0.1 | 0.7337 | 0.1 | 0.7631 |
| WR | 0.8 | 0.3589 | 1.3 | 0.2594 | 1 | 0.3151 | 1.3 | 0.2607 | 1.7 | 0.1911 |
| Hypoxia | 3.2 | 0.0734 | 4 | 0.0462 | 3.2 | 0.0758 | 3.4 | 0.0642 | 4.1 | 0.0421 |
| RS | 0.5 | 0.468 | 0.6 | 0.4208 | 0.5 | 0.4719 | 1.2 | 0.2651 | 1.2 | 0.2691 |
| EP | 0.1 | 0.7334 | 0.2 | 0.6695 | 0.1 | 0.7808 | 0.5 | 0.5006 | 0.4 | 0.5251 |
| Time trend for signature | ρ | P | ρ | P | ρ | P | ρ | P | ρ | P |
| Intrinsic-RORs | -0.377 | 0.0069 | -0.173 | 0.2094 | -0.171 | 0.2074 | -0.185 | 0.1875 | -0.171 | 0.1931 |
| PAM50-RORs | -0.127 | 0.3676 | -0.182 | 0.1873 | -0.220 | 0.1108 | -0.214 | 0.1175 | -0.186 | 0.1571 |
| 70-gene | -0.244 | 0.0702 | -0.180 | 0.1912 | -0.205 | 0.1266 | -0.221 | 0.1056 | -0.175 | 0.1811 |
| 76-gene | -0.260 | 0.0565 | -0.215 | 0.1069 | -0.248 | 0.0657 | -0.206 | 0.1303 | -0.212 | 0.0921 |
| GGI | -0.294 | 0.0296 | -0.191 | 0.1644 | -0.165 | 0.2325 | -0.206 | 0.1284 | -0.181 | 0.1671 |
| WR | -0.432 | 0.0002 | -0.260 | 0.0503 | -0.089 | 0.5184 | -0.150 | 0.2677 | -0.222 | 0.0811 |
| Hypoxia | -0.038 | 0.7132 | -0.194 | 0.1579 | -0.227 | 0.099 | -0.219 | 0.1093 | -0.167 | 0.2051 |
| RS | -0.226 | 0.0628 | -0.190 | 0.1647 | -0.178 | 0.1902 | -0.209 | 0.1271 | -0.174 | 0.1861 |
| EP | -0.184 | 0.2457 | -0.195 | 0.154 | -0.195 | 0.1564 | -0.212 | 0.1196 | -0.183 | 0.1621 |

Table S5. Univariate analysis on gene signatures with G1, G2, G3 separately in ER+ samples.

(A) Analysis of deviance & time trend test. Prognosis of individual signature was tested in univariate Cox model: $Risk = Signature$ in ER+ group (n= 715; column *Univariate*), G1 samples of the ER+ group, (n= 153; column *G1*), G2 samples of the ER+ group, (n= 311; column *G2*) and G3 samples of the ER+ group, (n=149; column *G3*). For each Cox model, the added (type I) effect of each subsequent covariate is reported under *Analysis of deviance* as the reduction in the residual deviance χ^2 with its corresponding p value. Time trend associated with individual gene signature covariate was assessed by testing for violation of proportional hazard (PH) assumption in the corresponding Cox model (“*Time trend for signature*”). Violation of the PH assumption (significant p value for correlation ρ) indicates significant time dependency of individual signatures on prognosis.

| Deviance (type I) | ER+ | | ER+ / G1 | | ER+ / G2 | | ER+ / G3 | |
|---------------------------------|--------------------------|----------|--------------------------|----------|--------------------------|----------|--------------------------|----------|
| | χ^2 | p | χ^2 | p | χ^2 | p | χ^2 | p |
| <i>Gene signature (df=1):</i> | | | | | | | | |
| Intrinsic-RORs | 9.8 | 0.0018 | <0.0001 | 0.8443 | 5.1 | 0.0238 | 0.5 | 0.4877 |
| PAM50-RORs | 58 | <0.0001 | 15.8 | 0.0001 | 24.5 | <0.0001 | 2.1 | 0.1434 |
| 70-gene | 31.2 | <0.0001 | 3.9 | 0.0469 | 27.1 | <0.0001 | 0.1 | 0.7575 |
| 76-gene | 42.9 | <0.0001 | 12.8 | 0.0003 | 11.2 | 0.0008 | 7 | 0.008 |
| GGI | 56.1 | <0.0001 | 10.5 | 0.0012 | 23.2 | <0.0001 | 6.4 | 0.0113 |
| WR | 46.5 | <0.0001 | 6 | 0.0144 | 19 | <0.0001 | 7.3 | 0.0069 |
| Hypoxia | 0.1 | 0.723 | <0.0001 | 0.9628 | 1.2 | 0.2737 | 0 | 0.9412 |
| RS | 42.4 | <0.0001 | 2.2 | 0.1395 | 19.6 | <0.0001 | 6.2 | 0.0125 |
| EP | 49.5 | <0.0001 | 7.5 | 0.0061 | 21 | <0.0001 | 9 | 0.0028 |
| Time trend for signature | ρ | p | ρ | p | ρ | p | ρ | p |
| Intrinsic-RORs | -0.233 | 0.0032 | -0.228 | 0.3061 | -0.161 | 0.1738 | 0.161 | 0.3238 |
| PAM50-RORs | -0.269 | 0.0005 | -0.700 | 0.0005 | -0.107 | 0.3355 | 0.131 | 0.3856 |
| 70-gene | -0.180 | 0.0232 | -0.458 | 0.0215 | -0.101 | 0.4128 | 0.282 | 0.0423 |
| 76-gene | -0.203 | 0.0092 | -0.529 | 0.007 | 0.001 | 0.9963 | -0.042 | 0.7763 |
| GGI | -0.324 | <0.0001 | -0.667 | 0.0034 | -0.149 | 0.2146 | -0.021 | 0.8881 |
| WR | -0.283 | 0.0001 | -0.565 | 0.0037 | -0.112 | 0.2966 | -0.049 | 0.7045 |
| Hypoxia | -0.020 | 0.7717 | -0.144 | 0.3479 | 0.033 | 0.7404 | -0.153 | 0.3078 |
| RS | -0.250 | 0.0019 | -0.541 | 0.0597 | -0.154 | 0.2079 | 0.200 | 0.1711 |
| EP | -0.274 | 0.0004 | -0.641 | 0.0079 | -0.204 | 0.1016 | 0.152 | 0.2448 |

(B) Standardized Hazard Ratio. Risk scores for individual gene signatures were standardized, and prognostic effects of signatures were compared using Hazard Ratio from univariate Cox model: $Risk = Signature$ in ER+ group (n= 715; column *ER+*), G1 samples of the ER+ group, (n= 153; column *ER+/G1*), G2 samples of the ER+ group, (n= 311; column *ER+/G2*) and G3 samples of the ER+ group, (n=149; column *ER+/G3*).

| Gene signature | ER+ | | ER+ / G1 | | ER+ / G2 | | ER+ / G3 | |
|----------------|------------------|---------|------------------|---------|------------------|----------|------------------|--------|
| | HR[95%CI] | p | HR[95%CI] | p | HR[95%CI] | p | HR[95%CI] | p |
| Intrinsic-RORs | 1.26 [1.09-1.45] | 0.0014 | 1.04 [0.7-1.54] | 0.8431 | 1.28 [1.04-1.58] | 0.0213 | 1.1 [0.84-1.45] | 0.4871 |
| PAM50-RORs | 1.8 [1.54-2.1] | <0.0001 | 2.13 [1.49-3.05] | <0.0001 | 1.76 [1.41-2.21] | <0.0001 | 1.24 [0.92-1.67] | 0.1587 |
| 70-gene | 1.51 [1.31-1.74] | <0.0001 | 1.45 [1.02-2.07] | 0.0391 | 1.8 [1.44-2.25] | <0.0001 | 1.04 [0.79-1.38] | 0.7579 |
| 76-gene | 1.62 [1.4-1.87] | <0.0001 | 1.98 [1.39-2.83] | 0.0002 | 1.45 [1.17-1.79] | 6.00E-04 | 1.46 [1.1-1.93] | 0.009 |
| GGI | 1.76 [1.52-2.03] | <0.0001 | 1.79 [1.3-2.45] | 0.0003 | 1.71 [1.38-2.12] | <0.0001 | 1.47 [1.08-2] | 0.0155 |
| WR | 1.69 [1.45-1.96] | <0.0001 | 1.59 [1.11-2.28] | 0.0114 | 1.64 [1.32-2.05] | <0.0001 | 1.51 [1.11-2.06] | 0.0083 |
| Hypoxia | 1.03 [0.88-1.2] | 0.7225 | 0.99 [0.64-1.53] | 0.9628 | 1.14 [0.9-1.43] | 0.2707 | 0.99 [0.75-1.3] | 0.9413 |
| RS | 1.58 [1.39-1.79] | <0.0001 | 1.26 [0.95-1.68] | 0.1036 | 1.56 [1.3-1.87] | <0.0001 | 1.44 [1.08-1.92] | 0.0135 |
| EP | 1.69 [1.46-1.96] | <0.0001 | 1.66 [1.18-2.32] | 0.0032 | 1.67 [1.35-2.08] | <0.0001 | 1.56 [1.15-2.1] | 0.0038 |

Table S6. Univariate analysis on gene signatures with T1, T2, T3 separately in ER+ samples.

(A) Analysis of deviance & time trend test. Prognosis of individual signature was tested in univariate Cox model: Risk = *Signature* in ER+ group (n= 715; column *ER+*), T1 samples of the ER+ group, (n= 349; column *ER+/T1*), T2 samples of the ER+ group, (n= 335; column *ER+/T2*) and T3 samples of the ER+ group, (n=26; column *ER+/T3*). For each Cox model, the added (type I) effect of each subsequent covariate is reported under *Analysis of deviance* as the reduction in the residual deviance χ^2 with its corresponding p value. Time trend associated with individual gene signature covariate was assessed by testing for violation of proportional hazard (PH) assumption in the corresponding Cox model (“*Time trend for signature*”). Violation of the PH assumption (significant p value for correlation ρ) indicates significant time dependency of individual signatures on prognosis.

| Deviance (type I) | <i>ER+</i> | | <i>ER+/T1</i> | | <i>ER+/T2</i> | | <i>ER+/T3</i> | |
|---------------------------------|--------------------------|----------|--------------------------|----------|--------------------------|----------|--------------------------|----------|
| | χ^2 | p | χ^2 | p | χ^2 | p | χ^2 | p |
| <i>Gene signature (df=1):</i> | | | | | | | | |
| Intrinsic-RORs | 9.8 | 0.0018 | 1.1 | 0.2901 | 8.2 | 0.0043 | 0.3 | 0.569 |
| PAM50-RORs | 58 | <0.0001 | 18.2 | <0.0001 | 28.5 | <0.0001 | 2 | 0.159 |
| 70-gene | 31.2 | <0.0001 | 8.2 | 0.0042 | 18.2 | <0.0001 | 0.8 | 0.3653 |
| 76-gene | 42.9 | <0.0001 | 22.2 | <0.0001 | 12.5 | 0.0004 | 1.9 | 0.1685 |
| GGI | 56.1 | <0.0001 | 15.9 | 0.0001 | 28.8 | <0.0001 | 3.7 | 0.0531 |
| WR | 46.5 | <0.0001 | 11.6 | 0.0006 | 21.2 | <0.0001 | 3.7 | 0.0543 |
| Hypoxia | 0.1 | 0.723 | 0 | 0.8616 | 0.5 | 0.4996 | 0.1 | 0.7227 |
| RS | 42.4 | <0.0001 | 11.7 | 0.0006 | 23.5 | <0.0001 | 0.3 | 0.6108 |
| EP | 49.5 | <0.0001 | 11.1 | 0.0009 | 29.2 | <0.0001 | 0.9 | 0.3487 |
| Time trend for signature | ρ | p | ρ | p | ρ | p | ρ | p |
| Intrinsic-RORs | -0.233 | 0.0032 | -0.452 | 0.0006 | -0.117 | 0.2537 | 0.306 | 0.4464 |
| PAM50-RORs | -0.269 | 0.0005 | -0.178 | 0.1766 | -0.266 | 0.0083 | 0.182 | 0.664 |
| 70-gene | -0.180 | 0.0232 | -0.241 | 0.0821 | -0.135 | 0.1812 | -0.005 | 0.9866 |
| 76-gene | -0.203 | 0.0092 | -0.108 | 0.4056 | -0.241 | 0.0166 | 0.309 | 0.4765 |
| GGI | -0.324 | <0.0001 | -0.202 | 0.1397 | -0.355 | 0.0004 | 0.270 | 0.4749 |
| WR | -0.283 | 0.0001 | -0.165 | 0.1981 | -0.311 | 0.0005 | 0.536 | 0.2178 |
| Hypoxia | -0.020 | 0.7717 | -0.103 | 0.377 | 0.083 | 0.3817 | -0.241 | 0.3351 |
| RS | -0.250 | 0.0019 | -0.343 | 0.0139 | -0.217 | 0.0365 | 0.292 | 0.4172 |
| EP | -0.274 | 0.0004 | -0.274 | 0.028 | -0.249 | 0.0171 | 0.031 | 0.9275 |

(B) Standardized Hazard Ratio. Risk scores for individual gene signatures were standardized, and prognostic effects of signatures were compared using Hazard Ratio from univariate Cox model: Risk = *Signature* in ER+ group (n= 715; column *ER+*), T1 samples of the ER+ group, (n= 349; column *ER+/T1*), T2 samples of the ER+ group, (n= 335; column *ER+/T2*) and T3 samples of the ER+ group, (n=26; column *ER+/T3*).

| <i>Gene signature</i> | <i>ER+</i> | | <i>ER+/T1</i> | | <i>ER+/T2</i> | | <i>ER+/T3</i> | |
|-----------------------|------------------|---------|------------------|----------|------------------|----------|------------------|--------|
| | HR[95%CI] | p | HR[95%CI] | p | HR[95%CI] | p | HR[95%CI] | p |
| Intrinsic-RORs | 1.26 [1.09-1.45] | 0.0014 | 1.15 [0.89-1.47] | 0.2834 | 1.32 [1.09-1.58] | 0.0036 | 1.22 [0.61-2.43] | 0.5679 |
| PAM50-RORs | 1.8 [1.54-2.1] | <0.0001 | 1.74 [1.35-2.25] | <0.0001 | 1.71 [1.4-2.1] | <0.0001 | 1.62 [0.82-3.19] | 0.1626 |
| 70-gene | 1.51 [1.31-1.74] | <0.0001 | 1.43 [1.12-1.82] | 0.004 | 1.51 [1.25-1.84] | <0.0001 | 1.35 [0.72-2.54] | 0.3538 |
| 76-gene | 1.62 [1.4-1.87] | <0.0001 | 1.8 [1.42-2.29] | <0.0001 | 1.4 [1.16-1.68] | 4.00E-04 | 1.67 [0.78-3.58] | 0.1893 |
| GGI | 1.76 [1.52-2.03] | <0.0001 | 1.64 [1.3-2.09] | <0.0001 | 1.71 [1.4-2.08] | <0.0001 | 2.09 [0.93-4.69] | 0.075 |
| WR | 1.69 [1.45-1.96] | <0.0001 | 1.54 [1.21-1.97] | 0.0005 | 1.59 [1.3-1.95] | <0.0001 | 1.95 [0.93-4.12] | 0.0783 |
| Hypoxia | 1.03 [0.88-1.2] | 0.7225 | 0.98 [0.75-1.27] | 0.8617 | 1.07 [0.88-1.3] | 0.4974 | 1.14 [0.56-2.32] | 0.7199 |
| RS | 1.58 [1.39-1.79] | <0.0001 | 1.49 [1.2-1.84] | 0.0002 | 1.58 [1.32-1.89] | <0.0001 | 1.18 [0.64-2.15] | 0.5979 |
| EP | 1.69 [1.46-1.96] | <0.0001 | 1.53 [1.2-1.96] | 7.00E-04 | 1.68 [1.39-2.04] | <0.0001 | 1.44 [0.67-3.08] | 0.3459 |

Table S7. Time- & ER-dependent effect assessment of individual gene signatures in predicting Disease-specific Survival on the METABRIC set. (A) On the complete METABRIC set; (B) On the systemically untreated samples and (C) On the systemically treated samples . Main effect associated with a signature for Disease-specific Survival prediction in a certain follow-up time interval was estimated by a Cox model within each ER stratification. The Hazard Ratio (HR) along with its 95% confidence interval and the p value from the Wald test are shown. Numbers of patients at risk (n_{risk}) were computed at time point 0, 5 and 10 year, respectively.

(A)

| Gene signature | Time | <i>ER + (n=801)</i> | | | | <i>ER - (n=195)</i> | | | |
|----------------|--------|---------------------|-------------|------------------|---------|---------------------|-------------|------------------|--------|
| | | n_{risk} | n_{event} | HR [95% CI] | p | n_{risk} | n_{event} | HR [95% CI] | p |
| Intrinsic-RORs | 0-5yr | 801 | 101 | 2.00 [1.66-2.41] | <0.0001 | 195 | 73 | 1.11 [0.87-1.43] | 0.4039 |
| | 5-10yr | 700 | 80 | 0.96 [0.77-1.20] | 0.7223 | 122 | 10 | 0.67 [0.47-0.95] | 0.0235 |
| | >10yr | 620 | 37 | 1.03 [0.74-1.43] | 0.8423 | 112 | 5 | 0.83 [0.38-1.80] | 0.6328 |
| PAM50-RORs | 0-5yr | 801 | 101 | 2.20[1.78-2.72] | <0.0001 | 195 | 73 | 1.03 [0.82-1.30] | 0.7855 |
| | 5-10yr | 700 | 80 | 1.32 [1.07-1.64] | 0.0107 | 122 | 10 | 0.68 [0.45-1.03] | 0.0658 |
| | >10yr | 620 | 37 | 1.04 [0.75-1.43] | 0.8285 | 112 | 5 | 0.27 [0.09-0.81] | 0.0187 |
| 70-gene | 0-5yr | 801 | 101 | 1.99 [1.63-2.41] | <0.0001 | 195 | 73 | 0.95 [0.76-1.18] | 0.6242 |
| | 5-10yr | 700 | 80 | 1.11 [0.89-1.38] | 0.3514 | 122 | 10 | 0.74 [0.43-1.29] | 0.2877 |
| | >10yr | 620 | 37 | 1.21 [0.87-1.68] | 0.2545 | 112 | 5 | 0.85 [0.39-1.89] | 0.6986 |
| 76-gene | 0-5yr | 801 | 101 | 1.57 [1.31-1.87] | <0.0001 | 195 | 73 | 0.89 [0.70-1.14] | 0.3622 |
| | 5-10yr | 700 | 80 | 1.23 [0.99-1.52] | 0.0574 | 122 | 10 | 1.32 [0.73-2.42] | 0.3605 |
| | >10yr | 620 | 37 | 0.76 [0.54-1.09] | 0.1346 | 112 | 5 | 1.27 [0.56-2.88] | 0.5727 |
| GGI | 0-5yr | 801 | 101 | 1.91 [1.59-2.31] | <0.0001 | 195 | 73 | 1.11 [0.88-1.42] | 0.3799 |
| | 5-10yr | 700 | 80 | 1.35 [1.09-1.67] | 0.0060 | 122 | 10 | 0.83 [0.44-1.57] | 0.5736 |
| | >10yr | 620 | 37 | 0.87 [0.62-1.22] | 0.4269 | 112 | 5 | 0.24 [0.07-0.88] | 0.0318 |
| WR | 0-5yr | 801 | 101 | 1.70 [1.41-2.06] | <0.0001 | 195 | 73 | 1.28 [1.00-1.65] | 0.0509 |
| | 5-10yr | 700 | 80 | 1.15 [0.93-1.43] | 0.1974 | 122 | 10 | 0.97 [0.53-1.79] | 0.9320 |
| | >10yr | 620 | 37 | 0.84 [0.6-1.17] | 0.2950 | 112 | 5 | 0.36 [0.13-1.04] | 0.0602 |
| Hypoxia | 0-5yr | 801 | 101 | 1.32 [1.11-1.56] | 0.0015 | 195 | 73 | 1.12 [0.90-1.40] | 0.3011 |
| | 5-10yr | 700 | 80 | 1.09 [0.88-1.36] | 0.4194 | 122 | 10 | 0.76 [0.36-1.57] | 0.4554 |
| | >10yr | 620 | 37 | 1.26 [0.88-1.80] | 0.2102 | 112 | 5 | 1.47 [0.50-4.27] | 0.4837 |
| RS | 0-5yr | 801 | 101 | 1.94 [1.69-2.24] | <0.0001 | 195 | 73 | 1.22 [0.99-1.51] | 0.0669 |
| | 5-10yr | 700 | 80 | 1.11 [0.89-1.38] | 0.3481 | 122 | 10 | 0.60 [0.33-1.10] | 0.0975 |
| | >10yr | 620 | 37 | 1.19 [0.86-1.65] | 0.2856 | 112 | 5 | 1.19 [0.56-2.54] | 0.6535 |
| EP | 0-5yr | 801 | 101 | 1.96 [1.64-2.33] | <0.0001 | 195 | 73 | 0.91 [0.74-1.13] | 0.4069 |
| | 5-10yr | 700 | 80 | 1.29 [1.04-1.59] | 0.0183 | 122 | 10 | 0.73 [0.41-1.28] | 0.2690 |
| | >10yr | 620 | 37 | 1.13 [0.82-1.55] | 0.4593 | 112 | 5 | 0.71 [0.26-1.93] | 0.5050 |

(B)

| Gene signature | Time | <i>ER + (n=203)</i> | | | | <i>ER - (n=50)</i> | | | |
|----------------|--------|-------------------------|--------------------------|------------------|---------|-------------------------|--------------------------|-----------------------|--------|
| | | <i>n_{risk}</i> | <i>n_{event}</i> | HR [95% CI] | p | <i>n_{risk}</i> | <i>n_{event}</i> | HR [95% CI] | p |
| Intrinsic-RORs | 0-5yr | 203 | 12 | 1.67 [1.03-2.71] | 0.0367 | 50 | 13 | 0.75 [0.47-1.21] | 0.2407 |
| | 5-10yr | 191 | 24 | 1.14 [0.78-1.67] | 0.491 | 37 | 2 | 2.3 [0.23-23.05] | 0.4788 |
| | >10yr | 167 | 12 | 0.59 [0.27-1.32] | 0.1994 | 35 | 0 | - | - |
| PAM50-RORs | 0-5yr | 203 | 12 | 2.22 [1.27-3.88] | 0.0049 | 50 | 13 | 0.97 [0.58-1.64] | 0.9191 |
| | 5-10yr | 191 | 24 | 1.4 [0.95-2.05] | 0.0881 | 37 | 2 | 4.81 [0.3-76.04] | 0.2645 |
| | >10yr | 167 | 12 | 0.85 [0.46-1.57] | 0.6022 | 35 | 0 | - | - |
| 70-gene | 0-5yr | 203 | 12 | 3.25 [1.94-5.45] | <0.0001 | 50 | 13 | 0.68 [0.42-1.11] | 0.121 |
| | 5-10yr | 191 | 24 | 1.68 [1.14-2.48] | 0.0083 | 37 | 2 | 49.96 [0.21-11631.36] | 0.1596 |
| | >10yr | 167 | 12 | 0.78 [0.43-1.42] | 0.4183 | 35 | 0 | - | - |
| 76-gene | 0-5yr | 203 | 12 | 1.97 [1.18-3.32] | 0.0101 | 50 | 13 | 0.83 [0.42-1.65] | 0.5916 |
| | 5-10yr | 191 | 24 | 1.64 [1.14-2.38] | 0.0082 | 37 | 2 | 1.02 [0.18-5.62] | 0.9839 |
| | >10yr | 167 | 12 | 0.61 [0.35-1.08] | 0.0919 | 35 | 0 | - | - |
| GGI | 0-5yr | 203 | 12 | 2.24 [1.33-3.77] | 0.0025 | 50 | 13 | 0.99 [0.58-1.71] | 0.9787 |
| | 5-10yr | 191 | 24 | 1.68 [1.17-2.41] | 0.0051 | 37 | 2 | 3.43 [0.51-23.07] | 0.2043 |
| | >10yr | 167 | 12 | 0.72 [0.4-1.3] | 0.2712 | 35 | 0 | - | - |
| WR | 0-5yr | 203 | 12 | 2.06 [1.18-3.59] | 0.0111 | 50 | 13 | 1.35 [0.76-2.42] | 0.3077 |
| | 5-10yr | 191 | 24 | 1.49 [1.01-2.2] | 0.0455 | 37 | 2 | 1.63 [0.34-7.69] | 0.5391 |
| | >10yr | 167 | 12 | 0.71 [0.41-1.23] | 0.223 | 35 | 0 | - | - |
| Hypoxia | 0-5yr | 203 | 12 | 1.33 [0.83-2.14] | 0.2352 | 50 | 13 | 1.25 [0.69-2.28] | 0.4552 |
| | 5-10yr | 191 | 24 | 1.05 [0.71-1.56] | 0.7919 | 37 | 2 | 0.57 [0.12-2.61] | 0.4675 |
| | >10yr | 167 | 12 | 0.98 [0.52-1.85] | 0.9439 | 35 | 0 | - | - |
| RS | 0-5yr | 203 | 12 | 1.86 [1.23-2.79] | 0.0031 | 50 | 13 | 1.21 [0.66-2.23] | 0.532 |
| | 5-10yr | 191 | 24 | 1.05 [0.71-1.53] | 0.8169 | 37 | 2 | 1.04 [0.25-4.35] | 0.9546 |
| | >10yr | 167 | 12 | 0.94 [0.5-1.76] | 0.8476 | 35 | 0 | - | - |
| EP | 0-5yr | 203 | 12 | 1.75 [1.08-2.85] | 0.0229 | 50 | 13 | 0.74 [0.46-1.2] | 0.2208 |
| | 5-10yr | 191 | 24 | 1.58 [1.12-2.22] | 0.0092 | 37 | 2 | 3.98 [0.74-21.42] | 0.108 |
| | >10yr | 167 | 12 | 0.96 [0.53-1.73] | 0.895 | 35 | 0 | - | - |

(C)

| Gene signature | Time | <i>ER + (n=598)</i> | | | | <i>ER - (n=145)</i> | | | |
|----------------|--------|-------------------------|--------------------------|------------------|---------|-------------------------|--------------------------|------------------|--------|
| | | <i>n_{risk}</i> | <i>n_{event}</i> | HR [95% CI] | p | <i>n_{risk}</i> | <i>n_{event}</i> | HR [95% CI] | p |
| Intrinsic-RORs | 0-5yr | 598 | 89 | 1.99 [1.62-2.45] | <0.0001 | 145 | 60 | 1.21 [0.89-1.64] | 0.2269 |
| | 5-10yr | 509 | 56 | 0.87 [0.67-1.14] | 0.3228 | 85 | 8 | 0.63 [0.45-0.87] | 0.0048 |
| | >10yr | 453 | 25 | 1.07 [0.75-1.53] | 0.7023 | 77 | 5 | 0.89 [0.46-1.73] | 0.7357 |
| PAM50-RORs | 0-5yr | 598 | 89 | 2.05 [1.63-2.57] | <0.0001 | 145 | 60 | 1.02 [0.79-1.31] | 0.8705 |
| | 5-10yr | 509 | 56 | 1.25 [0.96-1.61] | 0.0962 | 85 | 8 | 0.41 [0.24-0.7] | 0.0011 |
| | >10yr | 453 | 25 | 1.01 [0.7-1.46] | 0.969 | 77 | 5 | 0.4 [0.2-0.81] | 0.0111 |
| 70-gene | 0-5yr | 598 | 89 | 1.76 [1.43-2.18] | <0.0001 | 145 | 60 | 1.02 [0.79-1.32] | 0.8568 |
| | 5-10yr | 509 | 56 | 0.9 [0.69-1.18] | 0.4468 | 85 | 8 | 0.52 [0.29-0.95] | 0.0324 |
| | >10yr | 453 | 25 | 1.26 [0.85-1.86] | 0.2485 | 77 | 5 | 0.96 [0.42-2.19] | 0.9274 |
| 76-gene | 0-5yr | 598 | 89 | 1.45 [1.2-1.76] | 0.0002 | 145 | 60 | 0.86 [0.66-1.12] | 0.267 |
| | 5-10yr | 509 | 56 | 1.07 [0.82-1.38] | 0.6245 | 85 | 8 | 1.33 [0.71-2.51] | 0.3763 |
| | >10yr | 453 | 25 | 0.85 [0.55-1.29] | 0.443 | 77 | 5 | 1.23 [0.59-2.57] | 0.5853 |
| GGI | 0-5yr | 598 | 89 | 1.77 [1.45-2.18] | <0.0001 | 145 | 60 | 1.09 [0.83-1.42] | 0.535 |
| | 5-10yr | 509 | 56 | 1.19 [0.92-1.54] | 0.196 | 85 | 8 | 0.57 [0.27-1.19] | 0.1348 |
| | >10yr | 453 | 25 | 0.89 [0.59-1.34] | 0.5863 | 77 | 5 | 0.24 [0.06-0.91] | 0.0363 |
| WR | 0-5yr | 598 | 89 | 1.56 [1.27-1.91] | <0.0001 | 145 | 60 | 1.22 [0.92-1.6] | 0.1677 |
| | 5-10yr | 509 | 56 | 1.01 [0.78-1.32] | 0.9172 | 85 | 8 | 0.81 [0.41-1.6] | 0.5433 |
| | >10yr | 453 | 25 | 0.87 [0.59-1.28] | 0.4812 | 77 | 5 | 0.32 [0.11-0.95] | 0.0404 |
| Hypoxia | 0-5yr | 598 | 89 | 1.29 [1.07-1.55] | 0.0064 | 145 | 60 | 1.07 [0.84-1.36] | 0.5828 |
| | 5-10yr | 509 | 56 | 1.1 [0.85-1.41] | 0.4786 | 85 | 8 | 0.8 [0.35-1.85] | 0.6055 |
| | >10yr | 453 | 25 | 1.26 [0.84-1.9] | 0.2621 | 77 | 5 | 1.47 [0.51-4.22] | 0.477 |
| RS | 0-5yr | 598 | 89 | 1.91 [1.63-2.24] | <0.0001 | 145 | 60 | 1.18 [0.94-1.49] | 0.1505 |
| | 5-10yr | 509 | 56 | 1.11 [0.85-1.43] | 0.4434 | 85 | 8 | 0.53 [0.27-1.02] | 0.0579 |
| | >10yr | 453 | 25 | 1.15 [0.79-1.66] | 0.4602 | 77 | 5 | 1.11 [0.53-2.31] | 0.7872 |
| EP | 0-5yr | 598 | 89 | 1.91 [1.58-2.31] | <0.0001 | 145 | 60 | 0.94 [0.74-1.2] | 0.6272 |
| | 5-10yr | 509 | 56 | 1.12 [0.86-1.46] | 0.3846 | 85 | 8 | 0.56 [0.32-0.97] | 0.0397 |
| | >10yr | 453 | 25 | 1.11 [0.76-1.62] | 0.6028 | 77 | 5 | 0.65 [0.24-1.77] | 0.3996 |

Table S8. Time trend analysis on METABRIC set. Analysis is carried out on ER-positive and ER-negative groups separately. Time trend associated with individual gene signature covariate was assessed by testing for violation of proportional hazard (PH) assumption in the corresponding Cox model (“*Time trend for signature*”). Violation of the PH assumption (significant p value for correlation ρ) indicates significant time dependency of individual signatures on prognosis. The following Cox models were fitted: **(Model 1)** *Risk = Signature*; **(Model 2)** *Risk = Signature + Grade*; **(Model 3)** *Risk = Signature + TumorSize*.

| ER+ | Model 1 | | Model 2 | | Model 3 | |
|----------------|---------|---------|---------|--------|---------|--------|
| | ρ | p | ρ | p | ρ | p |
| Intrinsic-RORs | -0.3038 | <0.0001 | 0.0003 | 0.9963 | -0.0245 | 0.7195 |
| PAM50-RORs | -0.2832 | 0.0001 | 0.0199 | 0.7697 | 0.0023 | 0.9728 |
| 70-gene | -0.2533 | 0.0001 | 0.0116 | 0.8646 | -0.0048 | 0.9439 |
| 76-gene | -0.3112 | 0.0001 | 0.0185 | 0.7844 | 0.0038 | 0.9548 |
| GGI | -0.3364 | <0.0001 | 0.0298 | 0.6610 | 0.0093 | 0.8916 |
| WR | -0.3317 | <0.0001 | 0.0146 | 0.8304 | 0.015 | 0.8250 |
| Hypoxia | -0.0215 | 0.7391 | -0.0016 | 0.9816 | -0.0237 | 0.7286 |
| RS | -0.2572 | 0.0001 | 0.0044 | 0.9479 | -0.0159 | 0.8151 |
| EP | -0.2661 | 0.0003 | 0.0139 | 0.8375 | -0.0077 | 0.9097 |
| ER- | ρ | p | ρ | p | ρ | p |
| Intrinsic-RORs | -0.299 | 0.0030 | 0.0318 | 0.7683 | 0.1517 | 0.1547 |
| PAM50-RORs | -0.2512 | 0.0493 | -0.0025 | 0.9808 | 0.1915 | 0.0674 |
| 70-gene | -0.0987 | 0.3992 | -0.0594 | 0.5871 | 0.1594 | 0.1339 |
| 76-gene | -0.0259 | 0.8024 | -0.0607 | 0.5726 | 0.1627 | 0.1281 |
| GGI | -0.2564 | 0.0144 | -0.0299 | 0.7782 | 0.1681 | 0.1122 |
| WR | -0.2792 | 0.0050 | -0.0317 | 0.7651 | 0.1642 | 0.1218 |
| Hypoxia | -0.0432 | 0.7032 | -0.0579 | 0.5895 | 0.1763 | 0.1056 |
| RS | -0.1254 | 0.2382 | -0.0374 | 0.7272 | 0.1725 | 0.1040 |
| EP | -0.0998 | 0.3776 | -0.055 | 0.6115 | 0.1668 | 0.1163 |