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# Prognostic and Predictive Value of Immune-Related Gene Expression Signatures vs Tumor-Infiltrating Lymphocytes in Early-Stage ERBB2/HER2-Positive Breast Cancer

## A Correlative Analysis of the CALGB 40601 and PAMELA Trials

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**IMPORTANCE** Both tumor-infiltrating lymphocytes (TILs) assessment and immune-related gene expression signatures by RNA profiling predict higher pathologic complete response (pCR) and improved event-free survival (EFS) in patients with early-stage ERBB2/HER2-positive breast cancer. However, whether these 2 measures of immune activation provide similar or additive prognostic value is not known.

**OBJECTIVE** To examine the prognostic ability of TILs and immune-related gene expression signatures, alone and in combination, to predict pCR and EFS in patients with early-stage ERBB2/HER2-positive breast cancer treated in 2 clinical trials.

**DESIGN, SETTING, AND PARTICIPANTS** In this prognostic study, a correlative analysis was performed on the Cancer and Leukemia Group B (CALGB) 40601 trial and the PAMELA trial. In the CALGB 40601 trial, 305 patients were randomly assigned to weekly paclitaxel with trastuzumab, lapatinib, or both for 16 weeks. The primary end point was pCR, with a secondary end point of EFS. In the PAMELA trial, 151 patients received neoadjuvant treatment with trastuzumab and lapatinib for 18 weeks. The primary end point was the ability of the HER2-enriched subtype to predict pCR. The studies were conducted from October 2013 to November 2015 (PAMELA) and from December 2008 to February 2012 (CALGB 40601). Data analyses were performed from June 1, 2020, to January 1, 2022.

**MAIN OUTCOMES AND MEASURES** Immune-related gene expression profiling by RNA sequencing and TILs were assessed on 230 CALGB 40601 trial pretreatment tumors and 138 PAMELA trial pretreatment tumors. The association of these biomarkers with pCR (CALGB 40601 and PAMELA) and EFS (CALGB 40601) was studied by logistic regression and Cox analyses.

**RESULTS** The median age of the patients was 50 years (IQR, 42-50 years), and 305 (100%) were women. Of 202 immune signatures tested, 166 (82.2%) were significantly correlated with TILs. In both trials combined, TILs were significantly associated with pCR (odds ratio, 1.01; 95% CI, 1.01-1.02; $P = .02$). In addition to TILs, 36 immune signatures were significantly associated with higher pCR rates. Seven of these signatures outperformed TILs for predicting pCR, 6 of which were B-cell related. In a multivariable Cox model adjusted for clinicopathologic factors, including PAM50 intrinsic tumor subtype, the immunoglobulin G signature, but not TILs, was independently associated with EFS (immunoglobulin G signature–adjusted hazard ratio, 0.63; 95% CI, 0.42-0.93; $P = .02$; TIL-adjusted hazard ratio, 1.00; 95% CI, 0.98-1.02; $P = .99$).

**CONCLUSIONS AND RELEVANCE** Results of this study suggest that multiple B-cell–related signatures were more strongly associated with pCR and EFS than TILs, which largely represent T cells. When both TILs and gene expression are available, the prognostic value of immune-related signatures appears to be superior.

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Supplemental content

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During the last 2 decades, the outcome of patients with early-stage ERBB2/HER2-positive breast cancer has markedly improved owing to new treatment strategies combining polychemotherapy and multiple ERBB2/HER2-targeted drugs.[1-10] However, it is increasingly evident that many patients are overtreated by the recommended regimens, whereas others still experience metastatic relapse. A primary research focus in breast cancer is to better tailor treatments to risk; to accomplish this, effective prognostic and predictive biomarkers are needed.

Increasing evidence suggests that the activation of the host immune system mediates the response to ERBB2/HER2-targeted therapies in breast cancer.[11] Currently, there are several methods to assess intratumor immune activation. The presence of tumor-infiltrating lymphocytes (TILs) in the hematoxylin-eosin-stained tumor slides is one of these methods, and an international working group has established standardized tools for measuring TILs.[12] The percentage of TILs that infiltrate the breast tumor is positively prognostic in patients with early-stage ERBB2/HER2-positive breast cancer treated with anti-ERBB2/HER2 therapies in multiple scenarios: in the neoadjuvant and adjuvant setting, in the presence or absence of chemotherapy, with single and dual ERBB2/HER2 blockade, and when assessed at baseline and during treatment.[13-18] Other than TILs, immune activation can also be measured by gene expression.[19,20] In patients with early-stage ERBB2/HER2-positive breast cancer treated in the neoadjuvant setting, immune-related gene expression signatures (iGESs) are associated with higher pathologic complete response (pCR) rates and prolonged survival.[21-23] Specifically, the immunoglobulin G (IgG) signature[24] has previously shown strong and independent prognostic value across many studies.[2,19,22,25] However, the comparative prognostic ability of these different means of measuring immune activation has not been well examined. In this retrospective predictive and prognostic study, we tested which biomarker, or combination of biomarkers, is the most powerful for response and survival in 2 independent clinical trials: the Cancer and Leukemia Group B (CALGB) 40601 trial (NCT00770809) and the PAMELA trial (NCT01973660), respectively. The CALGB is now part of the Alliance for Clinical Trials in Oncology.

### Key Points

**Question** Which immune-related biomarker provides the most valuable information to predict pathologic complete response and event-free survival in patients with early-stage ERBB2/HER2-positive breast cancer: tumor-infiltrating lymphocytes, immune-related gene expression signatures, or both?

**Findings** In this predictive prognostic study in which a combined correlative analysis of the CALGB 40601 and PAMELA trials was conducted, 305 patients with early-stage ERBB2/HER2-positive breast cancer, 6 B-cell–related signatures were more strongly associated with pathologic complete response than were tumor-infiltrating lymphocytes. In a multivariable Cox model performed in the CALGB 40601 trial, the immunoglobulin G signature, but not tumor-infiltrating lymphocytes, was independently associated with event-free survival.

**Meaning** Findings suggest that when both tumor-infiltrating lymphocytes and gene expression are available, the prognostic and predictive value of RNA sequencing–based immune signatures is superior.

## Methods

### Neoadjuvant Trials

The CALGB 40601 trial study design, pCR, event-free survival (EFS), overall survival, and genomic correlative studies have been previously published.[2,22] In this predictive and prognostic study, a total of 305 women with stage II to III ERBB2/HER2-positive breast cancer were randomly assigned to receive neoadjuvant weekly paclitaxel with the addition of trastuzumab, lapatinib, or both for 16 weeks. The primary end point was pCR, defined as no invasive tumor in the breast at surgery, and secondary end points included EFS. The PAMELA trial study design, pCR, and biomarker correlative studies have also been previously published.[14,26,27] In this phase 2 trial, 151 patients with stage I to IIIA ERBB2/HER2-positive breast cancer received neoadjuvant lapatinib plus trastuzumab for 18 weeks. The primary outcome was the ability of the HER2-enriched subtype to predict pCR, defined as no invasive tumor in the breast at surgery. Each trial participant signed an institutional review board–approved (National Cancer Institute Central institutional review board for the CALGB 40601 trial and Hospital Universitari Vall d'Hebron for the PAMELA trial), protocol-specific informed consent document following federal and institutional guidelines.

### Tumor Gene Expression Analyses and iGESs

Gene expression profiles from pretreatment core biopsies were obtained from 264 of 305 CALGB 40601 trial participants (86.6%) and 142 of 151 PAMELA trial participants (94.0%) (eFigure 1 in the Supplement). Whole-transcriptome analyses by messenger RNA sequencing (RNA-Seq) were performed in the University of North Carolina High-Throughput Sequencing Facility and analyzed by the university's Lineberger Comprehensive Cancer Center Bioinformatics Core. The RNA sequencing libraries were made from total RNA with the TruSeq (Illumina) messenger RNA kit in the CALGB 40601 trial and the TruSeq RNA Access kit in the PAMELA trial and were sequenced on an Illumina HiSeq 2000 using a 2 × 50-base pair configuration. The CALGB 40601 trial RNA-Seq FASTQ files are available on the dbGAP repository (phs001570.v3.p1). The PAMELA trial RNA-Seq FASTQ files are available on EGA (EGAS00001006410/EGAD00001009054). Purity-filtered reads were aligned to the human reference GRCh38/hg38 genome, using Spliced Transcripts Aligned to a Reference, version 2.4.2a.[28] Transcript (GENCODE, version 22) abundance estimates were generated by Salmon, version 0.6.0[29] in "-quant" mode, based on the Spliced Transcripts Aligned to a Reference alignments. Raw read counts for all RNA-Seq samples were normalized to a fixed upper quartile.[30] Messenger RNA sequencing-normalized gene counts were then $\log_2$ transformed, and genes were filtered for those expressed in 70% of samples. The batch effect between the gene expression



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from the CALGB 40601 and PAMELA trials was corrected by applying the distance-weighted discrimination method,[31,32] version 1.0.2[33] (SlicerSALT) and using the CALGB 40601 trial as reference. Intrinsic subtypes were obtained from RNA-Seq gene expression data as described elsewhere.[22]

Expression of 202 iGESs from 43 publications (eReferences in the Supplement) was calculated. The list of iGESs and the genes within each signature are summarized in eTable 1 in the Supplement, and the R code is provided.[34] Finally, the iGESs were classified into 22 immune classes based on their gene ontology, with CIBERSORT as reference.[35]

### TIL Evaluation

In the CALGB 40601 and PAMELA trials, slides from core biopsies were available for 230 of 264 patients (87.1%) and 138 of 142 patients (97.2%) from the RNA-Seq cohort (eFigure 1 in the Supplement), respectively. The stromal TILs from both clinical trials were scored by the CALGB 40601 trial lead study pathologist (B.S.), following the International TILs Working Group recommendations.[12] In patients with more than 1 core biopsy available, the mean of the 2 TILs assessments was calculated, and patients without TILs assessment were censored.

### Statistical Analysis

The criteria of the Reporting Recommendations for Tumour Marker Prognostic Studies (REMARK) guidelines were followed for this study.[36] Comparisons of differences in baseline clinicopathologic variables between the CALGB 40601 trial and the PAMELA trial were made with the Wilcoxon rank sum test (continuous variables) and the $\chi^2$ test (categorical variables).

For pCR and EFS modeling, the iGES scores were analyzed as continuous variables. Stromal TILs were analyzed as continuous and discrete variables with different prespecified cutoffs (ie, 20%, 40%, and 60%). Immune-related gene expression signatures and TILs were also categorized by tertiles (ie, low, medium, and high) for visualization purposes.

The association between TILs and iGESs was measured with Spearman correlation coefficients. For differential gene expression analysis, we performed a multiclass significance analysis of microarrays.[37]

The association of immune biomarkers with pCR was evaluated in the CALGB 40601 and PAMELA combined cohort by logistic regression models. *P* values were adjusted for multiple testing with a Benjamini-Hochberg method to control the false discovery rate. To compare the goodness of fit of 2 models, we used the Akaike information criterion (AIC). As accuracy metric, we calculated the area under the receiver operating characteristic curve (AUC) for pCR, using the CALGB 40601 trial as a train set and the PAMELA trial as validation. In the CALGB 40601 trial, a mean of the AUC was calculated with 10-fold cross-validation.

In the CALGB 40601 trial, EFS was defined as the time from randomization to a breast cancer relapse after surgery, second primary malignant neoplasm, or death without recurrence for women who underwent surgery. For individuals who did not undergo surgery, the event was defined as death during clinical follow-up or noncompletion of neoadjuvant therapy due to progressive disease. The median follow-up was 9.1 years (IQR, 8.10-9.84). The association of immune biomarkers with EFS was evaluated with Cox regression models. *P* values were adjusted for multiple testing with a Benjamini-Hochberg correction. To compare the goodness of fit, we used the AIC. To evaluate the accuracy, we calculated an average C index using 5-fold cross-validation. To avoid a potential guarantee time bias in the multivariable EFS models including pCR status, we performed a 30-week landmark analysis. The landmark subpopulation included only patients without events who were followed up at 30 weeks after randomization.[38,39] Finally, to compare the prognostic ability of 2 nested models, we used the likelihood ratio test (LRT).

All the analyses were based on the study clinical database frozen on June 10, 2021. All tests were 2-sided, and a .05 level of significance was used. All statistical analyses were performed with R version 3.5.2 (R Foundation for Statistical Computing) and Python version 3.6 (Python Software Foundation). Data analyses were performed from June 1, 2020, to January 1, 2022.

## Results

### Baseline Patient Characteristics and TIL Distribution

The characteristics of the 305 patients included in the study are summarized in **Table 1**. Data on race and ethnicity were collected in the CALGB 40601 trial but not the PAMELA trial; therefore, we decided not to include the information in this study. The median age of the patients was 50 years (IQR, 42-50 years), and 305 (100%) were women. Patients enrolled in the CALGB 40601 trial were significantly younger, more likely to be premenopausal, and at a more advanced clinical stage at diagnosis than those enrolled in the nonchemotherapy PAMELA trial. There were no significant differences between the trials in the hormone receptor status and intrinsic subtype distribution. In the CALGB 40601 trial, there were no statistically significant differences in the baseline clinicopathologic characteristics between the TIL cohort (n = 230) and the landmark cohort (n = 227) (eTable 2 in the Supplement).

In the CALGB 40601 trial, the median TIL count was 20% (IQR, 13.1%-45%) (eFigure 2A in the Supplement). In the PAMELA trial, the median TIL count was 30% (IQR, 20%-50%) (eFigure 2B in the Supplement); the TILs distribution was not significantly different between the studies (eFigure 2C in the Supplement). The proportion of TILs was significantly higher in hormone receptor–negative compared with hormone receptor–positive disease in the CALGB 40601 trial (median in hormone receptor–negative disease = 30 [IQR, 15-60]; median in hormone receptor–positive disease = 20 [IQR, 10-35]; *P* = .03), the PAMELA trial (median in hormone receptor–negative disease = 30 [IQR, 20-65]; median in hormone receptor–positive disease = 20 [IQR, 10-35]; *P* = .04), and the combined cohort (median in hormone receptor–negative disease = 30 [IQR, 19-60]; median in hormone receptor–positive disease = 20 [IQR, 10-36]; *P* = .001) (eFigure 3A and C in the Supplement; **Figure 1**A). There was a significant difference in the proportion of TILs by tumor intrinsic subtype, with a significantly higher proportion of TILs in nonluminal (ie,



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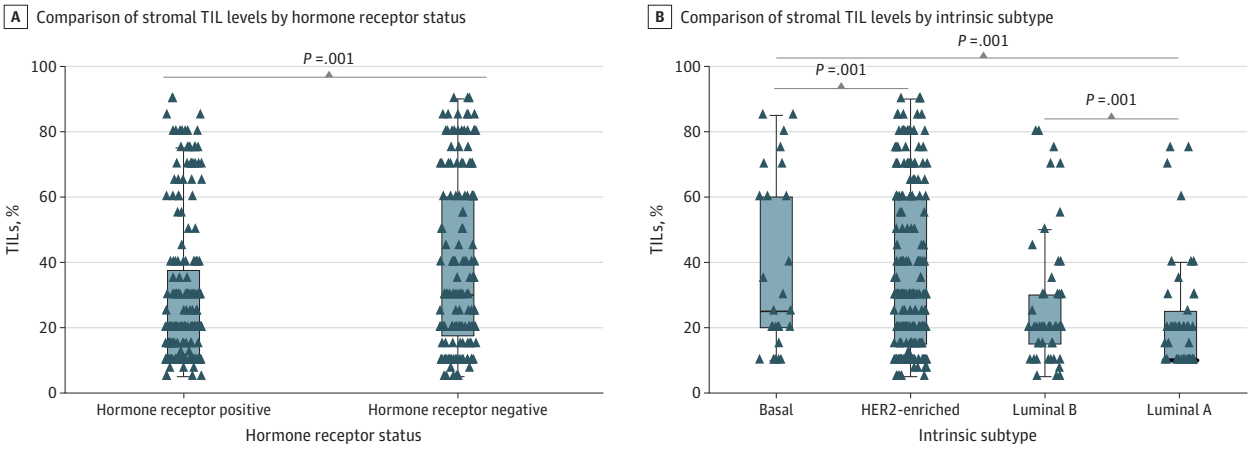
Table 1. Baseline Characteristics of Patients From the Study Population by Clinical Trial

| Characteristic | Patients, No. (%) | | | *P* value[a] |
|---|---|---|---|---|
| | CALGB 40601 trial (n = 230) | PAMELA trial (n = 138) | All (N = 368) | |
| Age, median (IQR), y | 49 (41-56) | 54 (44-64) | 50 (42-59) | |
| Menopause status | | | | |
| Postmenopausal | 89 (38.7) | 81 (58.7) | 170 (46.2) | <.001 |
| Premenopausal | 141 (61.3) | 57 (41.3) | 198 (53.8) | |
| Hormone receptor status | | | | |
| Negative | 93 (40.4) | 67 (48.6) | 160 (43.5) | .13 |
| Positive | 137 (59.6) | 71 (51.4) | 208 (56.5) | |
| Clinical stage | | | | |
| I | 0 | 45 (32.6) | 45 (12.2) | <.001 |
| II | 157 (68.3) | 86 (62.3) | 242 (65.8) | |
| III | 73 (31.7) | 8 (5.8) | 81 (22.0) | |
| Treatment | | | | |
| HL ± ET | 0 | 138 (100) | 138 (37.5) | <.001 |
| TH | 89 (38.7) | 0 | 89 (24.2) | |
| THL | 95 (41.3) | 0 | 95 (25.8) | |
| TL | 46 (20.0) | 0 | 46 (12.5) | |
| Intrinsic subtype | | | | |
| Basal-like | 19 (8.3) | 7 (5.1) | 26 (7.1) | .06 |
| HER2-enriched | 131 (57.0) | 91 (65.9) | 222 (60.3) | |
| Luminal A | 26 (11.3) | 20 (14.5) | 46 (12.5) | |
| Luminal B | 32 (13.9) | 16 (11.6) | 48 (13.0) | |
| Normal-like | 22 (9.5) | 4 (2.9) | 26 (7.1) | |

Abbreviations: CALGB, Cancer and Leukemia Group B 40601 trial; ET, endocrine therapy; HL, trastuzumab plus lapatinib; TH, weekly paclitaxel plus trastuzumab; THL, TH plus lapatinib; TL, weekly paclitaxel plus lapatinib.

[a] Statistical differences were assessed with the Wilcoxon rank sum test (for age) and the Pearson $\chi^2$ test (for the rest of the variables).

Figure 1. Comparison of Stromal Tumor-Infiltrating Lymphocyte (TIL) Levels by Hormone Receptor Status (A) and Intrinsic Subtype (B) in the Combined Cohort of the Cancer and Leukemia Group B 40601 Trial and the PAMELA Trial




Statistical differences were assessed with the Kruskal-Wallis test. The horizontal line in each box plot indicates the median of the distribution.

basal-like and HER2-enriched) compared with luminal tumors (CALGB 40601 trial: median nonluminal tumors = 25 [IQR, 15-60], median luminal tumors = 20 [IQR, 10-30], *P* = .01; PAMELA trial: median nonluminal tumors = 30 [IQR, 20-60], median luminal tumors = 20 [IQR, 10-30], *P* = .004; combined cohort: median nonluminal tumors = 30 [IQR, 15-60], median luminal tumors = 20 [IQR, 10-30], *P* < .001) (eFigure 3B and D in the Supplement; Figure 1B).

## Association Between TILs and iGESs

We found that 166 of 202 iGESs (82.2%) were significantly correlated with TILs in both studies, 179 in the CALGB 40601 trial and 174 in the PAMELA trial (eTable 3 in the Supplement). Spearman correlation coefficients are summarized in eTable 3 in the Supplement, and the coefficients from the 20 signatures that were the most correlated with TILs in both studies are represented in eFigure 4 in the Supplement. The iGESs most



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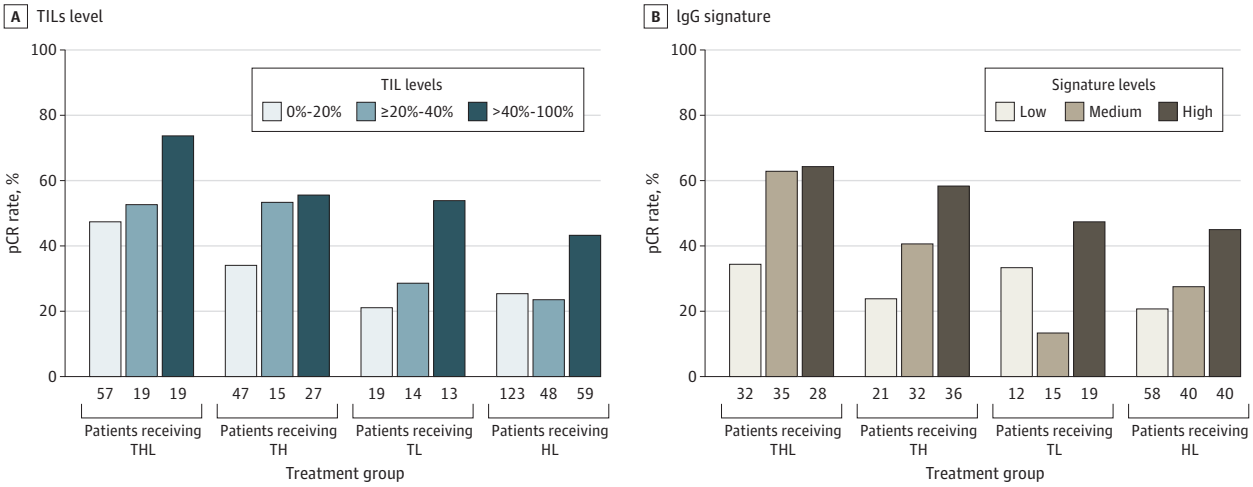
Figure 3. Rates of Pathologic Complete Response (pCR) According to Levels of Tumor-Infiltrating Lymphocytes (TILs) (A) and Immunoglobulin G (IgG) Gene Expression Signature (B)




Both variables were divided by tertiles to illustrate their association with pCR. HL indicates trastuzumab plus lapatinib; TH, weekly paclitaxel plus trastuzumab; THL, TH plus lapatinib; and TL, weekly paclitaxel plus lapatinib.

correlated with TILs were largely T-cell related. The highest Spearman correlation coefficient for TILs was 0.61 in the CALGB 40601 trial and 0.71 in the PAMELA trial. Three signatures associated with resistance to immunotherapy, inflammation, and immunosuppression were significantly negatively correlated with TILs in both studies (Spearman correlation coefficients for the CALGB 40601 and PAMELA trials: −0.29 and −0.37, −0.26 and −0.22, and −0.17 and −0.23, respectively) (eFigure 5 and eTable 3 in the Supplement).

To further study the association between TILs and iGESs, we compared the differences in immune cell infiltration, using our CIBERSORT-derived signatures to perform a multiclass significance analysis of microarrays by TIL levels (ie, low, medium, and high) and by IgG signature levels (ie, low, medium, and high) in the CALGB 40601 and PAMELA trials. The standardized mean differences between the iGESs in 1 class vs the overall mean expression are represented in **Figure 2**A (the CALGB 40601 trial) and Figure 2B (the PAMELA trial). Tumors with high TIL and IgG levels were significantly enriched for T cells compared with those with low TIL and IgG levels. However, although tumors with high IgG levels were enriched for B-cell and plasma cell signatures compared with those with low levels, in both studies, samples with high and low TIL levels showed a high expression of B-cell and plasma cell signatures. This analysis suggests that TILs do not recapitulate B-cell and plasma cell immune infiltration, and the 2 biomarkers should not be considered the same.

## Association of TILs and iGESs With pCR in the CALGB 40601 and PAMELA Trials

In the combined cohort, the percentage of TILs as a continuous variable was significantly associated with pCR, with an odds ratio of 1.01 (95% CI, 1.01-1.02; $P$ = .02) for each 1% increase in TILs. This association was observed regardless of the clinical trial and treatment group (**Figure 3**A). High vs low levels of TILs using a cutoff of 20% and 40% were also significantly associated with pCR (20%: odds ratio, 1.86; 95% CI, 1.20-2.91; $P$ = .04; 40%: odds ratio, 2.29; 95% CI, 1.40-3.77; $P$ = .02). The model including TILs with a cutoff of 40% rather than TILs as a continuous variable better predicted pCR (AIC, 471.68 for TILs with a cutoff of 40% vs 472.23 for TILs as a continuous variable; AUC, 0.59 for TILs with a cutoff of 40% in the PAMELA trial vs 0.57 for TILs as a continuous variable).

Thirty-six of 202 iGESs (17.8%) were also significantly associated with pCR independently of the treatment group and study (eTable 4 in the Supplement; Figure 3B; eFigure 6 in the Supplement). The biomarker models from 13 of these signatures better predicted the response end point than the best TILs model for pCR prediction, showing lower AIC values (AIC, 450.06-471.30 for iGESs vs 471.68 for TILs with a cutoff of 40%) (eTable 4 in the Supplement). When the accuracy metrics were examined, 7 iGESs outperformed TILs for pCR, showing higher AUC values in the train (CALGB 40601 trial) and the validation set (PAMELA trial) (eTable 5 in the Supplement). Moreover, in multivariable models adjusted by multiple clinical parameters (study, treatment group, stage, age, hormone receptor status, menopausal status, and subtype), these signatures but not TILs were significantly associated with pCR (eTable 5 in the Supplement). Most of these signatures were associated with B cells, plasma cells, and immunoglobulins (eFigure 7 in the Supplement).

## Association of TILs and iGESs With EFS in the CALGB 40601 Trial

In the CALGB 40601 trial, 37 iGESs, but not TILs, were significantly associated with EFS in Cox regression models adjusted by treatment group (eTable 6 in the Supplement). As with pCR, the top-performing immune signatures were also associated with B cells.



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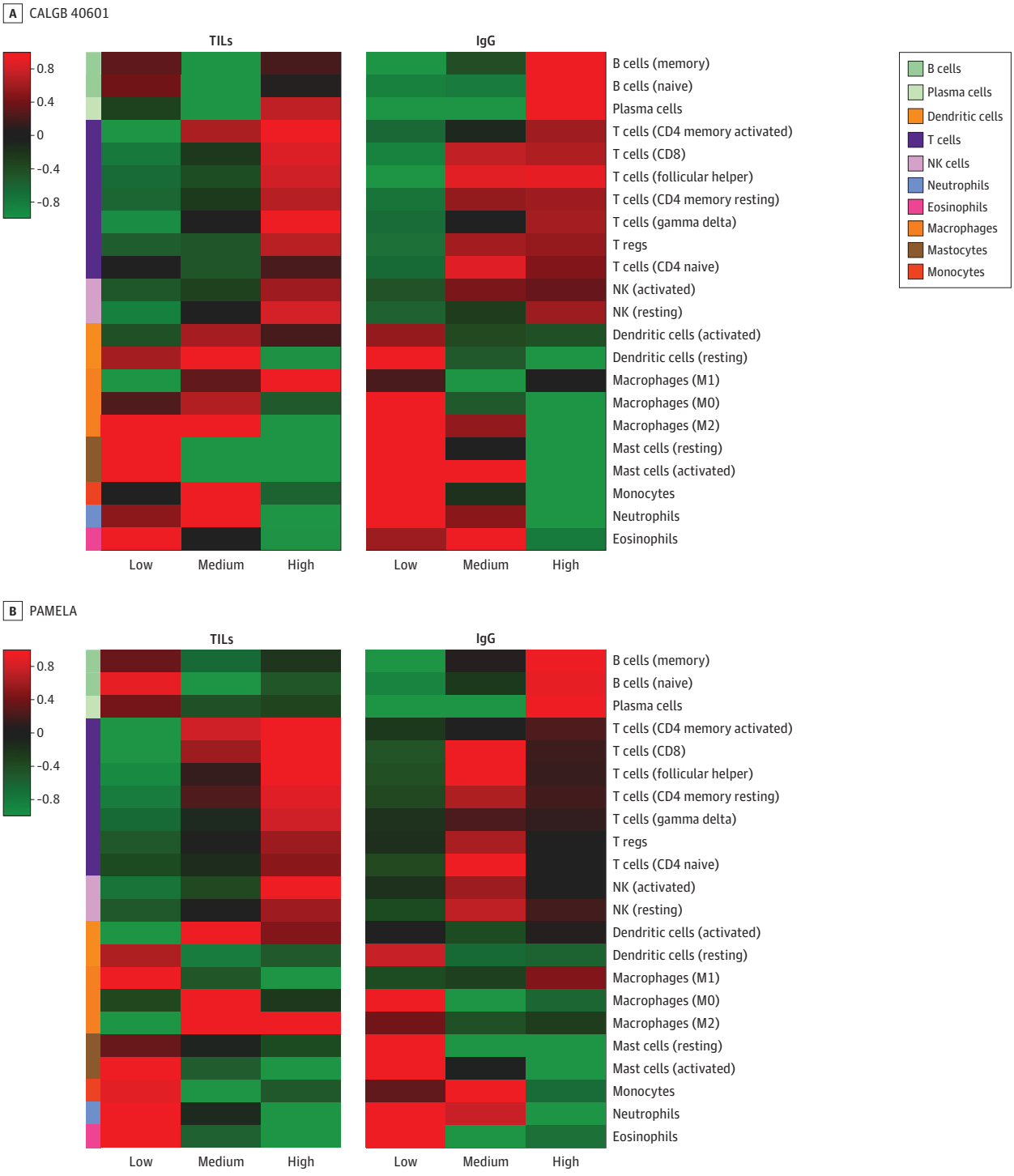
Figure 2. Heatmap Representing the Different Distributions of the CIBERSORT-Derived Gene Expression Signatures by Tumor-Infiltrating Lymphocyte (TIL) and Immunoglobulin G (IgG) Levels




Cancer and Leukemia Group B 40601 (CALGB 40601) and PAMELA trial samples were classified into 3 different groups by study, depending on the TIL and IgG levels by tertiles (ie, low, medium, and high TILs; and low, medium, and high IgG). Then, a multiclass significance analysis of microarrays was performed. The standardized mean differences between the immune signatures in 1 class vs the overall mean expression for each study are represented in 4 heatmaps. NK indicates natural killer; T regs, T regulatory cells.



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Finally, we wanted to test whether the combination of iGESs and TILs was more prognostic than each alone by comparing multiple multivariable Cox regression models. To test this, we selected 6 immune signatures that outperformed TILs for pCR and were also prognostic in the CALGB 40601 trial: 3 IgG signatures, 2 B-cell signatures, and 1 plasma cell signature. The results for 1 of the IgG signatures are shown in **Table 2**. We first built a base model that included known prognostic variables: pCR status, treatment group (weekly paclitaxel plus trastuzumab plus lapatinib, weekly paclitaxel plus lapatinib, or weekly paclitaxel plus trastuzumab, where the latter is the reference group), hormone receptor status, clinical stage, and PAM50 intrinsic tumor subtype (HER2-enriched vs other subtypes) (model 1). In this model, treatment group, clinical stage, pCR status, and intrinsic subtype were significantly associated with EFS. Adding TILs (model 2) did not provide additional prognostic information (LRT $P = .12$). We then built a model adding our previously published IgG signature to model 1; in this model (model 3), treatment group, clinical stage, pCR status, intrinsic subtype, and the IgG signature were all significantly associated with EFS (IgG-adjusted hazard ratio, 0.63; 95% CI, 0.45-0.87; $P = .006$). Also, model 3 was significantly better than model 1 for EFS (LRT $P = .005$). The last model (model 4) included both TILs and the IgG signature. In this model, the IgG signature, but not TILs, was significantly associated with EFS (IgG-adjusted hazard ratio, 0.63; 95% CI, 0.42-0.93; $P = .02$; TIL-adjusted hazard ratio, 1.00; 95% CI, 0.98-1.02; $P = .99$) (Table 2). Model 4, including both TILs and the IgG signature, was significantly better than the model including only TILs (model 4 vs model 2; LRT $P = .02$), but it was not significantly better than model 3, which included only the IgG signature (model 4 vs model 3; LRT $P = .99$). Similar results were observed with the other 5 iGESs (eTable 7 in the Supplement) when TILs was used as a discrete variable with a cutoff of 40% (eTable 8 in the Supplement) and when a landmark analysis was performed (eTable 9 in the Supplement). When different multivariate models including clinical parameters and 1 iGES were compared, the immunoglobulin-The Cancer Genome Atlas signature model performed slightly better than the rest (eTable 10 and eTable 11 in the Supplement).

## Discussion

In the CALGB 40601 and PAMELA trials, both the proportion of TILs and the multiple iGESs were significantly associated with pCR. Moreover, in the CALGB 40601 trial, several immune signatures were also associated with EFS in univariable and multivariable Cox analyses that included clinical factors and intrinsic subtype, whereas TILs were not significantly associated with outcome. B-cell signatures outperformed TILs and T-cell signatures for pCR and EFS.[40] Combining TILs and iGESs did not provide additional prognostic information. These results are especially relevant in early-stage ERBB2/HER2-positive breast cancer, in which multiple trials focus on developing prognostic tools combining tumor and immune cell biomarkers to guide treatment escalation and de-escalation.[25,41-43]

The proportion of TILs as a continuous variable has proven to be an independent prognostic biomarker in early-stage ERBB2/HER2-positive breast cancer.[13-18] Thus, the evaluation of TILs has been proposed as a readily available tool to identify different prognostic groups in this setting. Despite the standardization of TIL scoring by the International TILs Working Group, this biomarker still has low reproducibility rates across pathologists, with κ values in the 0.4 to 0.6 range[44,45] even after efforts to define the optimal TIL cutoff.[46] However, these are ongoing harmonization efforts, and TILs have value, particularly in resource-constrained settings.

Not surprisingly, quantitative gene expression of immune-related genes and signatures is strongly associated with the infiltration of TILs.[47,48] Immune genes and signatures have also proven to have prognostic and predictive value in patients with early-stage ERBB2/HER2-positive breast cancer, and the IgG signature is included in the HER2DX genomic test.[21-23,25] To our knowledge, this is the first study demonstrating that when both TILs and immune gene expression data are available, iGESs, particularly B-cell signatures, provide more prognostic information in ERBB2/HER2-positive breast cancer without the additional value of adding TILs. Similar results suggest the potential superiority of iGESs over TILs in triple-negative breast cancer treated with chemotherapy alone in the CALGB 40603 trial,[48] in which B-cell features, including IgG expression, were found to be the most prognostically valuable metric.

### Limitations

Our study has limitations. First, a substantial proportion of patients included in the CALGB 40601 and PAMELA trials received trastuzumab combined with lapatinib, a dual treatment used in the metastatic setting but not approved for early-stage ERBB2/HER2-positive breast cancer. Moreover, the PAMELA trial differed from the CALGB 40601 trial in that patients received only anti-ERBB2/HER2 therapy before surgery, without chemotherapy. Second, although EFS was a key secondary end point of the CALGB 40601 trial, the trial was not powered for long-term outcomes, so EFS prediction modeling should be interpreted with caution. Third, even when scored as a continuous variable, the proportion of TILs (ie, 0% to 100%) follows a semiquantitative pattern, with increments of 5% to 10%, and thus is not a true continuous variable like iGESs. However, when TILs were divided into high vs low levels based on multiple prespecified cutoffs, their ability to predict response and survival was lower than that of multiple B-cell–related signatures. Finally, we performed numerous statistical predictions simultaneously by building 1 model for each immune biomarker to predict pCR and EFS. To control type I error, we adjusted the models' $P$ values for multiple testing.

## Conclusions

To conclude, accumulating evidence supports the validity of using evidence of immune activation, which can be measured with TILs or immune-related gene expression



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Table 2. Association of TILs and Immune-Related Gene Expression Signatures With EFS in the Cancer and Leukemia Group B 40601 Trial

| Model, formula, and features | HR (95% CI) | *P* value | AIC | LRT *P* value[a] |
|---|---|---|---|---|
| Model 1: EFS ≈ treatment + HR + stage + pCRB + subtype | | | | |
| THL vs TH | 0.34 (0.14-0.78) | .01 | 395.68 | 1 [Reference] |
| TL vs TH | 1.27 (0.62-2.60) | .51 | | |
| HR (pos vs neg) | 1.86 (0.94-3.69) | .08 | | |
| Stage (III vs II) | 2.03 (1.07-3.87) | .03 | | |
| pCR (pCR vs RD) | 0.22 (0.10-0.48) | <.001 | | |
| HER2-enriched vs other | 4.20 (1.97-8.96) | <.001 | | |
| Model 2: EFS ≈ treatment + HR + stage + pCRB + subtype + TILs | | | | |
| THL vs TH | 0.31 (0.13-0.73) | .007 | 395.31 | Model 2 vs model 1 LRT: *P* = .12 |
| TL vs TH | 1.30 (0.63-2.67) | .48 | | |
| HR (pos vs neg) | 1.85 (0.93-3.69) | .08 | | |
| Stage (III vs II) | 1.95 (1.02-3.71) | .04 | | |
| pCR (pCR vs RD) | 0.24 (0.11-0.54) | <.001 | | |
| HER2-enriched vs not | 4.53 (2.11-9.73) | <.001 | | |
| TILs (continuous) | 0.99 (0.97-1.00) | .14 | | |
| Model 3: EFS ≈ treatment + HR + stage + pCRB + subtype + signature | | | | |
| THL vs TH | 0.31 (0.13-0.71) | .006 | 389.96 | Model 3 vs model 1 LRT: *P* = .005 |
| TL vs TH | 1.45 (0.70-3.02) | .32 | | |
| HR (pos vs neg) | 1.43 (0.71-2.90) | .32 | | |
| Stage (III vs II) | 2.01 (1.06-3.83) | .03 | | |
| pCR (pCR vs RD) | 0.30 (0.13-0.66) | .003 | | |
| HER2-enriched vs not | 4.28 (2.02-9.08) | <.001 | | |
| Signature (continuous) | 0.63 (0.45-0.87) | .006 | | |
| Model 4: EFS ≈ treatment + HR + stage + pCRB + subtype + signature + TILs | | | | |
| THL vs TH | 0.31 (0.13-0.72) | .006 | 391.96 | Model 4 vs model 2 LRT: *P* = .02 |
| TL vs TH | 1.45 (0.69-3.02) | .32 | | |
| HR (pos vs neg) | 1.43 (0.70-2.92) | .32 | | |
| Stage (III vs II) | 2.01 (1.05-3.84) | .03 | | |
| pCR (pCR vs RD) | 0.30 (0.13-0.66) | .003 | | Model 4 vs model 3 LRT: *P* = .99 |
| HER2-enriched vs not | 4.28 (2.01-9.12) | <.001 | | |
| TILs (continuous) | 1.00 (0.98-1.02) | .99 | | |
| Signature (continuous) | 0.63 (0.42-0.93) | .02 | | |

Abbreviations: AIC, Akaike information criterion; EFS, event-free survival; HR, hormone receptor; LRT, likelihood ratio test; neg, negative; pCR, pathologic complete response; pCRB, in-breast pCR; pos, positive; RD, residual disease; TH, weekly paclitaxel plus trastuzumab; THL, TH plus lapatinib; TIL, tumor infiltrating lymphocyte; TL, weekly paclitaxel plus lapatinib.

[a] This was a comparative analysis of nested multivariable Cox regression models using an LRT. The signature identification from the IgG signature is IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954.

biomarkers, to stratify patients with early-stage ERBB2/HER2-positive breast cancer into different prognostic groups. This study supports that measurement of immune activation, either by TIL measurement or by immune-related gene expression profiling, is predictive of treatment response and that immune-related gene expression is prognostic. In the presence of both immune biomarker types, iGESs, especially B-cell–related signatures, outperform TILs for both pCR and prognosis, and the combination of both biomarkers does not yield improved prognostic value. These results highlight the essential role of B cells in antitumor immunity and suggest that B-cell immune-related gene expression provides valuable prognostic information for treatment escalation and de-escalation in patients with early-stage ERBB2/HER2-positive breast cancer.

## ARTICLE INFORMATION

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Dr Fernandez-Martinez reported receiving grants from National Cancer Institute during the conduct of the study. Dr Pascual reported receiving consulting fees from Novartis, speakers' bureau fees from AstraZeneca outside the submitted work, and personal fees from Pfizer. Dr Nuciforo reported receiving grants from GSK to the institution to act as the central academic laboratory during the conduct of the study; and personal fees from Novartis, Bayer, MSD Oncology, and Targos Molecular Pathology outside the submitted work. Dr Ballman reported receiving grants from National Cancer Institute's National Clinical Trials Network for the Alliance during the conduct of the study and expert witness fees from Johnson & Johnson, Sanofi, Mylan Pharmaceuticals, and Janssen outside the submitted work. Dr Pare reported receiving a patent for an in vitro method for the prognosis of patients with ERBB2/HER2-positive breast cancer. Dr Brasó-Maristany reported receiving a pending patent for an HER2DX assay (EP21383165). Dr Krop reported receiving personal fees from Genentech-Roche; grants from Genentech-Roche, Pfizer, and MacroGenics to his institution; and personal fees from Bristol Meyers Squibb, Daiichi-Sankyo, AstraZeneca, Novartis, Merck, and Seagen outside the submitted work. Dr Cortés reported receiving personal fees and grants from Roche to his institution during the conduct of the study; consulting and honoraria fees from Roche, Celgene, Daiichi Sankyo, Lilly, and Merck Sharp & Dohme; consulting fees from Cellestia, AstraZeneca, Seattle Genetics, Erytech, Athenex, Polyphor, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, HiberCell, BioInvent, GEMoaB, Gilead, Menarini, Reveal Genomics, and Zymeworks; grants from Ariad Pharmaceuticals, AstraZeneca, Baxalta GmbH-Servier Affaires, Bayer Healthcare, Eisai, F. Hoffman-La Roche, Guardanth Health, Merck Sharp & Dohme, Pfizer, PIQUR Therapeutics, Puma C, and Queen Mary University of London to his institution; accommodation and expenses fees from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, and Gilead; honoraria from Novartis and Samsung Bioepis outside the submitted work; and receiving a patent for pharmaceutical combinations of a Pi3k inhibitor and a microtubule destabilizing agent (WO 2014/199294 A) and a patent for ERBB2/HER2 as a predictor of response to dual ERBB2/HER2 blockade in the absence of cytotoxic therapy (US 2019/0338368 A1). Dr Llombart-Cussac reported being a stockholder of Medsir; receiving grants from Genentech-Roche, Daiichi-Sanyo, Pfizer, and Novartis outside the submitted work; and receiving personal fees from Seagen. Dr Prat reported receiving personal fees from Reveal Genomics during the conduct of the study; personal fees from Oncolytics Biotech, Roche, Novartis, AstraZeneca, and Daiichi-Sankyo outside the submitted work; and receiving a patent for HER2DX licensed to Reveal Genomics. Dr Perou reported receiving grants from National Cancer Institute Breast SPORE program P50-CA58223 during the conduct of the study; being an equity stockholder in and receiving royalties from Bioclassifier LLC outside the submitted work; receiving a patent (US patent No. 12,995,459) with royalties paid from Bioclassifier; and being an equity owner in and consultant for Reveal Genomics. No other disclosures were reported.

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# Supplementary Online Content

Fernandez-Martinez A, Pascual T, Singh B, et al. Prognostic and predictive value of immune-related gene expression signatures vs tumor-infiltrating lymphocytes in early-stage ERBB2/HER2-positive breast cancer: a correlative analysis of the CALGB 40601 and PAMELA trials. *JAMA Oncol*. Published online January 5, 2023. doi:10.1001/jamaoncol.2022.6288



This supplementary material has been provided by the authors to give readers additional information about their work.

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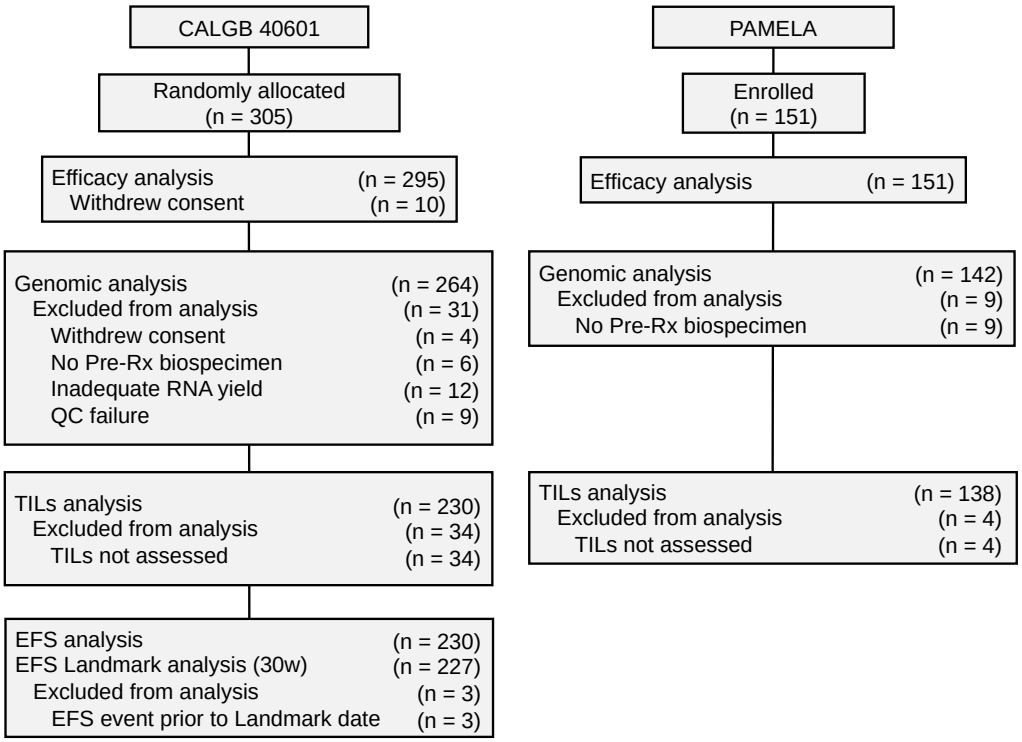
**eFigure 1. CONSORT Diagram**

TILs: Tumor-Infiltrating Lymphocytes; Rx: treatment; QC: quality control; w: weeks.

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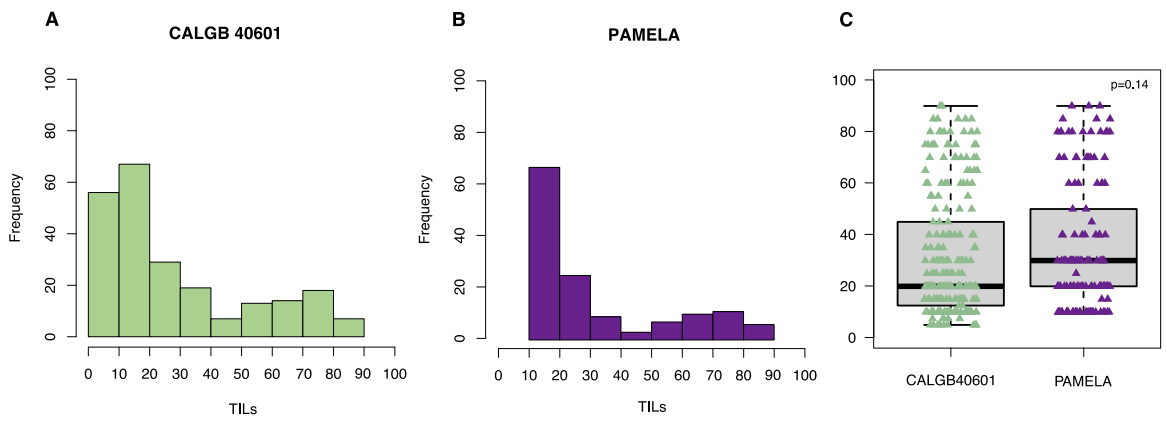
## eFigure 2. Distribution of Tumor-Infiltrating Lymphocytes Infiltration by Clinical Trial




A) Histogram of Tumor-Infiltrating Lymphocytes infiltration levels in CALGB 40601. B) Histogram of Tumor-Infiltrating Lymphocytes infiltration levels in PAMELA. C) Comparison of Tumor-Infiltrating Lymphocytes infiltration levels between both clinical trials. Statistical differences were assessed using an Kruskal Wallis test (P-value at the top of the figure). The horizontal line from the boxplots represents the median of the distribution. TILs: Tumor-Infiltrating Lymphocytes.

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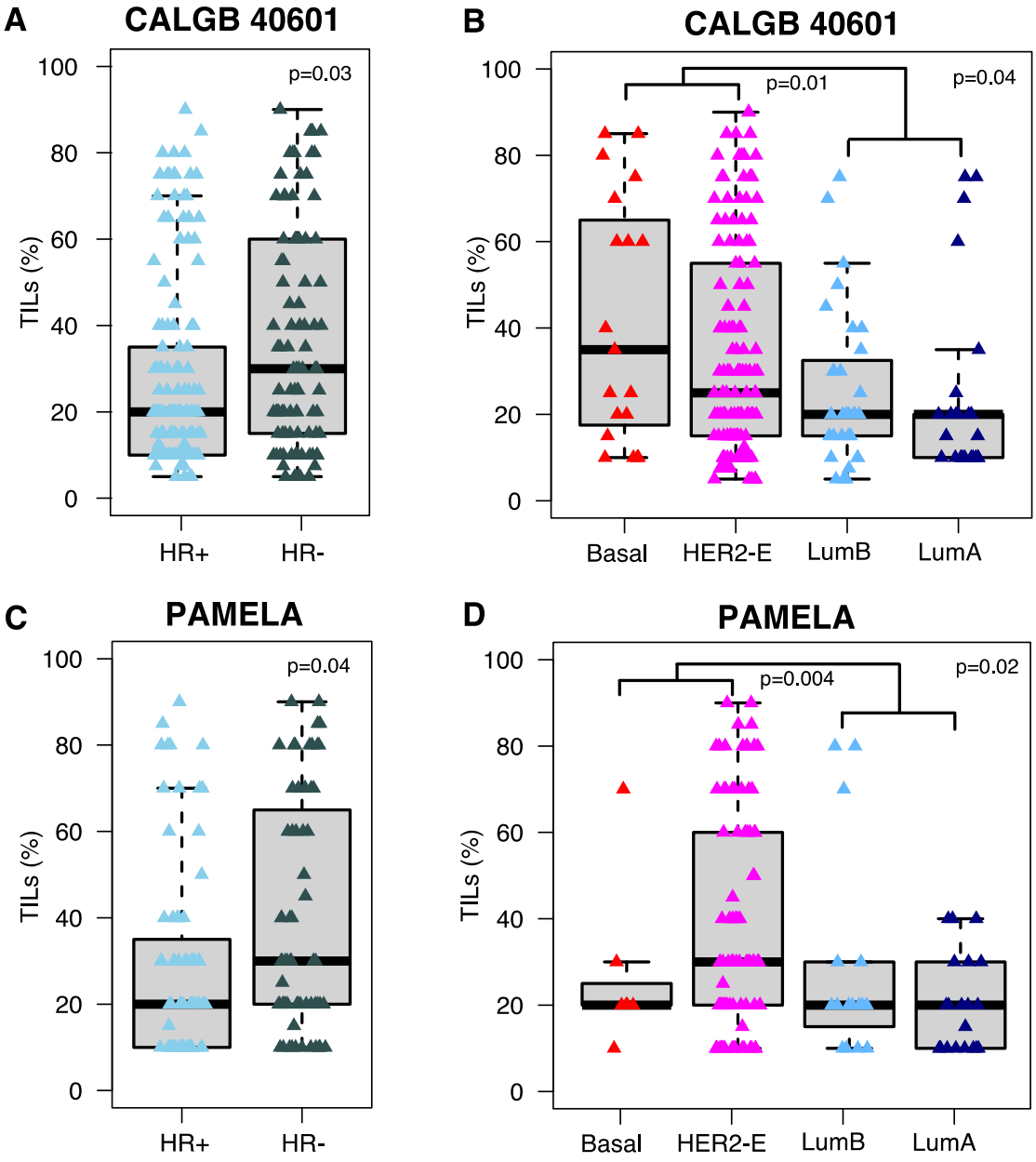
**eFigure 3. Comparison of Stromal Tumor-Infiltrating Lymphocytes (TILs) Levels by Hormone Receptor Status and Intrinsic Subtype in CALGB 40601 and PAMELA**




Comparison of stromal Tumor-Infiltrating Lymphocytes (TILs) levels by hormone receptor status and intrinsic subtype in CALGB 40601 (A, B) and PAMELA (C, D) trials. Statistical differences were assessed using an Kruskal Wallis test (P-value at the top of the figure). The horizontal line from the boxplots represents the median of the distribution.
TILs: Tumor-Infiltrating Lymphocytes; HR+: hormone receptor positive; HR-: hormone receptor negative; Basal: basal-like; HER2-E: HER2-Enriched; LumB: luminal B; LumA: luminal A.

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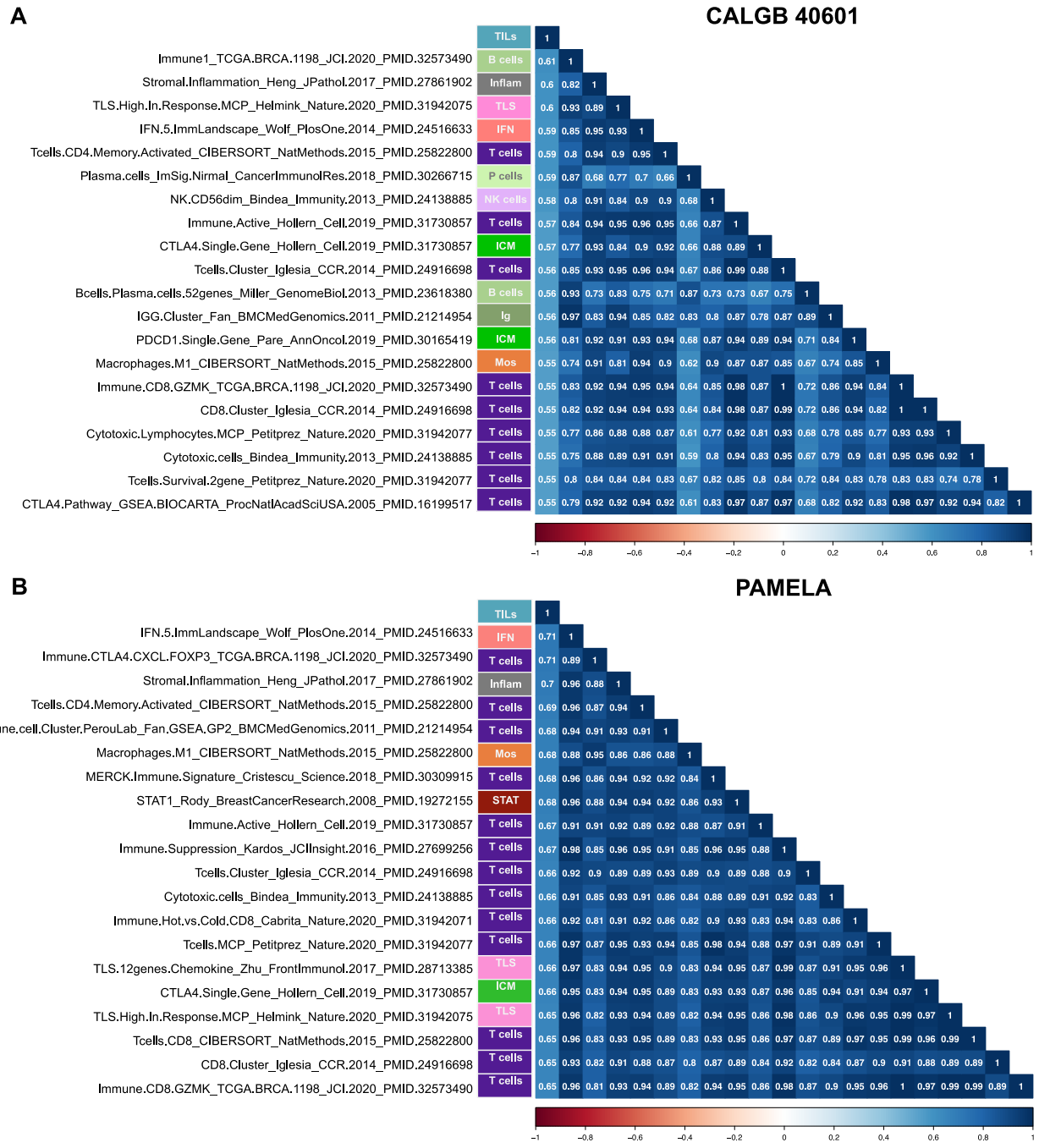
## eFigure 4. Correlation Between Tumor-Infiltrating Lymphocytes (TILs) Levels and Immune Gene Expression Signatures (iGES)




Spearman's Correlations between Tumor-Infiltrating Lymphocytes (TILs) levels and immune gene expression signatures. The 20 signatures with a p-value of 0.05 and the highest correlation coefficients are shown for A) CALGB 40601 and B) PAMELA.
TILs: Tumor-Infiltrating Lymphocytes; Inflam: inflammation; TLS: tertiary lymphoid structures; IFN: interferon; P: plasma; ICM: immune checkpoint molecules; Mos: macrophages; NK: natural killer; Ig: immunoglobulin; STAT: signal transducer and activator of transcription.

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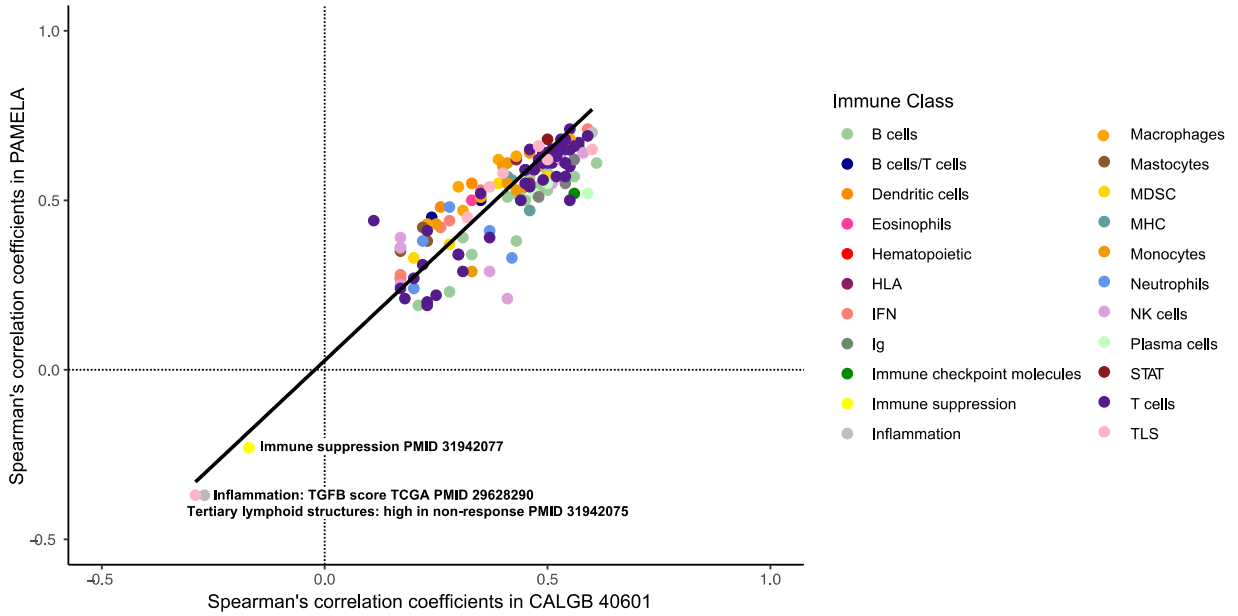
**eFigure 5. Association Between the Spearman Correlation Coefficients of Tumor-Infiltrating Lymphocytes (TILs) and Immune Gene Expression Signatures (iGES) in CALGB 40601 and PAMELA.**




Only the signatures significantly correlated with TILs in both studies (166/202, 81.2%) are represented (adjusted p-value < 0.05).
HLA: human leukocyte antigens; IFN: interferon; Ig: Immunoglobulin; MDSC: myeloid-derived-suppressor cells; MHC: major histocompatibility complex; NK: natural killer; STAT: signal transducer and activator of transcription; TLS: tertiary lymphoid structures.

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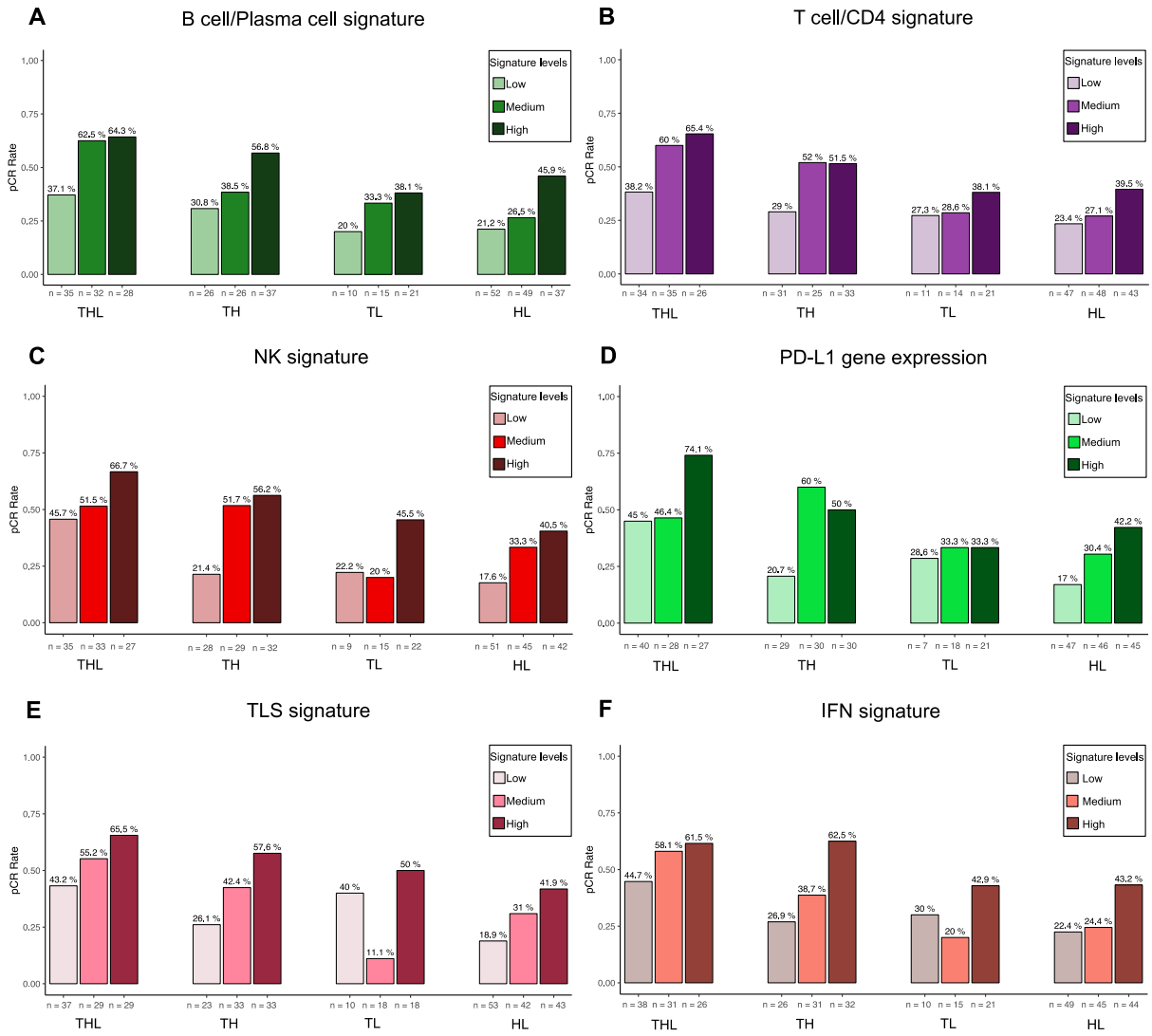
## eFigure 6. Rates of Pathologic Complete Response (pCR) According to Immune Gene Expression Signature (iGES) Levels




iGES have been divided by tertiles to illustrate their association with pCR rates.
pCR: pathologic complete response; T: weekly paclitaxel; H: trastuzumab; L: lapatinib; NK: natural killer; PD-L1: programmed death-1 ligand 1; TLS: tertiary lymphoid structures; IFN: interferon.

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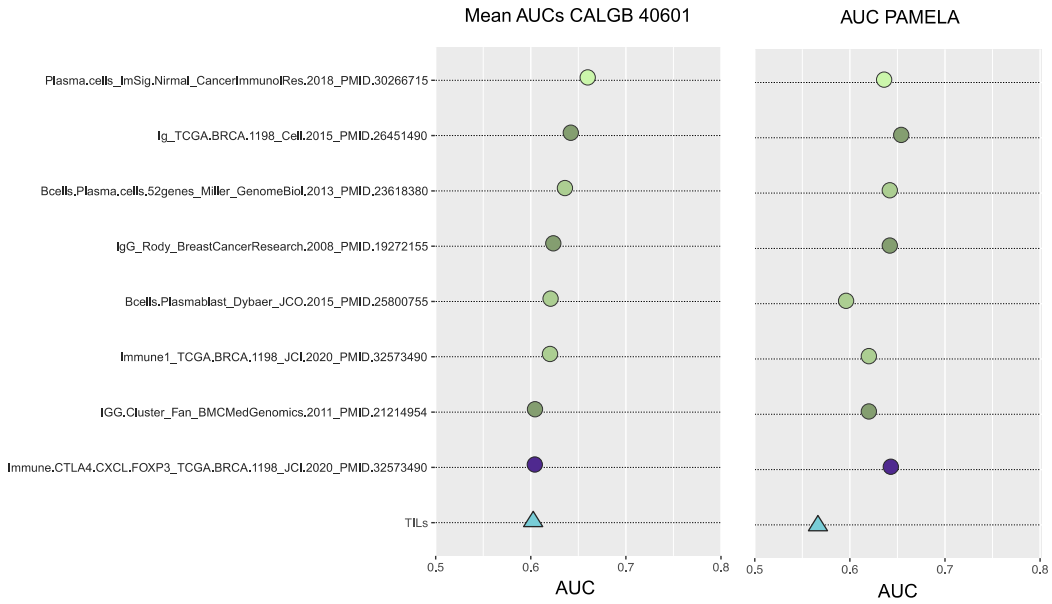
## eFigure 7. Accuracy Metrics of the Univariable Immune Biomarker Models for Pathologic Complete Response (pCR) Prediction




Using CALGB 40601 as training set, the average AUC of the different models was calculated across all the resamples using 10-fold cross validation. A second AUC for the different biomarkers was calculated using PAMELA as an external validation set. The gene expression signatures are represented as circles compared to TILs as continuous variable, that is represented as a triangle. The circle colors represent the immune signature class as shown in eTable 1.
TILs: Tumor-Infiltrating Lymphocytes; AUC: Area under the receiver operating characteristic curve.

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**eTable 1. List of Immune Gene Expression Signatures, Signature Class, PMID, and Genes Within a Signature**

| Signature ID paper | Immune class | Signature class | PMID | Genes |
|---|---|---|---|---|
| **Bcells.Cluster Iglesia CCR.2014 PMID.24916698** | **B cells** | Signature | PMID.24916698 | 3512; 9834; 608; 83416; 5450; 973; 96610; 8755; 389643; 150365; 974; 5079; 2208; 79368; 643; 930; 84824; 640; 115350; 931; 1269; 55024; 23495 |
| **Bcells.IL10.Minus Lin JImmunol.2014 PMID.25080484** | **B cells** | Signature | PMID.25080484 | 6504; 3586; 3569; 4049; 374; 50832; 1259; 5167; 2745; 54512; 92935; 6723; 760; 6507; 55176; 1960; 3280; 3662; 9021; 10406; 79005; 10794; 6503; 51559; 11147; 55784; 92002 |
| **Bcells.IL10.Plus Lin JImmunol.2014 PMID.25080484** | **B cells** | Signature | PMID.25080484 | 225; 481; 822; 901; 946; 1491; 1545; 1831; 2149; 2170; 2213; 2316; 2838; 3087; 3512; 3552; 3587; 3597; 3663; 3687; 3695; 3782; 3937; 3956; 4000; 4046; 4063; 4233; 4938; 4940; 5027; 5996; 6346; 6505; 6843; 9235; 9447; 9760; 10150; 10225; 10550; 10628; 10752; 10800; 11343; 22797; 23208; 25842; 26207; 26230; 28984; 51284; 51676; 55785; 55809; 55824; 57379; 79026; 81553; 84561; 118429; 128553; 130367; 143686; 151963; 162394; 166824; 167838; 201799; 219285; 219855; 257144; 285386; 374618; 388325; 402415 |
| **Bcells.Centroblast Dybaer JCO.2015 PMID.25800755** | **B cells** | Signature | PMID.25800755 | 10810; 7482; 148229; 651; 23710; 4086; 54443; 259266; 55635; 7153; 100126791; 283431; 9928; 10112; 80119; 1062; 25959; 8739; 4297; 157740; 101928620; 81930; 79071; 5450; 23089; 1063; 9787; 27109; 4751; 9582; 10733; 4798; 5577; 124989; 983; 100506844; 23766 |

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|---|---|---|---|---|
| **Bcells.Centrocyte Dybaer JCO.2015 PMID.25800755** | **B cells** | Signature | PMID.25800755 | 55448; 8622; 101929450; 639; 54820; 116931; 94121; 327657; 64805; 597; 6662; 88; 3117; 55971; 4023; 9638; 92737; 1960; 25953; 3119; 84102; 285313; 63971; 10170; 55785; 816; 285237; 5795; 1289; 53354; 23334; 54072; 55293; 147945; 3690; 100506930; 27197; 148808; 114614; 9782; 2956; 9133; 100509457; 406947; 724102 |
| **Bcells.Memory Dybaer JCO.2015 PMID.25800755** | **B cells** | Signature | PMID.25800755 | 6352; 170371; 946; 1230; 100506071; 3684; 27197; 374618; 1285; 1690; 440823; 27163; 2857; 2212; 79026; 195; 83417; 339005; 10382; 285972; 8082; 3310; 440253 |
| **Bcells.Naive Dybaer JCO.2015 PMID.25800755** | **B cells** | Signature | PMID.25800755 | 55211; 10252; 4345; 351; 8496; 5243; 167410; 140733; 643733; 100128252; 8531; 8115; 342926; 909; 5796; 9976; 646113; 4606; 1901; 6328; 2650; 401312; 646588; 63934; 2208 |
| **Bcells.Memory CIBERSORT NatMethods.2015 PMID.25822800** | **B cells** | Signature | PMID.25822800 | 10863; 60468; 55024; 640; 4064; 930; 911; 933; 951; 969; 971; 973; 974; 1380; 643; 9214; 2213; 79368; 2444; 2841; 91316; 3087; 3112; 3495; 3507; 3514; 91353; 3394; 80183; 4050; 9450; 931; 4829; 5026; 5368; 5790; 55103; 10235; 150094; 6557; 6689; 26228; 29802; 9447; 240; 1235; 939; 9629; 160518; 9750; 2788; 3446; 3574; 4153; 440348; 27240; 11262; 80008; 23495; 608; 9618; 27033 |
| **Bcells.Naive CIBERSORT NatMethods.2015 PMID.25822800** | **B cells** | Signature | PMID.25822800 | 5244; 10863; 60468; 55024; 605; 79656; 640; 673; 4064; 930; 911; 933; 951; 969; 971; 973; 974; 1380; 643; 55840; 9214; 2208; 2213; 79368; 2444; 2841; 91316; 3087; 3112; 3495; 3507; 3514; 91353; 3566; 3394; 80183; 283876; 4050; 9450; 4224; 57553; 931; 55335; 4829; |

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|---|---|---|---|---|
| | | | | 5026; 9934; 5368; 5670; 5790; 55103; 10235; 6402; 150094; 6557; 6689; 26228; 8115; 54576; 29802; 57335 |
| **Bcells Garber CellMolGastroenterol Hepatol.2017 PMID.28508029** | **B cells** | Signature | PMID.28508029 | 10863; 240; 60468; 55024; 53335; 53335; 53335; 53335; 640; 643; 930; 933; 951; 951; 958; 971; 973; 2208; 2788; 3087; 3112; 3117; 114884; 5368; 25780; 6689; 8115; 29802; 9934; 55103; 55103; 55103; 6039; 6328; 608 |
| **Bcells.Extended Garber CellMolGastroenterol Hepatol.2017 PMID.28508029** | **B cells** | Signature | PMID.28508029 | 3899; 65069; 10409; 695; 66033; 201895; 934; 100133941; 972; 972; 973; 26047; 51523; 378885; 9214; 84824; 23062; 3119; 3126; 23231; 4067; 4082; 55846; 256236; 5336; 5777; 10509; 51092; 6643 |
| **Bcells Bindea Immunity.2013 PMID.24138885** | **B cells** | Signature | PMID.24138885 | 608; 640; 930; 931; 971; 1380; 1690; 1838; 2731; 2788; 3112; 3117; 3493; 3500; 3507; 3514; 3535; 4208; 5244; 5368; 6328; 6565; 6689; 8115; 9834; 10803; 29064; 29760; 53335; 55278; 57553; 60468; 79368; 114884 |
| **Bcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184** | **B cells** | Signature | PMID.23382184 | 19; 330; 489; 605; 640; 643; 695; 930; 931; 933; 951; 958; 971; 972; 973; 974; 1185; 1235; 1380; 1387; 1456; 1657; 1960; 2181; 2185; 2208; 2841; 2872; 2889; 3280; 3399; 3592; 3662; 3708; 3915; 4033; 4064; 4208; 4209; 4214; 4641; 5079; 5106; 5142; 5287; 5290; 5336; 5451; 5452; 5530; 5579; 5777; 5925; 5966; 5993; 6480; 6565; 6598; 6643; 6689; 6721; 6850; 6925; 6929; 6949; 7187; 7430; 7799; 7942; 8202; 8527; 8564; 8930; 8942; 9015; 9026; 9135; 9308; 9450; 9451; 9467; 9640; 9657; 9665; 9681; 9711; 9734; 9779; 9788; 9873; 9896; 9922; 10193; 10447; 10564; 11108; 11142; 22837; 22876; 22898; |

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| | | | | 22906; 23035; 23062; 23075; 23216; 23325; 23411; 23495; 23515; 23596; 24149; 25780; 26040; 26051; 26228; 27314; 27334; 29116; 29760; 29802; 50618; 51284; 51363; 51585; 53335; 54468; 54920; 55016; 55024; 55114; 55149; 55278; 55500; 55565; 55589; 55702; 55788; 57102; 57157; 57396; 58513; 59339; 59342; 60468; 60485; 64376; 64783; 64853; 65117; 65986; 79161; 79365; 79591; 79600; 79622; 79651; 79874; 80021; 80183; 80221; 80237; 83478; 84159; 160518; 200576; 201895; 221037; 221749; 283232; 5450; 9712; 101928620; 100507213 |
| **Bcells.Activated Charoentong CellRep.2017 PMID.28052254** | **B cells** | Signature | PMID.28052254 | 79368; 3507; 931; 10863; 80709; 9938; 60468; 640; 6366; 4064; 930; 939; 952; 974; 388512; 283420; 160365; 1380; 2788; 3112; 3514; 57553; 5368; 6689; 8115; 608 |
| **Bcells.Immature Charoentong CellRep.2017 PMID.28052254** | **B cells** | Signature | PMID.28052254 | 115350; 26228; 933; 1536; 199786; 115352; 83416; 84824; 9734; 3117; 84329; 9711; 653361; 654816; 27334; 6672; 117289; 10628; 54877 |
| **Bcells.Memory Charoentong CellRep.2017 PMID.28052254** | **B cells** | Signature | PMID.28052254 | 4609; 57379; 890; 1033; 1184; 5167; 2205; 83417; 860; 6653; 6660; 6776; 6777; 54106 |
| **Bcells ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **B cells** | Signature | PMID.30266715 | 283663; 100507616; 29802; 640; 79368; 8115; 5079; 115350; 4063; 971; 83416; 115352; 8698; 5452; 931; 79856; 933; 199786; 3112; 81793; 1380; 26228; 3899; 4064; 5026; 151888; 951; 1235; 930; 28387; 5368; 1879; 974; 84824; 55024; 973 |
| **Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380** | **B cells** | Signature | PMID.23618380 | 973; 26586; 9917; 3662; 54900; 4917; 5450; 608; 3512; 91316; 100423062; 723778; 3500; 28461; |

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| | | | | 28937; 91353; 28862; 28939; 3507; 3525; 28797; 106481689; 28445; 3531; 28444; 28391; 28442; 3493; 28893; 28803; 3494; 28902; 28883; 28894; 28900; 3505; 106480274; 28921; 28452; 28930; 28815; 28931; 28908; 28458; 28912; 28793; 3538; 644731; 3532; 3537; 28392; 3539 |
| **Immune.CD19 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **B cells** | Signature | PMID.32573490 | 8115; 79368; 930; 640; 1269; 931; 84824; 5079 |
| **Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **B cells** | Signature | PMID.32573490 | 952; 9834; 973; 83416; 5450; 96610; 608; 8755; 3662; 54900; 389643 |
| **Bcells.Tcells.Cooperation Hollern Cell.2019 PMID.31730857** | **B cells/T cells** | Signature | PMID.31730857 | 115350; 640; 3502; 3502; 28776; 3500; 3502; 3514; 3512; 973; 100423062; 100423062; 3495; 930; 931; 5079; 3581; 6363; 51617; 2864; 959; 28558; 28621; 387923; 388507 |
| **Immune.14 Perez JCO.2015 PMID.2560586** | **B cells/T cells** | Signature | PMID.25605861 | 84632; 120425; 6366; 1233; 913; 959; 6387; 2534; 3112; 3487; 3394; 5729; 5734; 81793 |
| **Tcells.Bcells.Lymphocyte.Infiltration Calabro BreastCancerResTreat.2009 PMID.18592372** | **B cells/T cells** | Signature | PMID.18592372 | 6352; 930; 951; 915; 916; 917; 919; 973; 974; 925; 926; 3502; 3512; 3537; 929; 3932; 4050; 931 |
| **Immune.CD4.CD53.CD84.BTK TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **B cells/T cells** | Signature | PMID.32573490 | 221472; 257106; 1536; 8832; 22797; 313; 3394; 1234; 2124; 695; 920; 963; 5341; 1794; 3071; 3937; 2533; 5788; 10320; 3587; 3594; 64333; 54440; 5778; 124460; 6693; 388325; 89857; 64092; 23533; 286336; 951; 199; 7940; 79626; 3059; 27128; 4542; 83706; 6688; 7454; 4689; 64098; 6404 |
| **CD103.Negative Broz CancerCell.2014 PMID.25446897** | **Dendritic cells** | Signature | PMID.25446897 | 728; 10894; 8714; 4360; 6614; 23166; 713; 712; 140738; 10461; 714; 338773; 58475; 348; 8529; 54209; 51284 |

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|---|---|---|---|---|
| **Dendritic.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800** | **Dendritic cells** | Signature | PMID.25822800 | 51296; 1193; 6362; 54209; 6357; 6367; 7941; 6361; 910; 913; 2359; 4321; 55026; 6355; 10148; 6614; 3357; 80380; 6352; 3559; 5739; 1236; 6363; 3627; 6373; 79132; 8820; 3620; 10964; 8942; 27074; 51365; 83937; 91543; 11182; 7130; 1593; 7293; 6364; 58504; 330; 6346; 941; 942; 56548; 2117; 3593; 9175; 9242; 8013; 81796; 10402; 8792 |
| **Dendritic.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800** | **Dendritic cells** | Signature | PMID.25822800 | 51296; 1193; 968; 51313; 6362; 54209; 199; 50856; 2535; 246; 6357; 30835; 10462; 10261; 4688; 54; 79839; 6367; 7941; 56833; 945; 64581; 6039; 6335; 911; 2208; 79630; 6361; 909; 910; 913; 79154; 1959; 2205; 55640; 2359; 3117; 4321; 8496; 55026 |
| **Dendritic.cells.Activated Bindea Immunity.2013 PMID.24138885** | **Dendritic cells** | Signature | PMID.24138885 | 3620; 4940; 6346; 10148; 27074 |
| **Dendritic.cells Bindea Immunity.2013 PMID.24138885** | **Dendritic cells** | Signature | PMID.24138885 | 3290; 4881; 6357; 6361; 6367; 8495; 30835 |
| **Denditic.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184** | **Dendritic cells** | Signature | PMID.23382184 | 1471; 1776; 2322; 2828; 3383; 4610; 5058; 5199; 5547; 6252; 7045; 8321; 9314; 10875; 23677; 28955; 51177; 54802; 55022; 55509; 55521; 57118; 57698; 79887; 80005; 80176 |
| **Dendritic.cells.Activated Charoentong CellRep.2017 PMID.28052254** | **Dendritic cells** | Signature | PMID.28052254 | 822; 4843; 6503; 8926; 10011; 215; 10096; 506; 10632; 523; 598; 713; 714; 414062; 8900; 50489; 9936; 1088; 170482; 3118; 5861; 387; 8778; 89886; 51312; 60559; 7127; 8771; 8740; 54210; 340205; 285852; 10537; 8875; 23214 |
| **Dendritic.cells.Immature. Charoentong CellRep.2017 PMID.28052254** | **Dendritic cells** | Signature | PMID.28052254 | 400; 22876; 353514; 34; 10768; 8854; 224; 223; 246; 271; 275; 471; 498; 128346; 829; 1212; 1441; 5328; 23682; 5962; 58528; 6571; 4070 |

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| **Dendritic.cells.Immature. Bindea Immunity.2013 PMID.24138885** | **Dendritic cells** | Signature | PMID.24138885 | 645; 909; 910; 911; 913; 1436; 1497; 2162; 2167; 2535; 2952; 2978; 4070; 4321; 5468; 5550; 5909; 8566; 9023; 9429; 9956; 10462; 22846; 23428; 51760; 53343; 64170; 64231; 65010; 81501; 81562 |
| **Plasmacytoid.Dendritic.cell Charoentong CellRep.2017 PMID.28052254** | **Dendritic cells** | Signature | PMID.28052254 | 80325; 23466; 146722; 1601; 10521; 2014; 2022; 2204; 11337; 2876; 25994; 3419; 3479; 3563; 3674; 9903; 25984; 9500; 4925; 8481; 8473; 9601; 57661; 60675; 5899; 84666; 50862; 6397; 51734; 9792; 140885; 10959 |
| **Eosinophils CIBERSORT NatMethods.2015 PMID.25822800** | **Eosinophils** | Signature | PMID.25822800 | 8809; 671; 932; 6003; 1178; 9173; 9934; 719; 10402; 246; 4688; 53829; 23569; 6036; 51744; 8807; 8972; 26030; 5996; 55024; 597; 27202; 1602; 23604; 9681; 64174; 2015; 30817; 84658; 22905; 2867; 2696; 1880; 8477; 222487; 3568; 4033; 4117; 4084; 27334; 5029; 5146; 27039; 9185; 23223; 64092; 55512; 27293; 79865; 140803; 7673 |
| **Eosinophils Bindea Immunity.2013 PMID.24138885** | **Eosinophils** | Signature | PMID.24138885 | 32; 847; 1178; 1232; 2015; 2581; 3006; 3280; 3568; 3757; 6036; 6477; 7050; 7057; 7060; 8277; 8867; 9398; 9920; 11057; 11251; 22905; 23223; 25976; 51531; 55512; 55758; 57105; 59340; 91355; 728965; 80022 |
| **Eosinophils Charoentong CellRep.2017 PMID.28052254** | **Eosinophils** | Signature | PMID.28052254 | 1602; 23604; 9681; 84658; 2354; 2696; 1880; 8477; 3568; 442236; 4033; 8013; 9934; 5146; 27039; 23223; 10402 |
| **Hematopoietic.Stem.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184** | **Hematopoietic** | Signature | PMID.23382184 | 34; 284; 328; 332; 402; 444; 501; 594; 667; 672; 701; 759; 760; 783; 835; 947; 983; 1017; 1019; 1021; 1063; 1111; 1163; 1312; 1503; 1523; 1602; 1635; 1718; 1793; 1854; 1869; 1876; 1892; 1954; 1964; 2078; 2099; 2119; 2120; 2135; 2237; 2288; |

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| **Immune.HLA.A.F TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **HLA** | Signature | PMID.32573490 | 3133; 116071; 3659; 81030; 3902; 3107; 3105; 3106; 3134; 5698; 5696; 6890; 3965; 3601; 197259 |
| **Immune.HLA.D TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **HLA** | Signature | PMID.32573490 | 972; 3108; 3109; 3122; 3115; 3113 |
| **IFNa.Module10 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537** | **IFN** | Signature | PMID.20335537 | 51479; 23780; 80830; 11119; 11118; 10384; 55337; 9473; 834; 961; 8837; 56259; 3627; 23586; 55601; 23549; 10468; 2633; 2643; 2650; 51191; 55008; 3106; 3107; 10437; 3430; 10561; 10964; 2537; 3434; 3433; 3437; 24138; 8519; 3600; 3659; 3665; 9636; 3669; 3717; 3964; 26010; 4061; 4599; 4600; 4615; 4938; 4939; 4940; 8638; 11054; 5359; 5371; 5698; 55905; 91543; 64108; 6398; 51296; 81894; 8467; 3431; 9517; 6772; 6773; 6890; 6891; 23424; 7098; 80021; 10906; 11277; 9830; 6737; 7318; 9246; 11274; 54739; 56829 |
| **IFNg.Module11 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537** | **IFN** | Signature | PMID.20335537 | 23780; 80830; 406; 528; 55509; 604; 11119; 11118; 10384; 55337; 9473; 23607; 961; 1506; 3627; 6373; 4283; 23586; 23549; 2115; 2355; 10468; 2633; |

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| **IFN.Cluster.GSEA.GP11 Fan BMCMedGenomics.2011 PMID.21214954** | **IFN** | Signature | PMID.21214954 | 6772; 10068; 54739; 567; 91543; 94240; 5696; 5698; 56829; 3430; 23586; 388646; 3627; 6352; 163351; 4283; 29126; 85441; 7318; 3959; 83666; 10379; 103; 3433; 8638; 55601; 64135; 64108; 115361; 10561; 4599; 9636; 684; 11274; 3434; 4939; 81030; 54625; 345611; 6773; 64761; 6672; 2633; 116071; 9111; 146857; 387751; 3659 |
| **IFN Rody BreastCancerResearch.2008 PMID.19272155** | **IFN** | Signature | PMID.19272155 | 91543; 4940; 10561; 9636; 55601; 10964; 2537; 4599; 3437; 3429; 3434; 4938; 4939 |
| **IFN.Cluster Fan BMCMedGenomics.2011 PMID.21214954** | **IFN** | Signature | PMID.21214954 | 55337; 684; 3431; 64761; 24138; 4938; 10379; 11274; 23586; 4600; 3429; 4939; 2537; 3437; 10964; 10561; 3434; 9636; 4599; 91543; 4940; 55008; 51191; 55601; 5359; 9246; 54809; 64108; 54739; 9111; 8519; 10410; 3669; 5721; 5720; 3665 |
| **IFN.3.ImmLandscape Wolf PlosOne.2014 PMID.24516633** | **IFN** | Signature | PMID.24516633 | 3627; 23586; 55601; 51191; 55008; 3429; 10561; 10964; 2537; 64135; 3434; 3433; 3437; 9636; 4599; 4938; 4939; 4940; 8638; 91543; 64108; 54809; 6772; 6890 |
| **IFN.5.ImmLandscape Wolf PlosOne.2014 PMID.24516633** | **IFN** | Signature | PMID.24516633 | 27299; 9447; 597; 330; 10384; 6357; 6362; 6363; 6352; 6355; 1236; 930; 952; 917; 969; 973; 942; 926; 64581; 56253; 1075; |

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| **IFN.Pathway ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **IFN** | Signature | PMID.30266715 | 57169; 85441; 10964; 57674; 85363; 11274; 9636; 55601; 94240; 4599; 4600; 116071; 684; 151636; 55008; 51191; 10561; 3428; 84875; 51056; 6614; 64761; 54625; 115361; 2633; 64135; 64108; 8519; 4940; 5371; 91543; 4939; 3431; 219285; 3430; 84941; 129607; 6890; 51246; 26270; 54739; 79132; 9246; 51131; 6772; 10346; 6737; 6773; 55337; 5698; 23586; 10379; 3437; 3433; 8638; 3434; 8542; 27074; 83666; 24138; 3665; 54809; 10906; 80830; 441108; 2537 |
| **IFN.Score.module3 TCGA Immunity.2018 PMID.29628290** | **IFN** | Signature | PMID.29628290 | 10561; 10964; 23586; 2537; 3429; 3433; 3434; 3437; 8375; 8374; 8376; 3627; 4599; 4938; 4939; 4940; 51191; 54809; 55008; 55601; 64108; 64135; 6772; 6890; 8638; 91543; 9636 |
| **Immune.IFN TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **IFN** | Signature | PMID.32573490 | 10379; 24138; 51191; 55008; 55601; 54809; 3429; 2537; 9636; 23586; 64135; 3434; 10561; 10964; 3433; 3437; 129607; 91543; 4939; 4599; 8638; 4938; 4940; 54625; 83666; 6772; 11274; 54739; 4600; 64761; 5359; 9246; 6672; 3431 |

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| **IgG Rody BreastCancerResearch.2008 PMID.19272155** | **Ig** | Signature | PMID.19272155 | 391427; 96610; 339562; 28902; 651961; 90925; 651629; 91353; 28299; 28461; 5450; 28831; 91316; 3538; 28793; 3514; 28815; 3500; 3507; 28786; 3495; 3493; 3535; 3492; 3537; 652745 |
| **IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954** | **Ig** | Signature | PMID.21214954 | 939; 3561; 973; 11040; 5450; 3514; 28793; 3535; 3512; 608; 4917; 3576; 3107; 54900 |
| **Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490** | **Ig** | Signature | PMID.26451490 | 28904; 28467; 28875; 28426; 28776; 28474; 28919; 28424; 28923; 28874; 28420; 28784; 28423; 28817; 28937; 28457; 28876; 28943; 28778; 28400; 28396; 28793; 28434; 28391; 28941; 28938; 28935; 28408; 28394; 28797; 28914; 28395; 28465; 28809; 28450; 28822; 28448; 28933; 28468; 28388; 28813; 28921; 28444; 28815; 28893; 28392; 28299; 28442; 28912; 28908; 28913; 28825; 28439; 28796 |
| **Immune.Suppression Kardos JCIInsight.2016 PMID.27699256** | **Immune checkpoint molecules** | Signature | PMID.27699256 | 29126; 3620; 356; 1493; 5133; 3902; 84868; 80380; 3586; 7040; 5743; 4513 |
| **CD274.Single.Gene Hollern Cell.2019 PMID.31730857** | **Immune checkpoint molecules** | Gene | PMID.31730857 | 29126; 29126; 29126; 29126 |
| **CTLA4.Single.Gene Hollern Cell.2019 PMID.31730857** | **Immune checkpoint molecules** | Gene | PMID.31730857 | 1493; 1493; 1493; 1493 |
| **PDCD1.Single.Gene Pare AnnOncol.2019 PMID.30165419** | **Immune checkpoint molecules** | Gene | PMID.30165419 | 5133; 5133; 5133; 5133 |
| **Immunosuppression Petitprez Nature.2020 PMID.31942077** | **Immune suppression** | Signature | PMID.31942077 | 7043; 6387; 7040; 3956 |
| **Stromal.Inflammation Heng JPathol.2017 PMID.27861902** | **Inflammation** | Signature | PMID.27861902 | 1493; 27436; 50943; 2633; 9812; 11040; 23231; 9047; 56833; 201633; 79413 |
| **Wound.Healing Chang PlosBiol.2004 PMID.14737219** | **Inflammation** | Signature | PMID.14737219 | 292; 1111; 1178; 1326; 1633; 1663; 1841; 1978; 1981; 2023; 2107; 2171; 2193; 2224; 2923; 3015; 3037; 3146; 3151; 3157; |

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| **TGFB.score TCGA Immunity.2018 PMID.29628290** | **Inflammation** | Signature | PMID.29628290 | 4314; 65108; 3482; 3912; 6678; 2335; 3676; 6608; 4327; 3696; 3678; 4811; 7076; 6405; 23433; 1499; 4313; 5054; 2048; 1307; 1969; 3371; 3728; 3675; 6934; 1281; 1004; 7482; 8754; 1832; 3339; 392; 3693; 3488; 396; 4035; 3485; 1495; 10234; 4323; 4756; 1946; 3690; 2049; 960; 3487; 7132; 5879; 5829; 5327; 1295; 7479; |

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| **Immune.FOS.JUN.IL6 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **Inflammation** | Signature | PMID.32573490 | 8013; 3569; 9021; 467; 1959; 64651; 1843; 1958; 2354; 7538; 3164; 3725; 1839; 23645 |
| **Macrophages.M0 CIBERSORT NatMethods.2015 PMID.25822800** | **Macrophages** | Signature | PMID.25822800 | 366; 728; 968; 51313; 3101; 10261; 4688; 51296; 8876; 8740; 54; 27299; 79365; 79839; 6362; 6367; 6354; 1116; 1296; 1435; 2921; 6374; 1593; 81501; 2239; 8685; 4318; 7941; 5473; 25797; 56833; 84561; 54209 |
| **Macrophages.M1 CIBERSORT NatMethods.2015 PMID.25822800** | **Macrophages** | Signature | PMID.25822800 | 366; 51296; 27299; 1116; 200315; 11026; 10288; 64127; 51284; 51311; 6352; 80830; 8651; 3902; 3559; 5739; 10563; 79931; 1236; 952; 43; 80833; 408; 6363; 6355; 958; 1193; 3627; 6373; 4283; 1594; 79132; 10148; 2687; 8820; 3620; 10964; 643314; 8942; 27074; 51365; 83937; 91543; 6614; 6504; 11182; 7130; 54795 |
| **Macrophages.M2 CIBERSORT NatMethods.2015 PMID.25822800** | **Macrophages** | Signature | PMID.25822800 | 51296; 27299; 1116; 51311; 6355; 1193; 10148; 2687; 6614; 968; 51313; 6362; 54209; 199; 5199; 50856; 2242; 2535; 64231; 53829; 51314; 920; 246; 6357; 6358; 6368; 30835; 10462; 1414; 55691; 2952; 3269; 3357; 80896; 80380; 5973; 81029 |
| **Macrophages Bindea Immunity.2013 PMID.24138885** | **Macrophages** | Signature | PMID.24138885 | 348; 586; 950; 968; 1116; 1118; 1296; 1536; 2012; 2230; 2239; 2335; 2760; 3730; 4199; 4481; 5730; 6354; 6374; 6447; 6819; 8685; 8832; 9332; 10533; 23601; 26064; 26577; 51338; 58511; 81035; 259230; 1513 |
| **Macrophages.M2 Ghassabeh Blood.2006 PMID.16556895** | **Macrophages** | Signature | PMID.16556895 | 383; 84666; 7941; 5660; 6414; 54209; 5376; 10462; 1118; 27159; 374868; 999; 2350 |

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| **Macrophages.Th1.Cluster Iglesia CCR.2014 PMID.24916698** | **Macrophages** | Signature | PMID.24916698 | 26191; 5330; 50856; 3111; 752; 117289; 5552; 1436; 945; 713; 714; 712; 1520; 146722; 3394; 388325; 4332; 313; 57705; 8832; 22797; 1536; 5294; 11309; 3113; 3115; 3122; 3109; 3108; 972; 64092; 219972; 7133; 9938; 257106; 84433; 64231; 64098; 8477; 80231; 3594; 286336; 221472; 6404; 951; 3059; 7454; 4689; 3689; 83706; 6688; 4542; 27128; 79626; 199; 7940; 124460; 695; 3937; 5788; 2124; 3071; 963; 5341; 920; 54440; 3587; 1794; 2533; 10320; 1234; 6693; 64333; 10859; 11006; 2207; 9056; 3903; 84868; 7805; 942; 23533; 139716; 64926; 147138; 89857; 54518; 6503; 3635; 126364; 27180; 27036; 968; 3687; 55803; 719; 2123; 7456; 10875; 10261; 10288; 51411; 89790; 51311; 6039 |
| **Macrophages.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184** | **Macrophages** | Signature | PMID.23382184 | 136; 526; 719; 1026; 1051; 1317; 1436; 1462; 1508; 1827; 1848; 1861; 2131; 4035; 5271; 5326; 6051; 6237; 6256; 6614; 7045; 7056; 7133; 7941; 8522; 8754; 9056; 9732; 9777; 9935; 10577; 10855; 10924; 22918; 26509; 51311; 55022; 55160; 55486; 64127; 206358; 219654 |
| **Macrophages Charoentong CellRep.2017 PMID.28052254** | **Macrophages** | Signature | PMID.28052254 | 1268; 1269; 3101; 3269; 2206; 199; 10409; 6346; 6358; 6368; 10344; 124599; 920; 1414; 10209; 1973; 51313; 2242; 2357; 2358; 23401; 55691; 2535; 2850; 27202; 3176; 10261; 80896; 6036; 51296; 51314; 8876; 81029 |
| **Macrophages.Monocytes.CSF1.Response Beck CCR.2009 PMID.19188147** | **Macrophages** | Signature | PMID.19188147 | 113; 241; 272; 341; 348; 55843; 409; 567; 695; 80183; 79630; 719; 834; 6347; 6352; 9034; 9332; 945; 962; 1043; 963; 8832; 942; 925; 976; 51816; |

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| **Macrophages ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **Macrophages** | Signature | PMID.30266715 | 59342; 140; 4481; 51393; 6688; 51311; 55281; 9034; 313; 4125; 2215; 79895; 58475; 3903; 728; 23643; 1240; 597; 51816; 1520; 9332; 712; 10261; 713; 942; 10673; 409; 11006; 4332; 7941; 1508; 11326; 7127; 29887; 719; 1230; 27128; 10437; 3689; 2359; 64747; 79630; 972; 3684; 968; 7133; 1890; 7805; 3687; 2209; 3101; 2210; 80301; 2207; 3128; 920; 717; 1318; 10457; 7305; 10062; 1436; 51338; 3988; 6916; 80896; 3071; 4542; 56833; 11309; 1536; 11314; 64581; 1806; 2212; 51296; 27299 |
| **Immune.GIMAP.IL16 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **Macrophages** | Signature | PMID.32573490 | 54518; 55843; 1439; 9938; 170371; 1193; 2313; 55303; 168537; 474344; 55340; 4242; 139716; 7133; 4033; 10875; 219972; 3635; 3603 |
| **Mast.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800** | **Mastocytes** | Signature | PMID.25822800 | 945; 2205; 84561; 8809; 671; 932; 6003; 79895; 1178; 1215; 1359; 1511; 3067; 27306; 2206; 4602; 50508; 4914; 5023; 5553; 5874; 29091; 7177; 6364; 6346; 2921; 3002; 1437; 6351; 3562; 3198; 3552; |

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| **Mast.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800** | **Mastocytes** | Signature | PMID.25822800 | 945; 2205; 84561; 8809; 2672; 671; 1088; 932; 6489; 6003; 26228; 9934; 9508; 154; 79895; 55589; 719; 1178; 1215; 1359; 10321; 1511; 79843; 400451; 3067; 27306; 4056; 2206; 4602; 50508; 4914; 5023; 54852; 5553; 5874; 23176; 29091; 7177 |
| **Mast.cells Bindea Immunity.2013 PMID.24138885** | **Mastocytes** | Signature | PMID.24138885 | 116; 190; 794; 946; 1088; 1215; 1359; 1511; 1991; 2206; 2624; 3067; 3248; 3815; 4013; 4353; 5553; 5742; 6571; 6886; 7177; 7857; 10257; 27306; 57419; 57460; 64499; 79083; 339524; 4129 |
| **Mast.cell Charoentong CellRep.2017 PMID.28052254** | **Mastocytes** | Signature | PMID.28052254 | 1359; 9508; 55843; 1215; 1368; 1511; 1960; 2219; 2512; 3310; 3680; 29992; 5743; 6037; 6275; 27181; 6532 |
| **MDSC.Granulocytic Youn LeukocBiol.2012 PMID.21954284** | **MDSC** | Signature | PMID.21954284 | 100; 9133; 820; 8698; 2298; 2330; 2354; 2812; 3512; 3929; 4048; 4057; 4155; 4353; 5004; 5657; 641371; 55143; 8434; 1687; 55; 1992; 51449; 11065; 27333; 29942; 57509; 3039; 140460; 932; 55796; 55789; 353189; 10420; 9055; 25903 |
| **MDSC.Neutrophil Youn LeukocBiol.2012 PMID.21954284** | **MDSC** | Signature | PMID.21954284 | 894; 1154; 1234; 2919; 2921; 3383; 3557; 3569; 3627; 4023; 4323; 4502; 4794; 5196; 5900; 6275; 6281; 6354; 6385; 6648; 6696; 7057; 7124; 7185; 9641; 23328; 23657; 55686; 56895 |
| **MDSC.Tumor.Macrophages Schlecker JImmunol.2012 PMID.23152559** | **MDSC** | Signature | PMID.23152559 | 6351; 6348; 6354; 338442; 5008; 10409; 6369; 383; 967; 1339; 9034; 6696; 10022; 7070; 4323; 5996; 3303; 29923; 3553; 339210; 2920; 4360; 4322; 2919; 467; 3932; 1026; 9047; 2012; 929; 28984; 1601; 10912; 6385; 4283; 23179; 29126; 4643; 1263; 58191; 8877; 1958; 713; 8870; 1154; 101; 7124; 4818; 730249; 3123; 3725; |

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| **MDSC.Tumor Schlecker JImmunol.2012 PMID.23152559** | **MDSC** | Signature | PMID.23152559 | 123; 290; 383; 467; 712; 713; 714; 817; 839; 929; 958; 1026; 1154; 1234; 1462; 1476; 1522; 1601; 1643; 1827; 1845; 1846; 1893; 1910; 1958; 2012; 2078; 2155; 2159; 2213; 2309; 2549; 2697; 2799; 2810; 2919; 2920; 3119; 3123; 3162; 3303; 3304; 3383; 3557; 3617; 3680; 3725; 4000; 4239; 4261; 4283; 4322; 4323; 4360; 4794; 5008; 5025; 5026; 5146; 5209; 5236; 5328; 5553; 5597; 5641; 5817; 5866; 5973; 5996; 6347; 6348; 6351; 6354; 6369; 6385; 6535; 6643; 6692; 6696; 7052; 7076; 7124; 7167; 7185; 7431; 7982; 8360; 8364; 8553; 8808; 8835; 8877; 8892; 8991; 9034; 9043; 9046; 9308; 9518; 9522; 9546; 9641; 9732; 9788; 9797; 9934; 9953; 10046; 10062; 10268; 10312; 10417; 10457; 10461; 10493; 10630; 10915; 11172; 11186; 11238; 11282; 11316; 11346; 22862; 23049; 23099; 23166; 23179; 23207; 23216; |

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| **MDSC Charoentong CellRep.2017 PMID.28052254** | **MDSC** | Signature | PMID.28052254 | 929; 5660; 729230; 914; 942; 7852; 2212; 2213; 2214; 83706; 63940; 10068; 3566; 3683; 3684; 64098; 5732; 80142; 6279; 6280 |
| **MHC.11genes Forero CancerImmunolRes. 2016 PMID.26980599** | **MHC** | Signature | PMID.26980599 | 4261; 972; 3113; 3115; 3116; 3117; 3123; 3127; 3128; 1512; 8648; 100290966; 731247 |
| **MHC.24genes Forero CancerImmunolRes. 2016 PMID.26980599** | **MHC** | Signature | PMID.26980599 | 4261; 972; 3113; 3115; 3116; 3117; 3123; 3127; 3128; 1512; 8648; 100290966; 731247; 913; 2217; 3861; 57121; 89846; 6844; 120892; 4154; 4916; 84265; 5730; 6451; 9760; 399472 |
| **MHC.I Rody BreastCancerResearch.2008 PMID.19272155** | **MHC** | Signature | PMID.19272155 | 3135; 3105; 3106; 3107; 3134 |
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| **MHC.I.CoreGenes Lauss NatCommun.2017 PMID29170503** | **MHC** | Signature | PMID.29170503 | 3105; 3106; 3107; 6891; 84166; 6890; 5698; 5696; 567 |
| **CD68.Cluster Iglesia CCR.2014 PMID.24916698** | **Monocytes** | Signature | PMID.24916698 | 126364; 27180; 27036; 968; 3687; 55803; 719 |
| **Monocytes CIBERSORT NatMethods.2015 PMID.25822800** | **Monocytes** | Signature | PMID.25822800 | 8875; 2354; 199; 200315; 366; 432; 433; 683; 728; 729230; 912; 945; 968; 978; 5199; 51363; 50856; 64581; 9586; 1441; 51313; 2219; 2242; 2357; 2535; 3055; 3101; 3176; 10855; 10261; 11027; 11026; 10288; 7940; 4210; 4332; 64231; 4688; 4778; 114548; 64127; 53829; 23569; 6036; 6039; 6283; 51296; 7097; 51284; 51311; 7380; 8876 |
| **Tcells.Effector.Memory Bindea Immunity.2013 PMID.24138885** | **Monocytes** | Signature | PMID.24138885 | 1231; 2130; 2313; 4058; 4210; 4776; 5616; 6904; 6955; 7430; 9779; 10000; 10521; 27099; 81544 |
| **Monocytes.Dendritic.cell.Metagene Miller GenomeBiol.2013 PMID.23618380** | **Monocytes** | Signature | PMID.23618380 | 3113; 7940; 3133; 3115; 3119; 3108; 3122; 3123; 972 |
| **Monocytes Charoentong CellRep.2017 PMID.28052254** | **Monocytes** | Signature | PMID.28052254 | 1072; 4155; 71; 308; 432; 433; 526; 912; 5199; 1486; 9802; 326342; 3097; 10320; 65108; 4324; 10908; 10084; 51368; 7009; 7380 |
| **Monocytes ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **Monocytes** | Signature | PMID.30266715 | 7940; 2268; 199; 7077; 2242; 9056; 22918; 1200; 3162; 2219; 7045; 23313; 79168; 29108; 5265; 391; 29992; 5660; 3055; 150372; 84034; 126364; 57085; 2799; 4853; 10288; 11025; 2896; 945; 84106; 84898; 1509; 146722; 1462; 9473; 64115; 929 |
| **Monocytes.Dendritic.25genes Miller GenomeBiol.2013 PMID.23618380** | **Monocytes** | Signature | PMID.23618380 | 241; 920; 972; 1436; 1536; 1794; 2123; 2124; 10875; 3109; 3113; 3115; 3117; 3119; 3122; 3123; 3133; 7462; 7940; 5788; 5552; 3118; 3127; 3128; 3108 |
| **CSF1.Response TCGA Immunity.2018 PMID.29628290** | **Monocytes** | Signature | PMID.29628290 | 11151; 4332; 9034; 9056; 3108; 2533; 6039; 7097; 1075; 11006; 9595; 1520; 83937; 4478; 1536; 7805; |

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| **Immune.CD34.TIE1 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **Monocytes** | Signature | PMID.32573490 | 54810; 6403; 5243; 9452; 22915; 6358; 857; 6886; 79843; 22918; 2078; 947; 1003; 80177; 1901; 7075; 10252; 128553; 5168 |
| **HCK Rody BreastCancerResearch.2008 PMID.19272155** | **Monocytes** | Signature | PMID.19272155 | 64231; 11309; 51338; 7940; 199; 7305; 1794; 2207; 6039; 9056; 4332; 4688; 713; 7805; 10437; 22797; 9332; 3903; 942; 3689; 3055; 712; 1230 |
| **Influenza.11genes Khatri Immunity.2015 PMID.26682989** | **Monocytes** | Signature | PMID.26682989 | 952; 51191; 55008; 2537; 64135; 3959; 4061; 4599; 64761; 64108; 81030 |
| **Neutrophils.Activated.Blood Janiszewska NatCellBiol.2019 PMID.31263265** | **Neutrophils** | Signature | PMID.31263265 | 3043; 1514; 3039; 2791; 3043; 10398; 2815; 11313; 27013; 928; 51635; 10482; 3655; 5473; 1191; 8294; 10170; 64805; 65213; 4201; 6840; 11182; 3555; 7850; 653361; 5196; 3181; 84419; 6503; 3040; 4601; 820; 4792; 4282; 1831; 4001; 65125; 51274; 1611; 9246; 11345; 89875; 3187; 51499; 976; 4940; 259230; 26469; 23521; 54625; 54926; 51206; 4713; 6467; 7979; 128346; 10924; 6271; 3480; 5269; 1475; |

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| **Neutrophils.Activated.Lung Janiszewska NatCellBiol.2019 PMID.31263265** | **Neutrophils** | Signature | PMID.31263265 | 467; 8832; 79145; 143384; 115817; 3265; 80153; 92241; 123; 6222; 84919; 9698; 10905; 334; 23741; 2778; 51324; 23048; 10999; 63935; 1479; 11052; 22898; 54542; 7884; 258010; 23360; 63931; 64961; 23412; 5711; 58476; 26292; 4520; 9686; 1613; 7704; 85439; 26156; 9748; 56688; 5439; 9169; 6856; 10011; 6414; 64965; 79095; 151188; 10010; 5782; 4938; 3656; 55180; 60626; 388272; 4597; 64943; 4200; 8260; 139716; 84265; 8295; 255967; 119504; 22862; 5771; 9658; 23602; 57175; 79077; 6137; 10923; 1175; 54522; 91373; 10906; 2631; 79705; 55331; 9274; 203328; 4671; 51527; 4677; 8199; 84557; 3692; 10451; 11021; 51028; 51021; 64959; 2314; 4214; 4089; 51315; 3397; 53938; 3028; 1435; 79982; 6497; 389203; 55144; 155185; 79042; 4205; 5428; 1431; 5376; 140735; 22890; 51586; 7936; 79143; 1656; 29896; 196264; 54407; |

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| | | | | 23476; 8655; 2533; 23168; 79637; 10527; 64777; 10713; 1192; 57620; 91746; 4659; 56259; 84306; 8575; 81704; 6503; 59339; 80790; 122622; 7534; 8344; 5048; 55904; 65117; 57140; 58159; 10625; 10857; 9061; 51499; 9683; 136647; 54069; 81555 |
| **Neutrophils CIBERSORT NatMethods.2015 PMID.25822800** | **Neutrophils** | Signature | PMID.25822800 | 1178; 9934; 4688; 53829; 23569; 8807; 8972; 26030; 64174; 30817; 84658; 2867; 222487; 4117; 4084; 9185; 79865; 7130; 199; 10261; 1116; 51311; 5199; 366; 200315; 10288; 728; 8876; 25797; 8875; 978; 51363; 9586; 1441; 2357; 11027; 7940; 4210; 4332; 4778; 6283; 7097; 820; 79908; 838; 1232; 1084; 3577; 3579; 55924; 2215; 2358; 3034; 3310; 64386; 8993; 79689; 8794; 54210; 55350 |
| **Neutrophils Bindea Immunity.2013 PMID.24138885** | **Neutrophils** | Signature | PMID.24138885 | 249; 683; 1084; 1441; 2204; 2215; 2357; 2358; 3577; 3579; 3772; 4051; 4311; 5142; 6283; 6583; 8291; 8347; 8778; 8794; 8972; 9586; 9895; 10288; 10855; 22918; 50486; 51312; 55313; 55350; 83716 |
| **Granulocytes.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184** | **Neutrophils** | Signature | PMID.23382184 | 306; 366; 383; 526; 706; 719; 728; 820; 928; 929; 1116; 1436; 1441; 1675; 2896; 3082; 3162; 3176; 3934; 4057; 4814; 4973; 5154; 5329; 5724; 6280; 6403; 6688; 6813; 6916; 7057; 7077; 7097; 7099; 7130; 8301; 8972; 9764; 9826; 10159; 10170; 10457; 10562; 10634; 11237; 23569; 23601; 26253; 50486; 51257; 51311; 51734; 54210; 55350; 55625; 55647; 55793; 56729; 79689; 83716 |
| **Neutrophils.MCP Petitprez** | **Neutrophils** | Signature | PMID.31942077 | 762; 1084; 3577; 3579; 4051; 2215; 3034; 3772; |

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| **Nature.2020 PMID.31942077** | | | | 1955; 51312; 79689; 9895; 7090; 8794; 55350 |
| **Neutrophils Charoentong CellRep.2017 PMID.28052254** | **Neutrophils** | Signature | PMID.28052254 | 4117; 64386; 200315; 79908; 55924; 838; 978; 51363; 9586; 3577; 3579; 2867; 3034; 8972; 6283; 79689; 8794; 55350 |
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| **NK.Activated CIBERSORT NatMethods.2015 PMID.25822800** | **NK cells** | Signature | PMID.25822800 | 919; 3932; 4068; 3004; 3560; 3820; 79037; 3002; 6352; 3001; 8530; 10578; 2999; 3824; 22914; 5551; 5729; 28526; 51744; 8807; 7535; 10225; 924; 5790; 4818; 3595; 1521; 3823; 51348; 8809; 3802; 3812; 10004; 79899; 53637; 30009; 7294; 29909; 2841; 1803; 4050; 4049; 969; 1437; 3458; 9402; 5732; 259197; 60489; 80830; 6351; 894; 1021; 356; 3805; 3809; 5008; 8651; 8740 |
| **NK.Resting CIBERSORT NatMethods.2015 PMID.25822800** | **NK cells** | Signature | PMID.25822800 | 914; 919; 3932; 4068; 3004; 28639; 3560; 3820; 79037; 3002; 6352; 3001; 3003; 8530; 10578; 2999; 3824; 22914; 5551; 5729; 28526; 11126; 51744; 2672; 8807; 7535; 10225; 924; 5790; 4818; 3595; 1521; 3823; 8302; 51348; 566; 671; 820; 92211; 1088; 1669; 1991; 8809; 3802; 3812; 8972; 932; 10004; 51314; 79156; 79899; 53637; 30009; 7011; 55020; 7294; 7694 |
| **NK.CD56bright Bindea Immunity.2013 PMID.24138885** | **NK cells** | Signature | PMID.24138885 | 758; 1846; 2302; 6236; 6375; 8398; 8567; 10299; 57876; 83696; 254531 |

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| **NK.CD56dim Bindea Immunity.2013 PMID.24138885** | **NK cells** | Signature | PMID.24138885 | 2975; 3002; 3804; 3806; 3807; 3810; 3811; 3812; 3813; 10417; 50615; 53637; 55020; 56937; 115653 |
| **NK Bindea Immunity.2013 PMID.24138885** | **NK cells** | Signature | PMID.24138885 | 104; 219; 323; 596; 988; 2527; 2574; 2778; 3488; 5710; 6375; 6693; 6846; 6915; 7755; 8572; 8817; 8888; 9437; 9902; 11155; 22924; 25959; 27308; 51343; 55503; 55671; 57716; 64129; 64225; 64924; 65988; 79867; 84436; 259230; 643313; 730096 |
| **Tcells.Central.Memory Bindea Immunity.2013 PMID.24138885** | **NK cells** | Signature | PMID.24138885 | 360; 472; 841; 1540; 1678; 2533; 3187; 4214; 4297; 4747; 4775; 5108; 6482; 6638; 7294; 8287; 8556; 8675; 8821; 9057; 9397; 11278; 22990; 23059; 23177; 23348; 55729; 58487; 80012; 80342; 85021; 202134; 246721; 283970; 441155; 116828; 27086; 55269; 84663 |
| **NK.ImmuneProfiles. Mouse.Human Shay PNAS.2013 PMID.23382184** | **NK cells** | Signature | PMID.23382184 | 598; 864; 1521; 2151; 3001; 3140; 3458; 3560; 3673; 3824; 3982; 4818; 5782; 6574; 7008; 8459; 8530; 8807; 8809; 9437; 11030; 11092; 11126; 11145; 11178; 11285; 30009; 54438; 54843; 79158; 81563; 83988; 254531 |
| **NK.CD56bright Charoentong CellRep.2017 PMID.28052254** | **NK cells** | Signature | PMID.28052254 | 1001; 10866; 3067; 18; 64919; 56935; 56951; 92211; 1193; 9167; 148327; 1435; 1459; 1475; 1476; 1503; 1509; 1594; 25853; 8655; 10480; 84173; 957; 151194; 165186; 10468; 2624; 2766; 7107; 84717; 23462; 3198; 9653; 9957; 3892; 64223; 140465; 79612 |
| **NK.CD56dim Charoentong CellRep.2017 PMID.28052254** | **NK cells** | Signature | PMID.28052254 | 2902; 3806; 100132285; 3810; 22977; 1593; 57696; 8445; 55890; 3133; 50615; 4854; 64840; 5704; 6168; 7378 |
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| **NK ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **NK cells** | Signature | PMID.30266715 | 8302; 5551; 3822; 3823; 57292; 3810; 30009; 100132285; 3806; 3808; 154075; 115653; 3802; 3804; 117157; 3824; 3803; 3811; 3812; 3805 |
| **NK.MCP Helmink Nature.2020 PMID.31942077** | **NK cells** | Signature | PMID.31942077 | 11126; 3802; 3804; 3805; 3811; 3813; 9437; 5729; 117157 |
| **Bcells.Plasmablast Dybaer JCO.2015 PMID.25800755** | **Plasma cells** | Signature | PMID.25800755 | 639; 857; 999; 1534; 2081; 2487; 2549; 3493; 3537; 3655; 3662; 4121; 4189; 4695; 7421; 7494; 8339; 8343; 8344; 8346; 8347; 8349; 8970; 9236; 10788; 10802; 10970; 22862; 22936; 23446; 23710; 23766; 28396; 28831; 51237; 51303; 54502; 54855; 55132; 57823; 64764; 64778; 79694; 91319; 115908; 144535; 151556; 160428; 317649; 340542; 645784; 100533483; 101928615 |
| **Plasma.cells CIBERSORT NatMethods.2015 PMID.25822800** | **Plasma cells** | Signature | PMID.25822800 | 973; 79368; 91316; 3112; 3495; 3507; 3514; 91353; 5026; 5368; 150094; 939; 160518; 2788; 80008; 608; 55840; 23457; 270; 51378; 6315; 79703; 2826; 952; 2848; 3012; 8339; 3497; 3738; 26251; 54923; 100130100; 4121; 79694; 22983; 374977; 51237; 5081; 5163; 25780; 5972; 6003; 642741; 6676; |

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| **Bcells.Plasma.cells. Metagene Miller GenomeBiol.2013 PMID.23618380** | **Plasma cells** | Signature | PMID.23618380 | 3537; 3500; 3507; 3493; 3492; 3514; 28831; 50802; 28823; 100293211; 5450; 608; 91316; 3495; 91353; 100423062 |
| **Plasma.cells ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **Plasma cells** | Signature | PMID.30266715 | 3492; 3502; 28823; 91353; 81567; 91316; 51237; 28902; 608; 28831; 3546; 3514; 3537 |
| **STAT1 Rody BreastCancerResearch.2008 PMID.19272155** | **STAT** | Signature | PMID.19272155 | 6890; 2633; 64135; 5698; 4283; 3659; 6373; 3627; 3620; 6772 |
| **Proliferation.Pathway ImSig.Nirmal CancerImmunolRes. 2018 PMID.30266715** | **T cells** | Signature | PMID.30266715 | 6491; 2146; 79733; 7272; 6790; 9212; 9232; 55388; 113115; 81620; 9134; 11004; 55143; 83879; 11339; 55215; 157313; 55789; 7153; 113130; 890; 259266; 83461; 9928; 983; 990; 3832; 51514; 56992; 22974; 51203; 84057; 55635; 55872; 4171; 11065; 1894; 4173; 5888; 4175; 29128; 4085; 6241; 11130; 554282; 6240; 701; 3925; 9833; 79801; 1163; 24137; 3149; 4751; 2305; 9768; 54443; 55165; 3161; 7083; 57405; 7298; 5427; 64151; 54892; 55355; 1058; 699; 26271; 220134; 55055; 10721; 9319; 9837; 51659; 91687; 10635; 4288; 51053; 9787; 83540; 146909; 1063; 991; 10403; 332; 1062; 29980; 1033; 29127; 10592; 891; 10733; 9133; 55010; 5111; 6941; 10112 |
| **Immune.CTLA4.CXCL.FOXP3 TCGA.BRCA.1198 JCI.2020 PMID.32573490.** | **T cells** | Signature | PMID.32573490 | 1493; 6373; 3627; 4283; 3604; 50615; 56833; 50943; 3620; 94240; 2633 |
| **CD8.Cluster Iglesia CCR.2014 PMID.24916698** | **T cells** | Signature | PMID.24916698 | 256380; 151888; 925; 3003; 29909; 128611; 5790; 374403; 10663; 4063; 9744; 27240; 201633; 3932; 55423; 919; 84174; 3702; 10225; 4068; 921; 916; 914; 915; 2833; 114836; 3561; 53347; 6504; 149628; 939; 50852; |

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| **Tcells.CD8.MCP Petitprez Nature.2020 PMID.31942077** | **T cells** | Signature | PMID.31942077 | 926; 926; 926; 926 |
| **Tcells.CD4.Memory. Activated CIBERSORT NatMethods.2015 PMID.25822800** | **T cells** | Signature | PMID.25822800 | 914; 919; 915; 917; 924; 1803; 29851; 3932; 4068; 28755; 50852; 53347; 959; 923; 29909; 4818; 940; 1493; 3002; 3902; 6364; 993; 1437; 10563; 2842; 3458; 3595; 3605; 55801; 3559; 3562; 3565; 3578; 4049; 4998; 5367; 9136; 220134; 7293; 79931 |
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| **Tcells.Follicular.Helper CIBERSORT NatMethods.2015 PMID.25822800** | **T cells** | Signature | PMID.25822800 | 914; 919; 915; 917; 924; 29851; 3932; 4068; 28755; 50852; 53347; 959; 1493; 3902; 10563; 2842; 4049; 7293; 939; 642741; 9214; 64919; 3004; 3702; 51176; 55423; 6932; 28671; 28639; 7535; 969; 5790; 3820; 1606; 6489; 28680; 28677; 11184; 79884; 80162; 27040; 79037; 150094; 643; 767; 1117; 2354; 7976; 3382; 59067; 23178; 5133; 5996; 56301; 28951; 7253; 65986 |
| **Tcells.Gamma.Delta CIBERSORT NatMethods.2015 PMID.25822800** | **T cells** | Signature | PMID.25822800 | 914; 919; 915; 917; 3932; 4068; 53347; 3004; 55423; 28639; 11184; 29909; 27240; 3560; 8631; 3902; 6932; 3820; 27040; 79037; 3002; 4063; 6352; 3001; 3003; 925; 926; 8530; 1844; 10578; 2999; 3824; 22914; 5551; 5729; 28526; 2841; 631; 9024; 1234; 11126; 51744; 11314; 1010; 8292; 10663; 2672; 2996; 8807; 10219; 442236; 3973; 4110; 26030; 6335; 643503; 8875; 79973 |
| **Tcells.Regulatory.Tregs CIBERSORT NatMethods.2015 PMID.25822800** | **T cells** | Signature | PMID.25822800 | 914; 919; 915; 917; 29851; 3932; 4068; 28755; 50852; 53347; 1493; 2842; 939; 64919; 3004; 3702; 55423; 28639; 7535; 1606; 28677; 11184; 1803; 923; 29909; 940; 3559; 5367; 4050; 916; 10225; 920; 11123; 2825; 4153; 27240; 8538; 921; 970; 752014; 29121; 1946; 50943; 83786; 3090; 203510; 3560; 55243; 3904; 23547; 126987; 4861; 4917; 56143; 9651; |

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| **Cytolytic.Activity Rooney Cell.2015 PMID.25594174** | **T cells** | Signature | PMID.25594174 | 3001; 5551 |
| **Cytotoxic.Lymphocytes.MCP Petitprez Nature.2020 PMID.31942077** | **T cells** | Signature | PMID.31942077 | 925; 8320; 83888; 10578; 3823; 8302; 3824 |
| **Immune.Active Hollern Cell.2019 PMID.31730857** | **T cells** | Signature | PMID.31730857 | 12; 356; 433; 640; 718; 914; 915; 916; 917; 920; 923; 924; 925; 927; 930; 931; 933; 939; 940; 959; 969; 972; 973; 1233; 1380; 1493; 1776; 2634; 2841; 2864; 3002; 3109; 3111; 3112; 3117; 3120; 3135; 3274; 3363; 3458; 3495; 3500; 3502; 3512; 3514; 3559; 3560; 3581; 3593; 3595; 3627; 3682; 3702; 3816; 3820; 3824; 4049; 4050; 4261; 4283; 4332; 4818; 5079; 5133; 5551; 5790; 6039; 6346; 6352; 6363; 6367; 6373; 6434; 6504; 6518; 6773; 6846; 6909; 8302; 8530; 8740; 8798; 8942; 9402; 9476; 9934; 10019; 10100; 10225; 10420; 10563; 10612; 10663; 10666; 10803; 22806; 22914; 26191; 26279; 27334; 28557; 28558; 28621; 28683; 28776; 29126; 29851; 29909; 51617; 53347; 54929; 56253; 56949; 57823; 64386; 80380; 84327; 84636; 114132; 114770; 114836; 115350; 115362; 117157; 137970; 152789; 158067; 163351; 168537; 202309; 221150; 221830; 246778; 283420; 284486; 345611; 353345; 387914; 387923; 388507; 388646; 400410; 445347; 100423062; 100527949; 84824 |
| **CTLA4.Pathway GSEA.BIOCARTA ProcNatlAcadSciUSA.2005 PMID.16199517** | **T cells** | Signature | PMID.16199517 | 5781; 941; 942; 940; 915; 916; 917; 3702; 5290; 23308; 6957; 6955; 2885; 919; 29851; 5295; 3932; 3123; 3122; 1493; 3558 |

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| **Immune.cell.Cluster. PerouLab Fan.GSEA.GP2 BMCMedGenomics.2 011 PMID.21214954** | **T cells** | Signature | PMID.16 199517 | 7453; 3620; 6039; 8477; 4332; 27074; 25816; 4067; 7128; 51316; 3575; 1439; 3659; 7133; 27299; 56833; 55423; 4050; 5790; 1236; 9806; 5341; 972; 3108; 3122; 3109; 2207; 7305; 7805; 3689; 712; 6772; 6373; 3627; 2633; 6890; 5698; 55303; 5552; 10875; 3059; 9938; 3932; 2124; 55843; 9595; 3001; 3937; 963; 3587; 962; 6352; 915; 914; 3003; 5788; 4283; 9535; 3394; 1520; 22797; 6503; 9056; 7940; 199; 942; 3071; 9473; 4069; 1043; 6402; 3134; 3106; 3133; 3002; 10507; 11118; 10384; 834 |
| **Tcells.Bcell.KEGG.h ematopoietic.cell.line age GSEA.GP2 ProcNatlAcadSciUS A.2005 PMID.16199517** | **T cells** | Signature | PMID.16 199517 | 2811; 2812; 2056; 3581; 945; 7124; 2815; 3684; 947; 948; 2814; 3676; 3675; 4254; 3674; 2209; 3678; 2208; 2993; 7066; 7850; 3575; 4311; 3590; 930; 931; 7037; 933; 3815; 2322; 3690; 2323; 3552; 1380; 929; 1378; 7173; 2057; 3589; 1437; 3126; 920; 1436; 3127; 1435; 3125; 3563; 3562; 966; 652799; 928; 925; 926; 960; 924; 921; 1438; 1604; 1791; 1440; 3553; 3554; 3559; 3655; 3570; 3673; 3672; 1441; 3574; 951; 914; 915; 916; 952; 917; 910; 290; 911; 912; 913; 909; 3565; 3566; 3567; 3568; 3569; 3123; 3122 |
| **PD1.Signaling.React ome GSEA ProcNatlAcadSciUS A.2005 PMID.16199517** | **T cells** | Signature | PMID.16 199517 | 1445; 29126; 3113; 3115; 3117; 3118; 3123; 3125; 3127; 3932; 5133; 5777; 80380; 915; 916; 917; 919; 920 |
| **Tcells.CD8 Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24 138885 | 166; 321; 678; 687; 819; 925; 926; 1647; 1831; 2323; 3004; 3337; 5196; 5504; 5551; 5935; 6432; 6844; 6903; 6935; 7536; 7570; 7644; 7994; 9194; 11322; 23060; 23484; 29777; 51275; 54923; 55602; 55615; 55623; 79441; 91304 |

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| **Cytotoxic.cells Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 321; 864; 1521; 1844; 2999; 3001; 3820; 3824; 4818; 6095; 7704; 10578; 22914; 51348; 59307; 80833; 339005 |
| **Tcells Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 914; 915; 916; 917; 923; 940; 3932; 4068; 5588; 6955; 8631; 9452; 10225; 28639; 28755; 50852; 55340; 64919; 83988 |
| **Tcells.Thelper Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 940; 987; 1386; 4676; 5527; 6117; 6955; 7332; 8604; 9452; 9632; 10538; 10541; 10730; 10772; 23015; 25842; 29851; 55274; 57122; 63901; 79009; 79866; 285527 |
| **Tcells.Follicular.Helper Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 643; 753; 1114; 1117; 3382; 4086; 4094; 5783; 6489; 7253; 8362; 8645; 8851; 9760; 10563; 10585; 23178; 23462; 27087; 27347; 54436; 55423; 56301; 57496; 57535; 63892; 92595; 28986; 4646; 4647; 5133; 5816 |
| **Tcells.Gamma.Delta Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 6964; 6983; 9638; 10485; 11126; 445347 |
| **Tcells.Th1.cells Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 323; 347; 684; 952; 970; 1437; 1493; 1803; 1839; 1847; 2678; 3458; 3595; 4049; 6351; 6443; 7804; 8418; 9143; 9162; 10079; 10950; 25975; 27033; 50616; 54674; 55816 |
| **Tcells.Th17.cells Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 3605; 6097; 23765 |
| **Tcells.Th2.cells Bindea Immunity.2013 PMID.24138885** | **T cells** | Signature | PMID.24138885 | 107; 286; 332; 995; 1063; 1719; 2625; 2941; 3070; 3904; 4087; 4151; 5251; 5367; 5740; 6632; 7813; 8317; 9645; 10663; 11169; 23516; 51474; 54806; 55247; 55801; 728210 |
| **Immune.Hot.vs.Cold. CD8 Cabrita Nature.2020 PMID.31942071** | **T cells** | Signature | PMID.31942071 | 4069; 5552; 962; 51316; 1075; 9595; 939; 3123; 3394; 2533; 2124; 5880; 6352; 3122; 3119; 11151; 3512; 91353; 951; 3575; 6039; 4283; 3117; 27299; 963; 7805; 2207; 7852; |

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| **Immune.87 Perez JCO.2015 PMID.2560586** | **T cells** | Signature | PMID.2560586 | 3635; 729230; 3575; 3133; 3689; 3487; 7454; 10870; 3071; 7494; 81793; 6352; 7133; 3385; 3821; 4049; 3458; 4050; 959; 3394; 7412; 5729; 5734; 941; 4068; 54106; 973; 2833; 313; 695; 9934; 120425; 1235; 4069; 4065; 7852; 3683; 915; 5788; 976; 3561; 3766; 3932; 913; 2534; 11126; 6693; 5336; 3115; 3823; 9437; 3620; 916; 26191; 3112; 1233; 2826; 919; 10563; 84174; 3001; 718; 5168; 6932; 917; 6387; 10225; 54900; 974; 29126; 952; 5551; 1493; 84632; 5588; 80833; 1236; 29851; 6402; 10219; |

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| **LCK Rody BreastCancerResearch.2008 PMID.19272155** | **T cells** | Signature | PMID.19272155 | 55843; 22914; 54440; 9938; 6504; 55340; 4068; 1236; 3702; 28568; 5880; 11151; 5293; 9404; 5579; 6775; 9535; 6404; 10875; 2124; 1439; 3003; 64092; 55303; 3394; 3071; 3587; 28755; 3635; 51316; 6352; 919; 4050; 3561; 3059; 3575; 963; 1231; 3932; 915; 939; 3001; 6402; 28566; 914; 962; 6503; 3937; 5552; 5788 |
| **MCD3.CD8 Fan BMCMedGenomics.2011 PMID.21214954** | **T cells** | Signature | PMID.21214954 | 3932; 390243; 151888; 5450; 4242; 115350; 84824; 9214; 51617; 1840; 940; 26999; 4068; 3111; 921; 9840; 27040; 89857; 2833; 4050; 84329; 6689; 1380; 30009; 10750; 10870; 3603; 643; 974; 51237; 931; 55843; 26228; 923; 8631; 926; 915; 914; 3702; 925; 917; 6402; 399; 3695; 3560; 1731; 27334; 939; 6775; 80342; 26279; 393; 26191; 9476; 1269; 168537; 84433 |
| **MERCK.Immune.Signature Cristescu Science.2018 PMID.30309915** | **T cells** | Signature | PMID.30309915 | 6352; 939; 29126; 80381; 925; 1240; 4283; 10663; 3117; 3123; 3133; 3620; 3902; 4818; 80380; 5699; 6772; 201633 |
| **Tcells.NK.Metagene Miller GenomeBiol.2013 PMID.23618380** | **T cells** | Signature | PMID.23618380 | 4242; 10875; 3587; 916; 5579; 2841; 2124; 1521; 3820; 6375; 3059; 3635; 5293; 962; 951; 6402; 3932; 54440; 1439; 939; 3003; 729230; 11151; 3603; 28517; 3702; 10730; 5788; 5880; 4818; 55340; 55843; 474344; 9938 |
| **Tcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184** | **T cells** | Signature | PMID.23382184 | 23; 120; 158; 166; 360; 399; 406; 472; 476; 596; 814; 841; 894; 914; 915; 916; 917; 919; 921; 923; 939; 940; 944; 955; 1107; 1236; 1455; 1477; 1493; 1540; 1606; 1643; 1778; 1936; 2071; 2073; 2113; 2145; 2308; 2534; 2580; 2617; 2625; 3097; 3268; 3337; 3384; 3396; 3561; 3572; 3575; 3603; 3655; |

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| **Tcells.Regulatory.cell.2gene Petitprez Nature.2020 PMID.31942077** | **T cells** | Signature | PMID.31942077 | 50943; 8784 |
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| | | | | 389072; 5576; 7703; 51201; 2151; 10663; 5795; 3903; 6118; 3897; 3672; 22837; 960; 5214; 4542; 6095; 195; 4644; 93663; 1509; 84650; 2213; 23692; 3687; 301; 23175; 10809; 23604; 3764; 3004; 80005; 11345; 3595; 30009; 4818; 2149; 5783; 3683; 5551; 56994; 8807; 3821; 9497; 57412; 493869; 5911; 1524; 9839; 53637; 154075; 2034; 79156; 197259; 54331; 158219; 33; 4635; 79634; 127124; 63951; 3006; 8819; 214; 50515; 116496; 307; 11163; 29887; 3005; 22926; 3915; 7905; 6284; 23589; 8836; 11034; 639; 81615; 202; 1891; 5613; 29957; 80150; 168537; 333926; 10930; 55794; 8347; 11172; 83988; 3820; 3684; 3459; 8905; 54502; 199; 644; 84868; 11110; 114242; 160851; 79026; 84564; 89875; 91663; 93992 |
| **Tcells.CD8.Memory.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795** | **T cells** | Signature | PMID.27789795 | 941; 23670; 3559; 3662; 6504; 10538; 64092; 112574; 81553; 3555; 22936; 7227; 952; 5606; 5272; 4860; 3627; 3600; 3665; 64135; 11274; 5341; 366; 153020; 5966; 11080; 23429; 3606; 10260; 8444; 221079; 9693; 80149; 56300; 8767; 1647; 10950; 29933; 1326; 255231; 3475; 54206; 597; 8870; 1847; 9034; 23135; 23764; 6351; 2643; 6648; 2180; 1844; 7124; 3553; 3552; 2921; 7128; 4792; 29126; 64332; 8740; 80231; 1992; 25932; 1051; 51296; 10602; 11213; 3303; 1536; 929; 6280; 6279; 59342; 2212; 3162; 29992; 84419; 11006; 942; 967; 4067; 6775; 57823; 132864; 196383; 1880; 25976; 57485; 79720; 7050; 30015; 4793; 5932; 3725; |

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|---|---|---|---|---|
| | | | | 6236; 10221; 6520; 2669; 5996; 1164; 2717; 9456; 255758; 4783; 388; 22822; 7832; 1843; 3726; 9592; 3164; 2355; 467; 80219; 2354; 1390; 4929; 5734; 8013; 84275; 10253; 6498; 10206; 9683; 80824; 7185; 3383; 330; 65108; 4616; 85463; 4794; 1026; 6675; 5292; 127544; 338339; 8878; 4780; 222255; 51278; 7850 |
| **Serum.Response.Up TCGA Immunity.2018 PMID.29628290** | **T cells** | Signature | PMID.29628290 | 84131; 27258; 55631; 9263; 6184; 3726; 79902; 2318; 3151; 10799; 29796; 7965; 1111; 51534; 11340; 79172; 56902; 6566; 79084; 51465; 51491; 4521; 10592; 292; 9818; 8847; 11333; 56267; 10063; 56647; 5340; 85397; 6631; 10733; 10204; 25804; 6611; 10969; 93081; 7416; 10213; 26292; 64750; 2791; 2152; 3575; 83990; 8399183990; 83991; 3181; 1633; 84266; 56263; 9086156263; 90861; 4478; 7168; 219844; 115106; 9688; 6635; 3655; 55839; 53838; 8836; 5214; 2193; 27102; 387103; 7277; 6434; 7372; 51154; 55270; 5237; 55276; 79007; 6628; 4331; 129401; 6921; 51668; 84798; 3399; 79711; 10056; 1981; 220134; 79157; 5329; 153562; 4172; 1719; 10193; 3398; 3015; 1017; 56926; 55055; 6993; 56942; 55972; 389; 22948; 9601; 6626; 10432; 9260; 26207; 7170; 23603; 10613; 5059; 106065059; 10606; 51002; 348235; 4603; 80851; 675; 56681; 51728; 28957; 6494728957; 64947; 57122; 7283; 5411; 83648; 5983; 4637; 4176; 55110; 23625; 10452; 55038; 4504; 4522; 5718; 4605; 51192; 56675; 7430; |

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|---|---|---|---|---|
| | | | | 29902; 2822; 6723; 5865; 57486; 4494; 51330; 7167; 3037; 79135; 150726; 51253; 79807; 6382; 84058; 51444; 378708; 64777; 2023; 1326; 222865; 9784; 11103; 6876; 5036; 8607; 6632; 4017; 5427; 22919; 92856; 2013; 5708; 4233; 7866; 3999; 848233999; 84823; 5352; 57552; 4830; 6800; 201254; 86; 10301; 6627; 10951; 55646; 9199; 5216; 55835; 23406; 57213; 10208; 6182; 9510; 10539; 55884; 51021; 6495951021; 64959; 64858; 8195; 84319; 80315; 200162; 359815; 6675; 27235; 11169; 131566; 23065; 51128; 5688; 5702; 10980; 1854; 10465; 26147; 7169; 28985; 1978; 10236 |
| **Lymphocyte.Infiltration.Expression.Score TCGA Immunity.2018 PMID.29628290** | **T cells** | Signature | PMID.29628290 | 6352; 930; 951; 915; 916; 917; 919; 973; 974; 925; 926; 3502; 28219; 3512; 3537; 28840; 929; 3932; 4050; 931 |
| **Tcells.Follicular.Helper TCGA Immunity.2018 PMID.29628290** | **T cells** | Signature | PMID.29628290 | 27087; 643; 753; 8851; 1114; 1117; 10563; 23462; 8362; 3382; 8645; 57535; 4094; 28986; 57496; 4646; 4647; 23178; 5133; 10585; 5783; 5816; 54436; 55423; 56301; 4086; 7972; 6489; 27347; 63892; 9760; 7253; 92595 |
| **Tcells.Gamma.Delta TCGA Immunity.2018 PMID.29628290** | **T cells** | Signature | PMID.29628290 | 10485; 11126; 9638; 445347; 6964; 6983; 28531 |
| **Immune.CD8.GZMK TCGA.BRCA.1198 JCI.2020 PMID.32573490** | **T cells** | Signature | PMID.32573490 | 729230; 497189; 1236; 2672; 387357; 84636; 387751; 10666; 959; 115352; 5133; 100188949; 120425; 9840; 56253; 8320; 283897; 5579; 22914; 256380; 29851; 201633; 29909; 151888; 128611; 925; 10663; 154075; 50852; 3003; 149628; 30009; 3001; 939; 4063; 6504; 4068; 114836; 917; 3702; 10225; 55423; 53347; 3932; 2833; 27240; |

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|---|---|---|---|---|
| | | | | 915; 914; 916; 919; 921; 3561; 962; 84174; 6352; 4818; 5551; 923; 79037; 3004; 5790; 8698; 7535; 9744; 1731; 374403; 64926; 147138; 11184; 11151; 9051; 27040; 3718; 9806; 11262; 8530; 1043; 924; 80342 |
| **Immune.Cell.Content Verhaak NatCommun.2013 PMID.24113773** | **T cells** | Signature | PMID.24113773 | 10320; 9910; 3575; 55303; 3106; 3937; 4046; 2533; 5341; 3055; 3587; 10859; 3071; 3903; 4688; 1536; 5788; 7805; 963; 2124; 6503; 3689; 4542; 3059; 4332; 3561; 962; 313; 6352; 4050; 9535; 474344; 3003; 7940; 8477; 10288; 7456; 951; 51411; 2207; 7305; 10875; 2313; 3394; 55843; 10019; 7133; 1794; 914; 9459; 11151; 23643; 4069; 3683; 7128; 6039; 7040; 9051; 8530; 5996; 2268; 6402; 64780; 80342; 3676; 9935; 397; 3566; 399; 3113; 4818; 4689; 9404; 3702; 6404; 3115; 915; 11314; 3560; 113; 5734; 5552; 919; 1236; 4478; 241; 5732; 5880; 2634; 7409; 9976; 9934; 4792; 6280; 10437; 64747; 9770; 1200; 391; 50856; 3002; 79037; 6279; 834; 597; 3133; 3820; 10578; 5873; 8807; 8459; 2014; 51291; 3932; 9235; 5790; 3965; 26112; 25939; 6890; 2633; 1520; 2999; 101; 2745; 5551; 969; 3108; 972; 22914; 5791; 3122; 8875; 10312; 1475; 7535; 3134; 3135; 1043; 9936; 939 |
| **TLS.Hallmark Cabrita Nature.2020 PMID.31942071** | **TLS** | Signature | PMID.31942071 | 6363; 6366; 10563; 1236; 643; 27074; 6402 |
| **TLS.Known.Markers Cabrita Nature.2020 PMID.31942071** | **TLS** | Signature | PMID.31942071 | 1236; 10563; 6363; 7852; 6366; 27074; 942; 604; 6402 |
| **TLS.12genes.Chemokine Zhu FrontImmunol.2017 PMID.28713385** | **TLS** | Signature | PMID.28713385 | 6348; 6347; 10563; 6366; 4283; 6355; 6363; 6352; 6373; 6351; 6362; 3627 |

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|---|---|---|---|---|
| **TLS.High.In.No.Response Helmink Nature.2020 PMID.31942075** | **TLS** | Signature | PMID.31942075 | 51129; 7079; 80760; 4017; 5046; 5055; 374; 3451; 5212; 347; 8534; 133; 1917; 79884; 7056; 5522; 8862; 57722; 147495; 6098; 27295; 4099; 8515; 154664; 2260; 27237; 63982; 79054; 374946; 84929; 148281; 200162; 6620; 5009; 114788; 23743; 7087; 89886; 1770; 55511 |
| **TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075** | **TLS** | Signature | PMID.31942075 | 4283; 2633; 3001; 915; 3627; 8115; 973; 9235; 3620; 3512; 5450; 6890; 710; 51237; 3821; 923; 158471; 3659; 3458; 5920; 115361; 10396; 151888; 3824; 54900; 83416; 26279; 8368; 56145; 56146; 8395; 55118; 260436; 3738; 100423062; 91319; 389643 |
| **TLS.9genes Cabrita Nature.2020 PMID.31942071** | **TLS** | Signature | PMID.31942071 | 5730; 912; 974; 1235; 27040; 1071; 83758; 9086; 8631 |
| **TLS.Tumors.w.TLS.and.CD8.vs.CD8.alone Cabrita Nature.2020 PMID.31942071** | **TLS** | Signature | PMID.31942071 | 962; 4050; 1043; 915; 6402; 80342; 939; 51316; 9595; 973; 1236; 974; 4033; 952; 3957; 917; 919; 3512; 330; 51237; 6363; 8875; 6366; 730; 5790; 3112; 3394; 923; 27040; 912; 5730; 971; 54923; 1235; 7351; 54900; 64333; 374403; 81704; 11040; 9086; 54855; 1776; 5777; 5336; 8631; 55840; 114836; 160365; 202309; 115352; 83758; 1071; 79037 |

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## eTable 2. Comparison of Baseline Characteristics of the Patients From the CALGB 40601 Event-Free Survival (EFS) and Landmark Subpopulations

| Characteristic | CALGB40601 EFS cohort (N = 230) | CALGB40601 Landmark cohort (N = 227) | p-value |
|---|---|---|---|
| **Age (median, IQ range)** | 49 (41, 56) | 49 (41, 56) | NS |
| **Menopause status** | | | NS |
| Postmenopausal | 89 (38.70%) | 87 (38.33%) | |
| Premenopausal | 141 (61.30%) | 140 (61.67%) | |
| **HR status** | | | NS |
| HR-negative | 93 (40.43%) | 91 (40.09%) | |
| HR-positive | 137 (59.57%) | 136 (59.91%) | |
| **Clinical Stage** | | | NS |
| Stage I | 0 (0%) | 0 (0%) | |
| Stage II | 157 (68.26%) | 156 (68.72%) | |
| Stage III | 73 (31.74%) | 71 (31.28%) | |
| **Treatment** | | | NS |
| HL +/- ET | 0 (0%) | 0 (0%) | |
| TH | 89 (38.70%) | 87 (38.33%) | |
| THL | 95 (41.30%) | 95 (41.85%) | |
| TL | 46 (20%) | 45 (19.82%) | |
| **Intrinsic subtype** | | | NS |
| Basal-like | 19 (8.26%) | 19 (8.37%) | |
| HER2-Enriched | 131 (56.96%) | 129 (56.83%) | |
| Luminal A | 26 (11.30%) | 26 (11.45%) | |
| Luminal B | 32 (13.91%) | 31 (13.66%) | |
| Normal-like | 22 (9.57%) | 22 (9.69%) | |

Statistical differences were assessed using a Wilcoxon rank sum test (for the age) and Pearson's Chi-squared test (for the rest of the variables).
EFS: event-free survival; IQ: interquartile range; HR: hormone receptor; H: trastuzumab; L: lapatinib; ET: endocrine therapy; T: weekly paclitaxel; NS: no significant.

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## eTable 3. Correlation of Tumor-Infiltrating Lymphocytes (TILs) and Immune Gene Expression Signatures (iGES) in CALGB 40601 and PAMELA

| CALGB 40601 | Coefficient | p-value | Coefficient tertiles | p-value tertiles |
|---|---|---|---|---|
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.61 | <0.001 | 0.53 | <0.001 |
| Stromal.Inflammation Heng JPathol.2017 PMID.27861902 | 0.6 | <0.001 | 0.54 | <0.001 |
| TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075 | 0.6 | <0.001 | 0.53 | <0.001 |
| IFN.5.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.59 | <0.001 | 0.55 | <0.001 |
| Tcells.CD4.Memory.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.59 | <0.001 | 0.57 | <0.001 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.59 | <0.001 | 0.51 | <0.001 |
| NK.CD56dim Bindea Immunity.2013 PMID.24138885 | 0.58 | <0.001 | 0.52 | <0.001 |
| Immune.Active Hollern Cell.2019 PMID.31730857 | 0.57 | <0.001 | 0.50 | <0.001 |
| CTLA4.Single.Gene Hollern Cell.2019 PMID.31730857 | 0.57 | <0.001 | 0.51 | <0.001 |
| Tcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.56 | <0.001 | 0.49 | <0.001 |
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 0.56 | <0.001 | 0.52 | <0.001 |
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.56 | <0.001 | 0.51 | <0.001 |
| PDCD1.Single.Gene Pare AnnOncol.2019 PMID.30165419 | 0.56 | <0.001 | 0.50 | <0.001 |
| Macrophages.M1 CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | <0.001 | 0.51 | <0.001 |
| Immune.CD8.GZMK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.55 | <0.001 | 0.48 | <0.001 |
| CD8.Cluster Iglesia CCR.2014 PMID.24916698 | 0.55 | <0.001 | 0.47 | <0.001 |
| Cytotoxic.Lymphocytes.MCP Petitprez Nature.2020 PMID.31942077 | 0.55 | <0.001 | 0.51 | <0.001 |
| Cytotoxic.cells Bindea Immunity.2013 PMID.24138885 | 0.55 | <0.001 | 0.49 | <0.001 |
| Tcells.Survival.2gene Petitprez Nature.2020 PMID.31942077 | 0.55 | <0.001 | 0.49 | <0.001 |
| CTLA4.Pathway GSEA.BIOCARTA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.55 | <0.001 | 0.49 | <0.001 |
| Immune.CTLA4.CXCL.FOXP3 TCGA.BRCA.1198 JCI.2020 PMID.32573490. | 0.55 | <0.001 | 0.52 | <0.001 |
| Immune.Suppression Kardos JCIInsight.2016 PMID.27699256 | 0.54 | <0.001 | 0.52 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 0.54 | <0.001 | 0.50 | <0.001 |
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 0.54 | <0.001 | 0.49 | <0.001 |

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|---|---|---|---|---|
| Tcells.Gamma.Delta CIBERSORT NatMethods.2015 PMID.25822800 | 0.54 | <0.001 | 0.45 | <0.001 |
| MERCK.Immune.Signature Cristescu Science.2018 PMID.30309915 | 0.54 | <0.001 | 0.45 | <0.001 |
| Immune.87 Perez JCO.2015 PMID.2560586 | 0.54 | <0.001 | 0.46 | <0.001 |
| Tcells.Th1.cells Bindea Immunity.2013 PMID.24138885 | 0.54 | <0.001 | 0.53 | <0.001 |
| CD274.Single.Gene Hollern Cell.2019 PMID.31730857 | 0.54 | <0.001 | 0.51 | <0.001 |
| Bcells.Immature Charoentong CellRep.2017 PMID.28052254 | 0.54 | <0.001 | 0.48 | <0.001 |
| Tcells.CD8 CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | <0.001 | 0.47 | <0.001 |
| NK.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | <0.001 | 0.45 | <0.001 |
| Immune.cell.Cluster.PerouLab Fan.GSEA.GP2 BMCMedGenomics.2011 PMID.21214954 | 0.53 | <0.001 | 0.51 | <0.001 |
| Tcells.MCP Petitprez Nature.2020 PMID.31942077 | 0.53 | <0.001 | 0.48 | <0.001 |
| Immune.Hot.vs.Cold.CD8 Cabrita Nature.2020 PMID.31942071 | 0.53 | <0.001 | 0.48 | <0.001 |
| Immune.CD4.CD53.CD84.BTK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.53 | <0.001 | 0.48 | <0.001 |
| MHC.II Rody BreastCancerResearch.2008 PMID.19272155 | 0.53 | <0.001 | 0.47 | <0.001 |
| Tcells.Resident.Memory.Single.cell Savas NatMed.2018 PMID.29942092 | 0.52 | <0.001 | 0.46 | <0.001 |
| Tcells.Follicular.Helper CIBERSORT NatMethods.2015 PMID.25822800 | 0.52 | <0.001 | 0.45 | <0.001 |
| Tcells.CD4.Memory.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.52 | <0.001 | 0.42 | <0.001 |
| Tcells Bindea Immunity.2013 PMID.24138885 | 0.52 | <0.001 | 0.42 | <0.001 |
| Tcells.Th1.cells Charoentong CellRep.2017 PMID.28052254 | 0.52 | <0.001 | 0.46 | <0.001 |
| Cytolytic.Activity Rooney Cell.2015 PMID.25594174 | 0.51 | <0.001 | 0.45 | <0.001 |
| NK ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.51 | <0.001 | 0.48 | <0.001 |
| MCD3.CD8 Fan BMCMedGenomics.2011 PMID.21214954 | 0.51 | <0.001 | 0.43 | <0.001 |
| NK.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.51 | <0.001 | 0.46 | <0.001 |
| Dendritic.cells.Activated Bindea Immunity.2013 PMID.24138885 | 0.51 | <0.001 | 0.51 | <0.001 |
| Macrophages.Th1.Cluster Iglesia CCR.2014 PMID.24916698 | 0.51 | <0.001 | 0.48 | <0.001 |
| Tcells.CD8.Activated Charoentong CellRep.2017 PMID.28052254 | 0.51 | <0.001 | 0.45 | <0.001 |
| STAT1 Rody BreastCancerResearch.2008 PMID.19272155 | 0.5 | <0.001 | 0.48 | <0.001 |
| Tcells.Regulatory.Tregs CIBERSORT NatMethods.2015 PMID.25822800 | 0.5 | <0.001 | 0.41 | <0.001 |

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|---|---|---|---|---|
| TLS.Tumors.w.TLS.and.CD8.vs.CD8.alone Cabrita Nature.2020 PMID.31942071 | 0.5 | <0.001 | 0.44 | <0.001 |
| Plasma.cells CIBERSORT NatMethods.2015 PMID.25822800 | 0.5 | <0.001 | 0.45 | <0.001 |
| Bcells.IL10.Plus Lin JImmunol.2014 PMID.25080484 | 0.5 | <0.001 | 0.48 | <0.001 |
| Macrophages.Monocytes.CSF1.Response Beck CCR.2009 PMID.19188147 | 0.5 | <0.001 | 0.49 | <0.001 |
| CSF1.Response TCGA Immunity.2018 PMID.29628290 | 0.5 | <0.001 | 0.49 | <0.001 |
| MDSC Charoentong CellRep.2017 PMID.28052254 | 0.5 | <0.001 | 0.50 | <0.001 |
| Tcells.CD8.Exhausted.at.day.8.post.Imm.vs. Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.5 | <0.001 | 0.47 | <0.001 |
| Bcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.5 | <0.001 | 0.48 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.1 Pauken Science.2016 PMID.27789795 | 0.5 | <0.001 | 0.45 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.5 | <0.001 | 0.45 | <0.001 |
| Tcells.NK.51genes Miller GenomeBiol.2013 PMID.23618380 | 0.49 | <0.001 | 0.42 | <0.001 |
| Immune.Cell.Content Verhaak NatCommun.2013 PMID.24113773 | 0.49 | <0.001 | 0.46 | <0.001 |
| Tcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.49 | <0.001 | 0.42 | <0.001 |
| LCK Rody BreastCancerResearch.2008 PMID.19272155 | 0.49 | <0.001 | 0.46 | <0.001 |
| Tcells.Bcells.Lymphocyte.Infiltration Calabro BreastCancerResTreat.2009 PMID.18592372 | 0.49 | <0.001 | 0.39 | <0.001 |
| Lymphocyte.Infiltration.Expression.Score TCGA Immunity.2018 PMID.29628290 | 0.49 | <0.001 | 0.39 | <0.001 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.49 | <0.001 | 0.46 | <0.001 |
| Tcells.CD4.Activated Charoentong CellRep.2017 PMID.28052254 | 0.49 | <0.001 | 0.48 | <0.001 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 0.49 | <0.001 | 0.43 | <0.001 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 0.48 | <0.001 | 0.44 | <0.001 |
| TLS.12genes.Chemokine Zhu FrontImmunol.2017 PMID.28713385 | 0.48 | <0.001 | 0.45 | <0.001 |
| Tcells.Bcell.KEGG.hematopoietic.cell.lineage GSEA.GP2 ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.48 | <0.001 | 0.42 | <0.001 |
| Tcells.NK.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.48 | <0.001 | 0.44 | <0.001 |
| Monocytes.Dendritic.25genes Miller GenomeBiol.2013 PMID.23618380 | 0.48 | <0.001 | 0.46 | <0.001 |
| Bcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.48 | <0.001 | 0.43 | <0.001 |
| Tcells.CD4.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.47 | <0.001 | 0.41 | <0.001 |

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|---|---|---|---|---|
| Bcells.Plasma.cells.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.47 | <0.001 | 0.43 | <0.001 |
| Tcells.CD8.MCP Petitprez Nature.2020 PMID.31942077 | 0.46 | <0.001 | 0.35 | <0.001 |
| Bcells.Plasmablast Dybaer JCO.2015 PMID.25800755 | 0.46 | <0.001 | 0.39 | <0.001 |
| Dendritic.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.46 | <0.001 | 0.44 | <0.001 |
| Bcells.Memory CIBERSORT NatMethods.2015 PMID.25822800 | 0.46 | <0.001 | 0.41 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.Metagene.2 Pauken Science.2016 PMID.27789795 | 0.46 | <0.001 | 0.41 | <0.001 |
| MHC.11genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.46 | <0.001 | 0.42 | <0.001 |
| Immune.HLA.D TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.46 | <0.001 | 0.38 | <0.001 |
| Tcells.CD8.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.45 | <0.001 | 0.40 | <0.001 |
| Immune.CD19 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.45 | <0.001 | 0.38 | <0.001 |
| Tcells.Regulatory Charoentong CellRep.2017 PMID.28052254 | 0.45 | <0.001 | 0.43 | <0.001 |
| Tcells.Activation Petitprez Nature.2020 PMID.31942077 | 0.45 | <0.001 | 0.42 | <0.001 |
| Dendritic.cells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.45 | <0.001 | 0.44 | <0.001 |
| Bcells Bindea Immunity.2013 PMID.24138885 | 0.44 | <0.001 | 0.37 | <0.001 |
| Bcells.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.44 | <0.001 | 0.39 | <0.001 |
| PD1.Signaling.Reactome GSEA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.44 | <0.001 | 0.41 | <0.001 |
| Bcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.43 | <0.001 | 0.34 | <0.001 |
| Immune.HLA.A.F TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.43 | <0.001 | 0.41 | <0.001 |
| Bcells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.43 | <0.001 | 0.36 | <0.001 |
| Macrophages ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.43 | <0.001 | 0.46 | <0.001 |
| Monocytes.Dendritic.cell.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.43 | <0.001 | 0.34 | <0.001 |
| MHC.I Rody BreastCancerResearch.2008 PMID.19272155 | 0.42 | <0.001 | 0.35 | <0.001 |
| Neutrophils.Activated.Lung Janiszewska NatCellBiol.2019 PMID.31263265 | 0.42 | <0.001 | 0.36 | <0.001 |
| MHC.I.CoreGenes Lauss NatCommun.2017 PMID29170503 | 0.41 | <0.001 | 0.38 | <0.001 |
| Bcells Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.41 | <0.001 | 0.38 | <0.001 |
| NK.MCP Helmink Nature.2020 PMID.31942077 | 0.41 | <0.001 | 0.29 | <0.001 |
| Monocytes CIBERSORT NatMethods.2015 PMID.25822800 | 0.41 | <0.001 | 0.45 | <0.001 |

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|---|---|---|---|---|
| HCK Rody BreastCancerResearch.2008 PMID.19272155 | 0.41 | <0.001 | 0.43 | <0.001 |
| TLS.Known.Markers Cabrita Nature.2020 PMID.31942071 | 0.4 | <0.001 | 0.36 | <0.001 |
| Monocytes ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.4 | <0.001 | 0.35 | <0.001 |
| MDSC.Neutrophil Youn LeukocBiol.2012 PMID.21954284 | 0.39 | <0.001 | 0.36 | <0.001 |
| Macrophages.M0 CIBERSORT NatMethods.2015 PMID.25822800 | 0.39 | <0.001 | 0.44 | <0.001 |
| TLS.Hallmark Cabrita Nature.2020 PMID.31942071 | 0.37 | <0.001 | 0.30 | <0.001 |
| Tcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.37 | <0.001 | 0.34 | <0.001 |
| Tcells.Central.Memory Bindea Immunity.2013 PMID.24138885 | 0.37 | <0.001 | 0.26 | <0.001 |
| Neutrophils CIBERSORT NatMethods.2015 PMID.25822800 | 0.37 | <0.001 | 0.36 | <0.001 |
| Bcells.Tcells.Cooperation Hollern Cell.2019 PMID.31730857 | 0.35 | <0.001 | 0.28 | <0.001 |
| Immune.GIMAP.IL16 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.35 | <0.001 | 0.32 | <0.001 |
| Tcells.CD8.Exhausted.Anti.PDL1.vs.Control. Metagene.1 Pauken Science.2016 PMID.27789795 | 0.35 | <0.001 | 0.39 | <0.001 |
| IFNg.Module11 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 0.35 | <0.001 | 0.36 | <0.001 |
| IFN.Cluster.GSEA.GP11 Fan BMCMedGenomics.2011 PMID.21214954 | 0.35 | <0.001 | 0.37 | <0.001 |
| Bcells.IL10.Minus Lin JImmunol.2014 PMID.25080484 | 0.33 | <0.001 | 0.27 | <0.001 |
| Monocytes Charoentong CellRep.2017 PMID.28052254 | 0.33 | <0.001 | 0.27 | <0.001 |
| Dendritic.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.33 | <0.001 | 0.32 | <0.001 |
| Eosinophils CIBERSORT NatMethods.2015 PMID.25822800 | 0.33 | <0.001 | 0.31 | <0.001 |
| TLS.9genes Cabrita Nature.2020 PMID.31942071 | 0.32 | <0.001 | 0.24 | <0.001 |
| Bcells.Extended Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.31 | <0.001 | 0.29 | <0.001 |
| Macrophages Bindea Immunity.2013 PMID.24138885 | 0.31 | <0.001 | 0.31 | <0.001 |
| Tcells.Gamma.Delta Bindea Immunity.2013 PMID.24138885 | 0.31 | <0.001 | 0.26 | <0.001 |
| Tcells.Gamma.Delta TCGA Immunity.2018 PMID.29628290 | 0.31 | <0.001 | 0.26 | <0.001 |
| Tcells.CD8.Exhausted.vs.AntiPDL1.2 Pauken Science.2016 PMID.27789795 | 0.31 | <0.001 | 0.28 | <0.001 |
| Tcells.Follicular.Helper Bindea Immunity.2013 PMID.24138885 | 0.3 | <0.001 | 0.26 | <0.001 |
| Tcells.Follicular.Helper TCGA Immunity.2018 PMID.29628290 | 0.3 | <0.001 | 0.26 | <0.001 |

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|---|---|---|---|---|
| Macrophages.M2 CIBERSORT NatMethods.2015 PMID.25822800 | 0.3 | <0.001 | 0.27 | <0.001 |
| Bcells.Centrocyte Dybaer JCO.2015 PMID.25800755 | 0.28 | <0.001 | 0.25 | <0.001 |
| MDSC.Tumor.Macrophages Schlecker JImmunol.2012 PMID.23152559 | 0.28 | <0.001 | 0.30 | <0.001 |
| Bcells.Memory Dybaer JCO.2015 PMID.25800755 | 0.28 | <0.001 | 0.27 | <0.001 |
| IFNa.Module10 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 0.28 | <0.001 | 0.33 | <0.001 |
| Granulocytes.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.28 | <0.001 | 0.28 | <0.001 |
| Dendritic.cells Bindea Immunity.2013 PMID.24138885 | 0.26 | <0.001 | 0.26 | <0.001 |
| IFN.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.26 | <0.001 | 0.29 | <0.001 |
| Tcells.CD8.Exhausted.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 0.25 | 0.001 | 0.23 | 0.001 |
| Influenza.11genes Khatri Immunity.2015 PMID.26682989 | 0.25 | <0.001 | 0.26 | <0.001 |
| Immune.14 Perez JCO.2015 PMID.2560586 | 0.24 | <0.001 | 0.23 | 0.001 |
| Macrophages.M2 Ghassabeh Blood.2006 PMID.16556895 | 0.23 | 0.001 | 0.22 | 0.001 |
| CD68.Cluster Iglesia CCR.2014 PMID.24916698 | 0.23 | 0.001 | 0.21 | 0.002 |
| Proliferation.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.23 | 0.003 | 0.22 | 0.001 |
| Tcells.CD8.Effector.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 0.23 | 0.003 | 0.22 | 0.001 |
| Tcells.CD4.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.23 | <0.001 | 0.25 | <0.001 |
| Mast.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.23 | <0.001 | 0.18 | 0.01 |
| Mast.cell Charoentong CellRep.2017 PMID.28052254 | 0.22 | 0.001 | 0.23 | 0.001 |
| Tcells.Regulatory.cell.2gene Petitprez Nature.2020 PMID.31942077 | 0.22 | 0.001 | 0.17 | 0.01 |
| Neutrophils ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.22 | <0.001 | 0.27 | <0.001 |
| Denditic.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.21 | 0.003 | 0.24 | <0.001 |
| Bcells.Centroblast Dybaer JCO.2015 PMID.25800755 | 0.21 | 0.004 | 0.16 | 0.02 |
| Tcells.Follicular.Helper Charoentong CellRep.2017 PMID.28052254 | 0.2 | 0.001 | 0.21 | 0.002 |
| MDSC.Tumor Schlecker JImmunol.2012 PMID.23152559 | 0.2 | 0.001 | 0.22 | 0.001 |
| Serum.Response.Up TCGA Immunity.2018 PMID.29628290 | 0.2 | 0.001 | 0.12 | 0.07 |
| Neutrophils Bindea Immunity.2013 PMID.24138885 | 0.2 | 0.013 | 0.23 | 0.001 |
| Tcells.Th2 Charoentong CellRep.2017 PMID.28052254 | 0.18 | <0.001 | 0.17 | 0.01 |

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|---|---|---|---|---|
| Bcells.Naive Dybaer JCO.2015 PMID.25800755 | 0.17 | 0.002 | 0.14 | 0.04 |
| NK.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.17 | 0.002 | 0.17 | 0.01 |
| Wound.Healing Chang PlosBiol.2004 PMID.14737219 | 0.17 | 0.003 | 0.15 | 0.03 |
| MHC.24genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.17 | 0.008 | 0.15 | 0.03 |
| Mast.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.17 | 0.009 | 0.13 | 0.07 |
| NK Charoentong CellRep.2017 PMID.28052254 | 0.17 | 0.01 | 0.17 | 0.01 |
| NK.Tcell Charoentong CellRep.2017 PMID.28052254 | 0.17 | 0.01 | 0.22 | 0.001 |
| IFN.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.17 | 0.02 | 0.20 | 0.003 |
| Immune.IFN TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.17 | 0.03 | 0.20 | 0.003 |
| Tcells.CD8 Bindea Immunity.2013 PMID.24138885 | 0.17 | 0.03 | 0.05 | 0.47 |
| IFN.3.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.17 | 0.04 | 0.20 | 0.002 |
| IFN.Score.module3 TCGA Immunity.2018 PMID.29628290 | 0.17 | 0.04 | 0.20 | 0.002 |
| Eosinophils Charoentong CellRep.2017 PMID.28052254 | 0.15 | 0.03 | 0.17 | 0.014 |
| Tcells.Thelper Bindea Immunity.2013 PMID.24138885 | 0.14 | 0.012 | 0.07 | 0.29 |
| Tcells.Th17.cells Charoentong CellRep.2017 PMID.28052254 | 0.11 | 0.03 | 0.08 | 0.22 |
| Dendritic.cells.Immature. Charoentong CellRep.2017 PMID.28052254 | 0.1 | 0.04 | 0.14 | 0.05 |
| Mast.cells Bindea Immunity.2013 PMID.24138885 | -0.14 | 0.04 | -0.10 | 0.14 |
| Eosinophils Bindea Immunity.2013 PMID.24138885 | -0.16 | 0.03 | -0.07 | 0.34 |
| Immunosuppression Petitprez Nature.2020 PMID.31942077 | -0.17 | 0.01 | -0.11 | 0.10 |
| Tcells.Th17.cells Bindea Immunity.2013 PMID.24138885 | -0.18 | 0.04 | -0.16 | 0.02 |
| TGFB.score TCGA Immunity.2018 PMID.29628290 | -0.26 | <0.001 | -0.19 | 0.006 |
| TLS.High.In.No.Response Helmink Nature.2020 PMID.31942075 | -0.29 | <0.001 | -0.24 | <0.001 |
| **PAMELA** | **Coefficient** | **p-value** | | |
| IFN.5.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.71 | <0.001 | 0.64 | <0.001 |
| Stromal.Inflammation Heng JPathol.2017 PMID.27861902 | 0.7 | <0.001 | 0.63 | <0.001 |
| TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075 | 0.65 | <0.001 | 0.58 | <0.001 |
| Tcells.Bcell.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.68 | <0.001 | 0.62 | <0.001 |

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|---|---|---|---|---|
| Tcells.CD4.Memory.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.69 | <0.001 | 0.62 | <0.001 |
| Immune.Active Hollern Cell.2019 PMID.31730857 | 0.67 | <0.001 | 0.62 | <0.001 |
| Tcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.66 | <0.001 | 0.64 | <0.001 |
| Tcells.CD8 CIBERSORT NatMethods.2015 PMID.25822800 | 0.65 | <0.001 | 0.64 | <0.001 |
| CD8.Cluster Iglesia CCR.2014 PMID.24916698 | 0.65 | <0.001 | 0.62 | <0.001 |
| Cytotoxic.cells Bindea Immunity.2013 PMID.24138885 | 0.66 | <0.001 | 0.62 | <0.001 |
| Immune.CD8.GZMK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.65 | <0.001 | 0.62 | <0.001 |
| Macrophages.M1 CIBERSORT NatMethods.2015 PMID.25822800 | 0.68 | <0.001 | 0.62 | <0.001 |
| Tcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.63 | <0.001 | 0.63 | <0.001 |
| NK.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.63 | <0.001 | 0.59 | <0.001 |
| Tcells.Resident.Memory.Single.cell Savas NatMed.2018 PMID.29942092 | 0.64 | <0.001 | 0.60 | <0.001 |
| Immune.Hot.vs.Cold.CD8 Cabrita Nature.2020 PMID.31942071 | 0.66 | <0.001 | 0.64 | <0.001 |
| Tcells.Follicular.Helper CIBERSORT NatMethods.2015 PMID.25822800 | 0.65 | <0.001 | 0.61 | <0.001 |
| Immune.87 Perez JCO.2015 PMID.2560586 | 0.65 | <0.001 | 0.62 | <0.001 |
| Immune.Cell.Content Verhaak NatCommun.2013 PMID.24113773 | 0.64 | <0.001 | 0.63 | <0.001 |
| Tcells.Gamma.Delta CIBERSORT NatMethods.2015 PMID.25822800 | 0.61 | <0.001 | 0.54 | <0.001 |
| LCK Rody BreastCancerResearch.2008 PMID.19272155 | 0.64 | <0.001 | 0.59 | <0.001 |
| Tcells.CD4.Memory.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.63 | <0.001 | 0.63 | <0.001 |
| MCD3.CD8 Fan BMCMedGenomics.2011 PMID.21214954 | 0.62 | <0.001 | 0.54 | <0.001 |
| Tcells.MCP Petitprez Nature.2020 PMID.31942077 | 0.66 | <0.001 | 0.57 | <0.001 |
| Tcells.CD8.Activated Charoentong CellRep.2017 PMID.28052254 | 0.65 | <0.001 | 0.57 | <0.001 |
| TLS.Tumors.w.TLS.and.CD8.vs.CD8.alone Cabrita Nature.2020 PMID.31942071 | 0.62 | <0.001 | 0.59 | <0.001 |
| Tcells Bindea Immunity.2013 PMID.24138885 | 0.64 | <0.001 | 0.62 | <0.001 |
| Tcells.NK.51genes Miller GenomeBiol.2013 PMID.23618380 | 0.63 | <0.001 | 0.59 | <0.001 |
| MERCK.Immune.Signature Cristescu Science.2018 PMID.30309915 | 0.68 | <0.001 | 0.68 | <0.001 |
| NK.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.62 | <0.001 | 0.55 | <0.001 |
| Tcells.Bcells.Lymphocyte.Infiltration Calabro BreastCancerResTreat.2009 PMID.18592372 | 0.63 | <0.001 | 0.57 | <0.001 |

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|---|---|---|---|---|
| Lymphocyte.Infiltration.Expression.Score TCGA Immunity.2018 PMID.29628290 | 0.63 | <0.001 | 0.57 | <0.001 |
| Tcells.NK.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.61 | <0.001 | 0.56 | <0.001 |
| Immune.CTLA4.CXCL.FOXP3 TCGA.BRCA.1198 JCI.2020 PMID.32573490. | 0.71 | <0.001 | 0.67 | <0.001 |
| NK.CD56dim Bindea Immunity.2013 PMID.24138885 | 0.64 | <0.001 | 0.61 | <0.001 |
| CTLA4.Pathway GSEA.BIOCARTA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.65 | <0.001 | 0.61 | <0.001 |
| Dendritic.cells.Activated Bindea Immunity.2013 PMID.24138885 | 0.65 | <0.001 | 0.65 | <0.001 |
| Immune.CD4.CD53.CD84.BTK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.62 | <0.001 | 0.62 | <0.001 |
| Cytotoxic.Lymphocytes.MCP Petitprez Nature.2020 PMID.31942077 | 0.6 | <0.001 | 0.57 | <0.001 |
| TLS.12genes.Chemokine Zhu FrontImmunol.2017 PMID.28713385 | 0.66 | <0.001 | 0.64 | <0.001 |
| Tcells.Regulatory.Tregs CIBERSORT NatMethods.2015 PMID.25822800 | 0.61 | <0.001 | 0.57 | <0.001 |
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.62 | <0.001 | 0.52 | <0.001 |
| Macrophages.Th1.Cluster Iglesia CCR.2014 PMID.24916698 | 0.63 | <0.001 | 0.62 | <0.001 |
| Tcells.CD4.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.59 | <0.001 | 0.59 | <0.001 |
| Immune.Suppression Kardos JCIInsight.2016 PMID.27699256 | 0.67 | <0.001 | 0.64 | <0.001 |
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.61 | <0.001 | 0.54 | <0.001 |
| Tcells.CD4.Activated Charoentong CellRep.2017 PMID.28052254 | 0.64 | <0.001 | 0.60 | <0.001 |
| Macrophages.Monocytes.CSF1.Response Beck CCR.2009 PMID.19188147 | 0.62 | <0.001 | 0.60 | <0.001 |
| CSF1.Response TCGA Immunity.2018 PMID.29628290 | 0.62 | <0.001 | 0.60 | <0.001 |
| Tcells.Bcell.KEGG.hematopoietic.cell.lineage GSEA.GP2 ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.62 | <0.001 | 0.59 | <0.001 |
| STAT1 Rody BreastCancerResearch.2008 PMID.19272155 | 0.68 | <0.001 | 0.66 | <0.001 |
| CD274.Single.Gene Hollern Cell.2019 PMID.31730857 | 0.65 | <0.001 | 0.64 | <0.001 |
| Bcells.IL10.Plus Lin JImmunol.2014 PMID.25080484 | 0.58 | <0.001 | 0.51 | <0.001 |
| Tcells.CD8.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.59 | <0.001 | 0.58 | <0.001 |
| MHC.II Rody BreastCancerResearch.2008 PMID.19272155 | 0.65 | <0.001 | 0.63 | <0.001 |
| Tcells.CD8.Exhausted.at.day.8.post.Imm.vs. Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.62 | <0.001 | 0.56 | <0.001 |
| Dendritic.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.64 | <0.001 | 0.61 | <0.001 |

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|---|---|---|---|---|
| Cytolytic.Activity Rooney Cell.2015 PMID.25594174 | 0.61 | <0.001 | 0.59 | <0.001 |
| Tcells.Th1.cells Bindea Immunity.2013 PMID.24138885 | 0.57 | <0.001 | 0.54 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.1 Pauken Science.2016 PMID.27789795 | 0.64 | <0.001 | 0.60 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.64 | <0.001 | 0.60 | <0.001 |
| Bcells.Immature Charoentong CellRep.2017 PMID.28052254 | 0.57 | <0.001 | 0.56 | <0.001 |
| Immune.GIMAP.IL16 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.51 | <0.001 | 0.51 | <0.001 |
| TLS.Known.Markers Cabrita Nature.2020 PMID.31942071 | 0.58 | <0.001 | 0.53 | <0.001 |
| Immune.HLA.A.F TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.62 | <0.001 | 0.60 | <0.001 |
| NK ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.55 | <0.001 | 0.52 | <0.001 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 0.61 | <0.001 | 0.58 | <0.001 |
| Bcells.Memory CIBERSORT NatMethods.2015 PMID.25822800 | 0.57 | <0.001 | 0.47 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 0.61 | <0.001 | 0.55 | <0.001 |
| Tcells.CD8.MCP Petitprez Nature.2020 PMID.31942077 | 0.65 | <0.001 | 0.66 | <0.001 |
| Plasma.cells CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | <0.001 | 0.47 | <0.001 |
| Monocytes.Dendritic.25genes Miller GenomeBiol.2013 PMID.23618380 | 0.6 | <0.001 | 0.59 | <0.001 |
| Bcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.54 | <0.001 | 0.47 | <0.001 |
| TLS.Hallmark Cabrita Nature.2020 PMID.31942071 | 0.54 | <0.001 | 0.48 | <0.001 |
| MDSC Charoentong CellRep.2017 PMID.28052254 | 0.57 | <0.001 | 0.50 | <0.001 |
| HCK Rody BreastCancerResearch.2008 PMID.19272155 | 0.61 | <0.001 | 0.56 | <0.001 |
| Bcells.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | <0.001 | 0.44 | <0.001 |
| Macrophages.M0 CIBERSORT NatMethods.2015 PMID.25822800 | 0.62 | <0.001 | 0.60 | <0.001 |
| CTLA4.Single.Gene Hollern Cell.2019 PMID.31730857 | 0.66 | <0.001 | 0.63 | <0.001 |
| Macrophages ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.63 | <0.001 | 0.63 | <0.001 |
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 0.57 | <0.001 | 0.49 | <0.001 |
| Tcells.Th1.cells Charoentong CellRep.2017 PMID.28052254 | 0.57 | <0.001 | 0.55 | <0.001 |
| Bcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.53 | <0.001 | 0.44 | <0.001 |
| Tcells.Regulatory Charoentong CellRep.2017 PMID.28052254 | 0.55 | <0.001 | 0.50 | <0.001 |

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|---|---|---|---|---|
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 0.55 | <0.001 | 0.49 | <0.001 |
| Monocytes ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.6 | <0.001 | 0.57 | <0.001 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.56 | <0.001 | 0.53 | <0.001 |
| Bcells.Tcells.Cooperation Hollern Cell.2019 PMID.31730857 | 0.5 | <0.001 | 0.40 | <0.001 |
| Bcells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.52 | <0.001 | 0.41 | <0.001 |
| Bcells Bindea Immunity.2013 PMID.24138885 | 0.5 | <0.001 | 0.42 | <0.001 |
| Macrophages.M2 CIBERSORT NatMethods.2015 PMID.25822800 | 0.54 | <0.001 | 0.61 | <0.001 |
| Tcells.CD8.Memory.vs.Naive.Metagene.2 Pauken Science.2016 PMID.27789795 | 0.54 | <0.001 | 0.56 | <0.001 |
| MHC.I Rody BreastCancerResearch.2008 PMID.19272155 | 0.56 | <0.001 | 0.55 | <0.001 |
| Immune.HLA.D TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.55 | <0.001 | 0.50 | <0.001 |
| Dendritic.cells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.54 | <0.001 | 0.52 | <0.001 |
| PD1.Signaling.Reactome GSEA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.5 | <0.001 | 0.50 | <0.001 |
| Dendritic.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | <0.001 | 0.55 | <0.001 |
| TLS.9genes Cabrita Nature.2020 PMID.31942071 | 0.45 | <0.001 | 0.42 | <0.001 |
| MHC.I.CoreGenes Lauss NatCommun.2017 PMID29170503 | 0.57 | <0.001 | 0.59 | <0.001 |
| Tcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.39 | <0.001 | 0.43 | <0.001 |
| Bcells.Plasma.cells.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.52 | <0.001 | 0.44 | <0.001 |
| Immune.CD19 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.5 | <0.001 | 0.43 | <0.001 |
| Bcells Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.51 | <0.001 | 0.45 | <0.001 |
| MDSC.Neutrophil Youn LeukocBiol.2012 PMID.21954284 | 0.55 | <0.001 | 0.54 | <0.001 |
| MHC.11genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.47 | <0.001 | 0.39 | <0.001 |
| Monocytes CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | <0.001 | 0.51 | <0.001 |
| Bcells.Plasmablast Dybaer JCO.2015 PMID.25800755 | 0.47 | <0.001 | 0.40 | <0.001 |
| Tcells.CD8.Exhausted.Anti.PDL1.vs.Control. Metagene.1 Pauken Science.2016 PMID.27789795 | 0.52 | <0.001 | 0.53 | <0.001 |
| IFN.Cluster.GSEA.GP11 Fan BMCMedGenomics.2011 PMID.21214954 | 0.53 | <0.001 | 0.48 | <0.001 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.52 | <0.001 | 0.45 | <0.001 |

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|---|---|---|---|---|
| IFNg.Module11 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 0.51 | <0.001 | 0.49 | <0.001 |
| Monocytes.Dendritic.cell.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.53 | <0.001 | 0.59 | <0.001 |
| Tcells.Activation Petitprez Nature.2020 PMID.31942077 | 0.59 | <0.001 | 0.57 | <0.001 |
| Eosinophils CIBERSORT NatMethods.2015 PMID.25822800 | 0.5 | <0.001 | 0.42 | <0.001 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 0.51 | <0.001 | 0.41 | <0.001 |
| Tcells.Survival.2gene Petitprez Nature.2020 PMID.31942077 | 0.5 | <0.001 | 0.49 | <0.001 |
| Immune.14 Perez JCO.2015 PMID.2560586 | 0.45 | <0.001 | 0.45 | <0.001 |
| Dendritic.cells Bindea Immunity.2013 PMID.24138885 | 0.48 | <0.001 | 0.46 | <0.001 |
| Bcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.38 | <0.001 | 0.39 | <0.001 |
| Tcells.Th17.cells Charoentong CellRep.2017 PMID.28052254 | 0.44 | <0.001 | 0.33 | <0.001 |
| PDCD1.Single.Gene Pare AnnOncol.2019 PMID.30165419 | 0.52 | <0.001 | 0.45 | <0.001 |
| NK.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.39 | <0.001 | 0.40 | <0.001 |
| IFNa.Module10 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 0.44 | <0.001 | 0.39 | <0.001 |
| Mast.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.38 | <0.001 | 0.39 | <0.001 |
| Mast.cell Charoentong CellRep.2017 PMID.28052254 | 0.42 | <0.001 | 0.38 | <0.001 |
| TLS.High.In.No.Response Helmink Nature.2020 PMID.31942075 | -0.37 | <0.001 | -0.26 | <0.001 |
| Macrophages.M2 Ghassabeh Blood.2006 PMID.16556895 | 0.43 | <0.001 | 0.40 | <0.001 |
| Neutrophils CIBERSORT NatMethods.2015 PMID.25822800 | 0.41 | <0.001 | 0.39 | <0.001 |
| Granulocytes.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.48 | <0.001 | 0.53 | <0.001 |
| Influenza.11genes Khatri Immunity.2015 PMID.26682989 | 0.43 | <0.001 | 0.37 | <0.001 |
| MHC.24genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.36 | <0.001 | 0.35 | <0.001 |
| IFN.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.42 | <0.001 | 0.34 | <0.001 |
| Bcells.Extended Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.39 | <0.001 | 0.34 | <0.001 |
| Mast.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.35 | <0.001 | 0.37 | <0.001 |
| Macrophages Bindea Immunity.2013 PMID.24138885 | 0.47 | <0.001 | 0.48 | <0.001 |
| MDSC.Tumor.Macrophages Schlecker JImmunol.2012 PMID.23152559 | 0.37 | <0.001 | 0.37 | <0.001 |
| Monocytes Charoentong CellRep.2017 PMID.28052254 | 0.29 | <0.001 | 0.30 | 0.001 |

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|---|---|---|---|---|
| Tcells.CD4.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.41 | <0.001 | 0.36 | <0.001 |
| Neutrophils.Activated.Lung Janiszewska NatCellBiol.2019 PMID.31263265 | 0.33 | <0.001 | 0.40 | <0.001 |
| Tcells.Central.Memory Bindea Immunity.2013 PMID.24138885 | 0.29 | <0.001 | 0.26 | 0.003 |
| Tcells.Follicular.Helper Bindea Immunity.2013 PMID.24138885 | 0.34 | <0.001 | 0.36 | <0.001 |
| Tcells.Follicular.Helper TCGA Immunity.2018 PMID.29628290 | 0.34 | <0.001 | 0.36 | <0.001 |
| Neutrophils.Activated.Blood Janiszewska NatCellBiol.2019 PMID.31263265 | 0.33 | <0.001 | 0.28 | 0.002 |
| Neutrophils ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.38 | <0.001 | 0.38 | <0.001 |
| Bcells.Naive Dybaer JCO.2015 PMID.25800755 | 0.28 | <0.001 | 0.23 | 0.008 |
| Tcells.CD4.Central.Memory Charoentong CellRep.2017 PMID.28052254 | 0.25 | <0.001 | 0.32 | <0.001 |
| Tcells.CD8.Exhausted.vs.AntiPDL1.2 Pauken Science.2016 PMID.27789795 | 0.29 | 0.001 | 0.23 | 0.008 |
| NK.MCP Helmink Nature.2020 PMID.31942077 | 0.21 | 0.001 | 0.13 | 0.14 |
| TGFB.score TCGA Immunity.2018 PMID.29628290 | -0.22 | 0.001 | -0.10 | 0.25 |
| Tcells.CD8 Bindea Immunity.2013 PMID.24138885 | 0.24 | 0.001 | 0.19 | 0.03 |
| Tcells.Follicular.Helper Charoentong CellRep.2017 PMID.28052254 | 0.27 | 0.001 | 0.31 | <0.001 |
| Bcells.IL10.Minus Lin JImmunol.2014 PMID.25080484 | 0.34 | 0.002 | 0.28 | 0.001 |
| Immune.IFN TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.28 | 0.002 | 0.23 | 0.01 |
| IFN.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.27 | 0.003 | 0.24 | 0.007 |
| NK.CD56bright Bindea Immunity.2013 PMID.24138885 | 0.26 | 0.003 | 0.21 | 0.02 |
| NK.Tcell Charoentong CellRep.2017 PMID.28052254 | 0.36 | 0.003 | 0.37 | <0.001 |
| IFN.3.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.27 | 0.004 | 0.25 | 0.004 |
| IFN.Score.module3 TCGA Immunity.2018 PMID.29628290 | 0.27 | 0.004 | 0.25 | 0.004 |
| MDSC.Tumor Schlecker JImmunol.2012 PMID.23152559 | 0.33 | 0.004 | 0.30 | 0.001 |
| Tcells.Regulatory.cell.2gene Petitprez Nature.2020 PMID.31942077 | 0.31 | 0.007 | 0.34 | <0.001 |
| Immunosuppression Petitprez Nature.2020 PMID.31942077 | -0.23 | 0.009 | -0.14 | 0.13 |
| Bcells.Memory Dybaer JCO.2015 PMID.25800755 | 0.23 | 0.01 | 0.20 | 0.02 |
| Tcells.Th2 Charoentong CellRep.2017 PMID.28052254 | 0.21 | 0.01 | 0.22 | 0.01 |
| Tcells.CD8.Exhausted.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 0.22 | 0.01 | 0.17 | 0.05 |

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|---|---|---|---|---|
| NK Charoentong CellRep.2017 PMID.28052254 | 0.25 | 0.01 | 0.24 | 0.006 |
| Bcells.Memory Charoentong CellRep.2017 PMID.28052254 | 0.22 | 0.02 | 0.16 | 0.08 |
| Neutrophils Bindea Immunity.2013 PMID.24138885 | 0.24 | 0.03 | 0.24 | 0.006 |
| IFN Rody BreastCancerResearch.2008 PMID.19272155 | 0.21 | 0.03 | 0.21 | 0.02 |
| Bcells.Centroblast Dybaer JCO.2015 PMID.25800755 | 0.19 | 0.03 | 0.12 | 0.20 |
| Tcells.Effector.Memory Bindea Immunity.2013 PMID.24138885 | 0.14 | 0.03 | 0.22 | 0.01 |
| Hematopoietic.Stem.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | -0.14 | 0.04 | -0.17 | 0.06 |
| Proliferation.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.2 | 0.04 | 0.11 | 0.22 |
| CD103.Negative Broz CancerCell.2014 PMID.25446897 | 0.2 | 0.04 | 0.21 | 0.02 |
| Tcells.CD8.Effector.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 0.19 | 0.04 | 0.09 | 0.32 |

Only the immune signatures significantly associated with TILs as continuous variables in each study are shown. Spearman's correlation coefficients and p-values (95% CI) are included. P-values are adjusted for multiple testing using a Benjamini & Hochberg method to control the False Discovery Rate.

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**eTable 4. Association of Tumor-Infiltrating Lymphocytes (TILs) and Immune Gene Expression Signatures (iGES) With Pathologic Complete Response (pCR) in the Combined CALGB 40601 and PAMELA Data Set**

| All Signatures | OR | Lower CI | Upper CI | p value | AIC |
|---|---|---|---|---|---|
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 1.93 | 1.51 | 2.51 | <0.001 | 453.15 |
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 1.94 | 1.51 | 2.51 | <0.001 | 453.11 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 2.01 | 1.57 | 2.63 | <0.001 | 450.06 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 1.81 | 1.42 | 2.33 | <0.001 | 458.11 |
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.77 | 1.40 | 2.27 | <0.001 | 459.16 |
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 1.64 | 1.30 | 2.09 | 0.001 | 464.74 |
| NK.CD56dim Bindea Immunity.2013 PMID.24138885 | 1.65 | 1.31 | 2.12 | 0.001 | 464.57 |
| Bcells.Plasma.cells.Metagene Miller GenomeBiol.2013 PMID.23618380 | 1.65 | 1.30 | 2.11 | 0.001 | 464.76 |
| TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075 | 1.64 | 1.30 | 2.10 | 0.001 | 465.05 |
| Immune.CTLA4.CXCL.FOXP3 TCGA.BRCA.1198 JCI.2020 PMID.32573490. | 1.63 | 1.28 | 2.10 | 0.002 | 466.12 |
| CD274.Single.Gene Hollern Cell.2019 PMID.31730857 | 1.55 | 1.23 | 1.98 | 0.005 | 468.41 |
| Bcells.Centroblast Dybkae JCO.2015 PMID.25800755 | 1.55 | 1.23 | 1.98 | 0.005 | 468.37 |
| Denditic.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.48 | 1.18 | 1.88 | 0.02 | 471.30 |
| TILs 40 | 2.29 | 1.40 | 3.77 | 0.02 | 471.68 |
| TILs | 1.01 | 1.01 | 1.02 | 0.02 | 472.23 |
| Macrophages.M1 CIBERSORT NatMethods.2015 PMID.25822800 | 1.47 | 1.16 | 1.86 | 0.02 | 472.10 |
| STAT1 Rody BreastCancerResearch.2008 PMID.19272155 | 1.46 | 1.16 | 1.86 | 0.02 | 472.11 |
| IFN.5.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 1.44 | 1.15 | 1.83 | 0.02 | 472.63 |
| Bcells.Plasmablast Dybaer JCO.2015 PMID.25800755 | 1.43 | 1.14 | 1.80 | 0.02 | 472.66 |
| Tcells.CD4.Memory.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 1.44 | 1.14 | 1.82 | 0.02 | 472.81 |
| Stromal.Inflammation Heng JPathol.2017 PMID.27861902 | 1.43 | 1.14 | 1.80 | 0.03 | 473.18 |
| Bcells.Cluster Iglesia CCR.2014 PMID.24916698 | 1.40 | 1.12 | 1.77 | 0.03 | 473.77 |

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|---|---|---|---|---|---|
| Dendritic.cells.Activated Bindea Immunity.2013 PMID.24138885 | 1.41 | 1.12 | 1.79 | 0.03 | 473.91 |
| Immune.Suppression Kardos JCIInsight.2016 PMID.27699256 | 1.41 | 1.12 | 1.79 | 0.03 | 474.03 |
| Proliferation.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.41 | 1.12 | 1.78 | 0.03 | 473.78 |
| Tcells.CD8.Effector.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 1.40 | 1.12 | 1.78 | 0.03 | 473.84 |
| Tcells.CD8.Exhausted.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 1.40 | 1.12 | 1.78 | 0.03 | 473.88 |
| MDSC Charoentong CellRep.2017 PMID.28052254 | 1.41 | 1.12 | 1.79 | 0.03 | 474.17 |
| Plasma.cells CIBERSORT NatMethods.2015 PMID.25822800 | 1.38 | 1.11 | 1.74 | 0.03 | 474.31 |
| TLS.12genes.Chemokine Zhu FrontImmunol.2017 PMID.28713385 | 1.39 | 1.11 | 1.76 | 0.03 | 474.40 |
| Tcells.CD4.Activated Charoentong CellRep.2017 PMID.28052254 | 1.39 | 1.11 | 1.77 | 0.03 | 474.35 |
| TILs 20 | 1.86 | 1.20 | 2.91 | 0.04 | 474.98 |
| Immune.Active Hollern Cell.2019 PMID.31730857 | 1.37 | 1.09 | 1.73 | 0.04 | 475.04 |
| Dendritic.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 1.37 | 1.09 | 1.74 | 0.04 | 475.31 |
| PDCD1.Single.Gene Pare AnnOncol.2019 PMID.30165419 | 1.39 | 1.10 | 1.78 | 0.04 | 475.19 |
| Cytotoxic.Lymphocytes.MCP Petitprez Nature.2020 PMID.31942077 | 1.37 | 1.09 | 1.73 | 0.04 | 475.18 |
| Tcells.Activation Petitprez Nature.2020 PMID.31942077 | 1.38 | 1.09 | 1.77 | 0.04 | 475.16 |
| MHC.I.CoreGenes Lauss NatCommun.2017 PMID29170503 | 1.36 | 1.08 | 1.71 | 0.04 | 475.56 |
| MERCK.Immune.Signature Cristescu Science.2018 PMID.30309915 | 1.36 | 1.09 | 1.73 | 0.04 | 475.44 |
| Tcells.CD8.Exhausted.vs.AntiPDL1.2 Pauken Science.2016 PMID.27789795 | 1.35 | 1.08 | 1.70 | 0.05 | 475.70 |
| Tcells.Cluster Iglesia CCR.2014 PMID.24916698 | 1.35 | 1.08 | 1.70 | 0.05 | 475.80 |
| Tcells.Th1.cells Bindea Immunity.2013 PMID.24138885 | 1.34 | 1.07 | 1.68 | 0.06 | 476.16 |
| Tcells.CD8.Memory.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 1.34 | 1.07 | 1.70 | 0.06 | 476.18 |
| Monocytes Charoentong CellRep.2017 PMID.28052254 | 1.34 | 1.07 | 1.68 | 0.06 | 476.30 |
| Tcells.Central.Memory Bindea Immunity.2013 PMID.24138885 | 1.32 | 1.06 | 1.66 | 0.07 | 476.47 |
| Tcells.Th17.cells Charoentong CellRep.2017 PMID.28052254 | 1.32 | 1.06 | 1.66 | 0.07 | 476.47 |
| Immune.CD19 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.32 | 1.06 | 1.66 | 0.07 | 476.68 |
| Tcells.Follicular.Helper Bindea Immunity.2013 PMID.24138885 | 1.33 | 1.06 | 1.68 | 0.07 | 476.67 |

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|---|---|---|---|---|---|
| Tcells.Follicular.Helper TCGA Immunity.2018 PMID.29628290 | 1.33 | 1.06 | 1.68 | 0.07 | 476.67 |
| TLS.High.In.No.Response Helmink Nature.2020 PMID.31942075 | 0.76 | 0.61 | 0.95 | 0.07 | 476.90 |
| Mast.cells Bindea Immunity.2013 PMID.24138885 | 0.77 | 0.61 | 0.95 | 0.08 | 476.97 |
| Macrophages.M0 CIBERSORT NatMethods.2015 PMID.25822800 | 1.31 | 1.05 | 1.64 | 0.08 | 477.07 |
| MHC.11genes Forero CancerImmunolRes.2016 PMID.26980599 | 1.30 | 1.04 | 1.63 | 0.08 | 477.42 |
| NK.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 1.30 | 1.04 | 1.63 | 0.08 | 477.42 |
| CTLA4.Single.Gene Hollern Cell.2019 PMID.31730857 | 1.32 | 1.04 | 1.69 | 0.08 | 477.31 |
| Tcells.CD8 CIBERSORT NatMethods.2015 PMID.25822800 | 1.30 | 1.04 | 1.63 | 0.08 | 477.45 |
| Tcells.Follicular.Helper CIBERSORT NatMethods.2015 PMID.25822800 | 1.30 | 1.04 | 1.64 | 0.08 | 477.44 |
| CTLA4.Pathway GSEA.BIOCARTA ProcNatlAcadSciUSA.2005 PMID.16199517 | 1.31 | 1.04 | 1.65 | 0.08 | 477.17 |
| Immune.87 Perez JCO.2015 PMID.2560586 | 1.30 | 1.04 | 1.64 | 0.08 | 477.24 |
| Tcells.CD8.Activated Charoentong CellRep.2017 PMID.28052254 | 1.30 | 1.04 | 1.64 | 0.08 | 477.34 |
| Tcells.MCP Petitprez Nature.2020 PMID.31942077 | 1.30 | 1.04 | 1.65 | 0.08 | 477.38 |
| Immune.CD8.GZMK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.30 | 1.04 | 1.63 | 0.08 | 477.33 |
| Tcells.Effector.Memory Bindea Immunity.2013 PMID.24138885 | 0.78 | 0.62 | 0.97 | 0.08 | 477.50 |
| CD8.Cluster Iglesia CCR.2014 PMID.24916698 | 1.29 | 1.03 | 1.62 | 0.09 | 477.64 |
| Bcells.Centrocyte Dybkaer JCO.2015 PMID.25800755 | 1.28 | 1.02 | 1.61 | 0.10 | 478.00 |
| Bcells.Memory CIBERSORT NatMethods.2015 PMID.25822800 | 1.27 | 1.02 | 1.60 | 0.10 | 478.03 |
| Bcells.Activated Charoentong CellRep.2017 PMID.28052254 | 1.28 | 1.02 | 1.60 | 0.10 | 477.98 |
| Plasmacytoid.Dendritic.cell Charoentong CellRep.2017 PMID.28052254 | 0.78 | 0.62 | 0.98 | 0.10 | 477.92 |
| MDSC.Tumor.Macrophages Schlecker JImmunol.2012 PMID.23152559 | 1.29 | 1.02 | 1.63 | 0.10 | 478.03 |
| Cytotoxic.cells Bindea Immunity.2013 PMID.24138885 | 1.28 | 1.02 | 1.60 | 0.10 | 477.99 |
| Tcells.CD8.Central.Memory Charoentong CellRep.2017 PMID.28052254 | 0.79 | 0.63 | 0.98 | 0.10 | 478.03 |
| Tcells.Th2 Charoentong CellRep.2017 PMID.28052254 | 1.27 | 1.02 | 1.60 | 0.10 | 478.03 |
| TLS.Tumors.w.TLS.and.CD8.vs.CD8.alone Cabrita Nature.2020 PMID.31942071 | 1.27 | 1.02 | 1.60 | 0.10 | 478.03 |

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|---|---|---|---|---|---|
| MDSC.Granulocytic Youn LeukocBiol.2012 PMID.21954284 | 1.27 | 1.02 | 1.60 | 0.10 | 478.07 |
| Tcells.Gamma.Delta CIBERSORT NatMethods.2015 PMID.25822800 | 1.27 | 1.02 | 1.59 | 0.10 | 478.15 |
| MHC.II Rody BreastCancerResearch.2008 PMID.19272155 | 1.27 | 1.02 | 1.60 | 0.10 | 478.20 |
| Immune.CD34.TIE1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.80 | 0.64 | 0.99 | 0.11 | 478.37 |
| Tcells.Survival.2gene Petitprez Nature.2020 PMID.31942077 | 1.27 | 1.01 | 1.60 | 0.11 | 478.36 |
| Tcells.NK.51genes Miller GenomeBiol.2013 PMID.23618380 | 1.26 | 1.01 | 1.58 | 0.11 | 478.44 |
| Bcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.26 | 1.01 | 1.58 | 0.11 | 478.48 |
| PD1.Signaling.Reactome GSEA ProcNatlAcadSciUSA.2005 PMID.16199517 | 1.26 | 1.01 | 1.59 | 0.11 | 478.51 |
| Tcells.Bcells.Lymphocyte.Infiltration Calabro BreastCancerResTreat.2009 PMID.18592372 | 1.25 | 1.01 | 1.57 | 0.12 | 478.59 |
| Lymphocyte.Infiltration.Expression.Score TCGA Immunity.2018 PMID.29628290 | 1.25 | 1.01 | 1.57 | 0.12 | 478.59 |
| Bcells.Memory Charoentong CellRep.2017 PMID.28052254 | 1.25 | 1.00 | 1.57 | 0.12 | 478.66 |
| Macrophages Charoentong CellRep.2017 PMID.28052254 | 0.80 | 0.64 | 0.99 | 0.12 | 478.58 |
| NK.CD56bright Bindea Immunity.2013 PMID.24138885 | 1.25 | 1.00 | 1.57 | 0.12 | 478.64 |
| MHC.I Rody BreastCancerResearch.2008 PMID.19272155 | 1.26 | 1.00 | 1.58 | 0.12 | 478.75 |
| Tcells.CD8.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 1.25 | 1.00 | 1.57 | 0.12 | 478.75 |
| NK.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 1.25 | 1.00 | 1.57 | 0.12 | 478.79 |
| TILs 60 | 1.73 | 0.99 | 3.04 | 0.12 | 478.89 |
| Bcells.Tcells.Cooperation Hollern Cell.2019 PMID.31730857 | 1.24 | 1.00 | 1.55 | 0.12 | 478.86 |
| MCD3.CD8 Fan BMCMedGenomics.2011 PMID.21214954 | 1.24 | 1.00 | 1.56 | 0.12 | 478.89 |
| Tcells.CD8.Memory.vs.Naive.Metagene.2 Pauken Science.2016 PMID.27789795 | 1.24 | 1.00 | 1.56 | 0.12 | 478.88 |
| Tcells.Resident.Memory.Single.cell Savas NatMed.2018 PMID.29942092 | 1.25 | 1.00 | 1.57 | 0.12 | 478.91 |
| NK.CD56dim Charoentong CellRep.2017 PMID.28052254 | 1.23 | 0.99 | 1.54 | 0.13 | 479.07 |
| NK Charoentong CellRep.2017 PMID.28052254 | 0.81 | 0.65 | 1.01 | 0.13 | 479.13 |
| Tcells.Th2.cells Bindea Immunity.2013 PMID.24138885 | 1.23 | 0.99 | 1.54 | 0.13 | 479.12 |

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| | | | | | |
|---|---|---|---|---|---|
| Bcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.23 | 0.98 | 1.53 | 0.14 | 479.29 |
| Bcells.Immature Charoentong CellRep.2017 PMID.28052254 | 1.23 | 0.98 | 1.53 | 0.14 | 479.32 |
| Immune.HLA.A.F TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.23 | 0.98 | 1.55 | 0.14 | 479.28 |
| Bcells.Memory Dybaer JCO.2015 PMID.25800755 | 1.23 | 0.98 | 1.54 | 0.14 | 479.31 |
| Macrophages.Th1.Cluster Iglesia CCR.2014 PMID.24916698 | 1.23 | 0.98 | 1.54 | 0.15 | 479.37 |
| Immune.CD4.CD53.CD84.BTK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.22 | 0.98 | 1.54 | 0.15 | 479.42 |
| Immune.Hot.vs.Cold.CD8 Cabrita Nature.2020 PMID.31942071 | 1.22 | 0.98 | 1.54 | 0.15 | 479.45 |
| LCK Rody BreastCancerResearch.2008 PMID.19272155 | 1.22 | 0.98 | 1.53 | 0.15 | 479.50 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 1.22 | 0.98 | 1.54 | 0.15 | 479.48 |
| Tcells.Bcell.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 1.22 | 0.98 | 1.54 | 0.16 | 479.55 |
| Tcells Bindea Immunity.2013 PMID.24138885 | 1.22 | 0.98 | 1.54 | 0.16 | 479.56 |
| Bcells.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 1.21 | 0.98 | 1.52 | 0.16 | 479.61 |
| Tcells.Gamma.Delta Bindea Immunity.2013 PMID.24138885 | 1.21 | 0.98 | 1.51 | 0.16 | 479.63 |
| Tcells.Gamma.Delta TCGA Immunity.2018 PMID.29628290 | 1.21 | 0.98 | 1.51 | 0.16 | 479.63 |
| Tcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.21 | 0.97 | 1.52 | 0.16 | 479.68 |
| Tcells.CD8.Exhausted.at.day.8.post.Imm.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 1.22 | 0.97 | 1.53 | 0.16 | 479.71 |
| Bcells Bindea Immunity.2013 PMID.24138885 | 1.20 | 0.96 | 1.50 | 0.19 | 479.95 |
| Tcells.NK.Metagene Miller GenomeBiol.2013 PMID.23618380 | 1.20 | 0.96 | 1.50 | 0.20 | 480.03 |
| Macrophages.Monocytes.CSF1.Response Beck CCR.2009 PMID..19188147 | 1.20 | 0.96 | 1.50 | 0.20 | 480.09 |
| CSF1.Response TCGA Immunity.2018 PMID.29628290 | 1.20 | 0.96 | 1.50 | 0.20 | 480.09 |
| Neutrophils.Activated.Lung Janiszewska NatCellBiol.2019 PMID.31263265 | 1.20 | 0.96 | 1.51 | 0.20 | 480.05 |
| Tcells.CD4.Memory.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 1.20 | 0.96 | 1.50 | 0.20 | 480.08 |
| Tcells.Th1.cells Charoentong CellRep.2017 PMID.28052254 | 1.20 | 0.96 | 1.50 | 0.20 | 480.10 |
| NK ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.19 | 0.96 | 1.49 | 0.20 | 480.17 |

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|---|---|---|---|---|---|
| Tcells.CD8.Exhausted.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 1.20 | 0.96 | 1.50 | 0.20 | 480.17 |
| Tcells.CD8.MCP Petitprez Nature.2020 PMID.31942077 | 1.20 | 0.96 | 1.51 | 0.20 | 480.19 |
| Tcells.Regulatory.Tregs CIBERSORT NatMethods.2015 PMID.25822800 | 1.19 | 0.95 | 1.49 | 0.20 | 480.21 |
| Tcells.CD4.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 1.19 | 0.95 | 1.49 | 0.22 | 480.31 |
| Neutrophils ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.19 | 0.95 | 1.51 | 0.22 | 480.32 |
| Dendritic.cells.Immature. Bindea Immunity.2013 PMID.24138885 | 1.18 | 0.95 | 1.48 | 0.22 | 480.38 |
| MDSC.Neutrophil Youn LeukocBiol.2012 PMID.21954284 | 1.19 | 0.95 | 1.49 | 0.22 | 480.38 |
| Macrophages ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.18 | 0.95 | 1.48 | 0.22 | 480.42 |
| Immune.Cell.Content Verhaak NatCommun.2013 PMID.24113773 | 1.18 | 0.95 | 1.48 | 0.22 | 480.43 |
| IFNg.Module11 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 1.18 | 0.95 | 1.48 | 0.23 | 480.47 |
| Influenza.11genes Khatri Immunity.2015 PMID.26682989 | 1.18 | 0.95 | 1.47 | 0.23 | 480.47 |
| Bcells.IL10.Plus Lin JImmunol.2014 PMID.25080484 | 1.18 | 0.94 | 1.48 | 0.23 | 480.49 |
| TLS.Known.Markers Cabrita Nature.2020 PMID.31942071 | 1.17 | 0.94 | 1.47 | 0.24 | 480.56 |
| Neutrophils.Activated.Blood Janiszewska NatCellBiol.2019 PMID.31263265 | 0.85 | 0.67 | 1.06 | 0.24 | 480.57 |
| TLS.Hallmark Cabrita Nature.2020 PMID.31942071 | 1.17 | 0.94 | 1.47 | 0.24 | 480.61 |
| Monocytes CIBERSORT NatMethods.2015 PMID.25822800 | 1.17 | 0.94 | 1.46 | 0.24 | 480.62 |
| Dendritic.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 1.16 | 0.94 | 1.45 | 0.26 | 480.75 |
| Tcells.Regulatory Charoentong CellRep.2017 PMID.28052254 | 1.17 | 0.93 | 1.46 | 0.26 | 480.77 |
| Immune.HLA.D TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.17 | 0.93 | 1.46 | 0.26 | 480.78 |
| Monocytes..Dendritic.cell.Metagene Miller GenomeBiol.2013 PMID.23618380 | 1.17 | 0.93 | 1.46 | 0.26 | 480.80 |
| Tcells.CD8.Memory.vs.Naive.1 Pauken Science.2016 PMID.27789795 | 1.17 | 0.93 | 1.47 | 0.26 | 480.81 |
| Tcells.CD8.Memory.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 1.17 | 0.93 | 1.47 | 0.26 | 480.81 |
| Cytolytic.Activity Rooney Cell.2015 PMID.25594174 | 1.16 | 0.93 | 1.46 | 0.27 | 480.87 |
| Monocytes.Dendritic.25genes Miller GenomeBiol.2013 PMID.23618380 | 1.15 | 0.92 | 1.44 | 0.32 | 481.11 |

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|---|---|---|---|---|---|
| IFN.Cluster.GSEA.GP11 Fan BMCMedGenomics.2011 PMID.21214954 | 1.15 | 0.92 | 1.43 | 0.32 | 481.14 |
| Tcells.CD8 Bindea Immunity.2013 PMID.24138885 | 0.87 | 0.70 | 1.09 | 0.32 | 481.14 |
| Neutrophils Bindea Immunity.2013 PMID.24138885 | 0.88 | 0.70 | 1.09 | 0.34 | 481.25 |
| Tcells.CD4.Central.Memory Charoentong CellRep.2017 PMID.28052254 | 0.88 | 0.71 | 1.09 | 0.35 | 481.29 |
| Neutrophils CIBERSORT NatMethods.2015 PMID.25822800 | 1.13 | 0.91 | 1.42 | 0.35 | 481.33 |
| Dendritic.cells Bindea Immunity.2013 PMID.24138885 | 1.13 | 0.91 | 1.42 | 0.36 | 481.35 |
| Bcells.IL10.Minus Lin JImmunol.2014 PMID.25080484 | 1.13 | 0.91 | 1.41 | 0.39 | 481.46 |
| Serum.Response.Up TCGA Immunity.2018 PMID.29628290 | 1.13 | 0.90 | 1.41 | 0.40 | 481.54 |
| Bcells Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 1.12 | 0.90 | 1.39 | 0.41 | 481.57 |
| NK.MCP Helmink Nature.2020 PMID.31942077 | 1.12 | 0.90 | 1.39 | 0.41 | 481.60 |
| Tcells.Bcell.KEGG.hematopoietic.cell.lineage GSEA.GP2 ProcNatlAcadSciUSA.2005 PMID.16199517 | 1.12 | 0.90 | 1.40 | 0.41 | 481.59 |
| Macrophages.M2 CIBERSORT NatMethods.2015 PMID.25822800 | 1.12 | 0.90 | 1.40 | 0.42 | 481.62 |
| Tcells.CD4.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.90 | 0.72 | 1.12 | 0.43 | 481.66 |
| IFNa.Module10 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 1.12 | 0.90 | 1.39 | 0.43 | 481.67 |
| Wound.Healing Chang PlosBiol.2004 PMID.14737219 | 1.11 | 0.89 | 1.39 | 0.44 | 481.72 |
| Macrophages Bindea Immunity.2013 PMID.24138885 | 1.11 | 0.89 | 1.39 | 0.44 | 481.72 |
| Granulocytes.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.11 | 0.89 | 1.40 | 0.46 | 481.77 |
| MDSC.Tumor Schlecker JImmunol.2012 PMID.23152559 | 1.11 | 0.89 | 1.39 | 0.46 | 481.80 |
| Tcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.10 | 0.89 | 1.37 | 0.48 | 481.84 |
| Tcells.CD8.Exhausted.Anti.PDL1.vs.Control.Metagene.1 Pauken Science.2016 PMID.27789795 | 1.10 | 0.89 | 1.38 | 0.48 | 481.86 |
| Tcells.Thelper Bindea Immunity.2013 PMID.24138885 | 1.10 | 0.88 | 1.37 | 0.49 | 481.88 |
| HCK Rody BreastCancerResearch.2008 PMID.19272155 | 1.10 | 0.88 | 1.38 | 0.49 | 481.90 |
| NK.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.10 | 0.88 | 1.36 | 0.50 | 481.93 |

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|---|---|---|---|---|---|
| Bcells.Extended Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.91 | 0.73 | 1.14 | 0.50 | 481.94 |
| Dendritic.cells.Activated Charoentong CellRep.2017 PMID.28052254 | 1.09 | 0.88 | 1.37 | 0.52 | 481.98 |
| Mast.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 1.08 | 0.87 | 1.35 | 0.57 | 482.10 |
| Mast.cell Charoentong CellRep.2017 PMID.28052254 | 0.93 | 0.74 | 1.15 | 0.58 | 482.13 |
| Tcells.Th17.cells Bindea Immunity.2013 PMID.24138885 | 0.93 | 0.75 | 1.15 | 0.61 | 482.19 |
| Immune.14 Perez JCO.2015 PMID.2560586 | 1.07 | 0.86 | 1.33 | 0.65 | 482.27 |
| IFN Rody BreastCancerResearch.2008 PMID.19272155 | 0.94 | 0.75 | 1.16 | 0.65 | 482.26 |
| MHC.24genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.94 | 0.75 | 1.17 | 0.65 | 482.27 |
| Macrophages.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.06 | 0.85 | 1.33 | 0.68 | 482.32 |
| Immunosuppression Petitprez Nature.2020 PMID.31942077 | 0.95 | 0.76 | 1.18 | 0.71 | 482.37 |
| Hematopoietic.Stem.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 1.06 | 0.85 | 1.32 | 0.71 | 482.37 |
| Neutrophils Charoentong CellRep.2017 PMID.28052254 | 0.95 | 0.75 | 1.18 | 0.71 | 482.37 |
| Tcells.Follicular.Helper Charoentong CellRep.2017 PMID.28052254 | 1.06 | 0.85 | 1.32 | 0.71 | 482.36 |
| Eosinophils Charoentong CellRep.2017 PMID.28052254 | 1.06 | 0.85 | 1.32 | 0.71 | 482.38 |
| Tcells.Gamma.Delta Charoentong CellRep.2017 PMID.28052254 | 1.05 | 0.85 | 1.31 | 0.71 | 482.39 |
| NK Bindea Immunity.2013 PMID.24138885 | 0.95 | 0.77 | 1.18 | 0.73 | 482.41 |
| Tcells.Regulatory.cell.2gene Petitprez Nature.2020 PMID.31942077 | 0.95 | 0.76 | 1.19 | 0.73 | 482.41 |
| Immune.GIMAP.IL16 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.05 | 0.84 | 1.31 | 0.73 | 482.42 |
| NK.CD56bright Charoentong CellRep.2017 PMID.28052254 | 1.05 | 0.84 | 1.31 | 0.76 | 482.46 |
| Bcells.Naive Dybaer JCO.2015 PMID.25800755 | 0.97 | 0.78 | 1.20 | 0.83 | 482.52 |
| IFN.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.03 | 0.83 | 1.29 | 0.83 | 482.53 |
| Immune.FOS.JUN.IL6 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.97 | 0.77 | 1.21 | 0.83 | 482.53 |
| Macrophages.M2 Ghassabeh Blood.2006 PMID.16556895 | 1.03 | 0.83 | 1.29 | 0.83 | 482.52 |
| Monocytes ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.03 | 0.83 | 1.30 | 0.83 | 482.53 |

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|---|---|---|---|---|---|
| IFN.3.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.97 | 0.78 | 1.21 | 0.87 | 482.56 |
| IFN.Score.module3 TCGA Immunity.2018 PMID.29628290 | 0.97 | 0.78 | 1.21 | 0.87 | 482.56 |
| NK.Tcell Charoentong CellRep.2017 PMID.28052254 | 1.03 | 0.82 | 1.28 | 0.87 | 482.57 |
| Dendritic.cells.Immature. Charoentong CellRep.2017 PMID.28052254 | 1.02 | 0.82 | 1.27 | 0.88 | 482.58 |
| IFN.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.98 | 0.79 | 1.21 | 0.88 | 482.58 |
| Mast.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 1.02 | 0.82 | 1.27 | 0.88 | 482.57 |
| Immune.IFN TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.98 | 0.79 | 1.22 | 0.88 | 482.58 |
| Eosinophils Bindea Immunity.2013 PMID.24138885 | 1.02 | 0.82 | 1.27 | 0.90 | 482.59 |
| CD103.Negative Broz CancerCell.2014 PMID.25446897 | 1.01 | 0.81 | 1.26 | 0.95 | 482.61 |
| CD68.Cluster Iglesia CCR.2014 PMID.24916698 | 0.99 | 0.80 | 1.23 | 0.96 | 482.61 |
| Neutrophils.MCP Petitprez Nature.2020 PMID.31942077 | 0.99 | 0.80 | 1.24 | 0.97 | 482.61 |
| TLS.9genes Cabrita Nature.2020 PMID.31942071 | 1.00 | 0.81 | 1.25 | 0.98 | 482.62 |
| TGFB.score TCGA Immunity.2018 PMID.29628290 | 1.00 | 0.81 | 1.25 | 0.99 | 482.62 |
| Eosinophils CIBERSORT NatMethods.2015 PMID.25822800 | 1.00 | 0.81 | 1.24 | 0.99 | 482.62 |

Logistic regression multivariable models adjusted by study and treatment arm has been built for each biomarker. P-values are adjusted for multiple testing using a Benjamini & Hochberg method to control the False Discovery Rate.

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**eTable 5. Association of Tumor-Infiltrating Lymphocytes (TILs) and Immune Gene Expression Signatures (iGES) With Pathologic Complete Response (pCR) in the Presence of Clinical Parameters Using the Combined CALGB 40601 and PAMELA Cohort**

| Signatures | OR | Lower CI | Upper CI | p value | AIC |
|---|---|---|---|---|---|
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 1.82 | 1.39 | 2.40 | 0.002 | 429.72 |
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 1.80 | 1.38 | 2.37 | 0.002 | 420.23 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 1.82 | 1.40 | 2.42 | 0.002 | 429.49 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 1.67 | 1.29 | 2.19 | 0.005 | 434.08 |
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 1.66 | 1.29 | 2.17 | 0.005 | 434.23 |
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 1.55 | 1.21 | 2.01 | 0.02 | 438.13 |
| NK.CD56dim Bindea Immunity.2013 PMID.24138885 | 1.53 | 1.18 | 2.00 | 0.03 | 439.31 |
| Bcells.Plasma.cells.Metagene Miller GenomeBiol.2013 PMID.23618380 | 1.54 | 1.20 | 2.01 | 0.03 | 438.43 |
| TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075 | 1.57 | 1.22 | 2.05 | 0.02 | 437.57 |
| TILs | 1.01 | 1.00 | 1.02 | 0.18 | 444.48 |

Logistic regression multivariable models are adjusted by study, treatment arm, clinical stage, age, HR-status, menopausal status, and subtype.
Only the iGES significantly associated with pCR and TILs are shown.
P-values are adjusted for multiple testing using a Benjamini & Hochberg method to control the False Discovery Rate.

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**eTable 6. Accuracy Metrics (Area Under the Curve From the Receiver Operating Characteristic Curves: AUC ROC) of the Univariable Immune-Biomarker Models to Predict Pathologic Complete Response (pCR)**

| Signature | AUC CALGB 40601 | AUC PAMELA |
|---|---|---|
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 0.64 | 0.65 |
| Immune.CTLA4.CXCL.FOXP3 TCGA.BRCA.1198 JCI.2020 PMID.32573490. | 0.60 | 0.64 |
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 0.63 | 0.64 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 0.62 | 0.64 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.66 | 0.63 |
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.62 | 0.62 |
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.60 | 0.62 |
| Bcells.Plasmablast Dybaer JCO.2015 PMID.25800755 | 0.62 | 0.59 |
| TILs | 0.60 | 0.57 |
| Monocytes Charoentong CellRep.2017 PMID.28052254 | 0.62 | 0.56 |
| Denditic.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.62 | 0.56 |
| MDSC.Granulocytic Youn LeukocBiol.2012 PMID.21954284 | 0.61 | 0.53 |
| TILs 40 | 0.60 | 0.59 |
| TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075 | 0.60 | 0.63 |
| IFN.5.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.59 | 0.60 |
| Tcells.CD8.Exhausted.vs.AntiPDL1.2 Pauken Science.2016 PMID.27789795 | 0.59 | 0.53 |
| Plasma.cells CIBERSORT NatMethods.2015 PMID.25822800 | 0.59 | 0.55 |
| MDSC.Tumor.Macrophages Schlecker JImmunol.2012 PMID.23152559 | 0.59 | 0.61 |
| MHC.11genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.59 | 0.58 |
| PD1.Signaling.Reactome GSEA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.59 | 0.56 |
| TLS.High.In.No.Response Helmink Nature.2020 PMID.31942075 | 0.58 | 0.55 |
| TILs 20 | 0.58 | 0.55 |
| Bcells.Centrocyte Dybkaer JCO.2015 PMID.25800755 | 0.58 | 0.52 |
| Bcells.Plasma.cells.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.58 | 0.63 |
| Tcells.CD8.Exhausted.at.day.8.post.Imm.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.58 | 0.56 |
| Tcells.CD4.Activated Charoentong CellRep.2017 PMID.28052254 | 0.58 | 0.54 |
| Bcells.Centroblast Dybkae JCO.2015 PMID.25800755 | 0.58 | 0.63 |
| Macrophages.M0 CIBERSORT NatMethods.2015 PMID.25822800 | 0.58 | 0.60 |
| NK.CD56dim Bindea Immunity.2013 PMID.24138885 | 0.58 | 0.63 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 0.57 | 0.57 |

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| | | |
|---|---|---|
| Tcells.CD4.Memory.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.57 | 0.58 |
| CD274.Single.Gene Hollern Cell.2019 PMID.31730857 | 0.57 | 0.65 |
| Tcells.Th1.cells Bindea Immunity.2013 PMID.24138885 | 0.57 | 0.56 |
| Tcells.CD8.Exhausted.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.57 | 0.53 |
| Tcells.Th17.cells Charoentong CellRep.2017 PMID.28052254 | 0.57 | 0.53 |
| Tcells.CD8.Memory.vs.Naive.1 Pauken Science.2016 PMID.27789795 | 0.57 | 0.55 |
| MHC.II Rody BreastCancerResearch.2008 PMID.19272155 | 0.57 | 0.59 |
| MDSC Charoentong CellRep.2017 PMID.28052254 | 0.57 | 0.60 |
| PDCD1.Single.Gene Pare AnnOncol.2019 PMID.30165419 | 0.57 | 0.61 |
| Tcells.Activation Petitprez Nature.2020 PMID.31942077 | 0.57 | 0.62 |
| Tcells.Central.Memory Bindea Immunity.2013 PMID.24138885 | 0.57 | 0.59 |
| TLS.12genes.Chemokine Zhu FrontImmunol.2017 PMID.28713385 | 0.57 | 0.60 |
| Immune.CD8.GZMK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.56 | 0.56 |
| Tcells.Th2 Charoentong CellRep.2017 PMID.28052254 | 0.56 | 0.64 |
| TILs 60 | 0.56 | 0.55 |
| Neutrophils CIBERSORT NatMethods.2015 PMID.25822800 | 0.56 | 0.55 |
| Dendritic.cells.Activated Bindea Immunity.2013 PMID.24138885 | 0.56 | 0.60 |
| Bcells.Memory Dybaer JCO.2015 PMID.25800755 | 0.56 | 0.58 |
| STAT1 Rody BreastCancerResearch.2008 PMID.19272155 | 0.56 | 0.61 |
| LCK Rody BreastCancerResearch.2008 PMID.19272155 | 0.56 | 0.56 |
| Tcells.CD8.Effector.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 0.56 | 0.58 |
| MERCK.Immune.Signature Cristescu Science.2018 PMID.30309915 | 0.56 | 0.60 |
| CTLA4.Single.Gene Hollern Cell.2019 PMID.31730857 | 0.56 | 0.59 |
| Tcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.56 | 0.57 |
| Immune.Suppression Kardos JCIInsight.2016 PMID.27699256 | 0.56 | 0.61 |
| Tcells.CD8.Memory.vs.Naive.Metagene.3 Pauken Science.2016 PMID.27789795 | 0.56 | 0.57 |
| Immune.87 Perez JCO.2015 PMID.2560586 | 0.56 | 0.57 |
| Immune.Active Hollern Cell.2019 PMID.31730857 | 0.56 | 0.59 |
| Neutrophils.Activated.Blood Janiszewska NatCellBiol.2019 PMID.31263265 | 0.56 | 0.50 |
| Tcells.CD8.Central.Memory Charoentong CellRep.2017 PMID.28052254 | 0.56 | 0.54 |
| Tcells.CD8.Activated Charoentong CellRep.2017 PMID.28052254 | 0.56 | 0.56 |
| TLS.Known.Markers Cabrita Nature.2020 PMID.31942071 | 0.56 | 0.53 |
| Tcells.CD8.Exhausted.vs.Naive.2 Pauken Science.2016 PMID.27789795 | 0.56 | 0.59 |
| Stromal.Inflammation Heng JPathol.2017 PMID.27861902 | 0.56 | 0.60 |
| MHC.I.CoreGenes Lauss NatCommun.2017 PMID29170503 | 0.56 | 0.64 |
| Macrophages.M1 CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | 0.61 |

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| | | |
|---|---|---|
| NK ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.55 | 0.55 |
| Dendritic.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | 0.61 |
| CD8.Cluster Iglesia CCR.2014 PMID.24916698 | 0.55 | 0.56 |
| Bcells.Extended Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.55 | 0.55 |
| NK.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | 0.56 |
| Bcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.55 | 0.56 |
| Tcells.NK.51genes Miller GenomeBiol.2013 PMID.23618380 | 0.55 | 0.58 |
| Tcells.Gamma.Delta CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | 0.56 |
| TLS.Tumors.w.TLS.and.CD8.vs.CD8.alone Cabrita Nature.2020 PMID.31942071 | 0.55 | 0.55 |
| Bcells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.55 | 0.55 |
| Neutrophils Bindea Immunity.2013 PMID.24138885 | 0.55 | 0.53 |
| Hematopoietic.Stem.cells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.55 | 0.45 |
| TLS.Hallmark Cabrita Nature.2020 PMID.31942071 | 0.55 | 0.51 |
| NK Charoentong CellRep.2017 PMID.28052254 | 0.55 | 0.56 |
| Tcells.Th2.cells Bindea Immunity.2013 PMID.24138885 | 0.55 | 0.62 |
| Tcells.CD8.Memory.vs.Naive.Metagene.2 Pauken Science.2016 PMID.27789795 | 0.55 | 0.59 |
| Immune.GIMAP.IL16 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.55 | 0.53 |
| Tcells.Survival.2gene Petitprez Nature.2020 PMID.31942077 | 0.55 | 0.57 |
| Tcells.CD4.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.55 | 0.53 |
| Bcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.55 | 0.55 |
| NK.CD56bright Bindea Immunity.2013 PMID.24138885 | 0.55 | 0.59 |
| Bcells.Memory Charoentong CellRep.2017 PMID.28052254 | 0.55 | 0.58 |
| Tcells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.55 | 0.56 |
| MCD3.CD8 Fan BMCMedGenomics.2011 PMID.21214954 | 0.55 | 0.56 |
| Macrophages Charoentong CellRep.2017 PMID.28052254 | 0.55 | 0.52 |
| Bcells.Immature Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.55 |
| Proliferation.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.54 | 0.59 |
| Immune.FOS.JUN.IL6 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.54 | 0.50 |
| IFN.Score.module3 TCGA Immunity.2018 PMID.29628290 | 0.54 | 0.43 |
| TLS.9genes Cabrita Nature.2020 PMID.31942071 | 0.54 | 0.52 |
| Dendritic.cells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.60 |
| IFN.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.54 | 0.44 |
| Immune.IFN TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.54 | 0.44 |
| Tcells.CD8.Memory.vs.Naive.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.54 | 0.55 |
| CD68.Cluster Iglesia CCR.2014 PMID.24916698 | 0.54 | 0.47 |

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| | | |
|---|---|---|
| Tcells.Bcells.Lymphocyte.Infiltration Calabro BreastCancerResTreat.2009 PMID.18592372 | 0.54 | 0.57 |
| Tcells.Effector.Memory Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.54 |
| CD103.Negative Broz CancerCell.2014 PMID.25446897 | 0.54 | 0.54 |
| Bcells Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.57 |
| Tcells.Thelper Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.51 |
| TGFB.score TCGA Immunity.2018 PMID.29628290 | 0.54 | 0.48 |
| Mast.cells.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.54 | 0.53 |
| Neutrophils Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.44 |
| NK.Tcell Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.51 |
| Lymphocyte.Infiltration.Expression.Score TCGA Immunity.2018 PMID.29628290 | 0.54 | 0.57 |
| Eosinophils Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.45 |
| IFN.3.ImmLandscape Wolf PlosOne.2014 PMID.24516633 | 0.54 | 0.43 |
| NK Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.54 |
| Neutrophils.Activated.Lung Janiszewska NatCellBiol.2019 PMID.31263265 | 0.54 | 0.51 |
| NK.CD56bright Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.53 |
| Bcells.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.54 | 0.54 |
| Cytotoxic.cells Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.57 |
| Tcells.Bcell.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.54 | 0.59 |
| Macrophages.Th1.Cluster Iglesia CCR.2014 PMID.24916698 | 0.54 | 0.58 |
| Tcells.CD8.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.60 |
| CSF1.Response TCGA Immunity.2018 PMID.29628290 | 0.54 | 0.58 |
| Mast.cells Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.63 |
| Eosinophils Charoentong CellRep.2017 PMID.28052254 | 0.54 | 0.46 |
| Bcells.Naive Dybaer JCO.2015 PMID.25800755 | 0.54 | 0.44 |
| Monocytes.Dendritic.25genes Miller GenomeBiol.2013 PMID.23618380 | 0.54 | 0.57 |
| Tcells.Follicular.Helper TCGA Immunity.2018 PMID.29628290 | 0.54 | 0.62 |
| IFN Rody BreastCancerResearch.2008 PMID.19272155 | 0.54 | 0.58 |
| Tcells.Resident.Memory.Single.cell Savas NatMed.2018 PMID.29942092 | 0.54 | 0.61 |
| Tcells.Th17.cells Bindea Immunity.2013 PMID.24138885 | 0.54 | 0.44 |
| Bcells.IL10.Plus Lin JImmunol.2014 PMID.25080484 | 0.53 | 0.58 |
| MDSC.Neutrophil Youn LeukocBiol.2012 PMID.21954284 | 0.53 | 0.59 |
| Tcells.Regulatory.Tregs CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.54 |
| Dendritic.cells Bindea Immunity.2013 PMID.24138885 | 0.53 | 0.57 |
| Tcells.NK.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.53 | 0.57 |
| Bcells Garber CellMolGastroenterolHepatol.2017 PMID.28508029 | 0.53 | 0.52 |
| Bcells.Memory CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.55 |
| Tcells.Follicular.Helper Bindea Immunity.2013 PMID.24138885 | 0.53 | 0.62 |
| Tcells.MCP Petitprez Nature.2020 PMID.31942077 | 0.53 | 0.58 |

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| | | |
|---|---|---|
| Immune.HLA.D TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.53 | 0.59 |
| Tcells.CD4.Effector.Memory Charoentong CellRep.2017 PMID.28052254 | 0.53 | 0.57 |
| Immune.Cell.Content Verhaak NatCommun.2013 PMID.24113773 | 0.53 | 0.57 |
| Tcells.CD8 CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.57 |
| IFN.Pathway ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.53 | 0.48 |
| Macrophages.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.53 | 0.58 |
| NK.Activated CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.58 |
| Tcells.Follicular.Helper CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.57 |
| Serum.Response.Up TCGA Immunity.2018 PMID.29628290 | 0.53 | 0.48 |
| Dendritic.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.61 |
| Eosinophils CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.48 |
| Tcells.Follicular.Helper Charoentong CellRep.2017 PMID.28052254 | 0.53 | 0.54 |
| Tcells.CD4.Central.Memory Charoentong CellRep.2017 PMID.28052254 | 0.53 | 0.56 |
| Neutrophils.MCP Petitprez Nature.2020 PMID.31942077 | 0.53 | 0.52 |
| Tcells.Gamma.Delta Bindea Immunity.2013 PMID.24138885 | 0.53 | 0.49 |
| Immunosuppression Petitprez Nature.2020 PMID.31942077 | 0.53 | 0.54 |
| Tcells.CD4.Memory.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.55 |
| Bcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.53 | 0.53 |
| Monocytes..Dendritic.cell.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.53 | 0.59 |
| Immune.CD19 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.53 | 0.56 |
| Immune.CD34.TIE1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.53 | 0.60 |
| Tcells.CD8.MCP Petitprez Nature.2020 PMID.31942077 | 0.53 | 0.54 |
| Tcells.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.53 | 0.53 |
| HCK Rody BreastCancerResearch.2008 PMID.19272155 | 0.53 | 0.57 |
| CTLA4.Pathway GSEA.BIOCARTA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.53 | 0.59 |
| Tcells.Th1.cells Charoentong CellRep.2017 PMID.28052254 | 0.53 | 0.58 |
| Tcells.Gamma.Delta TCGA Immunity.2018 PMID.29628290 | 0.53 | 0.49 |
| Immune.HLA.A.F TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.53 | 0.58 |
| Tcells.Regulatory Charoentong CellRep.2017 PMID.28052254 | 0.53 | 0.58 |
| Tcells.CD8.Exhausted.Anti.PDL1.vs.Control.Metagene.1 Pauken Science.2016 PMID.27789795 | 0.53 | 0.51 |
| Immune.CD4.CD53.CD84.BTK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.53 | 0.58 |
| Macrophages.M2 CIBERSORT NatMethods.2015 PMID.25822800 | 0.53 | 0.60 |
| Tcells Bindea Immunity.2013 PMID.24138885 | 0.53 | 0.56 |

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| | | |
|---|---|---|
| Monocytes ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.53 | 0.40 |
| Macrophages.Monocytes.CSF1.Response Beck CCR.2009 PMID..19188147 | 0.53 | 0.58 |
| Macrophages Bindea Immunity.2013 PMID.24138885 | 0.53 | 0.57 |
| Dendritic.cells.Immature. Bindea Immunity.2013 PMID.24138885 | 0.53 | 0.48 |
| Dendritic.cells.Immature. Charoentong CellRep.2017 PMID.28052254 | 0.52 | 0.42 |
| Tcells.CD8 Bindea Immunity.2013 PMID.24138885 | 0.52 | 0.61 |
| Cytotoxic.Lymphocytes.MCP Petitprez Nature.2020 PMID.31942077 | 0.52 | 0.58 |
| MDSC.Tumor Schlecker JImmunol.2012 PMID.23152559 | 0.52 | 0.55 |
| NK.CD56dim Charoentong CellRep.2017 PMID.28052254 | 0.52 | 0.60 |
| Tcells.Gamma.Delta Charoentong CellRep.2017 PMID.28052254 | 0.52 | 0.51 |
| NK.MCP Helmink Nature.2020 PMID.31942077 | 0.52 | 0.48 |
| MHC.24genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.52 | 0.52 |
| Bcells.Tcells.Cooperation Hollern Cell.2019 PMID.31730857 | 0.52 | 0.55 |
| Immune.14 Perez JCO.2015 PMID.2560586 | 0.52 | 0.52 |
| MHC.I Rody BreastCancerResearch.2008 PMID.19272155 | 0.52 | 0.62 |
| IFNg.Module11 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 0.52 | 0.53 |
| Bcells.IL10.Minus Lin JImmunol.2014 PMID.25080484 | 0.51 | 0.46 |
| Neutrophils ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.51 | 0.59 |
| NK.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.51 | 0.48 |
| Immune.Hot.vs.Cold.CD8 Cabrita Nature.2020 PMID.31942071 | 0.51 | 0.58 |
| Macrophages.M2 Ghassabeh Blood.2006 PMID.16556895 | 0.51 | 0.53 |
| Monocytes CIBERSORT NatMethods.2015 PMID.25822800 | 0.51 | 0.59 |
| Mast.cells.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.51 | 0.52 |
| Cytolytic.Activity Rooney Cell.2015 PMID.25594174 | 0.51 | 0.55 |
| Plasmacytoid.Dendritic.cell Charoentong CellRep.2017 PMID.28052254 | 0.51 | 0.63 |
| IFNa.Module10 Gatza ProcNatlAcadSciUSA.2010 PMID.20335537 | 0.51 | 0.51 |
| IFN.Cluster.GSEA.GP11 Fan BMCMedGenomics.2011 PMID.21214954 | 0.51 | 0.51 |
| Tcells.Regulatory.cell.2gene Petitprez Nature.2020 PMID.31942077 | 0.51 | 0.45 |
| Influenza.11genes Khatri Immunity.2015 PMID.26682989 | 0.51 | 0.52 |
| Wound.Healing Chang PlosBiol.2004 PMID.14737219 | 0.50 | 0.50 |
| Tcells.Bcell.KEGG.hematopoietic.cell.lineage GSEA.GP2 ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.50 | 0.52 |
| Mast.cell Charoentong CellRep.2017 PMID.28052254 | 0.50 | 0.50 |
| Granulocytes.ImmuneProfiles.Mouse.Human Shay PNAS.2013 PMID.23382184 | 0.50 | 0.56 |
| Macrophages ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.49 | 0.60 |

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Using CALGB 40601 as train set, the average AUC of the different models was calculated across all the resamples using 10-fold cross validation. A second AUC was calculated using PAMELA as an external validation set.

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**eTable 7. Association of Tumor-Infiltrating Lymphocytes (TILs) and Immune Gene Expression Signatures (iGES) With Event-Free Survival (EFS) in CALGB 40601**

| Signature | HR | Lower CI | Upper CI | P-value | AIC |
|---|---|---|---|---|---|
| Bcells.Plasma.cells.Metagene Miller GenomeBiol.2013 PMID.23618380 | 0.55 | 0.42 | 0.73 | 0.007 | 401.97 |
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 0.56 | 0.42 | 0.74 | 0.007 | 403.55 |
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 0.56 | 0.42 | 0.75 | 0.007 | 403.91 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 0.60 | 0.45 | 0.80 | 0.02 | 406.92 |
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 0.59 | 0.44 | 0.80 | 0.02 | 406.97 |
| Immune.14 Perez JCO.2015 PMID.2560586 | 0.60 | 0.45 | 0.81 | 0.02 | 407.17 |
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.59 | 0.44 | 0.80 | 0.02 | 407.03 |
| Cytotoxic.Lymphocytes.MCP Petitprez Nature.2020 PMID.31942077 | 0.61 | 0.45 | 0.83 | 0.04 | 408.82 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.64 | 0.49 | 0.85 | 0.04 | 409.32 |
| MHC.24genes Forero CancerImmunolRes.2016 PMID.26980599 | 0.59 | 0.42 | 0.82 | 0.04 | 408.55 |
| Tcells.Follicular.Helper CIBERSORT NatMethods.2015 PMID.25822800 | 0.61 | 0.44 | 0.83 | 0.04 | 408.97 |
| Bcells.Tcells.Cooperation Hollern Cell.2019 PMID.31730857 | 0.62 | 0.46 | 0.84 | 0.04 | 408.91 |
| TLS.High.In.Response.MCP Helmink Nature.2020 PMID.31942075 | 0.63 | 0.47 | 0.84 | 0.04 | 409.27 |
| Immune.87 Perez JCO.2015 PMID.2560586 | 0.62 | 0.46 | 0.85 | 0.04 | 409.41 |
| Tcells.CD8.MCP Petitprez Nature.2020 PMID.31942077 | 0.60 | 0.43 | 0.84 | 0.04 | 409.44 |
| Tcells.CD4.Naive CIBERSORT NatMethods.2015 PMID.25822800 | 0.64 | 0.47 | 0.86 | 0.04 | 409.78 |
| Bcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.62 | 0.45 | 0.85 | 0.04 | 409.39 |
| Tcells.Cluster Iglesia CCR.2014 PMID.24916698 | 0.63 | 0.46 | 0.86 | 0.04 | 410.00 |
| Tcells.CD8 CIBERSORT NatMethods.2015 PMID.25822800 | 0.63 | 0.46 | 0.86 | 0.04 | 410.11 |
| Tcells.Gamma.Delta CIBERSORT NatMethods.2015 PMID.25822800 | 0.64 | 0.48 | 0.87 | 0.04 | 410.39 |
| NK ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 0.63 | 0.46 | 0.87 | 0.04 | 410.40 |
| PD1.Signaling.Reactome GSEA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.63 | 0.46 | 0.87 | 0.04 | 410.40 |
| Tcells.Bcells.Lymphocyte.Infiltration Calabro BreastCancerResTreat.2009 PMID.18592372 | 0.63 | 0.46 | 0.87 | 0.04 | 410.33 |
| Lymphocyte.Infiltration.Expression.Score TCGA Immunity.2018 PMID.29628290 | 0.63 | 0.46 | 0.87 | 0.04 | 410.33 |

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| | | | | | |
|---|---|---|---|---|---|
| TLS.Tumors.w.TLS.and.CD8.vs.CD8.alone Cabrita Nature.2020 PMID.31942071 | 0.63 | 0.45 | 0.87 | 0.04 | 410.21 |
| Tcells.CD8.Activated Charoentong CellRep.2017 PMID.28052254 | 0.65 | 0.47 | 0.88 | 0.04 | 410.91 |
| TLS.Hallmark Cabrita Nature.2020 PMID.31942071 | 0.63 | 0.46 | 0.87 | 0.04 | 410.83 |
| Immune.CD8.GZMK TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.64 | 0.47 | 0.88 | 0.04 | 410.73 |
| CD8.Cluster Iglesia CCR.2014 PMID.24916698 | 0.65 | 0.47 | 0.88 | 0.04 | 410.82 |
| Tcells.CD4.Memory.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.64 | 0.47 | 0.88 | 0.04 | 410.81 |
| Tcells.Regulatory.Tregs CIBERSORT NatMethods.2015 PMID.25822800 | 0.65 | 0.48 | 0.89 | 0.04 | 410.98 |
| NK.CD56dim Charoentong CellRep.2017 PMID.28052254 | 1.51 | 1.12 | 2.03 | 0.04 | 410.92 |
| CTLA4.Pathway GSEA.BIOCARTA ProcNatlAcadSciUSA.2005 PMID.16199517 | 0.65 | 0.48 | 0.89 | 0.04 | 411.16 |
| Immune.CD19 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 0.63 | 0.45 | 0.88 | 0.04 | 410.74 |
| Bcells.Activated Charoentong CellRep.2017 PMID.28052254 | 0.65 | 0.47 | 0.89 | 0.04 | 411.10 |
| NK.Resting CIBERSORT NatMethods.2015 PMID.25822800 | 0.64 | 0.46 | 0.89 | 0.04 | 411.14 |
| Bcells.Memory CIBERSORT NatMethods.2015 PMID.25822800 | 0.64 | 0.47 | 0.89 | 0.04 | 411.21 |

Cox regression models for EFS prediction in CALGB 40601 have been adjusted by treatment arm. Only the models significantly associated with EFS with a p-value <0.05 are shown. P-values are adjusted for multiple testing using a Benjamini & Hochberg method to control the False Discovery Rate.

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**eTable 8. Association of Tumor-Infiltrating Lymphocytes (TILs) as a Continuous Variable and Immune Gene Expression Signatures (iGES) With Event-Free Survival (EFS) in CALGB 40601**

Comparative analysis of nested multivariable Cox regression models.

| Signature:Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | | | | | | |
|---|---|---|---|---|---|---|
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.01** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.51 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 395.31 | Model 2 vs. Model 1 LRT p-value 0.12 |
| | TL vs. TH | 1.3 | 0.63, 2.67 | 0.48 | | |
| | HR (pos vs. neg) | 1.85 | 0.93, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 1.95 | 1.02, 3.71 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.24 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.53 | 2.11, 9.73 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.97, 1.00 | 0.14 | | |
| **Model 3** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 388.34 | Model 3 vs. Model 1 LRT p-value **<0.001** |
| | TL vs. TH | 1.55 | 0.74, 3.26 | 0.24 | | |
| | HR (pos vs. neg) | 1.84 | 0.93, 3.63 | 0.08 | | |
| | Stage (III vs. II) | 2.04 | 1.07, 3.89 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.32 | 0.14, 0.74 | **0.007** | | |
| | HER2-E vs. not | 5.43 | 2.47, 11.9 | **<0.001** | | |
| | Signature (cont) | 0.59 | 0.42, 0.82 | **0.002** | | |
| **Model 4** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 390.32 | Model 4 vs. Model 2 LRT p-value **0.008** |
| | TL vs. TH | 1.56 | 0.74, 3.29 | 0.24 | | |
| | HR (pos vs. neg) | 1.84 | 0.93, 3.62 | 0.08 | | |
| | Stage (III vs. II) | 2.05 | 1.07, 3.91 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.32 | 0.14, 0.74 | **0.007** | | Model 4 vs. Model 3 LRT p-value 0.90 |
| | HER2-E vs. not | 5.43 | 2.47, 12.0 | **<0.001** | | |
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.90 | | |
| | Signature (continuous) | 0.58 | 0.39, 0.86 | **0.007** | | |
| **Signature: Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.01** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.51 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 395.31 | Model 2 vs. Model 1 LRT p-value 0.12 |
| | TL vs. TH | 1.3 | 0.63, 2.67 | 0.48 | | |
| | HR (pos vs. neg) | 1.85 | 0.93, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 1.95 | 1.02, 3.71 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.24 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.53 | 2.11, 9.73 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.97, 1.00 | 0.14 | | |
| **Model 3** | THL vs. TH | 0.29 | 0.12, 0.68 | **0.005** | 385.04 | Model 3 vs. Model 1 LRT p-value **0.004** |
| | TL vs. TH | 1.57 | 0.75, 3.27 | 0.23 | | |
| | HR (pos vs. neg) | 1.36 | 0.68, 2.73 | 0.39 | | |
| | Stage (III vs. II) | 2.2 | 1.15, 4.19 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.76 | **0.008** | | |
| | HER2-E vs. not | 4.73 | 2.20, 10.1 | **<0.001** | | |
| | Signature (cont) | 0.53 | 0.38, 0.75 | **<0.001** | | |
| **Model 4** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 386.88 | Model 4 vs. Model 2 LRT p-value **0.001** |
| | TL vs. TH | 1.6 | 0.76, 3.36 | 0.22 | | |
| | HR (pos vs. neg) | 1.34 | 0.66, 2.69 | 0.42 | | |
| | Stage (III vs. II) | 2.23 | 1.17, 4.26 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.33 | 0.15, 0.75 | **0.008** | | Model 4 vs. Model 3 LRT p-value 0.69 |
| | HER2-E vs. not | 4.68 | 2.17, 10.1 | **<0.001** | | |
| | TILs (continuous) | 1 | 0.99, 1.02 | 0.68 | | |
| | Signature (continuous) | 0.51 | 0.34, 0.76 | **<0.001** | | |
| **Signature: Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.01** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.51 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 395.31 | Model 2 vs. Model 1 LRT p-value 0.12 |
| | TL vs. TH | 1.3 | 0.63, 2.67 | 0.48 | | |
| | HR (pos vs. neg) | 1.85 | 0.93, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 1.95 | 1.02, 3.71 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.24 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.53 | 2.11, 9.73 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.97, 1.00 | 0.14 | | |
| **Model 3** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 384.82 | Model 3 vs. Model 1 LRT p-value **<0.001** |
| | TL vs. TH | 1.71 | 0.81, 3.59 | 0.16 | | |
| | HR (pos vs. neg) | 1.48 | 0.74, 2.93 | 0.27 | | |
| | Stage (III vs. II) | 2.34 | 1.22, 4.47 | **0.01** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.77 | **0.01** | | |
| | HER2-E vs. not | 4.81 | 2.24, 10.3 | **<0.001** | | |
| | Signature (cont) | 0.53 | 0.37, 0.75 | **<0.001** | | |
| **Model 4** | THL vs. TH | 0.32 | 0.14, 0.75 | **0.009** | 386.66 | Model 4 vs. Model 2 LRT p-value **0.001** |
| | TL vs. TH | 1.75 | 0.82, 3.72 | 0.15 | | |
| | HR (pos vs. neg) | 1.47 | 0.74, 2.90 | 0.27 | | |
| | Stage (III vs. II) | 2.38 | 1.24, 4.59 | **0.01** | | |
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.76 | **0.009** | | Model 4 vs. Model 3 LRT p-value 0.69 |
| | HER2-E vs. not | 4.77 | 2.22, 10.2 | **<0.001** | | |
| | TILs (continuous) | 1 | 0.99, 1.02 | 0.69 | | |
| | Signature (continuous) | 0.5 | 0.33, 0.76 | **0.001** | | |
| **Signature: Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.01** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.51 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 395.31 | Model 2 vs. Model 1 LRT p-value 0.12 |
| | TL vs. TH | 1.3 | 0.63, 2.67 | 0.48 | | |
| | HR (pos vs. neg) | 1.85 | 0.93, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 1.95 | 1.02, 3.71 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.24 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.53 | 2.11, 9.73 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.97, 1.00 | 0.14 | | |
| **Model 3** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 389.43 | Model 3 vs. Model 1 LRT p-value **0.004** |
| | TL vs. TH | 1.49 | 0.72, 3.11 | 0.29 | | |
| | HR (pos vs. neg) | 1.47 | 0.73, 2.95 | 0.28 | | |
| | Stage (III vs. II) | 2.1 | 1.10, 4.00 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.71 | **0.005** | | |
| | HER2-E vs. not | 4.41 | 2.07, 9.38 | **<0.001** | | |
| | Signature (cont) | 0.6 | 0.43, 0.85 | **0.004** | | |
| **Model 4** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 391.41 | Model 4 vs. Model 2 LRT p-value **0.02** |
| | TL vs. TH | 1.5 | 0.72, 3.14 | 0.28 | | |
| | HR (pos vs. neg) | 1.46 | 0.72, 2.95 | 0.30 | | |
| | Stage (III vs. II) | 2.11 | 1.10, 4.03 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.71 | **0.005** | | Model 4 vs. Model 3 LRT p-value 0.88 |
| | HER2-E vs. not | 4.39 | 2.06, 9.36 | **<0.001** | | |
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.88 | | |
| | Signature (continuous) | 0.59 | 0.39, 0.90 | **0.014** | | |

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| Signature: IgG Rody BreastCancerResearch.2008 PMID.19272155 | | | | | | |
|---|---|---|---|---|---|---|
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.51 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 395.31 | Model 2 vs. Model 1 LRT p-value 0.12 |
| | TL vs. TH | 1.3 | 0.63, 2.67 | 0.48 | | |
| | HR (pos vs. neg) | 1.85 | 0.93, 3.69 | 0.08 | | |
| | Stage (III vs. II) | 1.95 | 1.02, 3.71 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.24 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.53 | 2.11, 9.73 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.97, 1.00 | 0.14 | | |
| **Model 3** | THL vs. TH | 0.33 | 0.14, 0.76 | **0.009** | 387.85 | Model 3 vs. Model 1 LRT p-value **0.002** |
| | TL vs. TH | 1.59 | 0.76, 3.32 | 0.22 | | |
| | HR (pos vs. neg) | 1.52 | 0.76, 3.02 | 0.24 | | |
| | Stage (III vs. II) | 2.3 | 1.20, 4.40 | **0.01** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.69 | **0.004** | | |
| | HER2-E vs. not | 4.71 | 2.20, 10.1 | **<0.001** | | |
| | Signature (cont) | 0.57 | 0.41, 0.81 | **0.002** | | |
| **Model 4** | THL vs. TH | 0.33 | 0.14, 0.77 | **0.01** | 389.85 | Model 4 vs. Model 2 LRT p-value **0.006** |
| | TL vs. TH | 1.59 | 0.76, 3.35 | 0.22 | | |
| | HR (pos vs. neg) | 1.51 | 0.76, 3.02 | 0.24 | | |
| | Stage (III vs. II) | 2.31 | 1.20, 4.45 | **0.01** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.69 | **0.004** | | Model 4 vs. Model 3 LRT p-value 0.96 |
| | HER2-E vs. not | 4.7 | 2.20, 10.1 | **<0.001** | | |
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.96 | | |
| | Signature (continuous) | 0.57 | 0.38, 0.85 | **0.006** | | |

CI: confident intervals; EFS: event-free survival; HR: hormone receptor; pCR: pathologic complete response; RD: residual disease; pos: positive; neg: negative; HER2-E: HER2-Enriched; AIC: Akaike Information Criterion; LR: likelihood-ratio test; TILs: tumor infiltrating lymphocytes; IgG: immunoglobulin G; T: weekly paclitaxel; H: trastuzumab; L: lapatinib. [1]Cox regression model p-value; [2]Likelihood-ratio test p-value.

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**eTable 9. Association of Tumor-Infiltrating Lymphocytes (TILs) Using a Cutoff of 40% and Immune Gene Expression Signatures (iGES) With Event-Free Survival (EFS) in CALGB 40601**

Comparative analysis of nested multivariable Cox regression models.

| Signature: IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | | | | | | |
|---|---|---|---|---|---|---|
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.511 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.076 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 394.78 | Model 2 vs. Model 1 LRT p-value 0.09 |
| | TL vs. TH | 1.27 | 0.62, 2.61 | 0.513 | | |
| | HR (pos vs. neg) | 1.87 | 0.94, 3.73 | 0.076 | | |
| | Stage (III vs. II) | 1.92 | 1.01, 3.66 | **0.046** | | |
| | pCR (pCR vs. RD) | 0.25 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.51 | 2.10, 9.68 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.49 | 0.20, 1.19 | 0.113 | | |
| **Model 3** | THL vs. TH | 0.31 | 0.13, 0.71 | **0.006** | 389.97 | Model 3 vs. Model 1 LRT p-value **0.005** |
| | TL vs. TH | 1.45 | 0.70, 3.02 | 0.322 | | |
| | HR (pos vs. neg) | 1.43 | 0.71, 2.90 | 0.319 | | |
| | Stage (III vs. II) | 2.01 | 1.06, 3.83 | **0.033** | | |
| | pCR (pCR vs. RD) | 0.3 | 0.13, 0.66 | **0.003** | | |
| | HER2-E vs. not | 4.28 | 2.02, 9.08 | **<0.001** | | |
| | Signature (cont) | 0.63 | 0.45, 0.87 | **0.006** | | |
| **Model 4** | THL vs. TH | 0.3 | 0.13, 0.70 | **0.006** | 391.74 | Model 4 vs. Model 2 LRT p-value **0.03** |
| | TL vs. TH | 1.43 | 0.69, 2.99 | 0.339 | | |
| | HR (pos vs. neg) | 1.46 | 0.72, 2.97 | 0.299 | | |
| | Stage (III vs. II) | 2 | 1.05, 3.80 | **0.035** | | |
| | pCR (pCR vs. RD) | 0.3 | 0.13, 0.68 | **0.004** | | Model 4 vs. Model 3 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | HER2-E vs. not | 4.33 | 2.04, 9.21 | **<0.001** | | LRT p-value 0.63 |
| | TILs High vs. Low (40%) | 0.79 | 0.29, 2.14 | 0.639 | | |
| | Signature (continuous) | 0.65 | 0.45, 0.95 | **0.024** | | |
| **Signature: Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.511 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.076 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 394.78 | Model 2 vs. Model 1 LRT p-value 0.09 |
| | TL vs. TH | 1.27 | 0.62, 2.61 | 0.513 | | |
| | HR (pos vs. neg) | 1.87 | 0.94, 3.73 | 0.076 | | |
| | Stage (III vs. II) | 1.92 | 1.01, 3.66 | **0.046** | | |
| | pCR (pCR vs. RD) | 0.25 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.51 | 2.10, 9.68 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.49 | 0.20, 1.19 | 0.113 | | |
| **Model 3** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 388.34 | Model 3 vs. Model 1 LRT p-value **0.002** |
| | TL vs. TH | 1.55 | 0.74, 3.26 | 0.243 | | |
| | HR (pos vs. neg) | 1.84 | 0.93, 3.63 | 0.081 | | |
| | Stage (III vs. II) | 2.04 | 1.07, 3.89 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.32 | 0.14, 0.74 | **0.007** | | |
| | HER2-E vs. not | 5.43 | 2.47, 11.9 | **<0.001** | | |
| | Signature (cont) | 0.59 | 0.42, 0.82 | **0.002** | | |
| **Model 4** | THL vs. TH | 0.3 | 0.13, 0.70 | **0.005** | 390.20 | Model 4 vs. Model 2 LRT p-value **0.01** |
| | TL vs. TH | 1.54 | 0.73, 3.23 | 0.257 | | |
| | HR (pos vs. neg) | 1.84 | 0.93, 3.64 | 0.08 | | |
| | Stage (III vs. II) | 2.03 | 1.06, 3.87 | **0.032** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | pCR (pCR vs. RD) | 0.33 | 0.14, 0.75 | **0.008** | | Model 4 vs. Model 3 LRT p-value 0.71 |
| | HER2-E vs. not | 5.4 | 2.46, 11.9 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.83 | 0.30, 2.26 | 0.714 | | |
| | Signature (continuous) | 0.61 | 0.42, 0.88 | **0.009** | | |
| **Signature: Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.511 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.076 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 394.78 | Model 2 vs. Model 1 LRT p-value 0.09 |
| | TL vs. TH | 1.27 | 0.62, 2.61 | 0.513 | | |
| | HR (pos vs. neg) | 1.87 | 0.94, 3.73 | 0.076 | | |
| | Stage (III vs. II) | 1.92 | 1.01, 3.66 | **0.046** | | |
| | pCR (pCR vs. RD) | 0.25 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.51 | 2.10, 9.68 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.49 | 0.20, 1.19 | 0.113 | | |
| **Model 3** | THL vs. TH | 0.29 | 0.12, 0.68 | **0.005** | 385.04 | Model 3 vs. Model 1 LRT p-value **<0.001** |
| | TL vs. TH | 1.57 | 0.75, 3.27 | 0.234 | | |
| | HR (pos vs. neg) | 1.36 | 0.68, 2.73 | 0.388 | | |
| | Stage (III vs. II) | 2.2 | 1.15, 4.19 | **0.016** | | |
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.76 | **0.008** | | |
| | HER2-E vs. not | 4.73 | 2.20, 10.1 | **<0.001** | | |
| | Signature (cont) | 0.53 | 0.38, 0.75 | **<0.001** | | |
| **Model 4** | THL vs. TH | 0.29 | 0.12, 0.68 | **0.005** | 387.03 | Model 4 vs. Model 2 LRT p-value **0.002** |
| | TL vs. TH | 1.56 | 0.74, 3.27 | 0.243 | | |
| | HR (pos vs. neg) | 1.36 | 0.68, 2.75 | 0.385 | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | Stage (III vs. II) | 2.19 | 1.15, 4.19 | **0.017** | | |
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.76 | **0.009** | | Model 4 vs. Model 3 LRT p-value 0.92 |
| | HER2-E vs. not | 4.73 | 2.20, 10.2 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.95 | 0.35, 2.59 | 0.915 | | |
| | Signature (continuous) | 0.54 | 0.37, 0.78 | **0.001** | | |
| **Signature: Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.511 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.076 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 394.78 | Model 2 vs. Model 1 LRT p-value 0.09 |
| | TL vs. TH | 1.27 | 0.62, 2.61 | 0.513 | | |
| | HR (pos vs. neg) | 1.87 | 0.94, 3.73 | 0.076 | | |
| | Stage (III vs. II) | 1.92 | 1.01, 3.66 | **0.046** | | |
| | pCR (pCR vs. RD) | 0.25 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.51 | 2.10, 9.68 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.49 | 0.20, 1.19 | 0.113 | | |
| **Model 3** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 384.82 | Model 3 vs. Model 1 LRT p-value **<0.001** |
| | TL vs. TH | 1.71 | 0.81, 3.59 | 0.16 | | |
| | HR (pos vs. neg) | 1.48 | 0.74, 2.93 | 0.265 | | |
| | Stage (III vs. II) | 2.34 | 1.22, 4.47 | **0.01** | | |
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.77 | **0.01** | | |
| | HER2-E vs. not | 4.81 | 2.24, 10.3 | **<0.001** | | |
| | Signature (cont) | 0.53 | 0.37, 0.75 | **<0.001** | | |
| **Model 4** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 386.82 | Model 4 vs. Model 2 |
| | TL vs. TH | 1.7 | 0.80, 3.61 | 0.169 | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | HR (pos vs. neg) | 1.48 | 0.74, 2.94 | 0.264 | | LRT p-value **0.002** |
| | Stage (III vs. II) | 2.33 | 1.21, 4.48 | **0.011** | | |
| | pCR (pCR vs. RD) | 0.34 | 0.15, 0.78 | **0.01** | | Model 4 vs. Model 3 LRT p-value 0.94 |
| | HER2-E vs. not | 4.81 | 2.25, 10.3 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.96 | 0.35, 2.63 | 0.942 | | |
| | Signature (continuous) | 0.53 | 0.36, 0.78 | **0.001** | | |
| **Signature: Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.511 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.076 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 394.78 | Model 2 vs. Model 1 LRT p-value 0.09 |
| | TL vs. TH | 1.27 | 0.62, 2.61 | 0.513 | | |
| | HR (pos vs. neg) | 1.87 | 0.94, 3.73 | 0.076 | | |
| | Stage (III vs. II) | 1.92 | 1.01, 3.66 | **0.046** | | |
| | pCR (pCR vs. RD) | 0.25 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.51 | 2.10, 9.68 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.49 | 0.20, 1.19 | 0.113 | | |
| **Model 3** | THL vs. TH | 0.3 | 0.13, 0.71 | **0.006** | 389.43 | Model 3 vs. Model 1 LRT p-value **0.004** |
| | TL vs. TH | 1.49 | 0.72, 3.11 | 0.285 | | |
| | HR (pos vs. neg) | 1.47 | 0.73, 2.95 | 0.282 | | |
| | Stage (III vs. II) | 2.1 | 1.10, 4.00 | **0.025** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.71 | **0.005** | | |
| | HER2-E vs. not | 4.41 | 2.07, 9.38 | **<0.001** | | |
| | Signature (cont) | 0.6 | 0.43, 0.85 | **0.004** | | |
| **Model 4** | THL vs. TH | 0.3 | 0.13, 0.70 | **0.005** | 391.31 | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | TL vs. TH | 1.48 | 0.71, 3.09 | 0.30 | | Model 4 vs. Model 2 LRT p-value **0.02** |
| | HR (pos vs. neg) | 1.49 | 0.73, 3.00 | 0.271 | | |
| | Stage (III vs. II) | 2.08 | 1.09, 3.97 | **0.027** | | |
| | pCR (pCR vs. RD) | 0.32 | 0.14, 0.71 | **0.006** | | Model 4 vs. Model 3 LRT p-value 0.73 |
| | HER2-E vs. not | 4.44 | 2.09, 9.46 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.84 | 0.30, 2.32 | 0.733 | | |
| | Signature (continuous) | 0.62 | 0.42, 0.92 | **0.019** | | |
| **Signature: IgG Rody BreastCancerResearch.2008 PMID.19272155** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.34 | 0.14, 0.78 | **0.011** | 395.68 | - |
| | TL vs. TH | 1.27 | 0.62, 2.60 | 0.511 | | |
| | HR (pos vs. neg) | 1.86 | 0.94, 3.69 | 0.076 | | |
| | Stage (III vs. II) | 2.03 | 1.07, 3.87 | **0.031** | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.48 | **<0.001** | | |
| | HER2-E vs. Other | 4.2 | 1.97, 8.96 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.31 | 0.13, 0.73 | **0.007** | 394.78 | Model 2 vs. Model 1 LRT p-value 0.09 |
| | TL vs. TH | 1.27 | 0.62, 2.61 | 0.513 | | |
| | HR (pos vs. neg) | 1.87 | 0.94, 3.73 | 0.076 | | |
| | Stage (III vs. II) | 1.92 | 1.01, 3.66 | **0.046** | | |
| | pCR (pCR vs. RD) | 0.25 | 0.11, 0.54 | **<0.001** | | |
| | HER2-E vs. not | 4.51 | 2.10, 9.68 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.49 | 0.20, 1.19 | 0.113 | | |
| **Model 3** | THL vs. TH | 0.33 | 0.14, 0.76 | **0.009** | 387.85 | Model 3 vs. Model 1 LRT p-value **0.002** |
| | TL vs. TH | 1.59 | 0.76, 3.32 | 0.217 | | |
| | HR (pos vs. neg) | 1.52 | 0.76, 3.02 | 0.236 | | |
| | Stage (III vs. II) | 2.3 | 1.20, 4.40 | **0.012** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.69 | **0.004** | | |
| | HER2-E vs. not | 4.71 | 2.20, 10.1 | **<0.001** | | |
| | Signature (cont) | 0.57 | 0.41, 0.81 | **0.002** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Model 4** | THL vs. TH | 0.32 | 0.14, 0.75 | **0.009** | 389.76 | Model 4 vs. Model 2 LRT p-value **0.008** |
| | TL vs. TH | 1.57 | 0.75, 3.30 | 0.234 | | |
| | HR (pos vs. neg) | 1.53 | 0.76, 3.06 | 0.229 | | |
| | Stage (III vs. II) | 2.27 | 1.18, 4.37 | **0.014** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.14, 0.69 | **0.004** | | Model 4 vs. Model 3 LRT p-value 0.77 |
| | HER2-E vs. not | 4.72 | 2.21, 10.1 | **<0.001** | | |
| | TILs High vs. Low (40%) | 0.86 | 0.32, 2.34 | 0.77 | | |
| | Signature (continuous) | 0.59 | 0.40, 0.87 | **0.007** | | |

CI: confident intervals; EFS: event-free survival; HR: hormone receptor; pCR: pathologic complete response; RD: residual disease; pos: positive; neg: negative; HER2-E: HER2-Enriched; AIC: Akaike Information Criterion; LR: likelihood-ratio test; TILs: tumor infiltrating lymphocytes; IgG: immunoglobulin G; T: weekly paclitaxel; H: trastuzumab; L: lapatinib. [1]Cox regression model p-value; [2]Likelihood-ratio test p-value.

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**eTable 10. Landmark Analysis Week 30**

Association of tumor-infiltrating lymphocytes (TILs) as continuous variable and immune gene expression signatures (iGES) with event-free survival (EFS) in CALGB 40601: comparative analysis of nested multivariable Cox regression models.

| Signature: IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | | | | | | |
|---|---|---|---|---|---|---|
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.37 | 0.16, 0.87 | **0.02** | 364.58 | - |
| | TL vs. TH | 1.34 | 0.63, 2.83 | 0.44 | | |
| | HR (pos vs. neg) | 2.13 | 1.03, 4.42 | **0.04** | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.2 | 0.09, 0.46 | **<0.001** | | |
| | HER2-E vs. Other | 4.6 | 2.09, 10.1 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 365.28 | Model 2 vs. Model 1 LRT p-value 0.25 |
| | TL vs. TH | 1.36 | 0.64, 2.90 | 0.42 | | |
| | HR (pos vs. neg) | 2.15 | 1.03, 4.45 | **0.04** | | |
| | Stage (III vs. II) | 1.89 | 0.96, 3.71 | 0.07 | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.51 | **<0.001** | | |
| | HER2-E vs. not | 4.9 | 2.21, 10.9 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.98, 1.01 | 0.27 | | |
| **Model 3** | THL vs. TH | 0.34 | 0.14, 0.81 | **0.015** | 361.31 | Model 3 vs. Model 1 LRT p-value **0.02** |
| | TL vs. TH | 1.54 | 0.71, 3.33 | 0.27 | | |
| | HR (pos vs. neg) | 1.71 | 0.81, 3.60 | 0.16 | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.27 | 0.11, 0.62 | **0.002** | | |
| | HER2-E vs. not | 4.6 | 2.10, 10.1 | **<0.001** | | |
| | Signature (cont) | 0.67 | 0.47, 0.94 | **0.02** | | |
| **Model 4** | THL vs. TH | 0.35 | 0.14, 0.83 | **0.02** | 363.27 | Model 4 vs. Model 2 LRT p-value **0.04** |
| | TL vs. TH | 1.55 | 0.72, 3.36 | 0.27 | | |
| | HR (pos vs. neg) | 1.68 | 0.79, 3.59 | 0.18 | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.85 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.26 | 0.11, 0.62 | **0.002** | | Model 4 vs. Model 3 LRT p-value 0.84 |
| | HER2-E vs. not | 4.55 | 2.07, 10.0 | **<0.001** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.84 | | |
| | Signature (continuous) | 0.65 | 0.43, 0.99 | **0.04** | | |
| **Signature: Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.37 | 0.16, 0.87 | **0.02** | 364.58 | - |
| | TL vs. TH | 1.34 | 0.63, 2.83 | 0.45 | | |
| | HR (pos vs. neg) | 2.13 | 1.03, 4.42 | **0.04** | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.2 | 0.09, 0.46 | **<0.001** | | |
| | HER2-E vs. Other | 4.6 | 2.09, 10.1 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 365.28 | Model 2 vs. Model 1 LRT p-value 0.25 |
| | TL vs. TH | 1.36 | 0.64, 2.90 | 0.42 | | |
| | HR (pos vs. neg) | 2.15 | 1.03, 4.45 | **0.04** | | |
| | Stage (III vs. II) | 1.89 | 0.96, 3.71 | 0.07 | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.51 | **<0.001** | | |
| | HER2-E vs. not | 4.9 | 2.21, 10.9 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.98, 1.01 | 0.27 | | |
| **Model 3** | THL vs. TH | 0.34 | 0.14, 0.80 | **0.01** | 360.66 | Model 3 vs. Model 1 LRT p-value **0.02** |
| | TL vs. TH | 1.61 | 0.74, 3.49 | 0.23 | | |
| | HR (pos vs. neg) | 2.11 | 1.02, 4.35 | **0.04** | | |
| | Stage (III vs. II) | 1.96 | 1.00, 3.86 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.28 | 0.12, 0.66 | **0.004** | | |
| | HER2-E vs. not | 5.58 | 2.47, 12.6 | **<0.001** | | |
| | Signature (cont) | 0.64 | 0.45, 0.91 | **0.01** | | |
| **Model 4** | THL vs. TH | 0.34 | 0.14, 0.82 | **0.02** | 362.61 | Model 4 vs. Model 2 LRT p-value **0.03** |
| | TL vs. TH | 1.62 | 0.74, 3.53 | 0.22 | | |
| | HR (pos vs. neg) | 2.11 | 1.02, 4.34 | **0.04** | | |
| | Stage (III vs. II) | 1.97 | 1.00, 3.89 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.28 | 0.12, 0.66 | **0.004** | | Model 4 vs. Model 3 LRT p-value 0.81 |
| | HER2-E vs. not | 5.59 | 2.47, 12.6 | **<0.001** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.81 | | |
| | Signature (continuous) | 0.62 | 0.41, 0.95 | **0.03** | | |
| **Signature: Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.37 | 0.16, 0.87 | **0.02** | 364.58 | - |
| | TL vs. TH | 1.34 | 0.63, 2.83 | 0.45 | | |
| | HR (pos vs. neg) | 2.13 | 1.03, 4.42 | **0.04** | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.2 | 0.09, 0.46 | **<0.001** | | |
| | HER2-E vs. Other | 4.6 | 2.09, 10.1 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 365.28 | Model 2 vs. Model 1 LRT p-value 0.25 |
| | TL vs. TH | 1.36 | 0.64, 2.90 | 0.42 | | |
| | HR (pos vs. neg) | 2.15 | 1.03, 4.45 | **0.04** | | |
| | Stage (III vs. II) | 1.89 | 0.96, 3.71 | 0.07 | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.51 | **<0.001** | | |
| | HER2-E vs. not | 4.9 | 2.21, 10.9 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.98, 1.01 | 0.27 | | |
| **Model 3** | THL vs. TH | 0.33 | 0.14, 0.78 | **0.01** | 357.02 | Model 3 vs. Model 1 LRT p-value **0.002** |
| | TL vs. TH | 1.68 | 0.78, 3.64 | 0.19 | | |
| | HR (pos vs. neg) | 1.62 | 0.77, 3.38 | 0.20 | | |
| | Stage (III vs. II) | 2.1 | 1.07, 4.13 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.3 | 0.13, 0.71 | **0.006** | | |
| | HER2-E vs. not | 5 | 2.27, 11.0 | **<0.001** | | |
| | Signature (cont) | 0.56 | 0.39, 0.81 | **0.002** | | |
| **Model 4** | THL vs. TH | 0.34 | 0.14, 0.82 | **0.02** | 358.57 | Model 4 vs. Model 2 LRT p-value **0.003** |
| | TL vs. TH | 1.74 | 0.80, 3.81 | 0.16 | | |
| | HR (pos vs. neg) | 1.56 | 0.74, 3.27 | 0.239 | | |
| | Stage (III vs. II) | 2.15 | 1.09, 4.24 | **0.03** | | |
| | pCR (pCR vs. RD) | 0.29 | 0.12, 0.69 | **0.005** | | Model 4 vs. Model 3 LRT p-value 0.51 |
| | HER2-E vs. not | 4.89 | 2.21, 10.8 | **<0.001** | | |

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|---|---|---|---|---|---|---|
| | TILs (continuous) | 1.01 | 0.99, 1.03 | 0.50 | | |
| | Signature (continuous) | 0.52 | 0.34, 0.79 | **0.002** | | |
| **Signature: Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.37 | 0.16, 0.87 | **0.02** | 364.58 | - |
| | TL vs. TH | 1.34 | 0.63, 2.83 | 0.45 | | |
| | HR (pos vs. neg) | 2.13 | 1.03, 4.42 | **0.04** | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.2 | 0.09, 0.46 | **<0.001** | | |
| | HER2-E vs. Other | 4.6 | 2.09, 10.1 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 365.28 | Model 2 vs. Model 1 LRT p-value 0.25 |
| | TL vs. TH | 1.36 | 0.64, 2.90 | 0.42 | | |
| | HR (pos vs. neg) | 2.15 | 1.03, 4.45 | **0.04** | | |
| | Stage (III vs. II) | 1.89 | 0.96, 3.71 | 0.07 | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.51 | **<0.001** | | |
| | HER2-E vs. not | 4.9 | 2.21, 10.9 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.98, 1.01 | 0.27 | | |
| **Model 3** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 356.98 | Model 3 vs. Model 1 LRT p-value **0.002** |
| | TL vs. TH | 1.81 | 0.83, 3.95 | 0.14 | | |
| | HR (pos vs. neg) | 1.73 | 0.84, 3.59 | 0.14 | | |
| | Stage (III vs. II) | 2.21 | 1.12, 4.37 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.31 | 0.13, 0.72 | **0.007** | | |
| | HER2-E vs. not | 5.06 | 2.30, 11.1 | **<0.001** | | |
| | Signature (cont) | 0.56 | 0.39, 0.81 | **0.002** | | |
| **Model 4** | THL vs. TH | 0.36 | 0.15, 0.87 | **0.02** | 358.58 | Model 4 vs. Model 2 LRT p-value **0.003** |
| | TL vs. TH | 1.89 | 0.85, 4.17 | 0.12 | | |
| | HR (pos vs. neg) | 1.7 | 0.82, 3.51 | 0.15 | | |
| | Stage (III vs. II) | 2.29 | 1.15, 4.56 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.3 | 0.13, 0.71 | **0.006** | | Model 4 vs. Model 3 LRT p-value 0.53 |
| | HER2-E vs. not | 4.97 | 2.25, 11.0 | **<0.001** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | TILs (continuous) | 1.01 | 0.99, 1.02 | 0.52 | | |
| | Signature (continuous) | 0.52 | 0.34, 0.80 | **0.003** | | |
| **Signature: Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.37 | 0.16, 0.87 | **0.02** | 364.58 | - |
| | TL vs. TH | 1.34 | 0.63, 2.83 | 0.45 | | |
| | HR (pos vs. neg) | 2.13 | 1.03, 4.42 | **0.04** | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.2 | 0.09, 0.46 | **<0.001** | | |
| | HER2-E vs. Other | 4.6 | 2.09, 10.1 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 365.28 | Model 2 vs. Model 1 LRT p-value 0.25 |
| | TL vs. TH | 1.36 | 0.64, 2.90 | 0.42 | | |
| | HR (pos vs. neg) | 2.15 | 1.03, 4.45 | **0.04** | | |
| | Stage (III vs. II) | 1.89 | 0.96, 3.71 | 0.07 | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.51 | **<0.001** | | |
| | HER2-E vs. not | 4.9 | 2.21, 10.9 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.98, 1.01 | 0.27 | | |
| **Model 3** | THL vs. TH | 0.34 | 0.14, 0.80 | **0.01** | 360.55 | Model 3 vs. Model 1 LRT p-value **0.01** |
| | TL vs. TH | 1.59 | 0.74, 3.45 | 0.24 | | |
| | HR (pos vs. neg) | 1.73 | 0.83, 3.63 | 0.14 | | |
| | Stage (III vs. II) | 2.02 | 1.02, 3.97 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.28 | 0.12, 0.66 | **0.004** | | |
| | HER2-E vs. not | 4.73 | 2.16, 10.4 | **<0.001** | | |
| | Signature (cont) | 0.64 | 0.44, 0.91 | **0.01** | | |
| **Model 4** | THL vs. TH | 0.34 | 0.14, 0.83 | **0.02** | 362.40 | Model 4 vs. Model 2 LRT p-value **0.03** |
| | TL vs. TH | 1.62 | 0.75, 3.52 | 0.22 | | |
| | HR (pos vs. neg) | 1.69 | 0.80, 3.57 | 0.17 | | |
| | Stage (III vs. II) | 2.04 | 1.03, 4.04 | **0.04** | | |
| | pCR (pCR vs. RD) | 0.28 | 0.12, 0.66 | **0.003** | | Model 4 vs. Model 3 LRT p-value 0.70 |
| | HER2-E vs. not | 4.64 | 2.11, 10.2 | **<0.001** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.70 | | |
| | Signature (continuous) | 0.6 | 0.39, 0.94 | **0.03** | | |
| **Signature: IgG Rody BreastCancerResearch.2008 PMID.19272155** | | | | | | |
| **Model** | **Features** | **HR** | **95% CI** | **p-value[1]** | **AIC** | **LR p-value[2]** |
| **Model 1** | THL vs. TH | 0.37 | 0.16, 0.87 | **0.02** | 364.58 | - |
| | TL vs. TH | 1.34 | 0.63, 2.83 | 0.45 | | |
| | HR (pos vs. neg) | 2.13 | 1.03, 4.42 | **0.04** | | |
| | Stage (III vs. II) | 1.95 | 0.99, 3.83 | 0.05 | | |
| | pCR (pCR vs. RD) | 0.2 | 0.09, 0.46 | **<0.001** | | |
| | HER2-E vs. Other | 4.6 | 2.09, 10.1 | **<0.001** | | |
| **Model 2** | THL vs. TH | 0.35 | 0.15, 0.83 | **0.02** | 365.28 | Model 2 vs. Model 1 LRT p-value 0.25 |
| | TL vs. TH | 1.36 | 0.64, 2.90 | 0.42 | | |
| | HR (pos vs. neg) | 2.15 | 1.03, 4.45 | **0.04** | | |
| | Stage (III vs. II) | 1.89 | 0.96, 3.71 | 0.07 | | |
| | pCR (pCR vs. RD) | 0.22 | 0.10, 0.51 | **<0.001** | | |
| | HER2-E vs. not | 4.9 | 2.21, 10.9 | **<0.001** | | |
| | TILs (continuous) | 0.99 | 0.98, 1.01 | 0.27 | | |
| **Model 3** | THL vs. TH | 0.36 | 0.15, 0.86 | **0.02** | 359.43 | Model 3 vs. Model 1 LRT p-value **0.007** |
| | TL vs. TH | 1.69 | 0.78, 3.67 | 0.18 | | |
| | HR (pos vs. neg) | 1.79 | 0.86, 3.71 | 0.12 | | |
| | Stage (III vs. II) | 2.19 | 1.11, 4.31 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.28 | 0.12, 0.65 | **0.003** | | |
| | HER2-E vs. not | 4.97 | 2.26, 10.9 | **<0.001** | | |
| | Signature (cont) | 0.61 | 0.43, 0.87 | **0.007** | | |
| **Model 4** | THL vs. TH | 0.37 | 0.15, 0.88 | **0.03** | 361.35 | Model 4 vs. Model 2 LRT p-value **0.02** |
| | TL vs. TH | 1.72 | 0.79, 3.75 | 0.17 | | |
| | HR (pos vs. neg) | 1.77 | 0.85, 3.68 | 0.13 | | |
| | Stage (III vs. II) | 2.22 | 1.11, 4.42 | **0.02** | | |
| | pCR (pCR vs. RD) | 0.28 | 0.12, 0.65 | **0.003** | | Model 4 vs. Model 3 LRT p-value 0.78 |
| | HER2-E vs. not | 4.93 | 2.24, 10.9 | **<0.001** | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | TILs (continuous) | 1 | 0.98, 1.02 | 0.78 | | |
| | Signature (continuous) | 0.59 | 0.39, 0.90 | **0.01** | | |

CI: confident intervals; EFS: event-free survival; HR: hormone receptor; pCR: in-breast pathologic complete response; RD: residual disease; pos: positive; neg: negative; HER2-E: HER2-Enriched; AIC: Akaike Information Criterion; LR: likelihood-ratio test; TILs: tumor infiltrating lymphocytes; IgG: immunoglobulin G; T: weekly paclitaxel; H: trastuzumab; L: lapatinib. [1]Cox regression model p-value; [2]Likelihood-ratio test p-value.

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## eTable 11. Summary Table of Akaike Information Criteria (AIC) and C-Index From Multivariable Cox Models Including Immune Gene Expression Signatures (iGES)

| iGES ID | AIC | c-index |
|---|---|---|
| IGG.Cluster Fan BMCMedGenomics.2011 PMID.21214954 | 389.97 | 0.76 |
| Plasma.cells ImSig.Nirmal CancerImmunolRes.2018 PMID.30266715 | 388.34 | 0.73 |
| Bcells.Plasma.cells.52genes Miller GenomeBiol.2013 PMID.23618380 | 385.04 | 0.77 |
| Ig TCGA.BRCA.1198 Cell.2015 PMID.26451490 | 384.82 | 0.77 |
| Immune1 TCGA.BRCA.1198 JCI.2020 PMID.32573490 | 389.43 | 0.74 |
| IgG Rody BreastCancerResearch.2008 PMID.19272155 | 387.85 | 0.74 |

A median c-index was calculated for each model using 5-folds cross validation.

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