# Supplementary Figures



**Supplementary Figure 1. P-value of selected prognostic genes based on univariate cox regression**
Scatter plots comparing the P-value of selected prognostic genes using different representative expressions. Hazardous (HR > 1, P-value < 0.01) and protective genes (HR < 1, P-value < 0.01) were selected based on average expression and compared with results using maximal and minimal expression separately. The text labels the percentage of genes in that area. The survival analysis measures disease-free survival.

# a Result of ORACLE (TRACERxC2)

| Method | Function | Hazard Ratio | P-value | C-index |
|---|---|---|---|---|
| Transformed gene expression (Method 1) | Avg. | 1.362 | 0.00955 | 0.581 |
| | Max. | 1.509 | 0.00029 | 0.607 |
| | Min. | 1.132 | 0.26325 | 0.537 |
| | Adj. | 1.528 | 1e−04 | 0.61 |
| | Rev. | 1.073 | 0.50677 | 0.527 |
| Region specific score (Method 2) | Avg. | 1.362 | 0.00955 | 0.581 |
| | Max. | 1.479 | 0.00072 | 0.603 |
| | Min. | 1.144 | 0.21736 | 0.54 |
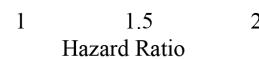
Hazard Ratio

# b Result of ORACLE (TRACERxLUAD)

| Method | Function | Hazard Ratio | P-value | C-index |
|---|---|---|---|---|
| Transformed gene expression (Method 1) | Avg. | 1.498 | 0.01218 | 0.58 |
| | Max. | 1.73 | 0.00016 | 0.616 |
| | Min. | 1.097 | 0.54225 | 0.526 |
| | Adj. | 1.777 | 3e−05 | 0.627 |
| | Rev. | 0.997 | 0.98361 | 0.491 |
| Region specific score (Method 2) | Avg. | 1.498 | 0.01218 | 0.58 |
| | Max. | 1.747 | 0.00031 | 0.616 |
| | Min. | 1.098 | 0.52101 | 0.525 |

Hazard Ratio

# c Result of ORACLE (MDAMPLC)
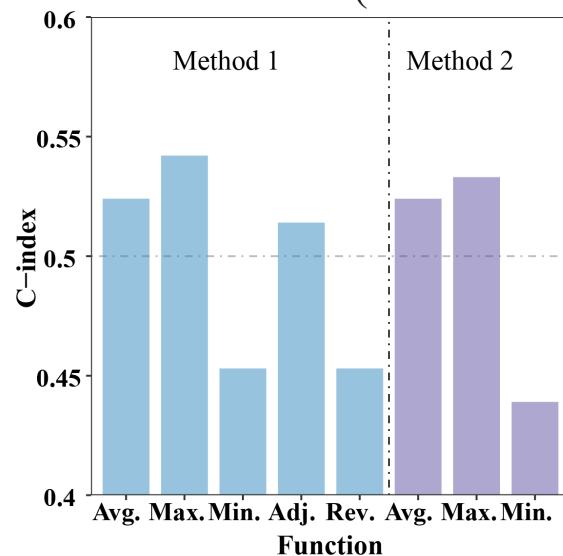


**Supplementary Figure 2. Survival analysis of the ORACLE signature in other cohorts**

(a-c) Performance of ORACLE signature applied with eight functions from two methods of quantifying patient-specific risk score in the (a) TRACERxC2, (b) TRACERxLUAD, and (c) MDAMPLC cohorts. In the Hazard Ratio column, 95% confidence interval was shown as dotted line. The survival analysis measures disease-free survival.

## a  Result of WTGS (TRACERxC2)

| Method | Function | | Hazard Ratio | P−value | C−index |
|---|---|---|---|---|---|
| Transformed gene expression (Method 1) | Avg. | | 0.985 | 0.0003374 | 0.604 |
| | Max. | | 0.983 | 0.0001469 | 0.607 |
| | Min. | | 0.985 | 0.0004749 | 0.596 |
| | Adj. | | 0.981 | 5e−07 | 0.65 |
| | Rev. | | 1 | 0.9705139 | 0.5 |
| Region specific score (Method 2) | Avg. | | 0.984 | 0.0003487 | 0.592 |
| | Max. | | 0.988 | 0.0032282 | 0.57 |
| | Min. | | 0.981 | 4.99e−05 | 0.623 |

Hazard Ratio: 0.975  1  1.025

## b  Result of WTGS (TRACERxLUAD)

| Method | Function | | Hazard Ratio | P−value | C−index |
|---|---|---|---|---|---|
| Transformed gene expression (Method 1) | Avg. | | 0.981 | 0.000756 | 0.622 |
| | Max. | | 0.979 | 0.0003265 | 0.629 |
| | Min. | | 0.983 | 0.0036095 | 0.605 |
| | Adj. | | 0.975 | 3e−07 | 0.687 |
| | Rev. | | 1.008 | 0.0717177 | 0.534 |
| Region specific score (Method 2) | Avg. | | 0.981 | 0.0009194 | 0.616 |
| | Max. | | 0.987 | 0.0192637 | 0.578 |
| | Min. | | 0.975 | 4.91e−05 | 0.65 |

Hazard Ratio: 0.975  1  1.025

## c  Result of WTGS (MDAMPLC)
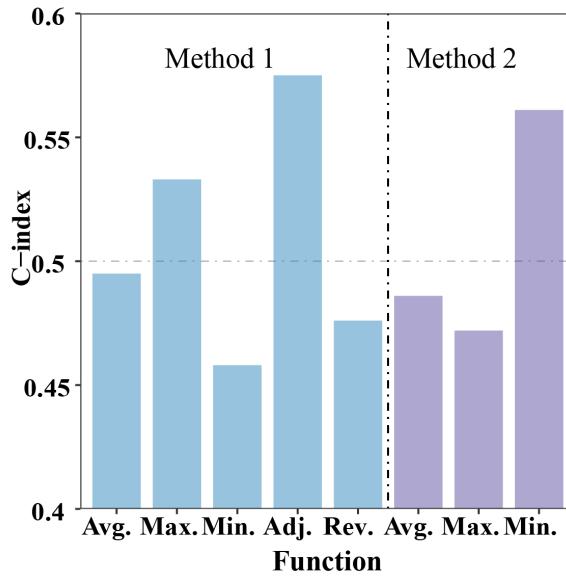


**Supplementary Figure 3. Survival analysis of the WTGS signature in other cohorts**

(a-c) Performance of WTGS signature applied with eight functions from two methods of quantifying patient-specific risk score in the (a) TRACERxC2, (c) TRACERxLUAD, and (c) MDAMPLC cohorts. In the Hazard Ratio column, 95% confidence interval was shown as dotted line. The survival analysis measures disease-free survival.

## a Result of PACEG (TRACERxC2)

| Method | Function | | Hazard Ratio | P−value | C−index |
|---|---|---|---|---|---|
| Transformed gene expression (Method 1) | Avg. | | 1.382 | 0.00778 | 0.576 |
| | Max. | | 1.55 | 0.00028 | 0.6 |
| | Min. | | 1.167 | 0.16463 | 0.542 |
| | Adj. | | 1.526 | 5e−05 | 0.614 |
| | Rev. | | 1.035 | 0.72955 | 0.512 |
| Region specific score (Method 2) | Avg. | | 1.382 | 0.00778 | 0.576 |
| | Max. | | 1.567 | 2e−04 | 0.603 |
| | Min. | | 1.154 | 0.19355 | 0.541 |

Hazard Ratio
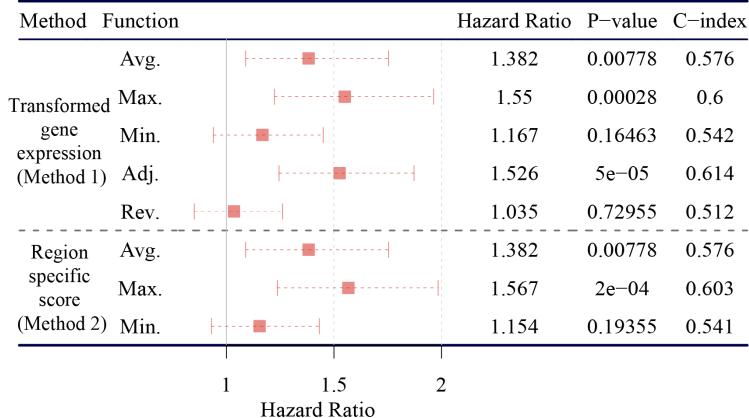
## b Result of PACEG (MDAMPLC)



## c Result of PACEG (TRACERxLUAD)

| Method | Function | | Hazard Ratio | P−value | C−index |
|---|---|---|---|---|---|
| Transformed gene expression (Method 1) | Avg. | | 1.536 | 0.012766 | 0.587 |
| | Max. | | 1.924 | 0.00017 | 0.615 |
| | Min. | | 1.106 | 0.496229 | 0.533 |
| | Adj. | | 1.994 | 3e−06 | 0.642 |
| | Rev. | | 0.909 | 0.45014 | 0.51 |
| Region specific score (Method 2) | Avg. | | 1.536 | 0.012766 | 0.587 |
| | Max. | | 1.99 | 8.4e−05 | 0.621 |
| | Min. | | 1.085 | 0.577392 | 0.529 |

Hazard Ratio
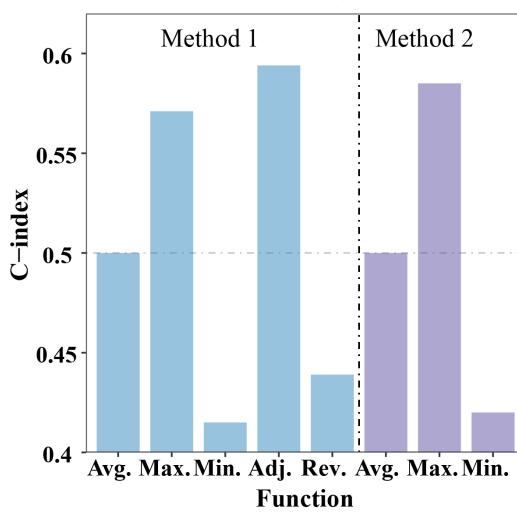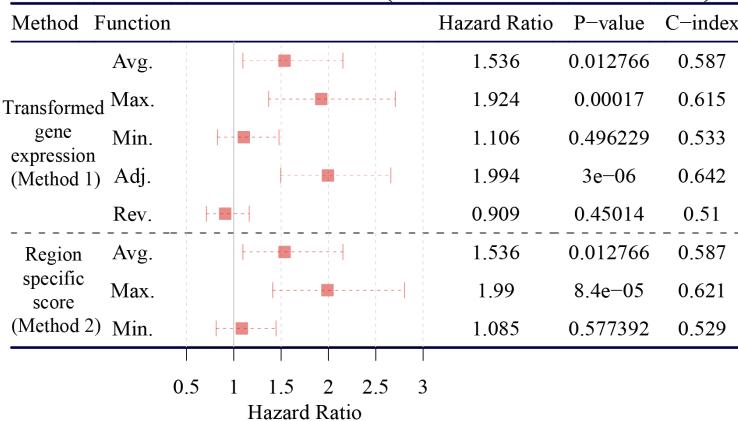
**Supplementary Figure 4. Survival analysis of the PACEG signature in other cohorts**

(a-c) Performance of PACEG signature applied with eight functions from two methods of quantifying patient-specific risk score in the (a) TRACERxC2, (b) MDAMPLC and (c) TRACERxLUAD cohorts. In the Hazard Ratio column, 95% confidence interval was shown as dotted line. The survival analysis measures disease-free survival.
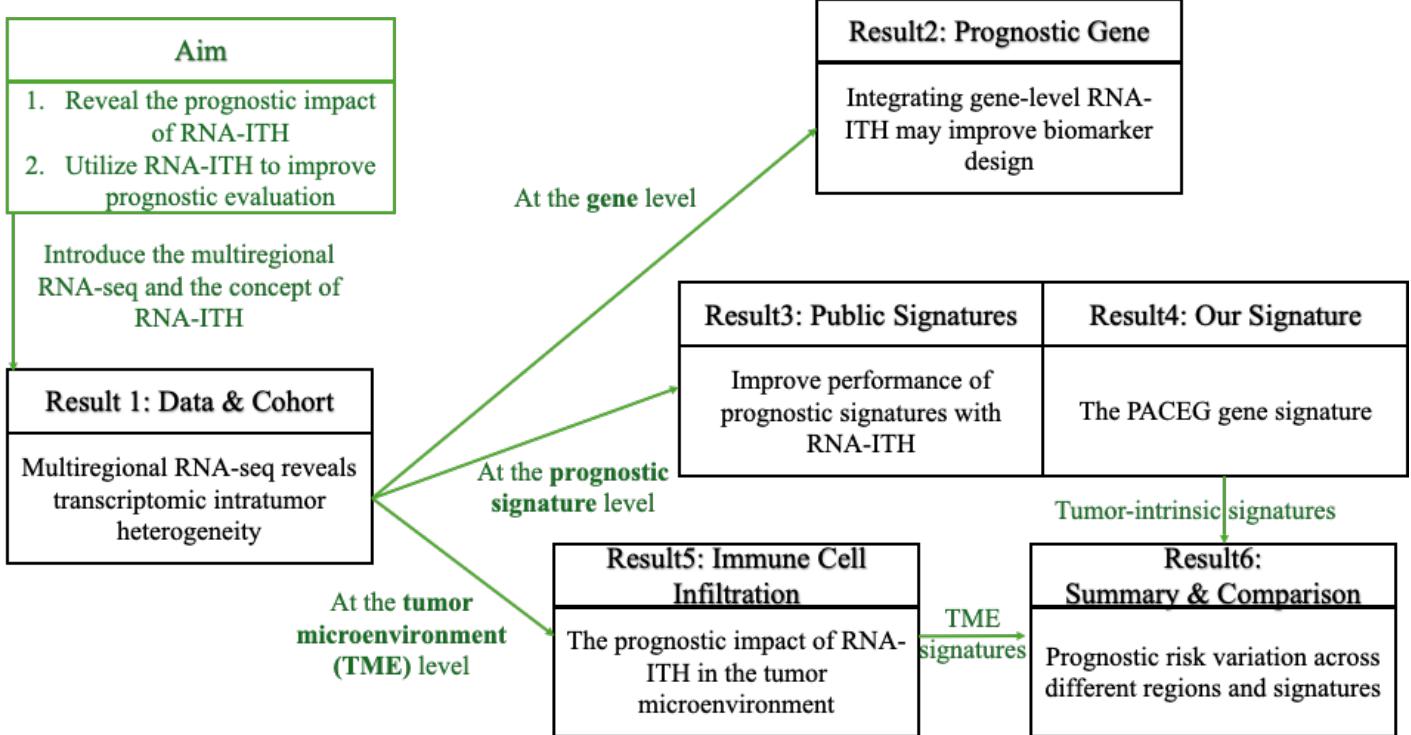
**Supplementary Figure 5. The flowchart of the study**

The flowchart provided an overview of the study. The black box represents the results, and the black text is the corresponding subtitle. The green box and text show the logic of the study.

**a** Region-Specific Risk Score (TRACERxC1, all patients with # Region ≥ 3)
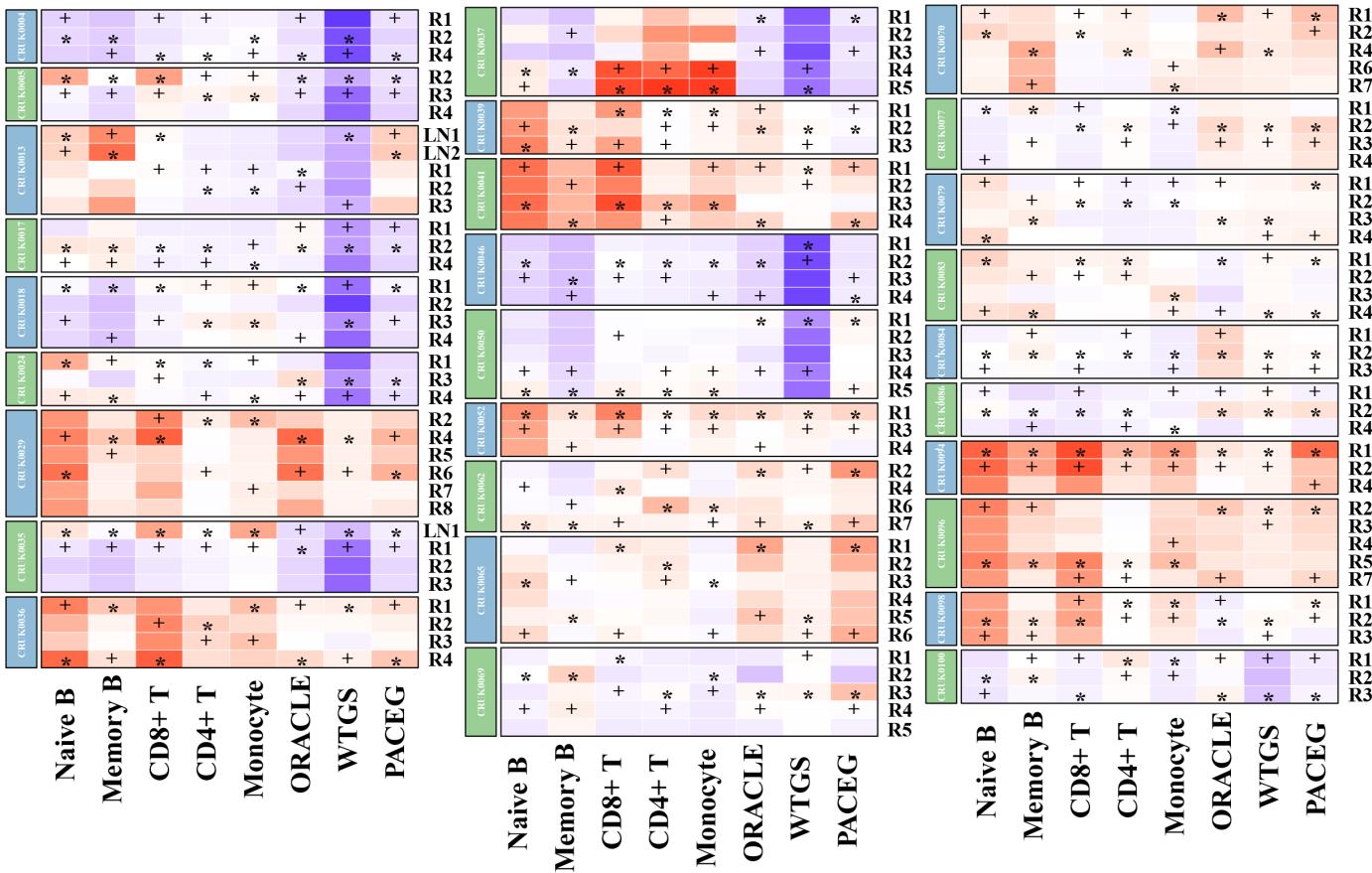
**b** Region-Specific Risk Score (MDAMPLC, all patients with # Region ≥ 3)

**Risk Score**

Risk Score Rank Across Regions
* 1st Highest
+ 2nd Highest
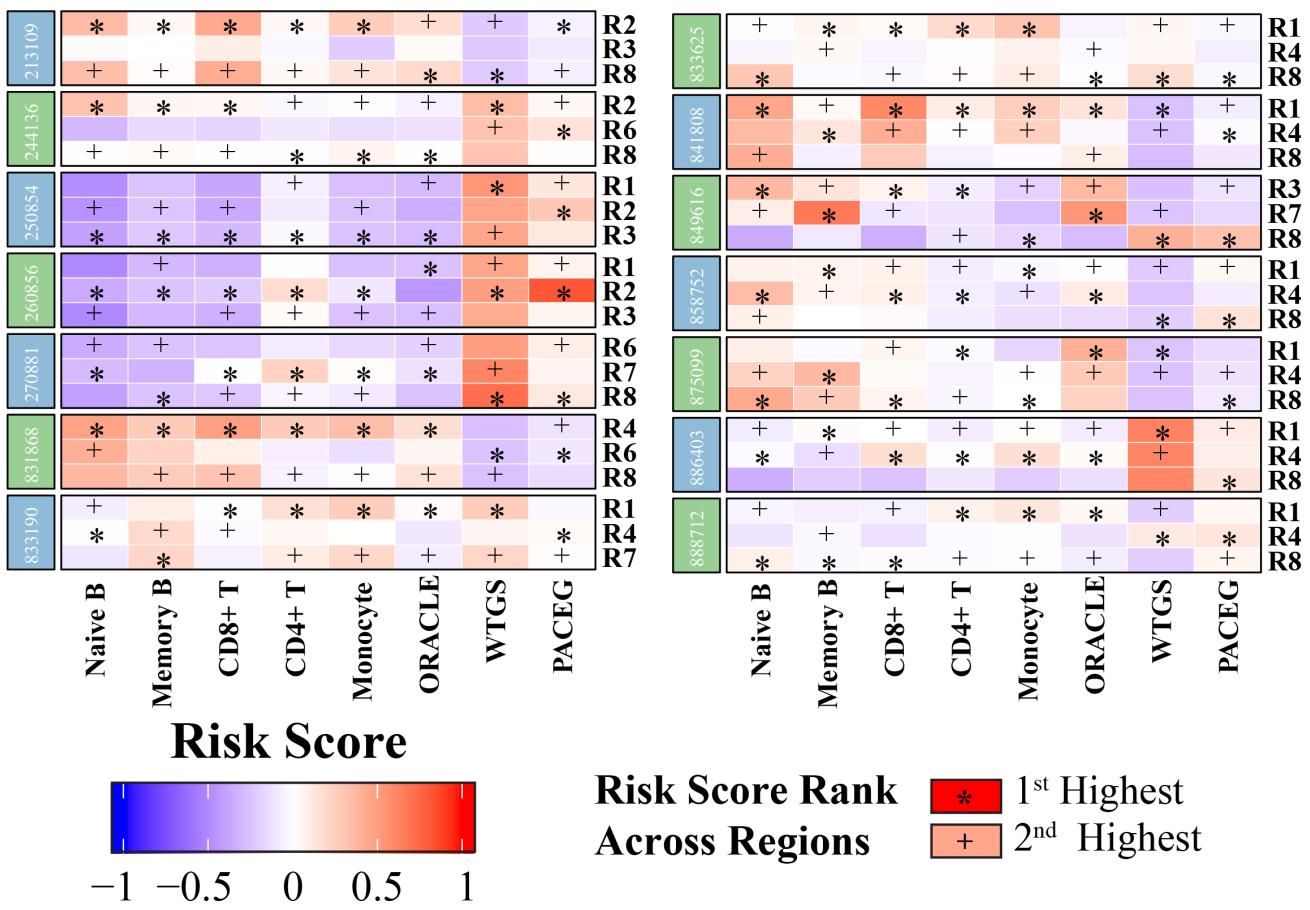
**Supplementary Figure 6. Region-specific risk scores predicted by different gene signatures.**

(a,b) Heatmap displaying the risk scores of different regions from all patients with at least three regions in (b) TRACERxC1 and (a) MDAMPLC cohorts predicted by eight gene signatures. The risk score was normalized by subtracting the median value and scaled to the [0, 1] interval "l" "*" represents the highest risk scores across different regions of the same patients. "+" shows the second highest risk scores.
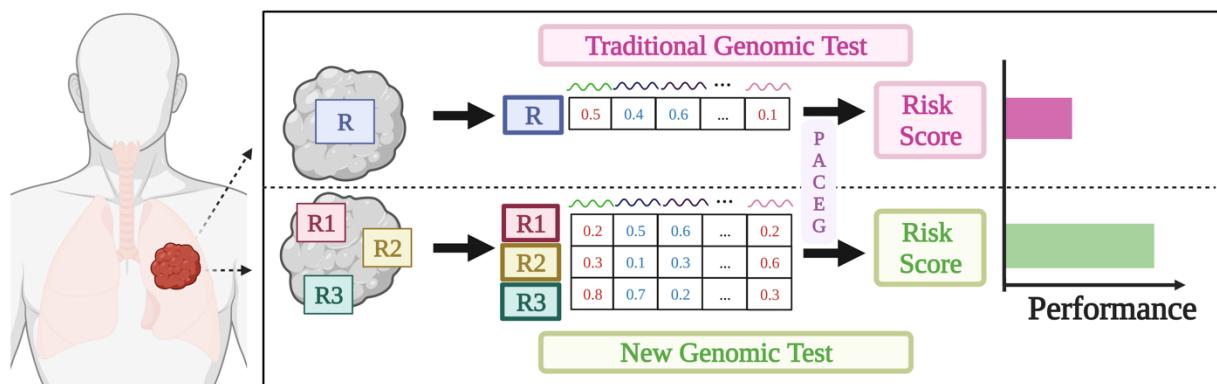


**Supplementary Figure 7. Schema of incorporation of PACEG and RNA-ITH**

We propose to integrate the PACEG signature developed in this study and the RNA-ITH obtained from multiregional profiling to achieve a reproducible and accurate prognostic analysis in clinical.

# Supplementary Tables

## Supplementary Table 1 Clinical characteristics of the patients

| Factor | | | TRACERxC1 | MDAMPLC | TRACERxC2 | TRACERxLUAD |
|---|---|---|---|---|---|---|
| No.patients | | | 64 | 25 | 261 | 187 |
| No.samples | | | 164 | 64 | 652 | 472 |
| No.patients with multiregions | | | 45 | 25 | 208 | 152 |
| No. regions per tumor | | | 2-6 | 2-3 | 1-8 | 2-8 |
| Age Range(median) | | | 34-83 (67.5) | 32-77 (62) | 37-92 (69) | 37-92 (68) |
| Sex | | Female | 23 | 12 | 115 | 91 |
| | | Male | 41 | 13 | 146 | 96 |
| Smoking History | | Current | 4 | 3 | 116 | 74 |
| | | Former | 29 | 18 | 130 | 95 |
| | | Never | 7 | 4 | 15 | 18 |
| | | Recent Former | 24 | 0 | 0 | 0 |
| Subtype | | Adenocarcinoma | 41 | 13 | 137 | 187** |
| | | Squamous cell carcinoma | 16 | 8 | 89 | 0 |
| | | Adenosquamous carcinoma | 3 | 0 | 9 | 0 |
| | | Carcinosarcoma | 2 | 0 | 0 | 0 |
| | | Large cell carcinoma | 1 | 0 | 5 | 0 |
| | | Large cell neuroendocrine carcinoma | 1 | 4 | 8 | 0 |
| | | Other | 0 | 0 | 13 | 0 |
| Aadjuvant Therapy | | Yes | 20 | 0 | 91 | 66 |
| | | No | 44 | 23 | 170 | 121 |
| | | Unknown | 0 | 2 | 0 | 0 |
| Stage | I | IA | 12 | 2 | 56 | 45 |
| | | IB | 25 | 9 | 58 | 45 |
| | II | IIA | 7 | 6 | 55 | 32 |
| | | IIB | 9 | 4 | 38 | 21 |
| | III | IIIA | 10 | 3 | 54 | 43 |
| | | IIIB | 1 | 0 | 0 | 1 |
| | | IV | 0 | 1 | 0 | 0 |

Note:

* TRACERxC2: TRACERxC1 cohort was excluded from the TRACERxC2 cohort.

** 4 patients in the TRACERxLUAD have both adenocarcinoma and squamous cell carcinoma and 1 patient in the cohort has both adenocarcinoma and other subtypes.

# Supplementary Table 2 Nine public signatures improved by TRACERxC2 multiregional RNA-seq data

| Signature | Method | Function | HR | P-Value | C-index |
|---|---|---|---|---|---|
| **Boutros et al., 2008 (N = 5)** | **Transformed gene expression (Method 1)** | Avg. | 1.393 | 0.01247485 | 0.575 |
| | | Max. | 1.491 | 0.00093265 | 0.591 |
| | | Min. | 1.136 | 0.32929494 | 0.529 |
| | | Adj. | 1.495 | 4.41E-05 | 0.609 |
| | | Rev. | 0.94 | 0.57130185 | 0.51 |
| | **Region specific score (Method 2)** | Avg. | 1.393 | 0.01247485 | 0.575 |
| | | Max. | 1.549 | 0.00038071 | 0.598 |
| | | Min. | 1.122 | 0.3708536 | 0.529 |
| **Krzystanek et al., 2016 (N = 6)** | **Transformed gene expression (Method 1)** | Avg. | 1.714 | 0.00039343 | 0.593 |
| | | Max. | 1.894 | 8.84E-06 | 0.614 |
| | | Min. | 1.389 | 0.02906403 | 0.554 |
| | | Adj. | 1.665 | 1.85E-06 | 0.623 |
| | | Rev. | 1.03 | 0.8289592 | 0.509 |
| | **Region specific score (Method 2)** | Avg. | 1.714 | 0.00039343 | 0.593 |
| | | Max. | 1.894 | 1.01E-05 | 0.612 |
| | | Min. | 1.41 | 0.02287783 | 0.56 |
| **Bianchi et al., 2007 (N = 10)** | **Transformed gene expression (Method 1)** | Avg. | 1.527 | 0.01482885 | 0.569 |
| | | Max. | 1.78 | 6.12E-04 | 0.597 |
| | | Min. | 1.219 | 0.24289328 | 0.533 |
| | | Adj. | 1.8 | 1.75E-05 | 0.622 |
| | | Rev. | 0.899 | 0.46312943 | 0.516 |
| | **Region specific score (Method 2)** | Avg. | 1.527 | 0.01482885 | 0.569 |
| | | Max. | 1.723 | 1.16E-03 | 0.592 |
| | | Min. | 1.25 | 0.18867976 | 0.537 |
| **Kratz et al., 2012 (N = 11)** | **Transformed gene expression (Method 1)** | Avg. | 1.654 | 0.00053067 | 0.592 |
| | | Max. | 1.702 | 0.00017328 | 0.602 |
| | | Min. | 1.527 | 0.00323929 | 0.575 |
| | | Adj. | 1.749 | 1.05E-05 | 0.627 |
| | | Rev. | 1.251 | 0.11709291 | 0.53 |
| | **Region specific score (Method 2)** | Avg. | 1.654 | 0.00053067 | 0.592 |
| | | Max. | 1.709 | 0.00009957 | 0.606 |
| | | Min. | 1.495 | 0.00638411 | 0.566 |
| **Zhu et al., 2010 (N = 15)** | **Transformed gene expression (Method 1)** | Avg. | 1.237 | 0.08407536 | 0.544 |
| | | Max. | 1.385 | 0.00609145 | 0.575 |
| | | Min. | 1.046 | 0.69273048 | 0.507 |
| | | Adj. | 1.394 | 0.00330562 | 0.582 |
| | | Rev. | 1.006 | 0.95392062 | 0.5 |
| | **Region specific score (Method 2)** | Avg. | 1.237 | 0.08407536 | 0.544 |
| | | Max. | 1.33 | 0.01806893 | 0.565 |
| | | Min. | 1.065 | 0.57951141 | 0.513 |
| **Garber et al., 2001(N = 24)** | **Transformed gene expression (Method 1)** | Avg. | 1.511 | 0.0126496 | 0.575 |
| | | Max. | 1.604 | 0.00216258 | 0.589 |
| | | Min. | 1.298 | 0.11498246 | 0.545 |
| | | Adj. | 1.645 | 4.01E-05 | 0.622 |
| | | Rev. | 0.906 | 0.49323607 | 0.511 |
| | **Region specific score (Method 2)** | Avg. | 1.511 | 0.0126496 | 0.575 |
| | | Max. | 1.568 | 0.00317732 | 0.587 |
| | | Min. | 1.302 | 0.10701124 | 0.547 |
| **Wistuba et al., 2013 (N = 30)** | **Transformed gene expression (Method 1)** | Avg. | 1.423 | 0.00058051 | 0.592 |
| | | Max. | 1.49 | 0.00004841 | 0.609 |
| | | Min. | 1.267 | 0.01651651 | 0.562 |
| | | Adj. | 1.193 | 3.04E-06 | 0.626 |
| | | Rev. | 0.899 | 0.02294407 | 0.557 |
| | **Region specific score (Method 2)** | Avg. | 1.423 | 0.00058051 | 0.592 |
| | | Max. | 1.526 | 0.00001673 | 0.621 |
| | | Min. | 1.259 | 0.0230048 | 0.556 |
| **Raz et al., 2008(N = 54)** | **Transformed gene expression (Method 1)** | Avg. | 1.11 | 0.02793449 | 0.56 |
| | | Max. | 1.15 | 0.00106967 | 0.59 |
| | | Min. | 1.026 | 0.57751577 | 0.515 |
| | | Adj. | 1.137 | 5.99E-05 | 0.614 |
| | | Rev. | 0.951 | 0.16687015 | 0.535 |
| | **Region specific score (Method 2)** | Avg. | 1.11 | 0.02793449 | 0.56 |
| | | Max. | 1.135 | 0.00383051 | 0.582 |
| | | Min. | 1.041 | 0.37825699 | 0.522 |
| **Beer et al., 2002(N = 92)** | **Transformed gene expression (Method 1)** | Avg. | 1.067 | 0.04898316 | 0.568 |
| | | Max. | 1.102 | 0.00164257 | 0.604 |
| | | Min. | 1.014 | 0.65252857 | 0.528 |
| | | Adj. | 1.057 | 2.25E-05 | 0.633 |
| | | Rev. | 0.96 | 6.32E-03 | 0.558 |
| | **Region specific score (Method 2)** | Avg. | 1.067 | 0.04898316 | 0.568 |
| | | Max. | 1.093 | 0.00448594 | 0.595 |
| | | Min. | 1.02 | 0.52369003 | 0.534 |

# Supplementary Table 3 Nine public signatures improved by TRACERxLUAD multiregional RNA-seq data

| Signature | Method | Function | HR | P-Value | C-index |
|---|---|---|---|---|---|
| **Boutros et al., 2008 (N = 5)** | **Transformed gene expression (Method 1)** | Avg. | 1.605 | 0.0088666 | 0.585 |
| | | Max. | 1.773 | 0.00018449 | 0.613 |
| | | Min. | 1.087 | 0.63792562 | 0.515 |
| | | Adj. | 1.658 | 6.97E-06 | 0.635 |
| | | Rev. | 0.826 | 0.19210966 | 0.534 |
| | **Region specific score (Method 2)** | Avg. | 1.605 | 0.0088666 | 0.585 |
| | | Max. | 1.822 | 0.00013544 | 0.616 |
| | | Min. | 1.131 | 0.49342495 | 0.522 |
| **Krzystanek et al., 2016 (N = 6)** | **Transformed gene expression (Method 1)** | Avg. | 1.876 | 0.00230328 | 0.602 |
| | | Max. | 2.074 | 7.25E-05 | 0.627 |
| | | Min. | 1.36 | 0.15576982 | 0.546 |
| | | Adj. | 1.804 | 4.91E-06 | 0.643 |
| | | Rev. | 0.815 | 0.31352806 | 0.509 |
| | **Region specific score (Method 2)** | Avg. | 1.876 | 0.00230328 | 0.602 |
| | | Max. | 2.109 | 5.35E-05 | 0.63 |
| | | Min. | 1.355 | 0.16009086 | 0.549 |
| **Bianchi et al., 2007 (N = 10)** | **Transformed gene expression (Method 1)** | Avg. | 2.024 | 0.00787399 | 0.584 |
| | | Max. | 2.63 | 5.92E-05 | 0.625 |
| | | Min. | 1.246 | 0.40355183 | 0.529 |
| | | Adj. | 2.561 | 1.40E-07 | 0.668 |
| | | Rev. | 0.651 | 0.04339652 | 0.547 |
| | **Region specific score (Method 2)** | Avg. | 2.024 | 0.00787399 | 0.584 |
| | | Max. | 2.541 | 9.31E-05 | 0.625 |
| | | Min. | 1.24 | 0.41799481 | 0.523 |
| **Kratz et al., 2012 (N = 11)** | **Transformed gene expression (Method 1)** | Avg. | 2.285 | 0.00280417 | 0.594 |
| | | Max. | 2.497 | 0.00042468 | 0.612 |
| | | Min. | 1.823 | 0.02960004 | 0.566 |
| | | Adj. | 2.726 | 1.79E-06 | 0.647 |
| | | Rev. | 0.901 | 0.6926792 | 0.514 |
| | **Region specific score (Method 2)** | Avg. | 2.285 | 0.00280417 | 0.594 |
| | | Max. | 2.433 | 0.00024071 | 0.618 |
| | | Min. | 1.711 | 0.06054803 | 0.555 |
| **Zhu et al., 2010 (N = 15)** | **Transformed gene expression (Method 1)** | Avg. | 1.372 | 0.07468283 | 0.552 |
| | | Max. | 1.799 | 0.00083192 | 0.6 |
| | | Min. | 0.985 | 0.92118644 | 0.501 |
| | | Adj. | 1.897 | 0.00016613 | 0.613 |
| | | Rev. | 0.911 | 0.53211701 | 0.514 |
| | **Region specific score (Method 2)** | Avg. | 1.372 | 0.07468283 | 0.552 |
| | | Max. | 1.702 | 0.00316334 | 0.589 |
| | | Min. | 1.014 | 0.92577751 | 0.507 |
| **Garber et al., 2001(N = 24)** | **Transformed gene expression (Method 1)** | Avg. | 1.51 | 0.07670698 | 0.56 |
| | | Max. | 1.868 | 0.00389186 | 0.592 |
| | | Min. | 1.111 | 0.64753818 | 0.519 |
| | | Adj. | 2.046 | 5.76E-06 | 0.64 |
| | | Rev. | 0.66 | 0.02144292 | 0.559 |
| | **Region specific score (Method 2)** | Avg. | 1.51 | 0.07670698 | 0.56 |
| | | Max. | 1.752 | 0.00805735 | 0.588 |
| | | Min. | 1.11 | 0.65077717 | 0.522 |
| **Wistuba et al., 2013 (N = 30)** | **Transformed gene expression (Method 1)** | Avg. | 1.474 | 0.00193559 | 0.604 |
| | | Max. | 1.48 | 0.00047893 | 0.621 |
| | | Min. | 1.316 | 0.03905611 | 0.565 |
| | | Adj. | 1.24 | 4.90E-07 | 0.656 |
| | | Rev. | 0.82 | 0.00035414 | 0.588 |
| | **Region specific score (Method 2)** | Avg. | 1.474 | 0.00193559 | 0.604 |
| | | Max. | 1.544 | 0.00012083 | 0.633 |
| | | Min. | 1.266 | 0.07758646 | 0.56 |
| **Raz et al., 2008(N = 54)** | **Transformed gene expression (Method 1)** | Avg. | 1.132 | 0.05199834 | 0.571 |
| | | Max. | 1.225 | 0.0005282 | 0.611 |
| | | Min. | 0.991 | 0.88017761 | 0.496 |
| | | Adj. | 1.216 | 3.03E-06 | 0.641 |
| | | Rev. | 0.898 | 0.01483498 | 0.564 |
| | **Region specific score (Method 2)** | Avg. | 1.132 | 0.05199834 | 0.571 |
| | | Max. | 1.22 | 0.00109238 | 0.607 |
| | | Min. | 1 | 0.99414774 | 0.51 |
| **Beer et al., 2002(N = 92)** | **Transformed gene expression (Method 1)** | Avg. | 1.1 | 0.03487677 | 0.574 |
| | | Max. | 1.158 | 0.00045574 | 0.615 |
| | | Min. | 1.005 | 0.906654 | 0.515 |
| | | Adj. | 1.083 | 6.00E-08 | 0.668 |
| | | Rev. | 0.933 | 5.14E-05 | 0.611 |
| | **Region specific score (Method 2)** | Avg. | 1.1 | 0.03487677 | 0.574 |
| | | Max. | 1.147 | 0.00105521 | 0.606 |
| | | Min. | 1.014 | 0.73748292 | 0.522 |

# Supplementary Table 4 PACEG information

| Gene | Coefficient | Role in Signature | Protein | Subcellular Location | Relevant Biological Functions |
|------|------------|------------------|---------|---------------------|-------------------------------|
| ADCY9 | -0.06 | Protective | Adenylate cyclase type 9 | Cell membrane | Adenylate cyclase; cAMP biosynthesis; PKA activation |
| AHSA1 | 0.04 | Hazardous | Activator of 90 kDa heat shock protein ATPase homolog 1 | Cytoplasm; Endoplasmic reticulum | Host-virus interaction; Stress response |
| AP2M1 | 0.01 | Hazardous | AP-2 complex subunit mu | Cell membrane; Membrane; coated pit | Endocytosis; Protein transport; CD4/CD8/CD28 Down-regulation |
| C1orf172 | -0.07 | Protective | Keratinocyte differentiation factor 1 | Cytoplasm; Cell junction | Differentiation |
| C9orf69 | 0.00 | Hazardous | Transmembrane protein 250 | Membrane; Nucleus; Cytoplasm | Host-virus interaction; Cell cycle |
| CCT6A | 0.00 | Hazardous | T-complex protein 1 subunit zeta | Cytoplasm | ATP hydrolysis; Regulating telomere maintenance. |
| CCT8 | 0.06 | Hazardous | T-complex protein 1 subunit theta | Cytoplasm | ATP hydrolysis; Stem cell maintenance. |
| CWC25 | -0.02 | Protective | Pre-mRNA-splicing factor CWC25 homolog | Nucleus | pre-mRNA splicing |
| EPN1 | 0.18 | Hazardous | Epsin-1 | Cytoplasm; Cell membrane; Nucleus; Membrane, clathrin-coated pit | Clathrin-mediated endocytosis; EGFR downregulation |
| FAF2 | 0.22 | Hazardous | FAS-associated factor 2 | Cytoplasm; Lipid droplet; Endoplasmic reticulum | Unfolded protein response; Neutrophil degranulation |
| GAPDH | 0.07 | Hazardous | Glyceraldehyde-3-phosphate dehydrogenase | Cytoplasm; Nucleus; Membrane | Apoptosis; Glycolysis; Innate immunity; Translation regulation |
| GSK3A | 0.03 | Hazardous | Glycogen synthase kinase-3 alpha | Axon; Cytoplasm; Nucleus; Mitochondrion | Carbohydrate metabolism; Glycogen metabolism; Neurogenesis; Wnt signaling pathway |
| HNRNPF | 0.11 | Hazardous | Heterogeneous nuclear ribonucleoprotein F | Nucleus | mRNA processing; mRNA splicing; JAK-STAT signaling |
| MED26 | -0.23 | Protective | Mediator of RNA polymerase II transcription subunit 26 | Nucleus | Transcription |
| MTUS1 | -0.03 | Protective | Microtubule-associated tumor suppressor 1 | Mitochondrion; Golgi apparatus; Cell membrane; Nucleus | Inhibit ERK2 activation and cell proliferation |
| PPFIBP1 | 0.12 | Hazardous | Liprin-beta-1 | Cell membrane; Cytoplasm | Receptor-type tyrosine-protein phosphatases; Signaling by ALK fusions and activated point mutants |
| RAD23B | 0.03 | Hazardous | UV excision repair protein RAD23 homolog B | Cytoplasm; Nucleus | DNA damage; DNA repair |
| RCOR1 | 0.14 | Hazardous | REST corepressor 1 | Nucleus | Chromatin regulator; Host-virus interaction; Transcription regulation |
| RUNDC1 | -0.04 | Protective | RUN domain-containing protein 1 | NA | Potential p53/TP53 inhibitor |
| SERBP1 | 0.11 | Hazardous | Plasminogen activator inhibitor 1 RNA-binding protein | Cytoplasm; Nucleus | mRNA stability |
| STK24 | 0.04 | Hazardous | Serine/threonine-protein kinase 24 | Cytoplasm; Nucleus; Membrane | Apoptosis |
| TBCC | 0.00 | Protective | Tubulin-specific chaperone C | Cytoplasm | Post-chaperonin tubulin folding pathway |
| TCP1 | 0.14 | Hazardous | T-complex protein 10A homolog 1 | Nucleus | Transcription regulation |
| USP4 | -0.12 | Protective | Ubiquitin carboxyl-terminal hydrolase 4 | Cytoplasm; Nucleus | TNFR1-induced NFkappaB signaling pathway |
| ZMYM6 | -0.05 | Protective | Zinc finger MYM-type protein 6 | Nucleus | Regulation of cell morphology and cytoskeletal organization |
| ZNF91 | -0.09 | Protective | Zinc finger protein 91 | Nucleus | Transcription regulation |

**Supplementary Table 5 Comparision between ORACLE and PACEG with M1-Adj**

| Signature | Method | Cohort | TRACERxC1 | TRACERxC2 | TRACERxLUAD |
|---|---|---|---|---|---|
| ORACLE | Transformed gene expression (Method 1) | HR | 2.932 | 1.528 | 1.777 |
| | | P-Value | 0.012 | 1.00E-04 | 3.00E-05 |
| | | C-index | 0.670 | 0.610 | 0.627 |
| PACEG | Ajusted Function *(M1-Adj)* | HR | 2.405 | 1.526 | **1.994** |
| | | P-Value | **0.006** | **5.00E-05** | **3.00E-06** |
| | | C-index | **0.693** | **0.614** | **0.642** |

**Supplementary Table 6 Multivariate Cox Regression Analysis of PACEG-*M1-Adj* and key clinical prognostic variables in TRACERxLUAD cohort**

| Factor | | Hazard Ratio | P-Value | Significance |
|---|---|---|---|---|
| **PACEG-*M1-Adj*** | | 1.69 | 0.000851 | *** |
| **Smoking_Status** | **Former vs Never** | 2.626 | 0.041001 | * |
| | **Current vs Never** | 1.648 | 0.318585 | |
| **StageIB** | **IB vs IA** | 1.439 | 3.25E-01 | |
| **StageIIA** | **IIA vs IA** | 2.565 | 0.015539 | * |
| **StageIIB** | **IIB vs IA** | 2.038 | 0.100541 | |
| **StageIIIA** | **IIIA vs IA** | 3.012 | 0.002342 | ** |
| **StageIIIB** | **IIIB vs IA** | 4.883 | 0.133415 | |
| **Age** | | 1.026 | 0.041944 | * |
| **Gender** | **Male vs Female** | 1.065 | 0.781166 | |

Note:

1. Signifance codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

2. Performance of the Multivariate model:

 1) C-Index = 0.728  (se = 0.028 )

 2) Likelihood ratio test = 56.84  on 10 df,   p=1e-08

 3) Wald test = 52.45  on 10 df,   p=9e-08

 4) Score (logrank) test = 56.84  on 10 df,   p=1e-08