

## SUPPLEMENTARY TABLES

**Supplementary Table 1. Early-stage LUAD prognosis-associated DNA methylation probes in discovery and validation phases.**

Probe	Discovery phase				Validation phase				
	HR	95% CI		<i>P</i>	FDR- <i>q</i>	HR	95% CI		<i>P</i>
cg06835509	0.2	0.1	0.5	1.27E-04	1.54E-03	0.1	0.0	0.6	1.03E-02
cg25702780	8.7	2.8	27.6	2.20E-04	1.54E-03	5.5	1.6	18.8	6.59E-03
cg11123595	4.1	1.9	9.1	4.47E-04	1.68E-03	3.1	1.1	8.7	3.58E-02
cg09916234	7.4	2.3	23.8	7.74E-04	2.32E-03	14.0	1.4	138.0	2.38E-02
cg04101194	5.4	1.8	16.2	2.91E-03	7.28E-03	6.5	2.2	19.2	7.64E-04
cg01431482	3.1	1.3	7.4	9.73E-03	1.37E-02	6.8	1.3	36.1	2.55E-02
cg05944877	0.4	0.2	0.8	7.69E-03	1.37E-02	0.2	0.1	0.8	2.37E-02
cg19196826	7.1	1.7	30.6	8.22E-03	1.37E-02	9.5	2.0	45.6	4.74E-03
cg20149022	4.7	1.5	14.2	6.49E-03	1.37E-02	16.8	1.4	197.0	2.46E-02
cg22122862	3.4	1.3	8.5	1.00E-02	1.37E-02	5.4	1.0	29.9	5.13E-02
cg25947773	2.7	1.1	6.4	2.44E-02	3.05E-02	18.1	2.5	129.0	3.87E-03
cg23780635	2.6	1.1	6.5	3.66E-02	4.53E-02	16.6	1.7	168.0	1.70E-02

Hazard ratios (HR), 95% confidence intervals (95% CI), and *P*-values were derived from Cox regression model adjusted for age, gender, clinical stage, and smoking status.

LUAD, lung adenocarcinoma; FDR, false discovery rate

**Supplementary Table 2. Early-stage LUAD prognosis-associated gene expression probes in discovery and validation phases.**

Gene	Discovery phase				Validation phase				
	HR	95% CI		<i>P</i>	FDR- <i>q</i>	HR	95% CI		<i>P</i>
<i>BLM</i>	2.6	1.4	5.1	4.11E-03	7.19E-03	1.4	1.1	1.9	1.02E-02
<i>CASC5</i>	2.7	1.5	4.9	1.43E-03	6.14E-03	1.3	1.1	1.6	3.21E-03
<i>FHIT</i>	0.2	0.1	0.8	2.01E-02	2.01E-02	0.6	0.4	0.7	5.17E-05
<i>GMPS</i>	4.1	1.7	10.0	1.75E-03	6.14E-03	1.9	1.3	3.0	3.08E-03
<i>MSH2</i>	4.3	1.6	11.4	4.04E-03	7.19E-03	1.5	1.0	2.2	3.13E-02
<i>SLC34A2</i>	0.5	0.2	0.8	1.23E-02	1.44E-02	0.8	0.7	0.9	1.58E-03
<i>ZNF429</i>	0.1	0.0	0.6	1.08E-02	1.44E-02	0.7	0.5	0.9	1.53E-02

Hazard ratios (HR), 95% confidence intervals (95% CI), and *P*-values were derived from Cox regression model adjusted for age, gender, clinical stage, and smoking status.

LUAD, lung adenocarcinoma; FDR, false discovery rate

**Supplementary Table 3. Potential DNA methylation–gene expression pathways associated with early-stage LUAD prognosis in causal mediation analysis.**

DNA methylation–gene expression	Discovery phase						Validation phase					
	HR <sub>DE</sub>	95% CI <sub>DE</sub>	P <sub>DE</sub>	HR <sub>IDE</sub>	95% CI <sub>IDE</sub>	P <sub>IDE</sub>	HR <sub>DE</sub>	95% CI <sub>DE</sub>	P <sub>DE</sub>	HR <sub>IDE</sub>	95% CI <sub>IDE</sub>	P <sub>IDE</sub>
cg25947773- <i>GMPS</i>	1.9	0.2–19.6	6.03E-01	3.3	1.3–8.6	1.52E-02	18.1	2.5–129	3.87E-03	2.9	1.4–6.0	5.77E-03
cg25947773- <i>BLM</i>	1.9	0.2–19.6	6.03E-01	2.7	1.2–6.2	2.08E-02	18.1	2.5–129	3.87E-03	2.2	1.2–4.3	1.57E-02
cg05944877- <i>MSH2</i>	0.6	0.1–5.2	6.76E-01	0.3	0.1–0.9	2.91E-02	0.2	0.1–0.8	2.37E-02	0.7	0.5–1.0	4.92E-02
cg23780635- <i>BLM</i>	3.6	0.3–44.2	3.23E-01	2.5	1.1–6.0	3.65E-02	16.6	1.7–167.6	1.70E-02	2.3	1.2–4.4	1.77E-02
cg23780635- <i>GMPS</i>	3.6	0.3–44.2	3.23E-01	2.6	1.0–6.7	4.73E-02	16.6	1.7–167.6	1.70E-02	2.8	1.3–5.8	7.43E-03
cg23780635- <i>MSH2</i>	3.6	0.3–44.2	3.23E-01	2.7	1.0–7.5	4.83E-02	16.6	1.7–167.6	1.70E-02	1.7	1.0–2.8	4.78E-02

Sobel method was used for calculations, with adjustment for age, gender, clinical stage, and smoking status.

HR<sub>DE</sub>, 95% CI<sub>DE</sub>, and P<sub>DE</sub> evaluated direct effects of DNA methylation on lung adenocarcinoma (LUAD) survival.

HR<sub>IDE</sub>, 95% CI<sub>IDE</sub>, and P<sub>IDE</sub> evaluated indirect effects of DNA methylation on LUAD survival, mediated through corresponding gene expression.

**Supplementary Table 4. Systematic review of accuracy of early-stage LUAD prognostic model.**

PMID	Author	Year	Stage	N	Validation	Outcome	Statistical model	Predictor	AUC/c-index
28122330	Chen M	2017	I, II	830	Yes	5-year survival	Cox proportional hazards model	7 lnc-RNA	0.65
28922552	Qi L	2017	I	542	Yes	5-year recurrence	Cox proportional hazards model	9 mRNA	0.55
29756233	Martínez-Terroba E	2018	I, II	353	Yes	5-year survival	Cox proportional hazards model	12 protein	0.65
24046125	Kim DH	2014	I	102	No	Recurrence after Curative surgical Resection	Cox proportional hazards model	F-18 fluoro-2-deoxyglucose Positron emission tomography	0.69
27524912	Sun Y	2016	I	92	No	First 7.5-year survival	Cox proportional hazards model	2 mRNA	0.75
26947549	Okayama A	2016	I	59	No	5-year recurrence	Multiple reaction monitoring	phospho-SSFA2	0.79

LUAD, lung adenocarcinoma

**Supplementary Table 5. DNA methylation information: 450K bead array from ENCODE/HAIB.**

<b>DNA methylation probes</b>	<b>Chromosome</b>	<b>Band</b>	<b>Base position</b>	<b>Gene</b>	<b>Name</b>	<b>Region</b>
cg01431482	1	1p36.32	2989086	<i>PRDM16</i>	PR domain containing 16	1-intron
cg22122862	1	1p36.32	2987915	<i>PRDM16</i>	PR domain containing 16	1-intron
cg25947773	2	2q36.1	223771011	<i>ACSL3</i>	Acyl-CoA synthetase long-chain family member 3	3-intron
cg25702780	3	3q26.2	169376299	<i>MECOM</i>	MDS1 and EVI1 complex locus	1-intron
cg11123595	3	3q26.2	169376619	<i>MECOM</i>	MDS1 and EVI1 complex locus	1-intron
cg09916234	4	4p16.3	1976220	<i>WHSC1</i>	Wolf-Hirschhorn syndrome candidate 1	18-intron
cg04101194	4	4p15.2	25656866	<i>SLC34A2</i>	Solute carrier family 34 (sodium phosphate), member 2	5'-UTR
cg19196826	7	7p22.2	3018392	<i>CARD11</i>	Caspase recruitment domain family, member 11	1-intron
cg23780635	8	8p23.3	1880114	<i>ARHGEF10</i>	Rho guanine nucleotide exchange factor (GEF) 10	15-intron
cg20149022	8	8p23.3	1863072	<i>ARHGEF10</i>	Rho guanine nucleotide exchange factor (GEF) 10	9-intron
cg06835509	16	16p12.2	23939098	<i>PRKCB</i>	Protein kinase C, beta	2-intron
cg05944877	16	16p12.2	24197864	<i>PRKCB</i>	Protein kinase C, beta	15-intron

**Supplementary Table 6. Interaction analysis (biomarkers vs. age) for overall survival.**

Interaction term with age	Discovery phase				Validation phase			
	HR	CL	CU	P value	HR	CL	CU	P value
cg01431482	0.93	0.73	1.19	5.89E-01	1.05	0.87	1.27	5.84E-01
cg22122862	1.01	0.77	1.33	9.46E-01	1.14	0.96	1.36	1.44E-01
cg25947773	1.15	0.91	1.46	2.45E-01	1.05	0.87	1.27	6.19E-01
cg11123595	0.86	0.65	1.16	3.28E-01	1.03	0.90	1.18	6.57E-01
cg25702780	0.95	0.66	1.35	7.58E-01	0.96	0.80	1.15	6.35E-01
cg04101194	0.90	0.58	1.39	6.42E-01	1.03	0.90	1.19	6.37E-01
cg09916234	1.04	0.64	1.68	8.77E-01	1.00	0.77	1.30	9.91E-01
cg19196826	0.99	0.77	1.29	9.60E-01	0.89	0.71	1.10	2.79E-01
cg20149022	0.90	0.57	1.41	6.40E-01	1.00	0.76	1.33	9.75E-01
cg23780635	1.07	0.81	1.41	6.43E-01	1.24	1.00	1.54	5.12E-02
cg05944877	0.95	0.72	1.26	7.26E-01	0.95	0.84	1.08	4.63E-01
cg06835509	0.89	0.68	1.16	3.79E-01	0.86	0.72	1.03	1.11E-01
SLC34A2	1.01	0.94	1.08	7.62E-01	1.00	0.97	1.02	7.43E-01
ACSL3	1.17	1.01	1.35	3.62E-02	0.99	0.97	1.02	5.76E-01
ARHGEF10	0.85	0.76	0.96	6.48E-03	1.00	0.98	1.01	4.71E-01
WHSC1	1.16	1.01	1.33	3.95E-02	1.03	0.99	1.07	1.56E-01
MECOM	1.01	0.94	1.09	7.55E-01	1.00	0.97	1.04	9.16E-01
PRKCB	0.98	0.90	1.06	5.62E-01	1.00	0.97	1.04	8.22E-01