

Table SI. Mass spectrometry parameters of metabolites and isotope internal standards.

Metabolite	Abbreviated ID	Retention time (min)	Q1 Mass (Da)	Q3 Mass (Da)	Fragment voltage	Collision energy
Methionine	—	1.54	150.1	104.1	90	5
				133.0	90	5
S-Adenosylmethionine	SAM	4.57	399.1	136.2	100	30
				250.2	100	10
S-Adenosylhomocysteine	SAH	2.70	385.0	134.1	80	20
				136.1	80	10
Homocysteine	—	1.71	136.1	56.2	80	15
				90.1	80	5
Methionine-d ₃	—	1.54	153.1	107.2	90	5
				136.1	90	5
S-Adenosylmethionine-d ₃	SAM-d ₃	4.56	402.0	136.2	100	35
				250.1	100	10
S-Adenosylhomocysteine-d ₄	SAH-d ₄	2.71	389.1	136.0	80	20
				138.1	80	10
Homocysteine-d ₄	—	1.70	140.0	60.1	80	15
				94.0	80	5

Table SII. Accuracy and precision of the QCs.

Metabolites	LLOQ	Low QC	Middle QC	High QC
Methionine	1.000	3.000	10.00	40.00
Mean	0.903	2.777	10.46	37.93
%Bias	-9.67	-7.44	4.630	-5.17
Intra-day Precision (%CV)	13.5	9.8	5.3	4.5
Inter-day Precision (%CV)	14.2	10.4	6.5	6.1
S-Adenosylmethionine	0.050	0.150	0.500	0.800
Mean	0.057	0.136	0.490	0.840
%Bias	13.33	-9.56	-2.07	4.96
Intra-day Precision (%CV)	16.8	10.6	6.4	4.1
Inter-day Precision (%CV)	18.2	12.5	6.8	6.9
S-Adenosylhomocysteine	0.010	0.030	0.100	0.400
Mean	0.011	0.032	0.092	0.409
%Bias	12.33	7.89	-8.33	2.33
Intra-day Precision (%CV)	15.3	10.7	7.8	5.3
Inter-day Precision (%CV)	19.4	12.6	8.9	6.7
Homocysteine	1.000	3.000	10.00	40.00
Mean	0.963	3.027	9.60	39.43
%Bias	-3.67	0.89	-4	-1.43
Intra-day Precision (%CV)	13.2	6.8	4.5	3.5
Inter-day Precision (%CV)	14.8	7.5	6.2	3.9

QC, quality control; LLOQ, lower limit of quantification; CV, coefficient of variation.

Table SIII. Comparison of metabolites concentration before and after age adjustment in patients with luminal breast cancer and HCs.

Metabolites	Group	Concentration, μM (unadjusted)	Concentration, μM (adjusted)	P-value (adjusted)
Methionine	Luminal	17.72 $\pm$ 6.69	17.74 $\pm$ 6.75	1.2 $\times 10^{-2}$
	HCs	21.08 $\pm$ 6.84	20.96 $\pm$ 6.82	
SAM	Luminal	0.25 $\pm$ 0.15	0.249 $\pm$ 0.145	2.0 $\times 10^{-6}$
	HCs	0.386 $\pm$ 0.137	0.389 $\pm$ 0.15	
SAH	Luminal	0.093 $\pm$ 0.052	0.092 $\pm$ 0.048	2.5 $\times 10^{-2}$
	HCs	0.113 $\pm$ 0.055	0.115 $\pm$ 0.054	
Homocysteine	Luminal	8.505 $\pm$ 4.484	8.494 $\pm$ 4.628	2.0 $\times 10^{-2}$
	HCs	10.49 $\pm$ 4.653	10.53 $\pm$ 4.668	
SAM/SAH	Luminal	3.848 $\pm$ 3.377	3.878 $\pm$ 3.733	7.7 $\times 10^{-2}$
	HCs	5.247 $\pm$ 4.904	5.127 $\pm$ 3.768	

HCs, healthy controls; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine.

Table SIV. DeLong test comparing the combined metabolites versus individual metabolite in receiver operating characteristics analysis.

Comparison	DeLong test		
	Luminal vs. HCs	Early-stage vs. Late-stage	Sensitive vs. Resistant
Combined vs. Methionine	$P < 1.0 \times 10^{-3}$	$P < 1.0 \times 10^{-3}$	$P = 1.4 \times 10^{-2}$
Combined vs. SAM	$P = 6.9 \times 10^{-2}$	$P = 3.0 \times 10^{-3}$	$P = 7.0 \times 10^{-3}$
Combined vs. SAH	$P < 1.0 \times 10^{-3}$	$P < 1.0 \times 10^{-3}$	$P = 5.1 \times 10^{-2}$
Combined vs. Homocysteine	$P < 1.0 \times 10^{-3}$	$P < 1.0 \times 10^{-3}$	$P = 1.1 \times 10^{-2}$
Combined vs. SAM/SAH	$P < 1.0 \times 10^{-3}$	$P < 1.0 \times 10^{-3}$	$P = 3.0 \times 10^{-3}$

HCs, healthy controls; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine.