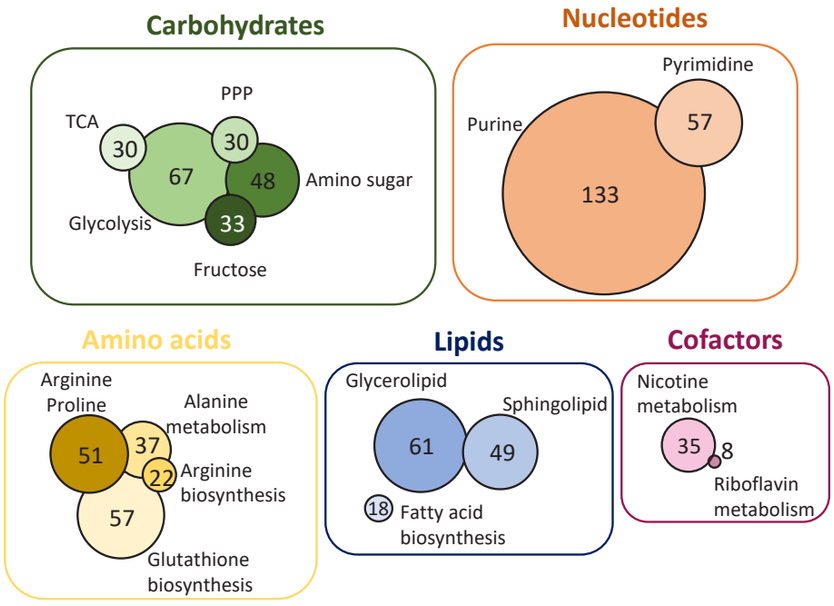

Figure S1 Diagram of 15 metabolic pathways, being altered in lung adenocarcinoma patients. Alanine metabolism- alanine, aspartate and glutamate metabolism; Arginine Proline, arginine and proline metabolism; Amino sugar, amino sugar metabolism; TCA, citric acid cycle; Fructose, fructose and mannose metabolism; Glycolysis, glycolysis and gluconeogenesis; PPP, pentose metabolism; Nicotine metabolism, nicotinate and nicotinamide metabolism; Glycerolipid, glycerolipid metabolism; Sphingolipid, sphingolipid metabolism; Purine, purine metabolism; Pyrimidine, pyrimidine metabolism.

Table S1 Lung adenocarcinoma cohorts demographic and clinical information

Characteristic	Lung adenocarcinoma Wikoff (n=39)	Lung adenocarcinoma Moreno (n=33)	Lung adenocarcinoma TCGA (n=522)
Age, y			
Gender	72.3±8.78	62.1±9.73	65.8±0.45
Male	15 (38%)	24 (73%)	242 (46%)
Female	24 (62%)	9 (23%)	280 (54%)
Race			
White			393 (75%)
Black or African American			53 (10%)
Other			9 (2%)
NA	39 (100%)	33 (100%)	67 (13%)
Smoking status			
Smoking	39 (100%)		402 (77%)
Non-smoking			120 (23%)
NA		33 (100%)	
AJCC stage, n (%)			
I	39 (100%)	17 (52%)	279 (53%)
II		10 (30%)	124 (24%)
III		6 (18%)	85 (16%)
IV			26 (5%)
NA			8 (2%)
Treatment			
Radiotherapy only			160 (31%)
Chemotherapy only			284 (54%)
Chemo-radiation			78 (15%)
NA	39 (100%)	33 (100%)	
Length of clinical follow-up from diagnosis, mo			23.93

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Gene	DF	Estimate	StdErr	ChiSq	HazardRatio	raw_p	pfdr_p
UAP1L1	1	4.9546	0.84573	34.3206	141.826	<.0001	<.0001
GBA	1	2.4793	0.52804	22.0461	11.933	<.0001	0.000735
GGT5	1	2.27617	0.59609	14.5808	9.739	0.0001	0.024706
LDHAL6A	1	2.43014	0.72568	11.2144	11.36	0.0008	0.094259
NMNAT3	1	3.45468	1.03597	11.1205	31.648	0.0009	0.094259
LAP3	1	1.81057	0.58831	9.4714	6.114	0.0021	0.146998
DLST	1	1.817	0.59158	9.4336	6.153	0.0021	0.146998
ACSS2	1	3.00126	1.0334	8.4347	20.111	0.0037	0.22578
CMAS	1	1.473	0.51464	8.1921	4.362	0.0042	0.232244
GMPPA	1	1.41237	0.51214	7.6054	4.106	0.0058	0.292024
MGST3	1	2.75469	1.02562	7.2139	15.716	0.0072	0.332766
RBKS	1	2.54643	1.01672	6.2728	12.762	0.0123	0.422517
P4HA2	1	1.28102	0.51174	6.2664	3.6	0.0123	0.422517
DGKG	1	1.14326	0.45821	6.2252	3.137	0.0126	0.422517
GNE	1	1.77386	0.71641	6.1308	5.894	0.0133	0.422517
ENPP3	1	0.90288	0.36658	6.0664	2.467	0.0138	0.422517
PMM1	1	1.70392	0.71761	5.638	5.495	0.0176	0.510612
AOC1	1	1.07126	0.46051	5.4114	2.919	0.02	0.552143
TK1	1	1.62524	0.71614	5.1503	5.08	0.0232	0.610941
GUCY2C	1	1.15127	0.51265	5.0434	3.162	0.0247	0.611207
ALDH1B1	1	1.13884	0.51352	4.9183	3.123	0.0266	0.611207
SMS	1	1.55249	0.71674	4.6917	4.723	0.0303	0.643458
PGM2	1	1.06793	0.51106	4.3666	2.909	0.0366	0.697599
GLS2	1	1.47655	0.71879	4.2198	4.378	0.04	0.732086
CS	1	2.06318	1.01018	4.1713	7.871	0.0411	0.732086
GSTA1	1	1.15091	0.58691	3.8453	3.161	0.0499	0.843039
PYCR2	1	1.14325	0.58629	3.8024	3.137	0.0512	0.843039
GSS	1	1.13911	0.58776	3.756	3.124	0.0526	0.843039
UGDH	1	0.98409	0.5105	3.7161	2.675	0.0539	0.843039
ADCY2	1	0.58736	0.30607	3.6827	1.799	0.055	0.843039
CARNS1	1	1.32751	0.71584	3.439	3.772	0.0637	0.917396
LPL	1	1.08953	0.58816	3.4315	2.973	0.064	0.917396
GSTM5	1	0.7746	0.4211	3.3836	2.17	0.0658	0.917396
CYB5RL	1	1.30852	0.7151	3.3483	3.701	0.0673	0.917396
ADA	1	1.85034	1.0144	3.3273	6.362	0.0681	0.917396
DGUOK	1	1.29131	0.71565	3.2558	3.638	0.0712	0.919178
ALDH3A1	1	1.05951	0.58808	3.2459	2.885	0.0716	0.919178
ENPP7	1	0.90736	0.51039	3.1604	2.478	0.0754	0.946461
PDE10A	1	-1.00389	0.58589	2.9359	0.366	0.0866	0.99805
AKR1B1	1	1.22208	0.71865	2.8918	3.394	0.089	0.99805
GAD2	1	-1.20873	0.71314	2.8728	0.299	0.0901	0.99805
BPGM	1	0.99282	0.58619	2.8686	2.699	0.0903	0.99805

Figure S2 Metabolic genes of clinical significance in non-squamous non-small cell lung cancer. Orange indicates hazard ratio of clinically relevant genes associated with shorter OS; green indicates Hazard Ratio of clinically relevant genes associated with longer OS. DF, degree of freedom; Std. Err, standard error; Chi Sq, Chi squared test; HR, hazard ratio; raw_p, raw P value; pfdr, p-FDR corrected P value; OS, overall survival.

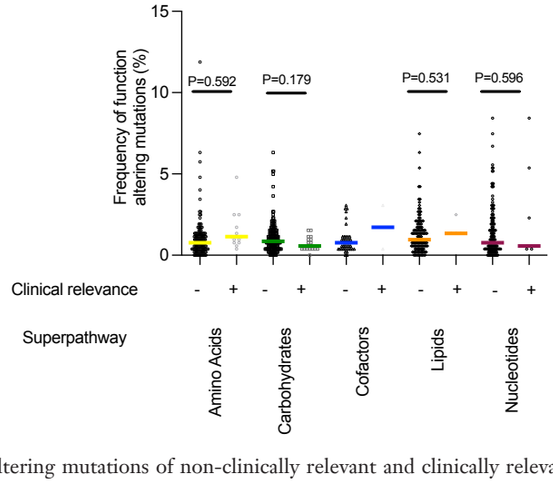

Figure S3 Incidence of function altering mutations of non-clinically relevant and clinically relevant genes controlling cellular metabolism in non-small cell lung cancer. Data presented as frequency of function altering mutations (%) per superpathway. Each point represents frequency of mutation in individual gene. Frequency of mutations in 522 patients from lung adenocarcinoma cohort.

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Table S2 RNA expression of metabolic genes of clinical significance in non-squamous non-small cell lung cancer

Gene	Non-mutated	Mutated	P value
UAP1L1	354.1±12.1	168.2±194.7	0.3412
GBA	1849.5±34.0	2440.3±289.7	0.0433*
GGT5	886.3±31.4	640.3±355.4	0.4910
LDHAL6A	2.8±0.7	0.9±11.6	0.8695
NMNAT3	65.3±2.0	42.0±31.2	0.4564
LAP3	2663.4±53.2	2655.3±537.4	0.9880
DLST	2200.4±32.8	1834.1±331.8	0.2724
ACSS2	1589.4±42.6	902.6±683.2	0.3161
CMAS	850.1±33.9	1021.2±312.9	0.5870
GMPPA	1000.7±17.1	958.7±136.2	0.7599
MGST3	1652.1±34.9	1928.8±559.3	0.6218
RBKS	125.4±3.4	70.5±55.0	0.3201
P4HA2	1699.8±43.7	1556.9±403.1	0.7246
DGKG	97.1±4.1	150.3±25.5	0.0401*
GNE	616.9±16.9	668.4±271.5	0.8498
ENPP3	206.9±15.1	114.4±84.6	0.2827
PMM1	956.7±33.3	631.4±376.8	0.3902
AOC1	900.6±71.0	792.9±441.8	0.8098
TK1	1243.7±44.0	1588.7±705.7	0.6258
GUCY2C	38.3±10.1	25.9±65.4	0.8511
ALDH1B1	880.5±24.2	928.3±181.4	0.7939
SMS	1601.3±37.1	1474.1±484.8	0.7938
PGM2	566.4±14.7	669.1±117.0	0.3840
GLS2	160.3±7.8	194.8±78.3	0.6611
CS	3828.5±56.5	3737.1±906.1	0.9199
GSTA1	788.5±145.8	17.2±1344.1	0.5686
PYCR2	1847.3±29.2	2326.4±249.3	0.0569
GSS	1215.5±20.2	1653.6±204.7	0.0336*
UGDH	3356.8±210.1	4794.2±2124.3	0.5010
ADCY2	27.2±4.3	21.6±14.1	0.7011
CARNS1	77.3±6.1	26.5±69.3	0.4649
LPL	1500.2±98.5	389.5±839.7	0.1896
GSTM5	80.5±3.8	57.4±23.8	0.3386
CYB5RL	70.6±1.7	75.2±28.0	0.8686
ADA	178.5±6.2	82.3±99.0	0.3325
DGUOK	845.8±15.5	789.8±202.2	0.7827
ALDH3A1	1762.6±320.7	475.4±2735.0	0.6404
ENPP7	0.7±0.1	1.0±0.40	0.3860
PDE10A	160.3±13.7	158.3±57.3	0.9723
AKR1B1	2062.0±111.9	2530.8±1131.5	0.6803
GAD2	0.2±0.1	0.00E+00	0.7037
BPGM	649.3±18.2	469.9±205.4	0.3847

Data presented as mean ± standard error. Putative differences between groups were tested using pair-wise comparison. Significant P values, i.e., P<0.05 between non-mutated *vs*. mutated metabolic genes of clinical significance are indicated by *.

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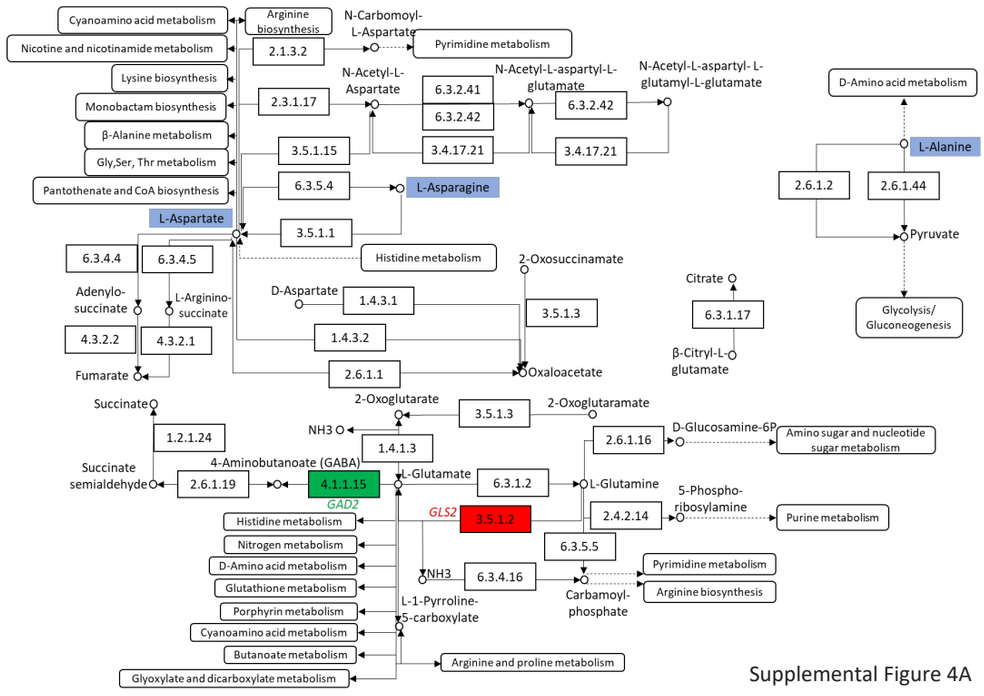
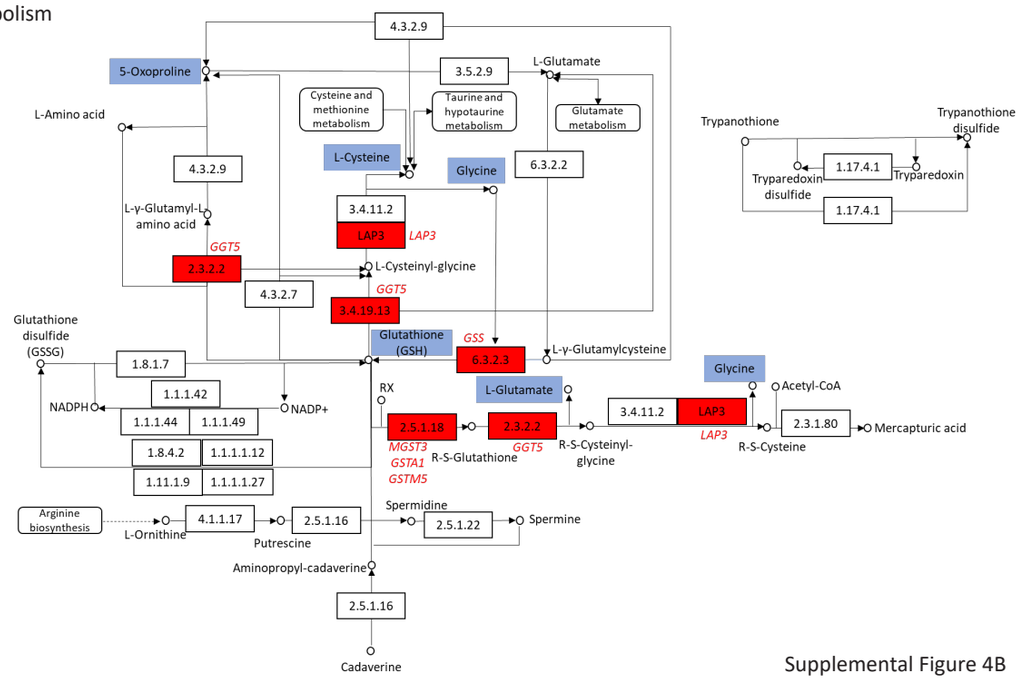
Alanine, aspartate and glutamate metabolism



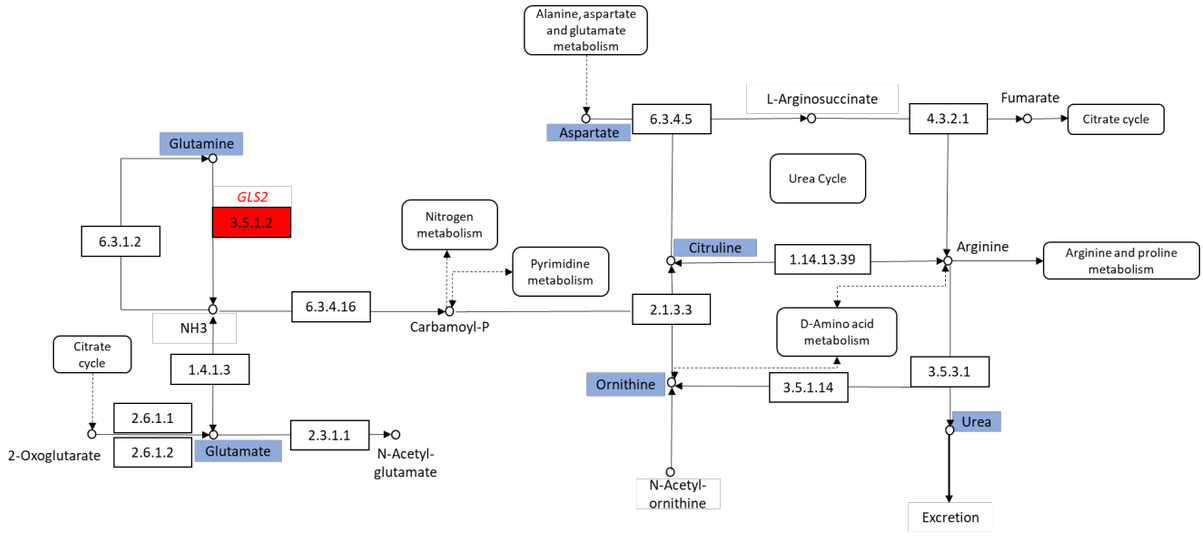
Supplemental Figure 4A

Glutathione metabolism



Supplemental Figure 4B

Arginine metabolism



Supplemental Figure 4C

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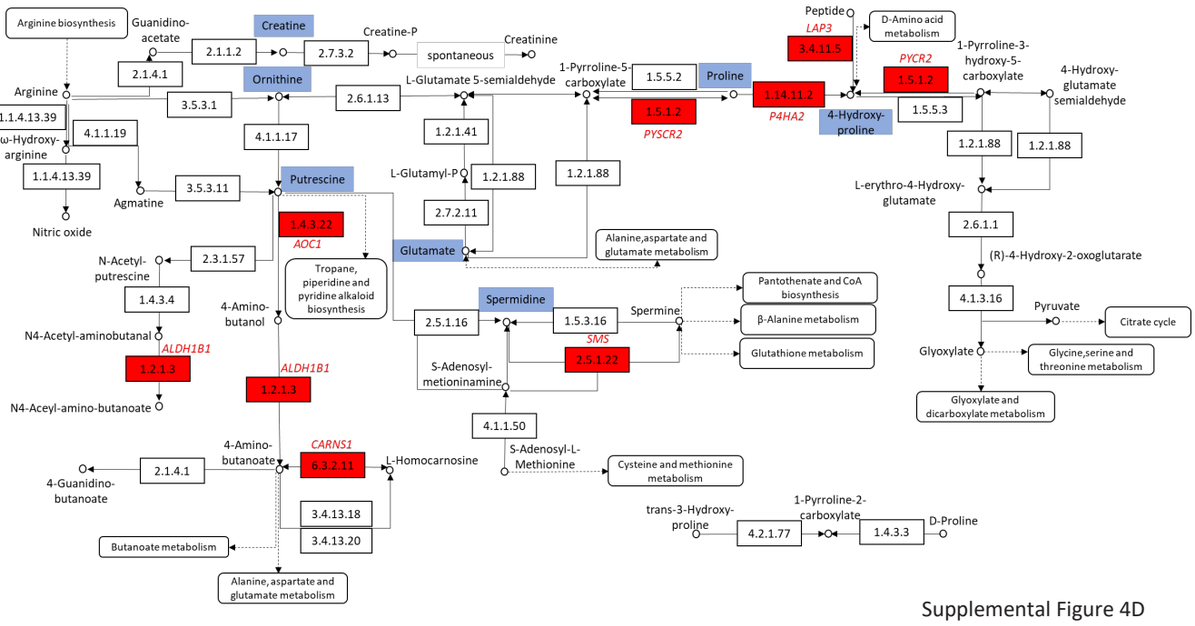
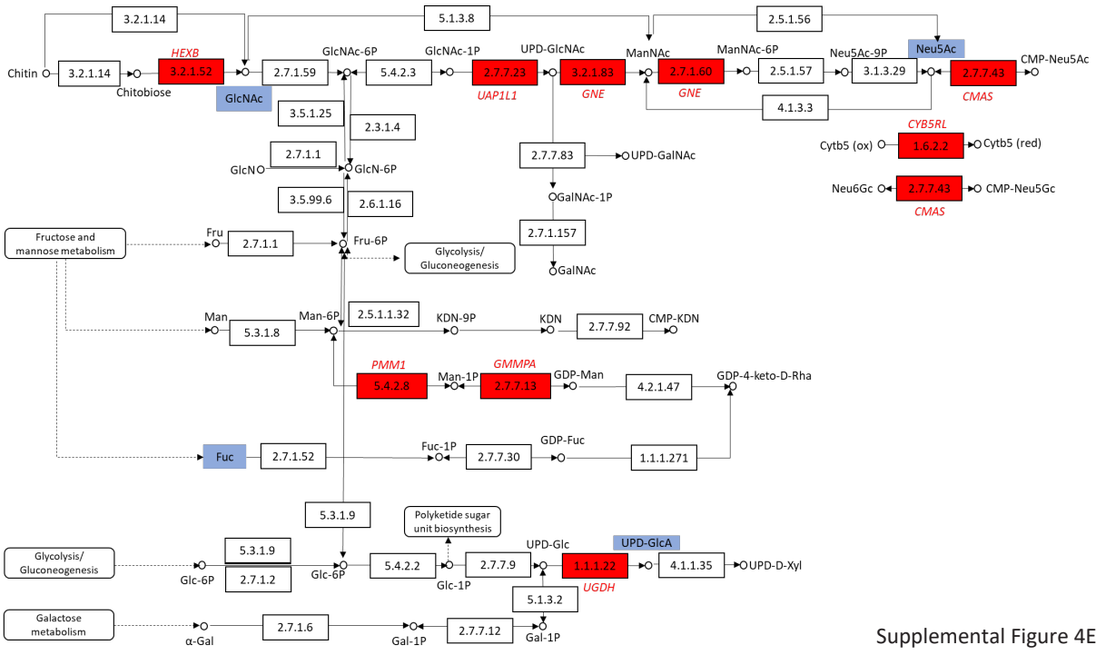
Arginine and proline metabolism



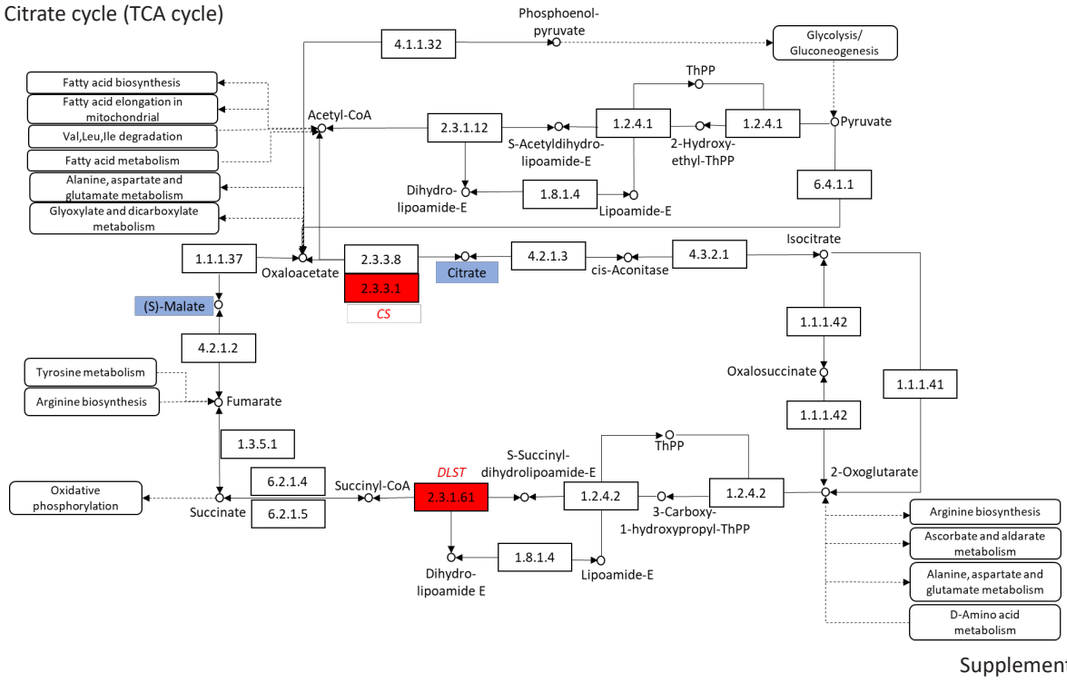
Supplemental Figure 4D

Amino sugar and nucleotide sugar metabolism



Supplemental Figure 4E

Citrate cycle (TCA cycle)



Supplemental Figure 4F

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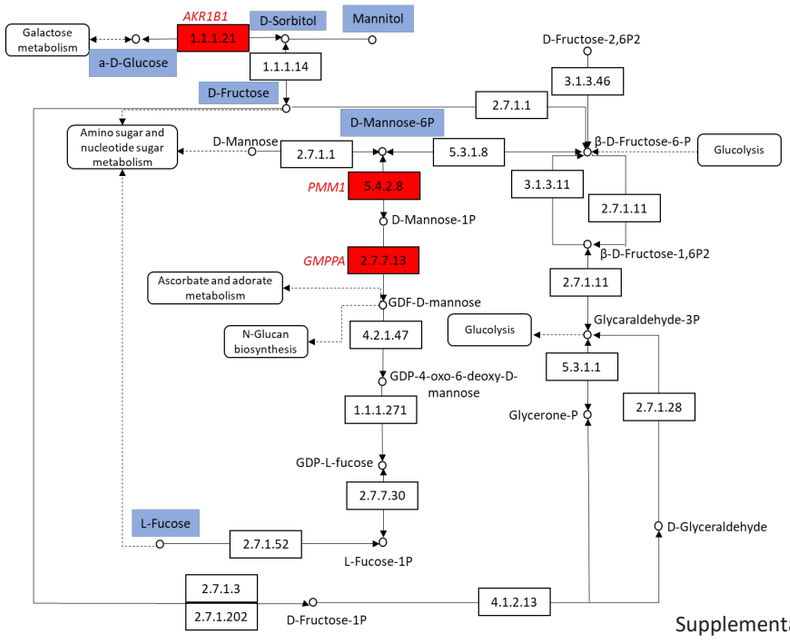
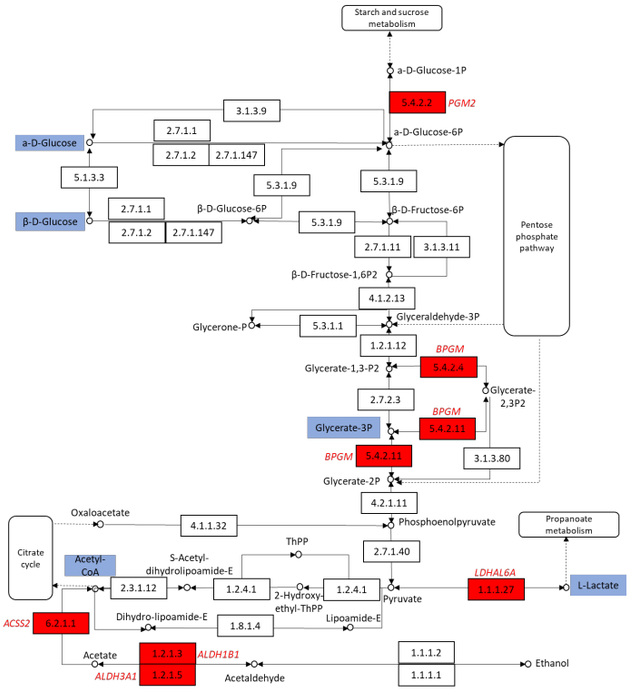
Fructose and mannose metabolism



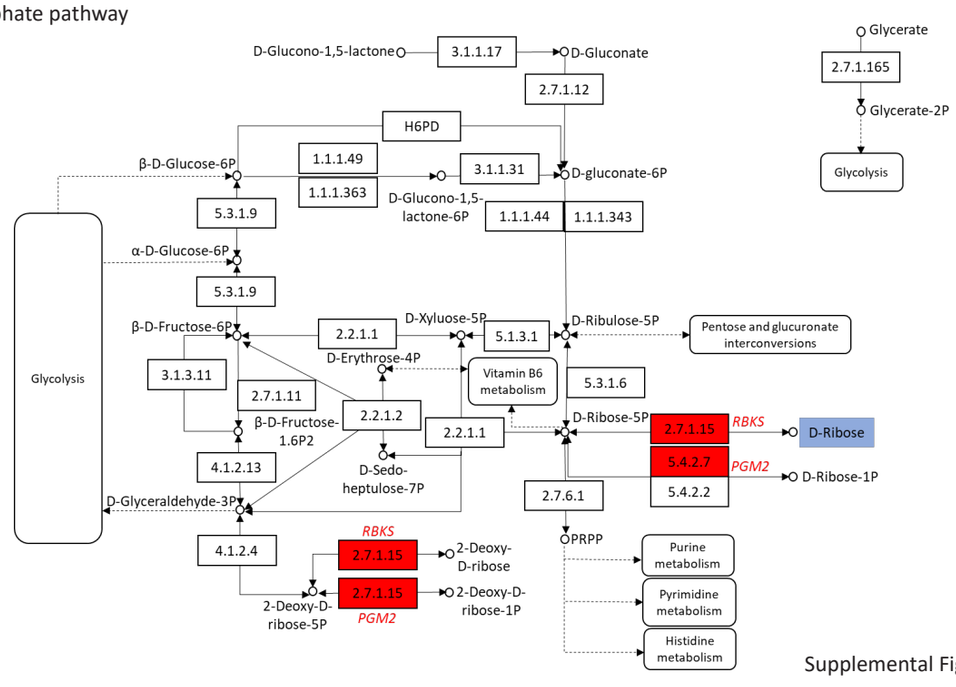
Supplemental Figure 4G

Glycolysis/gluconeogenesis



Supplemental Figure 4H

Pentose phosphate pathway



Supplemental Figure 4I

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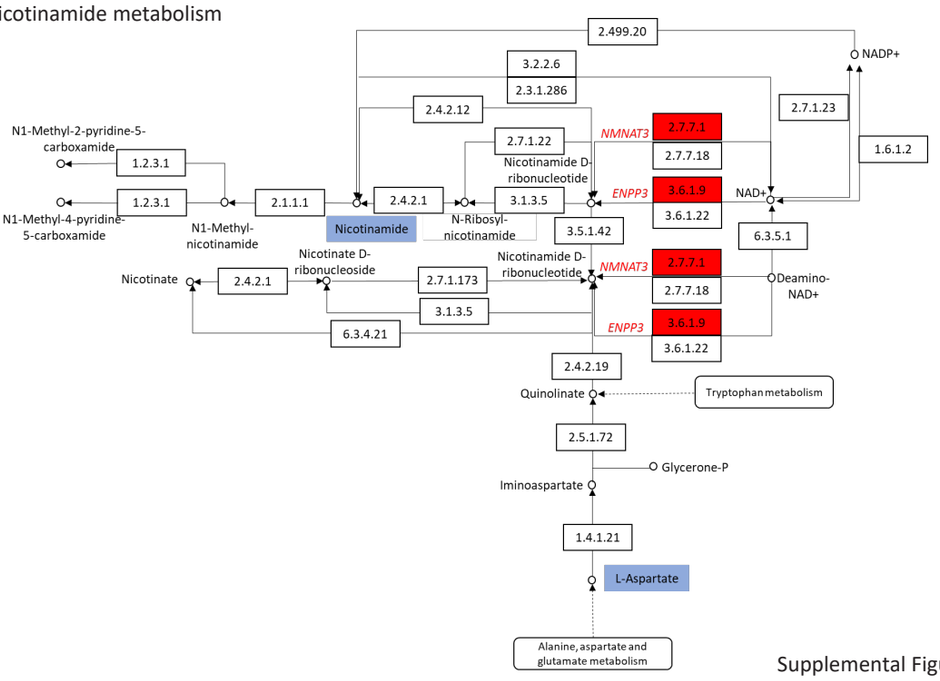
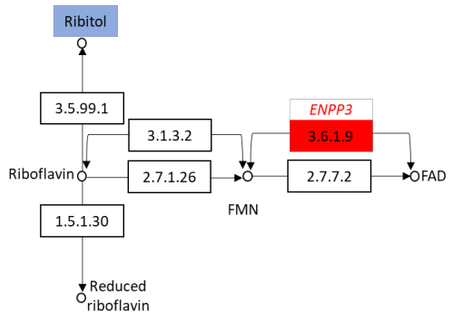
Nicotinate and nicotinamide metabolism



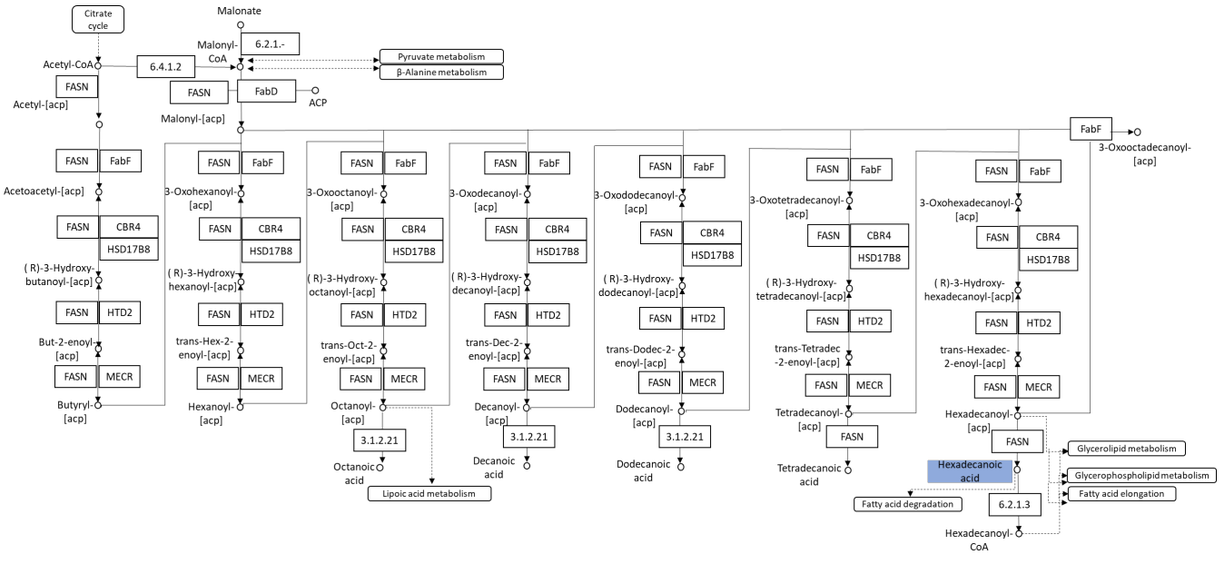
Supplemental Figure 4J

Riboflavin metabolism



Supplemental Figure 4K

Fatty acid biosynthesis



Supplemental Figure 4L

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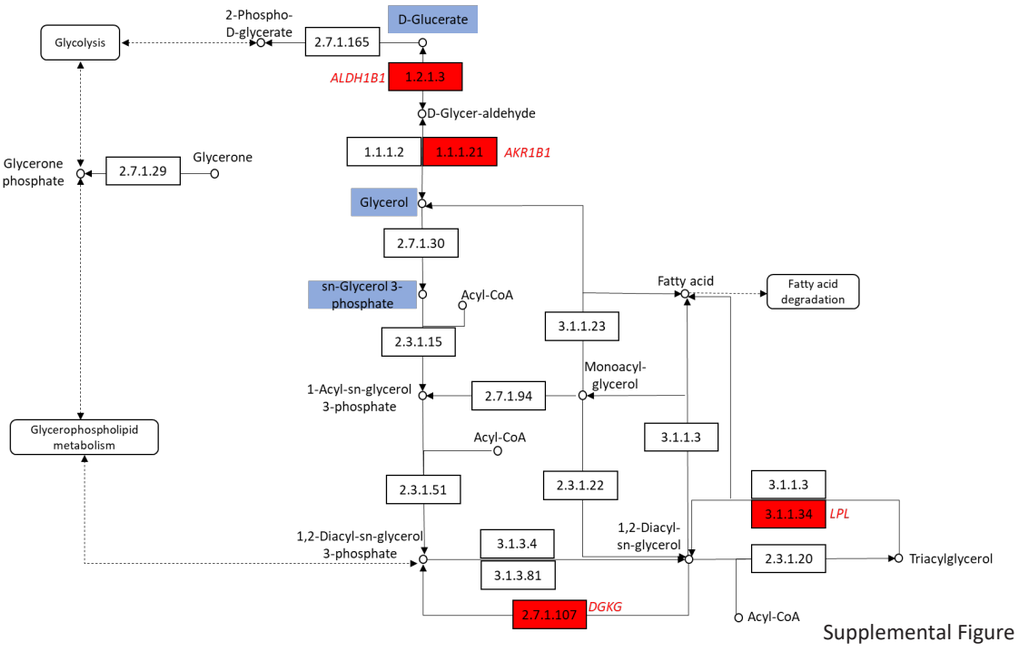
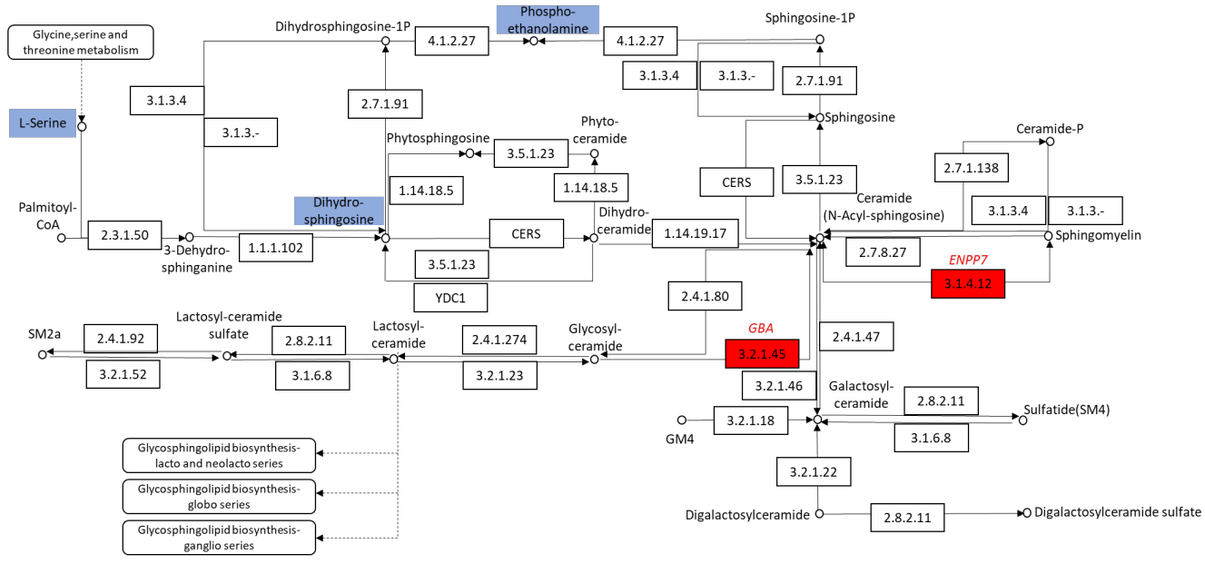
Glycerolipid metabolism



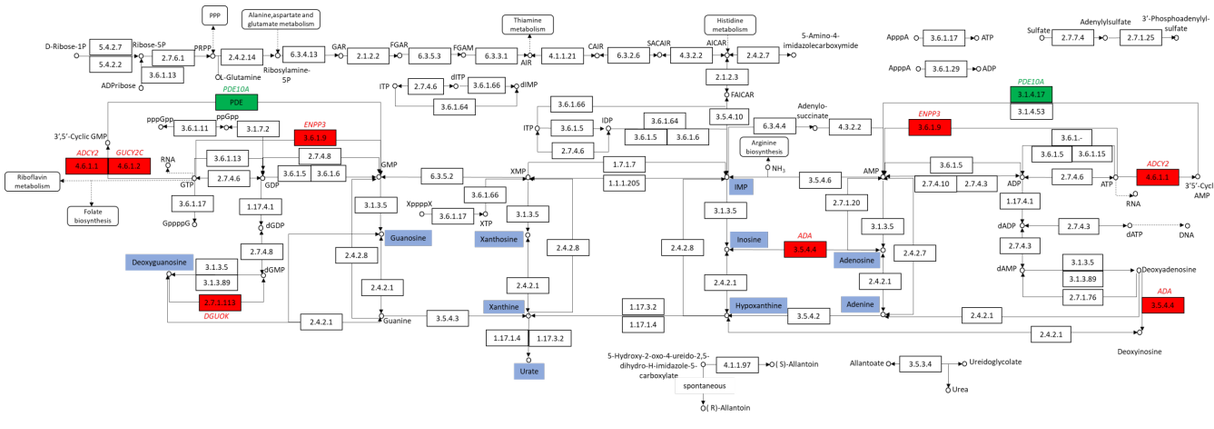
Supplemental Figure 4M

Sphingolipid metabolism



Supplemental Figure 4N

Purine metabolism



Supplemental Figure 4O

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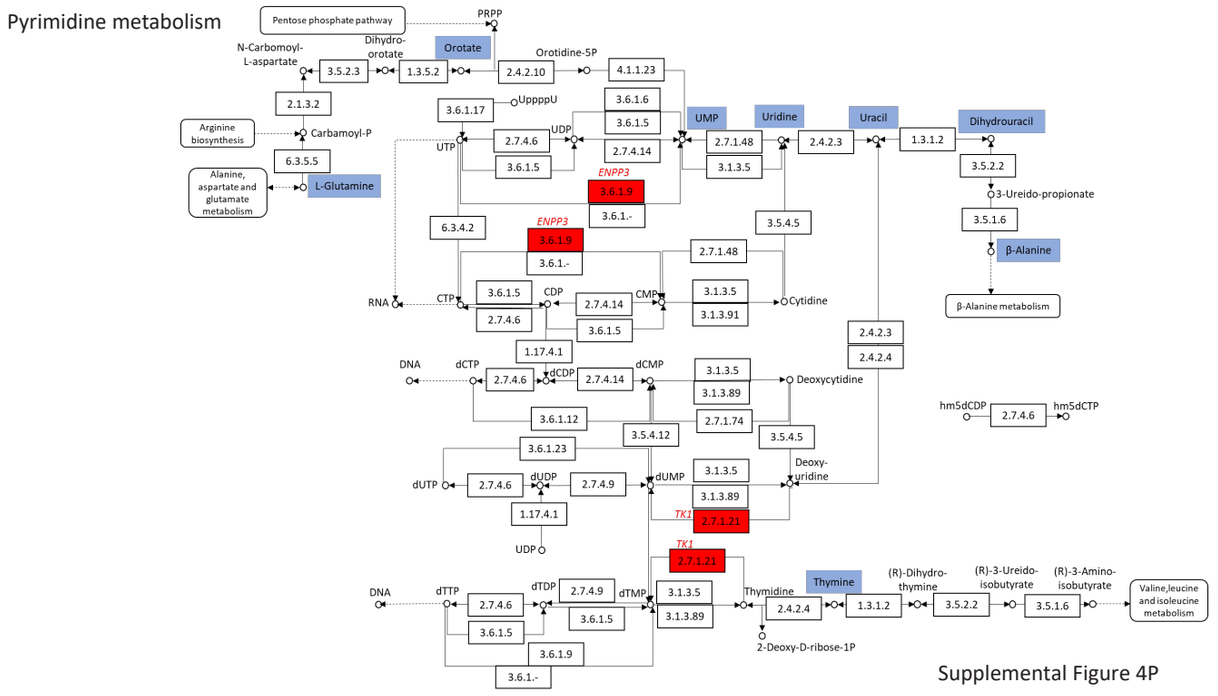

Figure S4 Metabolic maps with altered metabolites and clinically relevant genes in lung adenocarcinoma. (A) Alanine, aspartate and glutamate metabolism; (B) Glutathione metabolism; (C) Arginine biosynthesis; (D) Arginine and proline metabolism; (E) Amino sugar and nucleotide sugar metabolism; (F) Citrate cycle; (G) Fructose and mannose metabolism; (H) Glycolysis/gluconeogenesis; (I) Pentose phosphate pathway; (J) Nicotinate and nicotinamide metabolism; (K) Riboflavin metabolism; (L) Fatty acid biosynthesis; (M) Glycerolipid metabolism; (N) Sphingolipid metabolism; (O) Purine metabolism; (P) Pyrimidine metabolism. Metabolites, being altered in lung adenocarcinoma are colored in blue; genes, function altering mutations in which associated with worst prognosis colored in red; and genes, function altering mutations in which associated with good prognosis colored in green.

Table S3 Effect of clinical and demographic factors on frequency of mutations in metabolic superpathway of non-squamous non-small cell lung cancer

Factors	Metabolic superpathways				
	Amino acids	Carbohydrates	Cofactors	Lipids	Nucleotides
Gender (M *vs.* F, P value)	16.9% *vs.* 17.5%, P=0.866	12.0% *vs.* 10.4%, P=0.556	3.7% *vs.* 3.2%, P=0.753	9.5% *vs.* 7.5%, P=0.412	21.5% *vs.* 15.7%, P=0.090
Smoking status (non-smoking *vs.* smoking, P value)	10.8% *vs.* 19.2% P=0.027*	8.3% *vs.* 11.9%, P=0.273	2.5% *vs.* 3.7%, P=0.502	7.5% *vs.* 8.7%, P=0.673	10.0% *vs.* 20.9%, P=0.004*
AJCC stage (stages I + II *vs.* stages III + IV, P value)	16.6% *vs.* 19.8% P=0.437	10.2% *vs.* 14.4%, P=0.221	3.0% *vs.* 3.6%, P=0.741	7.9% *vs.* 10.9%, P=0.351	19.4% *vs.* 11.7%, P=0.052

Frequency of mutations is expressed in percentile value (%) between demographic and clinical groups. Putative differences between groups were tested using Fisher's exact test. Significant P values, i.e., P<0.05 between non-smoker vs. smokers are indicated by *.

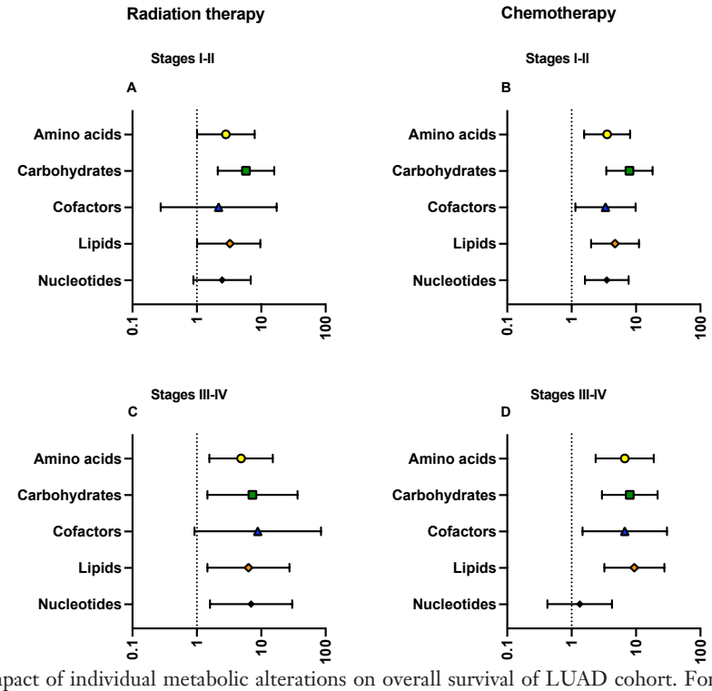

Figure S5 The relative impact of individual metabolic alterations on overall survival of LUAD cohort. Forest plots show the hazard ratio +/- 95% confidence intervals for each clinically relevant metabolic pathway in LUAD from the TCGA database. (A,C) LUAD patients received radiation therapy only. (B,D) LUAD patients received chemotherapy only. (A,B) Patients with early stages of disease (stages I and II are combined), (C,D) Patients with late stages of disease (stages III and IV are combined). LUAD, lung adenocarcinoma.

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