Appendix

Table A1. Characteristics of patients in the discovery cohort and replication cohort, stratified by impairment in executive function

	Discovery cohort		P-value	Replication cohort		P-value
	Not impaired N=60	Impaired N=81		Not impaired N=64	Impaired N=116	
Age, years	55.7 ± 16.9	57.2 ± 12.7	0.56	47.9 ± 13.6	52.0 ± 13.7	0.05
Male, %	71.7	59.3	0.13	60.9	62.1	0.88
White (vs. non-White) , %	43.3	42.0	0.87	23.4	27.6	0.54
Months receiving dialysis*	21 (10, 44)	38 (14, 76)	<0.01	41 (18, 100)	44 (21, 74)	0.99
Education, %			0.61			0.03
< High school	11.7	13.6		7.8	21.6	
High school graduate	23.3	29.6		21.9	25.9	
Post-high school	65.0	56.8		70.3	52.6	
English speaking (vs Spanish), %	98.3	92.6	0.12	85.9	77.6	0.18
Diabetes, %	40.0	50.6	0.21	39.1	43.1	0.60
Stroke, %	8.3	14.8	0.24	4.7	11.2	0.14
Systolic blood pressure (mm Hg)	144.7 ± 26.3	138.9 ± 25.9	0.21	145.5 ± 17.4	147.9 ± 18.7	0.38
Diastolic blood pressure (mm Hg)	79.4 ± 15.4	75.3 ± 14.4	0.12	80.0 ± 12.2	80.1 ± 11.9	0.95
URR (%)**	66.8 ± 7.9	68.5 ± 8.9	0.30	72.1 ± 5.9	73.5 ± 5.5	0.53
Blood urea nitrogen (mg/dL)	68.4 ± 19.8	66.3 ± 18.5	0.52	61.0 ± 18.5	56.3 ± 17.0	0.42
Hemoglobin (g/dL)	12.0 ± 1.1	11.9 ± 0.9	0.80	12.2 ± 1.1	12.0 ± 1.3	0.41
Peritoneal dialysis, %	13.3	2.5	0.01	-	-	
Day of week for blood draw, %	-	-				0.35
Monday/Tuesday				32.8	26.7	
Wednesday/Thursday				59.4	62.9	
Friday/Saturday				7.8	10.3	

*median (25^{th}, 75^{th} percentile)

**among hemodialysis patients

Table A2. Metabolite mean raw area counts and ratio in subjects with impaired executive function versus subjects without impaired executive function

Metabolite	Super pathway	Sub pathway	Mean raw area counts		Metabolite ratio impaired vs unimpaired	Nominal p-value
			unimpaired subjects	impaired subjects		
phenylacetylglutamine	Amino acid	Phenylalanine & tyrosine metabolism	6202417	8359483	1.35	0.000246
hippurate	Xenobiotics	Benzoate metabolism	7781270	12476702	1.60	0.000288
4-hydroxyphenylacetate	Amino acid	Phenylalanine & tyrosine metabolism	1893435	3165769	1.67	0.001565
pro-hydroxy-pro	Peptide	Dipeptide	530757	709257	1.34	0.002167
4-hydroxyhippurate	Xenobiotics	Benzoate metabolism	541371	760950	1.41	0.005096
N-acetylserine	Amino acid	Glycine, serine and threonine metabolism	2869339	3300228	1.15	0.005245
pyroglutamylvaline	Peptide	Dipeptide	16483	24615	1.49	0.005733
gluconate	Carbohydrate	Nucleotide sugars, pentose metabolism	6252327	7879092	1.26	0.007769
gamma-CEHC glucuronide	Cofactors and vitamins	Tocopherol metabolism	209397	310479	1.48	0.007891
C-glycosyltryptophan	Amino acid	Tryptophan metabolism	549866	641447	1.17	0.009085
phenylacetylglycine	Amino acid	Phenylalanine & tyrosine metabolism	20435	28523	1.40	0.021550
N6-carbamoylthreonyladenosine	Nucleotide	Purine metabolism, guanine containing	188555	218796	1.16	0.021921
N-acetylneuraminate	Carbohydrate	Aminosugars metabolism	5156751	6097823	1.18	0.025883
4-acetamidobutanoate	Amino	Guanidino	433626	503950	1.16	0.0312

	acid	and acetamido metabolism				11
phenylacetate	Amino acid	Phenylalanine & tyrosine metabolism	45852	60922	1.33	0.037733
1,7-dimethylurate	Xenobiotics	Xanthine metabolism	102733	139568	1.36	0.050153
N2,N2-dimethylguanosine	Nucleotide	Purine metabolism, guanine containing	106854	119749	1.12	0.050380
imidazole propionate	Amino acid	Histidine metabolism	29939	36983	1.24	0.053402
mannitol	Carbohydrate	Fructose, mannose, galactose, starch, and sucrose metabolism	24038780	39285795	1.63	0.068619
vanillylmandelate (VMA)	Amino acid	Phenylalanine & tyrosine metabolism	942554	1129213	1.20	0.074338
1,3,7-trimethylurate	Xenobiotics	Xanthine metabolism	73238	96016	1.31	0.078580
4-vinylphenol sulfate	Xenobiotics	Benzoate metabolism	300083	241395	0.80	0.079720
3-hydroxyhippurate	Xenobiotics	Benzoate metabolism	308339	439672	1.43	0.079785
N1-Methyl-2-pyridone-5-carboxamide	Cofactors and vitamins	Nicotinate and nicotinamide metabolism	627270	548938	0.88	0.083145
indoleacetate	Amino acid	Tryptophan metabolism	297968	324419	1.09	0.088865
xylose	Carbohydrate	Nucleotide sugars, pentose metabolism	2465713	3054639	1.24	0.093541
N-acetylalanine	Amino acid	Alanine and aspartate metabolism	95821	106633	1.11	0.094612
N-acetylcarnosine	Peptide	Dipeptide derivative	133551	117059	0.88	0.104598
4-methylcatechol sulfate	Xenobiotics	Benzoate metabolism	425105	487321	1.15	0.107580
phenol sulfate	Amino	Phenylalanin	2738973	3306931	1.21	0.1137

	acid	e & tyrosine metabolism				36
gulono-1,4-lactone	Cofactors and vitamins	Ascorbate and aldarate metabolism	4453394	5054035	1.13	0.116056
N-acetylthreonine	Amino acid	Glycine, serine and threonine metabolism	167997	178394	1.06	0.128644
citrulline	Amino acid	Urea cycle; arginine-, proline-, metabolism	465956	505698	1.09	0.132796
isobutyrylcarnitine	Amino acid	Valine, leucine and isoleucine metabolism	420827	360151	0.86	0.134419
3-methylhistidine	Amino acid	Histidine metabolism	271718	223986	0.82	0.135021
pyrophosphate (PPi)	Energy	Oxidative phosphorylation	4172830	4096503	0.98	0.162724
cytidine	Nucleotide	Pyrimidine metabolism, cytidine containing	31736	29092	0.92	0.169192
3-indoxyl sulfate	Amino acid	Tryptophan metabolism	8229092	9006599	1.09	0.176599
1-methylurate	Xenobiotics	Xanthine metabolism	308810	351490	1.14	0.199062
N-acetylhistidine	Amino acid	Histidine metabolism	35576	39174	1.10	0.216655
pseudouridine	Nucleotide	Pyrimidine metabolism, uracil containing	1019502	967399	0.95	0.222920
methyl indole-3-acetate	Amino acid	Tryptophan metabolism	202103	237148	1.17	0.230566
fumarate	Energy	Krebs cycle	858255	927874	1.08	0.235224
pyridoxate	Cofactors and vitamins	Pyridoxal metabolism	1475345	1219302	0.83	0.261521
N-formylmethionine	Amino acid	Cysteine, methionine, SAM, taurine metabolism	36573	34838	0.95	0.282701

gamma-glutamylisoleucine	Peptide	gamma-glutamyl	96877	101552	1.05	0.284870
3-methyl catechol sulfate 1	Xenobiotics	Benzoate metabolism	95132	82661	0.87	0.308822
xylonate	Carbohydrate	Nucleotide sugars, pentose metabolism	3607285	3895177	1.08	0.322077
scyllo-inositol	Lipid	Inositol metabolism	2054228	1839448	0.90	0.334212
arabitol	Carbohydrate	Nucleotide sugars, pentose metabolism	4198444	4114134	0.98	0.334214
arabinose	Carbohydrate	Nucleotide sugars, pentose metabolism	2024518	2162739	1.07	0.347572
homocitrulline	Amino acid	Urea cycle; arginine-, proline-, metabolism	210504	221754	1.05	0.352268
N-acetylphenylalanine	Amino acid	Phenylalanine & tyrosine metabolism	18262	20000	1.10	0.368985
androsterone sulfate	Lipid	Sterol/Steroid	881363	743738	0.84	0.394736
3-aminoisobutyrate	Nucleotide	Pyrimidine metabolism, thymine containing; Valine, leucine and isoleucine metabolism/	1097602	1009582	0.92	0.402789
galactitol (dulcitol)	Carbohydrate	Fructose, mannose, galactose, starch, and sucrose metabolism	2227651	2462831	1.11	0.407733
glycine	Amino acid	Glycine, serine and threonine metabolism	67942934	71434198	1.05	0.413798
p-cresol sulfate	Amino acid	Phenylalanine & tyrosine	12697550	13594933	1.07	0.424663

		metabolism				
tigloylglycine	Amino acid	Valine, leucine and isoleucine metabolism	76153	76623	1.01	0.459775
1-methylhistidine	Amino acid	Phenylalanine & tyrosine metabolism	739407	798603	1.08	0.463873
chiro-inositol	Xenobiotics	Benzoate metabolism	5121605	6033942	1.18	0.476810
3-methylglutarylcarnitine (C6)	Amino acid	Phenylalanine & tyrosine metabolism	446020	480350	1.08	0.492210
fucose	Peptide	Dipeptide	1461332	1557748	1.07	0.533595
urea	Xenobiotics	Benzoate metabolism	467766038	455841649	0.97	0.571285
threitol	Amino acid	Glycine, serine and threonine metabolism	10921136	11588525	1.06	0.572945
gamma-CEHC	Peptide	Dipeptide	54939	64868	1.18	0.594278
N-delta-acetylornithine	Carbohydrate	Nucleotide sugars, pentose metabolism	28398	26800	0.94	0.594374
phenylcarnitine	Cofactors and vitamins	Tocopherol metabolism	46712	49094	1.05	0.632275
acisoga	Amino acid	Tryptophan metabolism	437905	450373	1.03	0.636719
sucrose	Amino acid	Phenylalanine & tyrosine metabolism	457588	482518	1.05	0.648441
2-aminophenol sulfate	Nucleotide	Purine metabolism, guanine containing	137509	145415	1.06	0.654282
S-adenosylhomocysteine (SAH)	Carbohydrate	Aminosugars metabolism	27567	28331	1.03	0.655449
N-acetylmethionine	Amino acid	Guanidino and acetamido metabolism	30905	31827	1.03	0.655555
N-acetyltryptophan	Amino acid	Phenylalanine & tyrosine	12090	11519	0.95	0.656857

		metabolism				
2-hydroxyhippurate (salicylurate)	Xenobiotics	Xanthine metabolism	1683533	1150014	0.68	0.681595
erythritol	Nucleotide	Purine metabolism, guanine containing	32695382	23488774	0.72	0.727073
N-acetyl-3-methylhistidine	Amino acid	Histidine metabolism	163643	152921	0.93	0.733946
quinolinate	Carbohydrate	Fructose, mannose, galactose, starch, and sucrose metabolism	447729	461601	1.03	0.734424
arabonate	Amino acid	Phenylalanine & tyrosine metabolism	4725559	4840792	1.02	0.742937
beta-alanine	Xenobiotics	Xanthine metabolism	609130	575578	0.94	0.750724
5-methylthioadenosine (MTA)	Xenobiotics	Benzoate metabolism	15320	15604	1.02	0.785580
kynurenate	Xenobiotics	Benzoate metabolism	61473	59932	0.97	0.807418
N-acetyl-1-methylhistidine	Cofactors and vitamins	Nicotinate and nicotinamide metabolism	198751	168780	0.85	0.817888
allantoin	Amino acid	Tryptophan metabolism	546956	555333	1.02	0.839228
glutarylcarnitine (C5)	Carbohydrate	Nucleotide sugars, pentose metabolism	121940	120521	0.99	0.857937
isobutyrylglycine	Amino acid	Alanine and aspartate metabolism	47605	46716	0.98	0.863258
threonate	Peptide	Dipeptide derivative	8826790	8675367	0.98	0.865530
isovalerylglycine	Xenobiotics	Benzoate metabolism	32779	32191	0.98	0.908078
myo-inositol	Amino acid	Phenylalanine & tyrosine metabolism	88013858	87342654	0.99	0.915654
alpha-CEHC glucuronide*	Cofactors and vitamins	Ascorbate and aldarate metabolism	106392	92448	0.87	0.915672

erythronate	Amino acid	Glycine, serine and threonine metabolism	1967894 3	1979870 6	1.01	0.929999
1,6-anhydroglucose	Amino acid	Urea cycle; arginine-, proline-, metabolism	8319465	7684369	0.92	0.958421
pantothenate	Amino acid	Valine, leucine and isoleucine metabolism	211017	235029	1.11	0.966765
creatinine	Amino acid	Histidine metabolism	3100765	3103860	1.00	0.982767
indolelactate	Energy	Oxidative phosphorylation	4146250	4153602	1.00	0.986627

Table A3. Metabolite ratios associated with impaired executive function at false detection rate p-value <0.05. The p-gain statistic indicates that the association of the metabolite ratios with impaired executive function is not different from the association of individual metabolites.

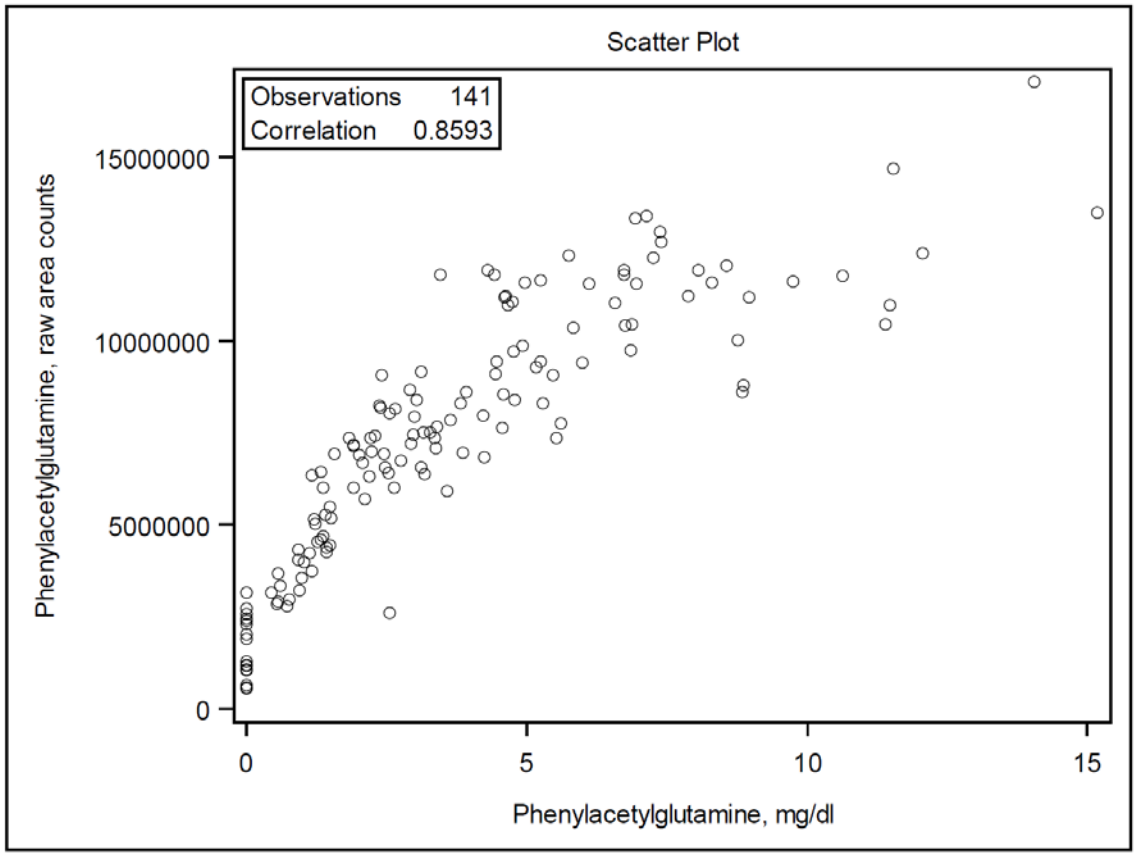
Metabolites	Log Metabolite ratio among impaired (SD)	Log Metabolite ratio among unimpaired (SD)	Nominal p-value	p-gain
1-arachidonoylglyercophosphate/ phenylacetylglutamine	-4.27 (0.71)	-3.6 (0.85)	2.10×10^{-6}	36.86
N1-Methyl-2-pyridone-5-carboxamide/ phenylacetylglutamine	-2.70 (0.53)	-2.15 (0.74)	9.78×10^{-7}	79.18
o-cresol sulfate/ phenylacetylglutamine	-6.28 (0.79)	-5.43 (1.20)	2.06×10^{-6}	37.54

Table A4. Relative risk of impaired executive function in discovery cohort and replication cohort. Models adjusted for all listed metabolites.

	Discovery cohort				Replication cohort			
Metabolite	4-hydroxyphenyl acetate	Phenylacetylglutamine	Hippurate	Prolyl-hydroxyproline	4-hydroxyphenyl acetate	Phenylacetylglutamine	Hippurate	Prolyl-hydroxyproline
Metabolite (per SD increase in log)	1.16 (1.03, 1.32)	1.39 (1.13, 1.71)	1.24 (1.03, 1.50)	1.20 (1.05, 1.38)	1.12 (1.02, 1.23)	1.11 (0.98, 1.26)	0.96 (0.86, 1.08)	1.11 (1.00, 1.24)
Age (per 10 years)	1.03 (0.92, 1.16)	1.03 (0.92, 1.16)	1.03 (0.92, 1.15)	1.05 (0.94, 1.18)	1.11 (1.01, 1.21)	1.10 (1.00, 1.21)	1.10 (1.01, 1.21)	1.12 (1.02, 1.22)
Education								
< High school	1.05 (0.67, 1.63)	1.17 (0.76, 1.81)	1.13 (0.72, 1.76)	1.14 (0.72, 1.79)	1.49 (1.17, 1.89)	1.43 (1.13, 1.81)	1.46 (1.15, 1.85)	1.51 (1.19, 1.92)
High school grad	0.89 (0.65, 1.21)	0.87 (0.65, 1.18)	0.88 (0.65, 1.20)	0.84 (0.61, 1.15)	1.25 (0.95, 1.66)	1.25 (0.95, 1.66)	1.27 (0.96, 1.68)	1.25 (0.94, 1.65)
Post-high school	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Spanish speaking (vs English)	1.59 (1.01, 2.51)	1.73 (1.00, 2.99)	1.62 (0.95, 2.77)	1.67 (1.03, 2.70)	1.14 (0.87, 1.49)	1.20 (0.93, 1.55)	1.24 (0.95, 1.62)	1.22 (0.94, 1.59)
Stroke	1.21 (0.84, 1.75)	1.34 (0.94, 1.91)	1.42 (0.97, 2.08)	1.23 (0.85, 1.79)	1.26 (0.98, 1.61)	1.24 (0.97, 1.59)	1.27 (0.99, 1.64)	1.27 (0.99, 1.62)
Vintage (per year)	1.05 (1.01, 1.08)	1.04 (1.00, 1.07)	1.04 (1.00, 1.07)	1.04 (1.01, 1.08)	0.93 (0.70, 1.23)	0.92 (0.68, 1.23)	0.95 (0.72, 1.26)	0.90 (0.67, 1.19)
Peritoneal dialysis (vs hemodialysis)	0.41 (0.12, 1.44)	0.44 (0.14, 1.44)	0.41 (0.13, 1.27)	0.39 (0.11, 1.35)				
Day of blood draw	-	-	-	-				
Mon/Tues					0.92 (0.71, 1.18)	0.90 (0.70, 1.17)	0.96 (0.73, 1.25)	0.96 (0.74, 1.28)
Wed/Thurs					1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Fri/Sat					1.11 (0.80, 1.54)	1.12 (0.81, 1.55)	1.15 (0.83, 1.60)	1.13 (0.83, 1.54)

Figure A1. Correlation of phenylacetylglutamine (Panel A) and hippurate (Panel B) measured by direct quantification versus metabolon platform.

Panel A. Phenylacetylglutamine



Panel B. Hippurate