Supplemental Table of Contents

1. Supplemental Table 1. Fractional clearances of solutes assayed employing chemical xtandards calculated using $U/P_{creatinine}$ for both control and CKD subjects

2. Supplemental Table 2. Fractional clearances of solutes assayed employing chemical standards calculated using U/P_{urea} for both control and CKD subjects

3. Supplemental Table 3. Ratios of average fractional clearance values in CKD subjects as compared to control subjects using different denominators to estimate the GFR

4. Supplemental Table 4. Solutes for which metabolomic analysis provided a comparison of fractional clearance values in control subjects and patients with advanced CKD.

5. Supplemental Table 5 – Comparison of fractional clearance values obtained by metabolomic analysis and by assays employing chemical standards.

6. Supplemental Table 6. Plasma concentrations in patients with advanced CKD relative to control subjects of solutes identified as secreted in control subjects.

Supplemental Table 1. Fractional Clearances of Solutes Assayed Employing Chemical Standards calculated using $U/P_{creatinine}$ for both Control and CKD subjects

Solute		Fractional Clearance				Free Fraction (%)		
		Control	CKD	CKD/ Control	*p value*	Control	CKD	*p value*
UreaN		0.53 ± 0.16	0.57 ± 0.10	1.1				
PAG	Total	3.9 ± 0.8	1.7 ± 0.4	0.44	<0.001	95 ± 17	97 ± 7	0.733
	Free	4.2 ± 0.6	1.8 ± 0.5	0.44	<0.001			
PCS	Total	0.18 ± 0.04	0.15 ± 0.04	0.81	0.03	2.2 ± 0.4	4.9 ± 1.2	<0.001
	Free	8.6 ± 2.6	3.2 ± 1.1	0.37	<0.001			
IS	Total	0.53 ± 0.11	0.32 ± 0.11	0.60	<0.001	2.4 ± 0.7	5.7 ± 1.7	<0.001
	Free	23.0 ± 7.3	5.8 ± 2.1	0.25	<0.001			
HIPP	Total	3.4 ± 1.2	3.2 ± 0.8	0.95	0.65	33 ± 2	49 ± 7	<0.001
	Free	10.2 ± 3.8	6.6 ± 2.1	0.65	0.003			

Different from Table 2 in the main manuscript in that urine/plasma creatinine was used as the denominator in calculating fractional clearance values for both Control and CKD subjects. The result is that the apparent reductions in fractional secretion are increased over those reported in the main manuscript as summarized further in Supplemental Table 3. Results are mean ± standard deviation. CKD, chronic kidney disease; PAG, phenylacetylglutamine; PCS, p-cresol sulfate; IS, indoxyl sulfate; HIPP, hippurate. The free fraction represents the proportion of solute that is not bound to protein and was calculated as the free level divided by the total level for each solute. CKD/Control is the ratio of the average value in the CKD subjects to the average value in the control subjects.

Supplemental Table 2. Fractional Clearances of Solutes Assayed Employing Chemical Standards calculated using U/P_{urea} for both Control and CKD subjects

Solute		Fractional Clearance				Free Fraction (%)		
		Control	CKD	CKD/ Control	*p value*	Control	CKD	*p value*
UreaN		1	1	1				
PAG	Total	9.3 ± 3.2	3.2 ± 1.4	0.38	<0.001	95 ± 17	97 ± 7	0.733
	Free	9.1 ± 4.4	3.3 ± 1.3	0.37	<0.001			
PCS	Total	0.37 ± 0.10	0.26 ± 0.08	0.72	0.004	2.2 ± 0.4	4.9 ± 1.2	<0.001
	Free	17.2 ± 5.3	5.8 ± 2.9	0.34	<0.001			
IS	Total	1.11 ± 0.42	0.57 ± 0.22	0.51	<0.001	2.4 ± 0.7	5.7 ± 1.7	<0.001
	Free	46.4 ± 15.3	10.7 ± 5.1	0.23	<0.001			
HIPP	Total	6.9 ± 3.0	5.7 ± 1.5	0.83	0.17	33 ± 2	49 ± 7	<0.001
	Free	20.7 ± 8.8	11.9 ± 4.1	0.57	<0.001			

Different from Table 2 in the main manuscript in that urine/plasma urea was used as the denominator in calculating factional clearance values for both Control and CKD subjects. The result is that the apparent reductions in fractional secretion are increased over those reported in the main manuscript as summarized further in Supplemental Table 3. Results are mean ± standard deviation. CKD, chronic kidney disease; PAG, phenylacetylglutamine; PCS, p-cresol sulfate; IS, indoxyl sulfate; HIPP, hippurate. The free fraction represents the proportion of solute that is not bound to protein and was calculated as the free level divided by the total level for each solute. CKD/Control is the ratio of the average value in the CKD subjects to the average value in the control subjects.

Supplemental Table 3. Ratios of Average Fractional Clearance Values in CKD Subjects as Compared to Control Subjects using Different Denominators to Estimate the GFR

		Fractional Clearance CKD/Control		
		creatinine and urea for CKD, creatinine for Control	**creatinine for CKD, creatinine for Control**	**urea for CKD, urea for Control**
UreaN		1.4	1.1	1
PAG	Total	0.57	0.44	0.38
	Free	0.56	0.44	0.37
PCS	Total	1.04	0.81	0.72
	Free	0.47	0.37	0.34
IS	Total	0.76	0.60	0.51
	Free	0.33	0.25	0.23
HIPP	Total	1.21	0.83	0.83
	Free	0.82	0.57	0.57

The use of combined urea/creatinine clearance for CKD patients and creatinine clearance for controls is conservative. This combination employs an overestimate of GFR and thus obtains an underestimate of fractional clearance in controls while using a lower GFR and obtaining a higher fractional clearance in CKD patients. The result is to minimize the estimated reduction in secretory clearance in CKD. Use of either creatinine or urea for both CKD patients and control subjects results in estimation of a relatively greater reduction in secretory clearances in CKD.

Supplemental Table 4 – Solutes for Which Fractional Clearance Values Were Calculated in Both Control Subjects and Patients with Advanced CKD

	Solute	HMDB #	Mass	Fractional Clearance Control	Fractional Clearance CKD
1	1,3,7-trimethylurate	HMDB02123	209.068	15.1 ± 5.5	11.5 ± 4.7
2	3-indoxyl sulfate	HMDB00682	212.0023	14.2 ± 4.8	6.1 ± 1.9
3	pyridoxate		182.0459	13.1 ± 7.8	7.8 ± 3.4
4	N-(2-furoyl)glycine		168.0302	11.8 ± 8.1	4 ± 1.4
5	guanidinoacetate	HMDB00128	118.0611	10.1 ± 8.5	8.8 ± 7.6
6	3-hydroxyhippurate	HMDB06116	194.0459	9.7 ± 6.3	9 ± 5
7	5-acetylamino-6-formylamino-3-methyluracil	HMDB11105	225.0629	9.6 ± 5	6.2 ± 2.6
8	4-methylcatechol sulfate		203.002	8.7 ± 4	2.6 ± 0.8
9	5-hydroxy-2-methylpyridine sulfate		188.0023	7.8 ± 5.6	2.2 ± 1
10	hippurate	HMDB00714	178.051	7.5 ± 2.7	6.2 ± 1.3
11	1,7-dimethylurate	HMDB11103	195.0524	6.4 ± 1.7	6 ± 1.8
12	4-hydroxyhippurate	HMDB13678	194.0459	6.2 ± 2.5	5.3 ± 1.1
13	N2,N5-diacetylornithine		217.1183	6.1 ± 3	2.6 ± 1.1
14	p-cresol sulfate	HMDB11635	187.0071	5.8 ± 1.2	3.8 ± 0.8
15	N-acetyl-2-aminooctanoate*	HMDB59745	200.1292	5.6 ± 4.6	2.6 ± 1.2
16	glutamine conjugate of C7H12O2*		255.135	5.2 ± 1.9	2.8 ± 0.9
17	N2,N2-dimethylguanosine	HMDB04824	312.1303	5.2 ± 1	3.2 ± 0.8
18	3-methyl catechol sulfate (1)		203.002	5.1 ± 1.9	3 ± 1.3
19	2-isopropylmalate	HMDB00402	175.0612	5 ± 4.1	4.4 ± 2.5
20	acisoga		185.1285	5 ± 3.2	4.2 ± 1.9
21	vanillylmandelate (VMA)	HMDB00291	197.0456	4.8 ± 1	3.3 ± 0.9
22	1-methylnicotinamide	HMDB00699	137.0709	4.8 ± 1.3	7.6 ± 3
23	3-methoxycatechol sulfate (1)		218.9969	4.7 ± 2	2.3 ± 0.6

24	acesulfame	HMDB33585	161.9867	4.7 ± 2.3	2.4 ± 1.5
25	1-methylurate	HMDB03099	183.0513	4.6 ± 1.4	3.6 ± 1
26	N-acetylasparagine	HMDB06028	173.0568	4.6 ± 1.6	1.2 ± 0.5
27	4-guanidinobutanoate	HMDB03464	146.0924	4.5 ± 1.7	2.1 ± 1.1
28	guaiacol sulfate	HMDB60013	203.002	4.5 ± 1.2	2.2 ± 0.7
29	p-cresol glucuronide*	HMDB11686	283.0823	4.3 ± 1.2	2.2 ± 0.7
30	2,6-dihydroxybenzoic acid	HMDB13676	153.0193	4.1 ± 1.9	3.4 ± 1.3
31	phenylacetylglutamine	HMDB06344	265.1183	4 ± 1.1	2.9 ± 0.9
32	hexanoylglutamine		243.135	4 ± 1.5	2.3 ± 0.6
33	1-methylxanthine		167.0564	3.9 ± 1.6	2.3 ± 0.9
34	N-acetyltaurine		166.018	3.7 ± 0.9	1.8 ± 0.4
35	glutamine conjugate of C6H10O2 (1)*		241.1194	3.5 ± 0.7	1.7 ± 0.5
36	N-acetylglucosamine/N-acetylgalactosamine		222.0972	3.4 ± 1	3.3 ± 0.8
37	4-hydroxyphenylacetylglutamine		279.0986	3.4 ± 0.9	1.5 ± 0.4
38	1-methyl-5-imidazoleacetate	HMDB04988	141.0659	3.3 ± 2.4	0.9 ± 0.5
39	glutamine conjugate of C6H10O2 (2)*		241.1194	3.3 ± 1.2	2 ± 0.6
40	3-aminoazepan-2-one		129.1022	3.2 ± 0.6	4.1 ± 0.8
41	N-acetylglutamine	HMDB06029	187.0724	2.9 ± 1.3	1 ± 0.4
42	methylsuccinate	HMDB01844	131.035	2.9 ± 0.7	4.6 ± 1.1
43	N-acetylputrescine	HMDB02064	131.1179	2.6 ± 0.3	3.2 ± 0.8
44	hydantoin-5-propionate	HMDB01212	171.0411	2.6 ± 0.8	1.6 ± 0.4
45	7-methylxanthine	HMDB01991	167.0564	2.5 ± 0.9	1.7 ± 1
46	3-hydroxypyridine sulfate		173.9867	2.5 ± 1.8	1.4 ± 0.6
47	catechol sulfate	HMDB59724	188.9863	2.5 ± 0.7	1.4 ± 0.3
48	N2-acetyl,N6,N6-dimethyllysine		217.1547	2.4 ± 0.4	0.9 ± 0.3
49	N-acetylhistidine		196.0728	2.4 ± 0.8	0.8 ± 0.2
50	carboxysuccinate		161.0092	2.3 ± 0.7	2.4 ± 0.8
51	N2-acetyl,N6-methyllysine		203.139	2.3 ± 0.6	0.9 ± 0.3
52	gamma-carboxyglutamate		192.0503	2.2 ± 1.1	1.9 ± 0.9
53	suberate (C8-DC)	HMDB00893	173.0819	2.2 ± 1.1	1.5 ± 0.7
54	4-ureidobutyrate		145.0619	2.2 ± 1.3	1.7 ± 0.7
55	5-hydroxymethyl-2-furoic acid	HMDB02432	141.0193	2.1 ± 1	0.9 ± 0.8

56	lactose	HMDB00186	387.1144	2.1 ± 1.7	1.6 ± 0.9
57	isocitric lactone		173.0092	2.1 ± 1.2	0.7 ± 0.2
58	heptenedioate (C7:1-DC)*		157.0506	2.1 ± 0.5	1.6 ± 0.5
59	3-hydroxy-3-methylglutarate	HMDB00355	161.0456	2 ± 0.6	2.4 ± 0.7
60	N-acetylarginine	HMDB04620	217.1	2 ± 0.4	1.2 ± 0.5
61	dimethylguanidino valeric acid (DMGV)*		202.1186	2 ± 2	0.7 ± 0.5
62	malonate		103.0037	2 ± 2	2.1 ± 1.6
63	glycerol 3-phosphate	HMDB00126	173.021	1.9 ± 1.3	3.4 ± 1.7
64	N-acetylisoleucine	HMDB61684	174.1125	1.9 ± 0.9	1.3 ± 0.9
65	phenol sulfate	HMDB60015	172.9914	1.9 ± 0.7	1.8 ± 0.6
66	7-methylguanine		164.0578	1.9 ± 0.5	1.7 ± 0.4
67	N6-carbamoylthreonyladenosine	HMDB41623	411.127	1.8 ± 2.4	0.9 ± 0.2
68	3-ureidopropionate	HMDB00026	133.0608	1.8 ± 0.6	2.8 ± 0.9
69	N,N-dimethyl-5-aminovalerate		146.1176	1.8 ± 1.5	1.4 ± 1.1
70	3-hydroxypyridine glucuronide		272.0765	1.8 ± 1	0.6 ± 0.5
71	3-hydroxybutyroylglycine		162.0761	1.7 ± 0.6	1.6 ± 0.3
72	2-furoylcarnitine		256.118	1.6 ± 0.4	0.8 ± 0.5
73	pyrraline	HMDB33143	255.1339	1.6 ± 0.7	0.7 ± 0.5
74	3-amino-2-piperidone	HMDB00323	115.0866	1.5 ± 0.3	3.3 ± 0.6
75	3-hydroxyadipate*	HMDB00345	161.0455	1.5 ± 0.9	1.1 ± 0.6
76	N1-methylinosine		327.0946	1.5 ± 0.6	0.8 ± 0.4
77	imidazole propionate	HMDB02271	141.0659	1.5 ± 0.7	0.9 ± 0.5
78	1-methyl-4-imidazoleacetate	HMDB02820	141.0659	1.5 ± 0.2	1.6 ± 0.4
79	quinolinate		166.0146	1.5 ± 1	0.8 ± 0.5
80	O-sulfo-L-tyrosine		260.0234	1.4 ± 0.6	1.1 ± 0.4
81	1-ribosyl-imidazoleacetate*	HMDB02331	259.0925	1.4 ± 0.5	1.3 ± 0.4
82	N-carbamoylalanine		133.0608	1.4 ± 0.5	1.1 ± 0.2
83	N-acetyl-aspartyl-glutamate (NAAG)	HMDB01067	305.098	1.4 ± 0.5	0.6 ± 0.7
84	pimeloylcarnitine/3-methyladipoylcarnitine (C7-DC)		304.1755	1.4 ± 0.5	0.7 ± 0.2
85	beta-citrylglutamate		320.0623	1.4 ± 0.6	0.7 ± 0.6
86	1-methyladenosine	HMDB03331	282.1197	1.4 ± 0.2	1.4 ± 0.4
87	glucuronate	HMDB00127	193.0354	1.4 ± 0.2	1.3 ± 0.2

88	4-acetamidobutanoate	HMDB03681	146.0812	1.4 ± 0.2	1.3 ± 0.3
89	3-methylxanthine	HMDB01886	165.0418	1.3 ± 0.5	1 ± 0.4
90	galactonate	HMDB00565	195.051	1.3 ± 1.2	1.1 ± 0.6
91	suberoylcarnitine (C8-DC)		318.1911	1.3 ± 0.3	0.9 ± 0.2
92	succinoyltaurine		224.0234	1.3 ± 0.4	0.7 ± 0.4
93	N-methyltaurine		138.023	1.3 ± 0.4	0.6 ± 0.3
94	2-hydroxyphenylacetate	HMDB00669	151.0401	1.3 ± 0.6	1.1 ± 1
95	lanthionine		209.0591	1.3 ± 0.2	0.6 ± 0.2
96	trigonelline (N'-methylnicotinate)	HMDB00875	138.055	1.2 ± 0.3	1.7 ± 0.3
97	palmitoyl sphingomyelin (d18:1/16:0)		703.5749	1.2 ± 1.9	11.3 ± 17.6
98	prolylhydroxyproline	HMDB06695	229.1183	1.2 ± 0.2	0.9 ± 0.2
99	hydroxyasparagine	HMDB32332	149.0557	1.2 ± 0.4	0.9 ± 0.3
100	cytosine	HMDB00630	112.0505	1.2 ± 0.5	1.2 ± 0.4
101	imidazole lactate	HMDB02320	157.0608	1.1 ± 0.3	0.8 ± 0.2
102	S-carboxyethylcysteine		194.0482	1.1 ± 0.4	0.6 ± 0.3
103	3-methylglutaconate		99.0452	1.1 ± 0.2	0.9 ± 0.2
104	N-acetylcarnosine	HMDB12881	267.1099	1.1 ± 0.2	0.8 ± 0.3
105	adipoylcarnitine (C6-DC)	HMDB61677	290.1598	1.1 ± 0.4	0.7 ± 0.2
106	N-acetylglutamate		188.0564	1.1 ± 0.3	1.1 ± 0.3
107	tyramine O-sulfate	HMDB06409	216.0336	1.1 ± 0.4	0.7 ± 0.5
108	N-acetylproline		158.0812	1.1 ± 1.6	0.9 ± 0.4
109	sebacate (C10-DC)	HMDB00792	201.1132	1.1 ± 1.3	1.6 ± 1.8
110	succinylcarnitine (C4-DC)	HMDB61717	262.1285	1.1 ± 0.2	1 ± 0.2
111	3-methylglutarylcarnitine (2)	HMDB00552	290.1598	1.1 ± 0.4	0.7 ± 0.3
112	N-acetylglucosaminylasparagine	HMDB00489	336.1402	1.1 ± 0.4	0.7 ± 0.2
113	5-(galactosylhydroxy)-L-lysine		325.1606	1 ± 0.7	0.7 ± 0.3
114	N-acetyl-isoputreanine		201.1245	1 ± 0.4	0.4 ± 0.2
115	N6-carboxymethyllysine		205.1183	1 ± 0.4	0.7 ± 0.2
116	sucrose	HMDB00258	387.1144	1 ± 0.4	0.9 ± 0.2
117	isobutyrylglycine (C4)	HMDB00730	144.0666	1 ± 0.6	1 ± 0.4
118	2,3-dihydroxy-5-methylthio-4-pentenoate (DMTPA)*		177.0227	1 ± 0.2	0.7 ± 0.2
119	carboxyethyl-GABA	HMDB02201	176.0917	1 ± 0.3	2.2 ± 0.5

120	dupllicate creatinine	HMDB00562	114.0662	1 ± 0	1.5 ± 0.1
121	creatinine	HMDB00562	114.0662	1 ± 0	1.5 ± 0.1
122	trans-urocanate	HMDB00301	139.0502	1 ± 0.4	2.3 ± 1.6
123	5-acetylamino-6-amino-3-methyluracil	HMDB04400	197.068	1 ± 0.2	0.9 ± 0.2
124	glutarylcarnitine (C5-DC)	HMDB13130	276.1442	1 ± 0.2	0.7 ± 0.2
125	trimethylamine N-oxide	HMDB00925	76.0757	1 ± 0.4	1.6 ± 0.6
126	pseudouridine	HMDB00767	243.0623	0.9 ± 0.3	1 ± 0.4
127	(N(1) + N(8))-acetylspermidine		188.1757	0.9 ± 0.2	0.6 ± 0.3
128	N-acetylaspartate (NAA)	HMDB00812	174.0408	0.9 ± 0.5	1.3 ± 0.7
129	2'-O-methylcytidine		258.1085	0.9 ± 0.4	0.5 ± 0.4
130	2-aminophenol sulfate	HMDB61116	188.0023	0.9 ± 0.4	0.6 ± 0.3
131	methylsuccinoylcarnitine		276.1442	0.9 ± 0.2	0.7 ± 0.2
132	N-acetylneuraminate	HMDB00230	310.1133	0.9 ± 0.4	1.2 ± 0.2
133	ribonate	HMDB00867	165.0405	0.9 ± 0.5	0.8 ± 0.4
134	formiminoglutamate	HMDB00854	175.0713	0.9 ± 0.3	0.8 ± 0.3
135	fucitol		165.0768	0.9 ± 0.2	0.8 ± 0.1
136	C-glycosyltryptophan		365.1354	0.9 ± 0.3	0.7 ± 0.2
137	orotidine	HMDB00788	287.0521	0.8 ± 0.4	0.8 ± 0.4
138	indoleacetate	HMDB00197	174.0561	0.8 ± 0.9	0.6 ± 0.6
139	3-hydroxystachydrine*		160.0968	0.8 ± 0.3	0.7 ± 0.3
140	erythritol	HMDB02994	167.0561	0.8 ± 0.2	0.6 ± 0.2
141	argininate*	HMDB03148	176.103	0.8 ± 0.1	0.6 ± 0.1
142	N,N,N-trimethyl-alanylproline betaine (TMAP)		229.1547	0.8 ± 0.2	0.6 ± 0.1
143	tiglyl carnitine (C5)	HMDB02366	244.1543	0.8 ± 0.1	0.6 ± 0.1
144	adipate	HMDB00448	145.0506	0.8 ± 0.5	2 ± 1.4
145	maleate	HMDB00176	115.0037	0.8 ± 0.2	0.8 ± 0.1
146	orotate	HMDB00226	155.0098	0.8 ± 0.3	1.4 ± 0.5
147	quinate	HMDB03072	191.0561	0.8 ± 0.3	0.9 ± 0.3
148	citraconate/glutaconate		129.0194	0.8 ± 0.3	0.9 ± 0.4
149	aconitate [cis or trans]		173.0092	0.8 ± 0.2	1 ± 0.2
150	ascorbic acid 2-sulfate		254.9816	0.8 ± 0.2	0.7 ± 0.1
151	2,3-dihydroxyisovalerate	HMDB12141	133.0506	0.7 ± 0.2	0.7 ± 0.2

152	cyclo(gly-pro)		155.0815	0.7 ± 0.4	0.6 ± 0.1
153	gulonate*	HMDB03290	195.051	0.7 ± 0.5	0.6 ± 0.3
154	glycerophosphoglycerol		245.0432	0.7 ± 0.4	1.5 ± 1
155	arabitol/xylitol		151.0612	0.7 ± 0.3	0.8 ± 0.3
156	dopamine 3-O-sulfate	HMDB06275	232.0285	0.7 ± 0.3	0.8 ± 0.5
157	mannitol/sorbitol	HMDB00247	181.0718	0.7 ± 0.3	1 ± 0.2
158	5,6-dihydrouridine		245.0779	0.7 ± 0.3	0.7 ± 0.2
159	ethylmalonate	HMDB00622	131.035	0.7 ± 0.2	0.6 ± 0.2
160	ribitol	HMDB00508	151.0612	0.7 ± 0.1	0.6 ± 0.3
161	1,6-anhydroglucose	HMDB00640	207.051	0.7 ± 0.3	0.6 ± 0.3
162	pantothenate (Vitamin B5)	HMDB00210	218.1034	0.7 ± 0.2	1.1 ± 0.7
163	3-methylhistidine	HMDB00479	168.0779	0.7 ± 0.2	0.7 ± 0.2
164	homocitrulline		188.1041	0.6 ± 0.5	0.6 ± 0.5
165	2S,3R-dihydroxybutyrate	HMDB02453	119.035	0.6 ± 0.1	0.6 ± 0.2
166	N-acetylthreonine	HMDB62557	160.0615	0.6 ± 0.3	0.6 ± 0.3
167	erythronate*	HMDB00613	135.0299	0.6 ± 0.2	0.9 ± 0.3
168	2-O-methylascorbic acid		189.0405	0.6 ± 0.1	0.5 ± 0.2
169	mannonate*		195.051	0.6 ± 0.2	0.6 ± 0.2
170	beta-hydroxyisovaleroylcarnitine		262.1649	0.6 ± 0.1	0.9 ± 0.3
171	arabinose	HMDB00646	195.051	0.6 ± 0.2	1.2 ± 2.7
172	3-hydroxyhexanoylcarnitine (1)		276.1806	0.6 ± 0.2	0.8 ± 0.2
173	xanthine	HMDB00292	151.0262	0.6 ± 0.3	1.4 ± 1.1
174	arabonate/xylonate		165.0405	0.6 ± 0.3	0.5 ± 0.2
175	methylmalonate (MMA)	HMDB00202	117.0193	0.6 ± 0.2	0.6 ± 0.2
176	N-methylhydroxyproline		146.0812	0.6 ± 0.5	0.8 ± 0.8
177	pantoate		147.0663	0.6 ± 0.4	0.6 ± 0.5
178	2-oxoarginine*	HMDB04225	174.0873	0.6 ± 0.3	0.5 ± 0.3
179	pentose acid*		165.0405	0.6 ± 0.1	0.6 ± 0.1
180	3-aminoisobutyrate	HMDB03911	104.0706	0.6 ± 0.4	0.9 ± 0.4
181	dimethylarginine (ADMA + SDMA)	HMDB01539	203.1503	0.6 ± 0.1	0.5 ± 0.1
182	hydroxy-N6,N6,N6-trimethyllysine*		205.1547	0.6 ± 0.3	0.4 ± 0.2
183	2R,3R-dihydroxybutyrate	HMDB00498	119.035	0.6 ± 0.1	0.6 ± 0.1

184	ascorbic acid 3-sulfate*		254.9815	0.5 ± 0.4	0.5 ± 0.3
185	sulfate*	HMDB01448	96.9601	0.5 ± 0.1	0.9 ± 0.2
186	citrate		210.0608	0.5 ± 0.4	0.9 ± 0.5
187	2-keto-3-deoxy-gluconate	HMDB01353	177.0405	0.5 ± 0.2	0.7 ± 0.2
188	N-acetylphenylalanine		206.0823	0.5 ± 0.3	2.3 ± 1.2
189	N1-Methyl-2-pyridone-5-carboxamide	HMDB04193	151.0513	0.5 ± 0.1	0.8 ± 0.2
190	isobutyrylcarnitine (C4)	HMDB00736	232.1543	0.5 ± 0.1	0.5 ± 0.1
191	hypoxanthine		137.0458	0.5 ± 0.3	0.3 ± 0.4
192	N6-acetyllysine	HMDB00206	187.1088	0.5 ± 0.2	0.3 ± 0.2
193	gluconate	HMDB00625	195.051	0.5 ± 0.2	0.4 ± 0.1
194	gamma-glutamylisoleucine*	HMDB11170	261.1445	0.4 ± 0.2	0.5 ± 0.3
195	2-methylbutyrylcarnitine (C5)	HMDB00378	246.17	0.4 ± 0.3	0.4 ± 0.3
196	3,4-dihydroxybutyrate		119.035	0.4 ± 0.1	0.6 ± 0.1
197	1-methylhistidine	HMDB00001	168.0779	0.4 ± 0.2	0.4 ± 0.2
198	2-hydroxyglutarate	HMDB0059655	131.0339	0.4 ± 0.1	1.2 ± 0.8
199	cis-4-decenoylcarnitine (C10:1)		314.2326	0.4 ± 0.2	0.4 ± 0.1
200	N-acetylleucine	HMDB11756	172.0979	0.4 ± 0.3	0.8 ± 0.8
201	allo-threonine	HMDB04041	118.051	0.3 ± 0.4	0.6 ± 0.4
202	adenine	HMDB00034	136.0618	0.3 ± 0.2	1.4 ± 1
203	duplicate urea	HMDB00294	121.072	0.3 ± 0.1	0.5 ± 0.1
204	urea	HMDB00294	121.072	0.3 ± 0.1	0.5 ± 0.1
205	1-carboxyethylphenylalanine		236.0928	0.3 ± 0.3	0.7 ± 1
206	caprate (10:0)	HMDB00511	171.1391	0.3 ± 0.1	2.9 ± 1.3
207	N6,N6,N6-trimethyllysine	HMDB01325	189.1598	0.3 ± 0.1	0.2 ± 0.1
208	gamma-glutamylalanine	HMDB29142	219.0976	0.3 ± 0.3	3.5 ± 2.7
209	gamma-glutamylvaline	HMDB11172	247.1289	0.3 ± 0.2	0.4 ± 0.2
210	N6-carboxyethyllysine		219.1339	0.3 ± 0.3	0.3 ± 0.2
211	glutarate (C5-DC)	HMDB00661	131.035	0.3 ± 0.2	1 ± 0.7
212	phosphate	HMDB01429	98.9842	0.3 ± 0.1	1.2 ± 0.2
213	N6,N6-dimethyllysine	HMDB13287	175.1441	0.3 ± 0.1	0.3 ± 0.1
214	stachydrine	HMDB04827	144.1019	0.3 ± 0.1	0.6 ± 0.1
215	5-methylthioadenosine (MTA)	HMDB01173	298.0968	0.3 ± 0.1	0.2 ± 0.1

216	salicylate	HMDB01895	137.0242	0.2 ± 0.3	1 ± 0.8
217	glycerophosphoethanolamine	HMDB00114	216.0632	0.2 ± 0.2	1.4 ± 0.9
218	(S)-3-hydroxybutyrylcarnitine		248.1493	0.2 ± 0.1	0.6 ± 0.2
219	cysteine s-sulfate	HMDB00731	199.9693	0.2 ± 0.3	0.1 ± 0.1
220	ribulonate/xylulonate/lyxonate*		165.0405	0.2 ± 0.1	0.4 ± 0.1
221	chiro-inositol	HMDB34220	225.0616	0.2 ± 0.2	0.8 ± 0.2
222	5-oxoproline		128.0353	0.2 ± 0.1	1 ± 0.3
223	histidine	HMDB00177	154.0622	0.2 ± 0.1	0.7 ± 0.3
224	succinate		117.0193	0.2 ± 0.1	1.3 ± 0.7
225	urate	HMDB00289	167.0211	0.2 ± 0.1	0.6 ± 0.2
226	cysteine	HMDB00574	122.027	0.2 ± 0.1	0.3 ± 0.1
227	dimethylglycine	HMDB00092	104.0706	0.2 ± 0.1	0.5 ± 0.1
228	allantoin	HMDB00462	157.0367	0.2 ± 0.1	0.7 ± 0.2
229	theobromine	HMDB02825	181.072	0.2 ± 0.1	0.3 ± 0.2
230	kynurenine	HMDB00684	209.0921	0.2 ± 0.1	0.3 ± 0.2
231	gamma-glutamylthreonine	HMDB29159	249.1081	0.2 ± 0.1	0.3 ± 0.2
232	threonate	HMDB00943	135.0299	0.2 ± 0.1	0.6 ± 0.2
233	myo-inositol	HMDB00211	225.0616	0.14 ± 0.16	1.29 ± 0.6
234	oxalate (ethanedioate)	HMDB02329	88.988	0.14 ± 0.09	1.22 ± 0.53
235	S-methylcysteine sulfoxide	HMDB29432	152.0376	0.14 ± 0.07	0.21 ± 0.2
236	N,N-dimethylalanine		118.0863	0.14 ± 0.08	0.51 ± 0.24
237	nicotinamide	HMDB01406	123.0553	0.13 ± 0.08	1.36 ± 0.81
238	phosphocholine	HMDB01565	184.0733	0.12 ± 0.09	1.81 ± 0.78
239	3-methoxytyrosine	HMDB01434	212.0917	0.12 ± 0.06	0.22 ± 0.2
240	N-methylproline		130.0863	0.12 ± 0.1	0.47 ± 0.31
241	2-methylserine		120.0655	0.11 ± 0.06	0.32 ± 0.13
242	phosphoethanolamine (PE)		140.0118	0.1 ± 0.09	0.24 ± 0.23
243	methionine sulfone		182.0482	0.09 ± 0.04	0.22 ± 0.13
244	N,N,N-trimethyl-5-aminovalerate		160.1332	0.09 ± 0.04	0.28 ± 0.09
245	homostachydrine*	HMDB33433	158.1176	0.08 ± 0.04	1.17 ± 3.49
246	methionine	HMDB00696	150.0583	0.08 ± 0.02	0.86 ± 0.27
247	pelargonate (9:0)	HMDB00847	157.1234	0.08 ± 0.1	0.82 ± 0.82

248	creatine		130.0622	0.08 ± 0.08	0.2 ± 0.16
249	thioproline		134.027	0.08 ± 0.09	0.28 ± 0.31
250	tryptophan	HMDB00929	205.0972	0.07 ± 0.03	0.31 ± 0.17
251	N-acetylglycine	HMDB00532	118.0499	0.07 ± 0.09	0.24 ± 0.16
252	fumarate	HMDB00134	115.0037	0.07 ± 0.08	0.92 ± 0.62
253	N-acetylserine	HMDB02931	146.0459	0.07 ± 0.06	0.18 ± 0.14
254	glycine	HMDB00123	76.0393	0.07 ± 0.03	0.36 ± 0.15
255	taurine	HMDB00251	126.022	0.07 ± 0.06	0.26 ± 0.39
256	betaine	HMDB00043	118.0863	0.07 ± 0.08	0.63 ± 0.22
257	3-(4-hydroxyphenyl)lactate (HPLA)	HMDB00755	181.0506	0.07 ± 0.03	0.71 ± 0.23
258	malate	HMDB00156	133.0143	0.05 ± 0.05	0.53 ± 0.25
259	fructosyllysine		309.1656	0.05 ± 0.07	0.07 ± 0.04
260	acetylcarnitine (C2)	HMDB00201	204.123	0.05 ± 0.04	0.38 ± 0.22
261	fructose		179.0561	0.05 ± 0.04	0.14 ± 0.11
262	isovalerylcarnitine (C5)	HMDB00688	246.17	0.05 ± 0.03	0.29 ± 0.29
263	alpha-ketoglutarate	HMDB00208	145.0143	0.05 ± 0.04	0.35 ± 0.19
264	cystine	HMDB00192	241.0311	0.05 ± 0.08	0.08 ± 0.07
265	beta-alanine	HMDB00056	90.055	0.04 ± 0.07	0.21 ± 0.26
266	2-aminobutyrate	HMDB00650	104.0706	0.04 ± 0.02	0.67 ± 0.37
267	serine		104.0353	0.04 ± 0.03	0.27 ± 0.15
268	propionylcarnitine (C3)	HMDB00824	218.1387	0.03 ± 0.02	0.24 ± 0.11
269	tryptophan betaine	HMDB61115	247.1441	0.03 ± 0.02	0.17 ± 0.11
270	choline	HMDB00097	104.107	0.03 ± 0.01	1.02 ± 0.4
271	glycerate	HMDB00139	105.0193	0.03 ± 0.03	0.19 ± 0.13
272	carnitine	HMDB00062	162.1125	0.03 ± 0.02	0.24 ± 0.1
273	methionine sulfoxide	HMDB02005	166.0533	0.02 ± 0.01	0.17 ± 0.14
274	N-acetylalanine	HMDB00766	130.051	0.02 ± 0.02	0.09 ± 0.06
275	glycerophosphorylcholine (GPC)	HMDB00086	258.1101	0.02 ± 0.02	0.24 ± 0.15
276	N6-methyllysine	HMDB02038	161.1285	0.02 ± 0.03	0.06 ± 0.05
277	aspartate	HMDB00191	134.0448	0.02 ± 0.01	0.27 ± 0.29
278	caffeine	HMDB01847	195.0877	0.02 ± 0.02	0.17 ± 0.25
279	octanoylcarnitine (C8)	HMDB00791	288.2169	0.02 ± 0.01	0.09 ± 0.05

280	glucose	HMDB00122	225.0616	0.02 ± 0.03	0.18 ± 0.16
281	asparagine		131.0462	0.02 ± 0.02	0.16 ± 0.13
282	N-delta-acetylornithine		173.0932	0.015 ± 0.021	0.089 ± 0.11
283	tyrosine		180.0666	0.014 ± 0.009	0.122 ± 0.088
284	lysine		145.0983	0.014 ± 0.025	0.069 ± 0.085
285	alanine		88.0404	0.013 ± 0.015	0.108 ± 0.12
286	threonine	HMDB00167	120.0655	0.012 ± 0.008	0.156 ± 0.114
287	phenylalanine	HMDB00159	166.0863	0.011 ± 0.004	0.093 ± 0.057
288	cysteinylglycine disulfide*	HMDB00709	298.0526	0.011 ± 0.014	0.019 ± 0.011
289	hydroxyproline	HMDB00725	132.0655	0.011 ± 0.015	0.31 ± 0.168
290	deoxycarnitine	HMDB01161	146.1176	0.011 ± 0.006	0.13 ± 0.078
291	glutamine	HMDB00641	147.0764	0.008 ± 0.004	0.064 ± 0.055
292	1,5-anhydroglucitol (1,5-AG)	HMDB02712	163.0612	0.008 ± 0.017	0.114 ± 0.139
293	citrulline	HMDB00904	176.103	0.007 ± 0.01	0.163 ± 0.104
294	leucine		132.1019	0.005 ± 0.002	0.074 ± 0.047
295	ornithine	HMDB03374	133.0972	0.005 ± 0.006	0.052 ± 0.036
296	uridine		243.0623	0.004 ± 0.003	0.029 ± 0.023
297	glutamate	HMDB00148	148.0604	0.004 ± 0.002	0.027 ± 0.022
298	arginine	HMDB00517	175.119	0.003 ± 0.003	0.041 ± 0.026
299	isoleucine		132.1019	0.003 ± 0.002	0.046 ± 0.04
300	alpha-hydroxyisovalerate	HMDB00407	117.0557	0.003 ± 0.004	0.031 ± 0.031
301	lactate	HMDB00190	89.0244	0.002 ± 0.003	0.032 ± 0.029
302	valine		118.0863	0.001 ± 0.001	0.023 ± 0.034
303	proline	HMDB00162	116.0706	0.001 ± 0.001	0.052 ± 0.04

HMDB, entry in Human Metabolome Database if available. CKD, chronic kidney disease. For each solute the fractional clearance was calculated as the urine to the plasma concentration ratio for the solute divided by the urine to plasma concentration ratio for creatinine in control subjects and by the average of the urine to plasma concentration ratios for

creatinine and urea in CKD patients. The presence of a (#) after a solute name indicates the solute is one of two or more steroisomers that are indistinguishable by mass spectrometry. The presence of an asterisk (*) indicates a compound whose identity is considered known but has not been confirmed by use of a chemical standard. This list includes all solutes for which metabolomic analysis identified peaks in at least 10 of 16 samples in both urine and plasma ultrafiltrate in both control and CKD subjects. One solute (#24 acesulfame) which met our criteria of an estimated fractional clearance of greater than 3.0 based on the free level in control subjects was not included in Table 3 in the main manuscript because it is a food additive which is not known to be produced by mammalian metabolism. We cannot exclude, however, that there is unknown production of this substance by humans.

Supplemental Table 5 – Comparison of Fractional Clearances Values

Obtained by Metabolomic Analysis and by Assays Employing Chemical Standards

Solute		Fractional Clearance Chemical Standards				Fractional Clearance Metabolomic			
		Control	CKD	CKD/ Cont	p	Control	CKD	CKD/ Cont	p
PAG	Free	4.2 ± 0.6	2.3 ± 0.6	0.56	0.000	4.0 ± 1.1	2.9 ± 0.9	0.73	0.004
	Total	3.9 ± 0.8	2.2 ± 0.6	0.57	0.000	3.4 ± 0.8	2.4 ± 0.5	0.71	0.000
PCS	Free	8.6 ± 2.6	4.1 ± 1.5	0.47	0.000	5.8 ± 1.2	3.8 ± 0.8	0.65	0.000
	Total	0.18 ± 0.04	0.19 ± 0.05	1.04	0.69	0.28 ± 0.06	0.27 ± 0.04	0.96	0.50
IS	Free	23.0 ± 7.3	7.5 ± 2.8	0.33	0.000	14.2 ± 4.8	6.1 ± 1.9	0.43	0.000
	Total	0.53 ± 0.11	0.40 ± 0.14	0.76	0.007	0.54 ± 0.13	0.45 ± 0.12	0.85	0.07
HIPP	Free	10.2 ± 3.8	8.4 ± 2.6	0.82	0.13	7.5 ± 2.7	6.2 ± 1.3	0.83	0.11
	Total	3.4 ± 1.2	4.0 ± 1.0	1.21	0.92	2.7 ± 1.0	3.0 ± 1.0	1.08	0.48

Results are mean ± standard deviation. CKD, chronic kidney disease; PAG, phenylacetylglutamine; PCS, p-cresol sulfate; IS, indoxyl sulfate; HIPP, hippurate. For each solute the fractional clearance was calculated as the urine to the plasma concentration ratio for the solute divided by the urine to plasma concentraton ratio for creatinine in control subjects and by the average of the urine to plasma concentration ratios for creatinine and urea in CKD patients.

Supplemental Table 6. Metabolomic Analysis of Accumulation of Secreted Solutes in Advanced CKD

Solute	Fractional Clearance [Free] Control	CKD /Control [Free]	CKD /Control [Total]
1,3,7-trimethylurate	15.1 ± 5.5	3.7	2.7
3-indoxyl sulfate	14.2 ± 4.8	22.4	10.3
pyridoxate	13.1 ± 7.8	3.5	
N-(2-furoyl)glycine	11.8 ± 8.1	2.6	
guanidinoacetate	10.1 ± 8.5	0.8	0.9
3-hydroxyhippurate	9.7 ± 6.3	5.9	4.9
5-acetylamino-6-formylamino-3-methyluracil	9.6 ± 5.0	4.0	6.5
4-methylcatechol sulfate	8.7 ± 4.0	8.6	3.7
5-hydroxy-2-methylpyridine sulfate	7.8 ± 5.6	3.1	1.6
hippurate	7.5 ± 2.7	7.6	5.2
1,7-dimethylurate	6.4 ± 1.7	4.1	2.6
4-hydroxyhippurate	6.2 ± 2.5	9.8	10.3
N2,N5-diacetylornithine	6.1 ± 3.0	15.5	15.1
p-cresol sulfate	5.8 ± 1.2	9.9	6.3
N-acetyl-2-aminooctanoate*	5.6 ± 4.6	4.6	2.6

glutamine conjugate of C7H12O2*	5.2 ± 1.9	25.9	24.5
N2,N2-dimethylguanosine	5.2 ± 1.0	8.4	7.0
3-methyl catechol sulfate (1)	5.1 ± 1.9	1.6	1.3
2-isopropylmalate	5.0 ± 4.1	3.9	4.0
acisoga	5.0 ± 3.2	3.7	
vanillylmandelate (VMA)	4.8 ± 1.0	10.0	8.2
1-methylnicotinamide	4.8 ± 1.3	1.7	1.6
3-methoxycatechol sulfate (1)	4.7 ± 2.0	5.2	3.4
1-methylurate	4.6 ± 1.4	7.3	6.8
N-acetylasparagine	4.6 ± 1.6	8.2	8.6
4-guanidinobutanoate	4.5 ± 1.7	2.7	2.4
guaiacol sulfate	4.5 ± 1.2	19.9	12.6
p-cresol glucuronide*	4.3 ± 1.2	30.1	32.4
2,6-dihydroxybenzoic acid	4.1 ± 1.9	3.1	2.0
phenylacetylglutamine	4.0 ± 1.1	13.1	12.7
hexanoylglutamine	4.0 ± 1.5	10.9	9.1
1-methylxanthine	3.9 ± 1.6	1.2	
N-acetyltaurine	3.7 ± 0.9	7.6	4.9
glutamine conjugate of C6H10O2 (1)*	3.5 ± 0.7	20.9	15.2

N-acetylglucosamine/N-acetylgalactosamine	3.4 ± 1.0	2.7	2.5
4-hydroxyphenylacetylglutamine	3.4 ± 0.9	42.7	46.5
1-methyl-5-imidazoleacetate	3.3 ± 2.4	31.3	37.2
glutamine conjugate of C6H10O2 (2)*	3.3 ± 1.2	23.2	19.7
3-aminoazepan-2-one	3.2 ± 0.6	4.5	4.5

Solutes identified as secreted in the metabolomic analysis are listed in order of their average estimated fractional clearance values expressed in terms of the free solute levels in the control subjects, denoted Fractional Clearance [Free]. CKD/Control [Free] is the ratio of the average metabolomic peak area in plasma ultrafiltrates of the control subjects divided by the average metabolomic peak area in plasma ultrafiltrates of the patients with advanced CKD. CKD/Control [Total] is the ratio of the average metabolomic peak area in plasma of the control subjects divided by the average metabolomic peak area in plasma of the patients with advanced CKD. Among the 39 solutes listed, values for CKD/Control [Total] could not be calculated for 4 solutes because peak areas were quantifiable in ultrafiltrate samples but not in plasma samples. The presence of a (#) after a solute name indicates the solute is one or two or more steroisomers that are indistinguishable by mass spectrometry. The presence of an asterisk (*) indicates a compound whose identity is considered known but has not been confirmed by use of a chemical standard.