

**Supplemental Table 1. Baseline Characteristics of Validation Group Separated by type of diabetes**

	T2DM+CKD	T1DM+CKD
n	49	12
Age, years	64.2 ± 10.2	46.2 ± 5.7
Race		
White	21 (44%)	1 (8%)
Non-White	27 (56%)	11 (92%)
Gender: Male	27 (55%)	9 (75%)
Gender: Female	22 (45%)	3 (25%)
BMI, kg/m <sup>2</sup>	33.3 ± 7.4	29 ± 5.6
Smoking: Ever	23 (49%)	7 (58%)
Smoking: Never	24 (51%)	5 (42%)
Systolic BP, mmHg	130.7 ± 12.9	132.3 ± 22.1
Diastolic BP, mmHg	71.2 ± 7.3	75.9 ± 10
Type 2 DM Duration, yrs*	15 (9.5, 23)	
Type 1 DM Duration, yrs*		30 (24.2, 37.8)
HbA1c, %	7.4 ± 1.3	7.4 ± 1.2
Serum Creatinine, mg/dL	2.1 ± 0.8	2.5 ± 1.4
Albumin/Creatinine Ratio*	0.18 (0.06, 0.73)	0.65 (0.33, 1.61)
eGFR, ml/min/1.73m <sup>2</sup>	35.4 ± 11.5	38.2 ± 19.8

\*Median (Quartile 1, Quartile 3) ; otherwise, mean ± SD or n (%) are presented.

**Supplemental Table 2 : Geometric Mean Metabolite Levels by Group**

Metabolite	Control, n=23	Screening, n=24	Validation, n=61	Type 1 DM w/o CKD, n=32	Type 2 DM w/o CKD, n=41	Type I&II DM w/o CKD, n=73
3-Hydroxy Isovalerate	37.47 (28.57,49.16)	11.39 (9.35,13.88)	12 (10.48,13.74)	42.45 (33.03,54.55)	34.27 (30.43,38.6)	37.64 (33.14,42.76)
Aconitic Acid	78.02 (67.75,89.84)	54.08 (46.38,63.06)	42.43 (34.75,51.81)	96.19 (78.92,117.25)	91.5 (85.81,97.56)	93.53 (85.36,102.48)
Citric Acid	523.69 (427.88,640.95)	201.26 (159.58,253.84)	183.56 (148.59,226.76)	719.71 (591.33,875.97)	610.26 (547.79,679.86)	656.03 (591.07,728.12)
2-Ethyl 3-OH Propionate	2.04 (1.65,2.52)	1.48 (1.32,1.66)	1.19 (1.12,1.28)	2.42 (2.03,2.89)	2.19 (1.99,2.42)	2.29 (2.08,2.51)
Glycolic Acid	84.39 (71.94,99)	35.36 (29.56,42.31)	37.95 (34.12,42.21)	111.19 (90.96,135.93)	85.75 (78.87,93.22)	96.09 (86.81,106.36)
Homovanillic Acid	15.77 (13.84,17.97)	8 (5.97,10.71)	8.39 (7.18,9.81)	13.89 (10.58,18.23)	15.94 (14.54,17.48)	15.01 (13.22,17.04)
3-Hydroxy Isobutyrate	46.91 (37.31,58.99)	27.24 (21.96,33.78)	22.34 (17.92,27.87)	82.98 (66.36,103.75)	64.59 (58.32,71.53)	72.09 (64.31,80.8)
2-Methyl Acetoacetate	7.77 (4.39,13.74)	3.74 (2.76,5.06)	1.25 (1.1,1.42)	9.47 (6.62,13.54)	1.62 (1.38,1.89)	3.51 (2.68,4.6)
3-Methyl Adipic Acid	8.1 (5,13.13)	1.88 (1.41,2.5)	1.16 (1.07,1.24)	3.04 (2.59,3.57)	2.53 (2.26,2.83)	2.74 (2.49,3.01)
3-Methyl Crotonyl Glycine	4.02 (2.93,5.51)	1.52 (1.25,1.85)	1.16 (1.03,1.31)	3.5 (2.41,5.11)	2.01 (1.69,2.39)	2.56 (2.1,3.12)
3-Hydroxy Propionate	3.57 (2.93,4.34)	1.62 (1.32,1.98)	1.54 (1.33,1.78)	2.02 (1.6,2.54)	3.18 (2.57,3.92)	2.6 (2.22,3.06)
Tiglylglycine	2.52 (2.15,2.94)	1.62 (1.39,1.88)	1.23 (1.09,1.38)	2.08 (1.62,2.68)	2.46 (2.04,2.97)	2.29 (1.97,2.66)
Uracil	10.57 (8.5,13.16)	3.05 (2.18,4.27)	5.72 (4.83,6.77)	8.59 (6.88,10.71)	15.38 (13.06,18.13)	11.91 (10.29,13.8)

**Supplementary Table 3: Comparison of Candidate Urine Metabolites between DM CKD vs DM without CKD based on diabetic types\***

Metabolite	T1 DM CKD	p-value**	T2 DM CKD	p-value**
	vs. T1DM w/o CKD Percent <sup>†</sup> (95% CI)		vs.T2DM w/o CKD Percent <sup>†</sup> (95% CI)	
3-Hydroxy Isovalerate	-63.05 (-78.74, -35.78)	0.0008182	-60.46 (-70.32, -47.32)	4.67E-09
Aconitic Acid	-56.21 (-71.31, -33.16)	0.0003387	-37.47 (-47.38, -25.7)	4.48E-07
Citric Acid	-70.15 (-82.4, -49.39)	4.45E-05	-63.38 (-74.3, -47.83)	1.64E-07
2-Ethyl 3-OH Propionate	-50.25 (-64.74, -29.8)	0.0002165	-39.01 (-49.25, -26.7)	6.22E-07
Glycolic Acid	-55.52 (-71.31, -31.05)	0.0006246	-53.3 (-62.64, -41.61)	9.10E-10
Homovanillic Acid	-47.37 (-70, -7.66)	0.02639	-33.82 (-51.63, -9.46)	0.01037
3-Hydroxy Isobutyrate	-62.99 (-76.71, -41.19)	0.0001062	-54.72 (-69.26, -33.3)	9.81E-05
2-Methyl Acetoacetate	-76.19 (-88.28, -51.64)	0.0002198	-14.47 (-43.36, 29.15)	0.4535
3-Methyl Adipic Acid	-58.54 (-70.84, -41.06)	1.19E-05	-41.28 (-56.06, -21.52)	0.000432
3-Methyl Crotonyl Glycine	-57.36 (-81.53, -1.57)	0.04603	-25.86 (-44.98, -0.1)	0.04927
3-Hydroxy Propionate	14.7 (-30.56, 89.48)	0.5828	-36.26 (-56.74, -6.09)	0.0232
Tiglylglycine	-39.25 (-64.82, 4.9)	0.07248	-34.32 (-52.21, -9.75)	0.01005
Uracil	-35.7 (-62.07, 9.01)	0.09838	-59.73 (-73.49, -38.82)	3.75E-05

+ Percent difference between DM+CKD vs DM w/o CKD groups, respectively

\*\* p-values based on linear models adjusted for age, race and gender, MAP, BMI, HbA1C and DM duration ; Bonferroni corrected p-value cutoff for 13 metabolite comparisons is 0.0038.

**Supplemental Table 4: Principal Components (PC1 and PC2) and weighted value (loadings)**

	PC1 loadings	PC2 loadings
3-Hydroxy Isovalerate	0.756	0.537
Aconitic Acid	0.703	0.364
Citric Acid	0.795	0.35
2-Ethyl 3-OH Propionate	0.61	0.547
Glycolic Acid	0.755	0.482
Homovanillic Acid	0.696	0.293
3-Hydroxy Isobutyrate	0.754	0.417
2-Methyl Acetoacetate	0.093	0.896
3-Methyl Adipic Acid	0.319	0.772
3-Methyl Crotonyl Glycine	0.274	0.736
3-Hydroxy Propionate	0.515	0.168
Tiglylglycine	0.518	0.308
Uracil	0.791	-0.174

**Supplemental Table 5. Comparison of Candidate Urine Metabolites between DM CKD vs CKD without DM (FSGS) \***

Metabolite	DM CKD	p-value**
	vs. CKD w/o DM (FSGS) Percent <sup>†</sup> (95% CI)	
3-Hydroxy Isovalerate	-3.25 (-33.72, 41.23)	0.8626
Aconitic Acid	6.74 (-27.08, 56.25)	0.7345
Citric Acid	27.45 (-25.96, 119.37)	0.3774
2-Ethyl 3-OH Propionate	-15.44 (-30.82, 3.37)	0.1006
Glycolic Acid	21.63 (-8.43, 61.56)	0.1741
Homovanillic Acid	-2.08 (-36.02, 49.87)	0.9222
3-Hydroxy Isobutyrate	-18.54 (-52.47, 39.62)	0.4516
2-Methyl Acetoacetate	-88.02 (-92.99, -79.52)	7.35E-12
3-Methyl Adipic Acid	-68.14 (-77.57, -54.76)	4.63E-09
3-Methyl Crotonyl Glycine	-73.21 (-82.85, -58.14)	7.18E-08
3-Hydroxy Propionate	-54.29 (-69.79, -30.84)	0.0003053
Tiglylglycine	-54.46 (-68.76, -33.6)	7.66E-05
Uracil	24.95 (-27.11, 114.17)	0.4138

\*Adjusted for age, race and gender.

+ Percent difference between DM+CKD vs CKD w/o DM (FSGS) groups

\*\*p-values based on ANCOVAs comparison of DM+CKD vs CKD without DM (FSGS); Bonferonni adjusted p-value cutoff is 0.0038 for 13 metabolite comparisons.

**Supplemental Table 6. Association of eGFR and ACR with Candidate Metabolites in patients with Diabetes and CKD\***

Metabolite	Type 1 and 2 DM+CKD % change in metabolite with change in eGFR Percent <sup>+</sup> (95% CI)	p-value**	Type 1 and 2 DM+CKD % change in metabolite with change in ACR Percent <sup>+</sup> (95% CI)	p-value**
3-Hydroxy Isovalerate	1.94 (1.14, 2.74)	6.78E-06	2.57 (-2.2, 7.58)	0.2919
Aconitic Acid	1.01 (0.43, 1.59)	0.0008407	0.21 (-3.06, 3.59)	0.8996
Citric Acid	1.81 (0.64, 3)	0.00282	1.09 (-5.24, 7.85)	0.7387
2-Ethyl 3-OH Propionate	0.43 (-0.05, 0.91)	0.07982	2.2 (-0.39, 4.85)	0.09534
Glycolic Acid	1.6 (0.96, 2.23)	3.04E-06	-0.97 (-4.69, 2.9)	0.6142
Homovanillic Acid	-0.06 (-1.08, 0.97)	0.9111	2.94 (-2.57, 8.75)	0.2971
3-Hydroxy Isobutyrate	0.96 (-0.28, 2.21)	0.1284	5.52 (-1.23, 12.73)	0.1094
2-Methyl Acetoacetate	-0.34 (-1.62, 0.95)	0.5963	10.07 (3.09, 17.51)	0.004648
3-Methyl Adipic Acid	-0.3 (-1.17, 0.58)	0.5047	5.45 (0.74, 10.37)	0.02336
3-Methyl Crotonyl Glycine	0.83 (-0.01, 1.67)	0.05354	4.99 (0.41, 9.77)	0.0327
3-Hydroxy Propionate	0.5 (-0.45, 1.46)	0.3008	0.37 (-4.67, 5.67)	0.8883
Tiglylglycine	0.12 (-0.65, 0.89)	0.7634	0.64 (-3.45, 4.89)	0.7607
Uracil	1.54 (0.28, 2.82)	0.0173	-4.53 (-10.88, 2.26)	0.1828

\* eGFR untransformed in ml/min/1.73m<sup>2</sup>; Log-transformed albumin/creatinine ratio and metabolites

\*\* p-values based on linear models adjusted for age, race and gender, MAP, BMI, HbA1C and DM duration ; Bonferroni corrected p-value cutoff for 13 metabolite comparisons is 0.0038.

+ Percent change in metabolite per unit change in eGFR or log-ACR

**Supplemental Table 7. Regulation of metabolites in OAT1 and OAT3 KO Mice**

	Oat1		Oat3		Oat1 Knockout
Metabolite	Km ( $\mu\text{M}$ )	Ki ( $\mu\text{M}$ )	Km ( $\mu\text{M}$ )	Ki ( $\mu\text{M}$ )	Ref <sup>13</sup>
3-Hydroxy Isovalerate					
Aconitic Acid					
Citric Acid	Inhibitory				
2-Ethyl 3-OH Propionate					
Glycolic Acid				203	
Homovanillic Acid	65		274		
3-Hydroxy Isobutyrate		3220			Reduced in urine
2-Methyl Acetoacetate					
3-Methyl Adipic Acid					
3-Methyl Crotonyl Glycine					Reduced in urine
3-Hydroxy Propionate					Reduced in urine
Tiglylglycine					
Uracil					Reduced in urine

