Supplemental Table S1: Discriminating features between DR patients and diabetic controls that were assigned tentative annotations with medium or high confidence level using xMSannotator

Features were selected using PLS-DA (VIP ≥ 2) and were significantly associated ($p < 0.05$) with DR status in linear regression analyses adjusting for age, sex, diabetes duration, and hemoglobin A1c. Fold change presented as diabetic controls/DR patients. Features were annotated by xMSannotator with medium or high confidence. All metabolites matches are M+H adducts unless otherwise specified.

m/z	Retention Time (seconds)	VIP	Fold Change	HMDB Match (Chemical ID)
219.0830	47.0	2.966	1.292	L-Arginine (HMDB00517) [M+2Na-H], D-Arginine (HMDB03416)[M+2Na-H], 1-(2-Thienyl)-1-heptanone (HMDB40241) [M+Na]
175.1191	47.9	2.778	1.262	L-Arginine (HMDB00517), D-Arginine (HMDB03416)
276.1462	343.6	2.664	1.445	Glutarylcarnitine (HMDB13130)
176.1030	56.8	2.613	1.440	Argininic acid (HMDB03148), Citrulline (HMDB00904)
1111.2909	47.8	2.547	0.916	Kaempferol 3-O-feruloyl-caffeoyl-sophoroside 7-O-glucoside (HMDB29266)
270.2795	352.8	2.429	1.540	Capsiamide (HMDB40940)
193.0989	58.8	2.372	0.645	Hydroxycotinine (HMDB01390), 5-Hydroxycotinine (HMDB01427), Cotinine N-oxide (HMDB01411), Oxoamide (HMDB01004), N-Hydroxymethylnorcotinine (HMDB01324)
796.5849	437.0	2.353	0.439	PE(20:1(11Z)20:3(8Z11Z14Z)) (HMDB09266), PE(18:3(6Z9Z12Z)22:1(13Z)) (HMDB09139), PE(22:1(13Z)18:3(6Z9Z12Z)) (HMDB09523), PE(20:2(11Z14Z)20:2(11Z14Z)) (HMDB09297), PE(20:1(11Z)20:3(5Z8Z11Z)) (HMDB09265), PE(18:3(9Z12Z15Z)22:1(13Z)) (HMDB09172), PE(22:4(7Z10Z13Z16Z)18:0) (HMDB09585), PE(22:2(13Z16Z)18:2(9Z12Z)) (HMDB09555), PE(18:4(6Z9Z12Z15Z)22:0) (HMDB09204), PC(22:4(7Z10Z13Z16Z)15:0) (HMDB08625), PE(18:2(9Z12Z)22:2(13Z16Z)) (HMDB09107), PE(22:1(13Z)18:3(9Z12Z15Z)) (HMDB09524), PE(18:022:4(7Z10Z13Z16Z)) (HMDB09009), PE(20:3(8Z11Z14Z)20:1(11Z)) (HMDB09362), PE(20:3(5Z8Z11Z)20:1(11Z)) (HMDB09329), PE(20:4(5Z8Z11Z14Z)20:0) (HMDB09394), PE(20:4(8Z11Z14Z17Z)20:0) (HMDB09427), PE(22:018:4(6Z9Z12Z15Z)) (HMDB09492), PC(15:022:4(7Z10Z13Z16Z)) (HMDB07955), PE(20:020:4(5Z8Z11Z14Z)) (HMDB09234), PE(20:020:4(8Z11Z14Z17Z)) (HMDB09235)
214.0564	50.9	2.338	1.695	3-Methylhistidine (HMDB00479), 1-Methylhistidine (HMDB00001)
220.0668	53.4	2.176	1.320	Argininic acid (HMDB03148) [M+2Na-H], Citrulline (HMDB00904) [M+2Na-H]

171.1380	402.3	2.163	0.894	()-6-Methyl-5-hepten-2-yl acetate (HMDB30031), xi-Tetrahydro-3-pentyl-2H-pyran-2-one (HMDB37632), Methyl (xi)-3-nonenoate (HMDB29859), 2-Hexenyl butanoate (HMDB34581), 2-Hydroxycineol (HMDB59852), trans-p-Menth-2-ene-14-diol (HMDB37021), cis-4-Decenoic acid (HMDB04980), Hexyl crotonate (HMDB36211), Isopentyl 3-methyl-2-butenoate (HMDB40530), 8-Methylnonenoate (HMDB12183), 1-Cyclopropyl-4-methyl-13-cyclohexanediol (HMDB36992), Ethyl 4Z-octenoate (HMDB39795), 26-Dimethyl-37-octadiene-26-diol (HMDB36990), Ethyl 3-octenoate (HMDB32275), cis-3-Hexenyl isobutyrate (HMDB40213), ()-trans-Linalyl oxide (HMDB40727), Ethyl (E)-2-octenoate (HMDB37497), (E)-3-(Tetrahydro-55-dimethyl-2-furanyl)-2-buten-1-ol (HMDB35839), trans-Dec-2-enoic acid (HMDB10726), 3-Methyl-24-nonanedione (HMDB34880), 9-Hydroxygeraniol (HMDB38744), 5-Decenoic acid (HMDB39768), ()-cis-Linalool 37-oxide (HMDB41630), Citronellic acid (HMDB35837), Linalool oxide (trans-pyranoid) (HMDB31440), xi-5-Hexyldihydro-2(3H)-furanone (HMDB37217), ()-6-Hydroxy-26-dimethyl-7-octen-4-one (HMDB39149), 9-Decenoic acid (HMDB31003), Lilac alcohol (HMDB36099), 1-Octen-3-yl acetate (HMDB32452), 6-Decenoic acid (HMDB41012), ()-cis-Linalyl oxide (HMDB40726), Cyclohexylethyl acetate (HMDB31362), cis-3-Hexenyl butyrate (HMDB33377), Linalool oxide III (HMDB31441), 2-Exo-hydroxy-18-cineole (HMDB59610), Methyl 2-nonenoate (HMDB40194), 5Z-Octenyl acetate (HMDB29358), 3-Decenoic acid (HMDB31002), Cnidiol C (HMDB35365), 4-Hydroxy-26-dimethyl-7-octen-3-one (HMDB32119), delta-Decalactone (HMDB37116), 2-Propenyl heptanoate (HMDB40208), 2-Octenyl acetate (HMDB31297), Cyclohexyl butanoate (HMDB34427), 6-Decanolide (HMDB33203), Menthone lactone (HMDB40330), (SE)-26-Dimethyl-57-octadiene-23-diol (HMDB35122), 2-Methylbutyl 3-methyl-2-butenoate (HMDB32393), Linalyl oxide (HMDB35907)
367.0294	53.5	2.156	0.884	3-O-Galloyl-14-galactarolactone (HMDB37201), Molybdopterin precursor Z (HMDB11683), 5-O-Galloyl-14-galactarolactone (HMDB37202), 2-O-Galloyl-14-galactarolactone (HMDB37199), all M+Na adduct
264.1807	210.7	2.120	1.628	Hydroxyvalerylcarnitine (HMDB13132)
255.2109	356.3	2.071	1.556	18-Nor-4(19)81113-abietatetraene (HMDB41371)
129.0658	55.3	2.056	1.475	Dihydrothymine (HMDB00079), L-Cyclo(alanylglycyl) (HMDB31547), Squamolone (HMDB29874)
171.0638	272.7	2.056	1.383	34-Methyleneadipic acid (HMDB59756), Furaneol acetate (HMDB32966), Herierin IV (HMDB38761), 34-Dihydroxyphenylglycol (HMDB00318), Herierin III (HMDB38760)
203.1278	254.8	2.034	1.724	Oxalic acid dibutyl ester (HMDB40196), 2-Ethylsuberic acid (HMDB59708), 3-Methylazelaic acid (HMDB59754), R-2-Hydroxy-3-methylbutanoic acid 3-Methylbutanoyl (HMDB31510), Sebacic acid (HMDB00792), Heptylmalonic acid (HMDB59719)
1560.0019	436.0	2.011	2.676	CL(18:2(9Z12Z)20:4(5Z8Z11Z14Z)22:6(4Z7Z10Z13Z16Z19Z)20:4(5Z8Z11Z14Z)) (HMDB58877), CL(18:2(9Z12Z)22:6(4Z7Z10Z13Z16Z19Z)20:4(5Z8Z11Z14Z)20:4(5Z8Z11Z14Z)) (HMDB58942), CL(18:2(9Z12Z)20:4(5Z8Z11Z14Z)20:4(5Z8Z11Z14Z)22:6(4Z7Z10Z13Z16Z19Z)) (HMDB58867), CL(20:4(5Z8Z11Z14Z)18:2(9Z12Z)20:4(5Z8Z11Z14Z)22:6(4Z7Z10Z13Z16Z19Z)) (HMDB59067), CL(20:4(5Z8Z11Z14Z)18:2(9Z12Z)22:6(4Z7Z10Z13Z16Z19Z)20:4(5Z8Z11Z14Z)) (HMDB59077), CL(20:4(5Z8Z11Z14Z)20:4(5Z8Z11Z14Z)22:6(4Z7Z10Z13Z16Z19Z)18:2(9Z12Z)) (HMDB59108)

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Supplemental Table S2: Discriminating features between NPDR and PDR patients that were assigned tentative annotations with medium or high confidence level using xMSannotator

Features were selected using PLS-DA (VIP ≥ 2) and were significantly associated ($p < 0.05$) with PDR in linear regression analyses adjusting for age, sex, diabetes duration, and hemoglobin A1c. Fold change presented as PDR patients/NPDR patients. Features were annotated by xMSannotator with medium or high confidence. All metabolite matches are M+H adducts unless otherwise specified.

m/z	Retention Time (seconds)	VIP	Fold Change	HMDB Match (Chemical ID)
307.1895	563	3.004	0.291	Capsiate (HMDB34780), 5-Carboxy-gamma-chromanol (HMDB12799)
447.3831	549.6	2.993	0.558	alpha-Tocopherolquinone (HMDB34408), Schleicherastatin 3 (HMDB35512), 13-Hydroxy-alpha-tocopherol (HMDB12559), Stigmastentriol (HMDB29607)
414.3580	419.6	2.976	1.323	Heptadecanoyl carnitine (HMDB06210)
275.2010	397.5	2.969	2.659	(10Z14E16E)-101416-Octadecatrien-12-ynoic acid (HMDB35963), Nandrolone (HMDB02725), Rhodinyl phenylacetate (HMDB37191), Citronellyl alpha-toluate (HMDB37230), 1-Phenyl-13-dodecanedione (HMDB35579)
209.1904	423.8	2.949	2.521	(E)-610-Dimethyl-9-methylene-5-undecen-2-one (HMDB35862), 2-Decylfuran (HMDB32215), 2-Cyclotetradecen-1-one (HMDB39884)
221.1900	420.9	2.821	1.495	Isoshyobunone (HMDB38193), Spathulenol+H20:I38 (HMDB36420), Humulenol I (HMDB38211), Epoxyguaiene (HMDB35645), 11-Copaen-4-ol (HMDB37395), (6Z9Z12Z)-6912-Pentadecatrien-2-one (HMDB39532), Bisacurol (HMDB38512), Calacone (HMDB38146), alpha-Bergamotenol (HMDB36402), Humulene epoxide II (HMDB38210), Preisocalamendiol (HMDB35391), beta-Betulenol (HMDB36788), 4-Nonylphenol (HMDB38982), Vetiverol (HMDB37811), 7(14)-Isodaucen-10-one (HMDB38160), alpha-Cyperol (HMDB35026), beta-Costol (HMDB35097), 315-Epoxy-6-caryophyllene (HMDB36793), 26-Di-tert-butyl-4-methylphenol (HMDB33826), Eremofukinone (HMDB38119), alpha-Santal-10-en-12-ol (HMDB34940), Acoragermacrone (HMDB37069), (R)-27(14)9-Bisabolatrien-11-ol (HMDB35739), Humuladienone (HMDB38208), Dihydronootkatone (HMDB32220), Acorenone (HMDB35704), Italicene ether (HMDB40763), Humulene epoxide I (HMDB38209), Isospathulenol (HMDB34718), Fukinone (HMDB35793), Bisabolene oxide (HMDB38134), Cabreuva oxide D (HMDB59836), Isocyperol (HMDB35718), 15-Epoxy-4(14)-salvialene (HMDB38123), 2-trans6-trans-Farnesal (HMDB60356), Humulenol II (HMDB38212), 4(15)-Copaen-11-ol (HMDB37392), (3S6E)-6-Caryophyllen-15-al (HMDB36118), Nootkatol (HMDB13688), Aromadendrene epoxide (HMDB39711), trans-beta-Santalol (HMDB36717), Isoacolamone (HMDB35720), Apritone (HMDB36192), Epishyobunone (HMDB35306), Caryophyllene alpha-oxide (HMDB36789), (2R6S7S10Z)-beta-Santala-3(15)10-dien-12-ol (HMDB30232), beta-Santalol (HMDB36716), Acolamone (HMDB350200), 8alpha-3-Copaen-8-ol (HMDB36798), alpha-Valerenol (HMDB34661)
444.3085	459.6	2.790	0.552	Dynorphin A (6-8) (HMDB12932)
800.6098	569.4	2.780	0.847	PE(22:1(13Z)18:1(11Z)) (HMDB09520), PE(18:1(11Z)22:1(13Z)) (HMDB09040), PE(22:1(13Z)18:1(9Z)) (HMDB09521), PE(20:1(11Z)20:1(11Z)) (HMDB09263), PE(20:2(11Z14Z)20:0) (HMDB09295), PE(18:1(9Z)22:1(13Z)) (HMDB09073), PE(16:1(9Z)24:1(15Z)) (HMDB08981), PE(18:022:2(13Z16Z)) (HMDB09008), PE(18:2(9Z12Z)22:0) (HMDB09105), PE(24:1(15Z)16:1(9Z)) (HMDB09749), PE(20:020:2(11Z14Z)) (HMDB09231), PE(22:018:2(9Z12Z)) (HMDB09489), PE(22:2(13Z16Z)18:0) (HMDB09552), PC(15:022:2(13Z16Z)) (HMDB07954), PC(22:2(13Z16Z)15:0) (HMDB08592),
162.1125	57.0	2.767	1.222	L-Carnitine (HMDB00062)
800.6740	436.3	2.692	1.758	SM(d17:124:1(15Z)) (HMDB11696)
248.0488	61.8	2.663	0.784	Emtricitabine (HMDB15017)
163.1158	53.4	2.623	1.220	L-Carnitine (HMDB00062) [M+H_[+1]], (S1)-Methoxy-3-heptanethiol (HMDB32380)

241.1547	58.1	2.535	1.342	Pirbuterol (HMDB15407)
506.3618	419	2.531	1.174	LysoPC(P-18:1(9Z)) (HMDB10408)
315.1778	563.8	2.471	0.589	()-trans-Carveol glucoside (HMDB29849), (-)-trans-Carveol glucoside (HMDB29848), Perilloside A (HMDB38706)
431.3156	454.3	2.439	0.783	Barogenin (HMDB34403), 7 alpha-Hydroxy-3-oxo-4-cholestenoate (HMDB12458), 25-Hydroxyvitamin D3-2623-lactol (HMDB60127), 24-Oxo-1alpha25-dihydroxyvitamin D3 (HMDB60128), Australigenin (HMDB30066), MG(0:024:6(6Z9Z12Z15Z18Z21Z)0:0) (HMDB11560), MG(24:6(6Z9Z12Z15Z18Z21Z)0:00:0) (HMDB11590), Schidigeragenin C (HMDB36249)
309.1308	567.3	2.435	1.497	8-Acetylegelolide (HMDB37772)
570.2570	418.8	2.424	0.729	LysoPE(22:6(4Z7Z10Z13Z16Z19Z)0:0) (HMDB11526), LysoPE(0:022:6(4Z7Z10Z13Z16Z19Z)) (HMDB11496) [all M+2Na-H adducts]
247.2056	244.8	2.416	0.536	Avocadynofuran (HMDB30933), Ginsenoyne J (HMDB40373), Avocadienofuran (HMDB30926), Isoavocadienofuran (HMDB30927)
566.2652	307.2	2.410	2.672	Hemorphin-4 (HMDB59788)
149.0447	280.5	2.389	1.344	D-2-Hydroxyglutaric acid (HMDB00606), 2-Hydroxyglutarate (HMDB59655), 1-Propenyl propyl disulfide (HMDB41392), 3-Hydroxyglutaric acid (HMDB00428), Ribonolactone (HMDB01900), L-2-Hydroxyglutaric acid (HMDB00694), 2-Propenyl propyl disulfide (HMDB33912), Citramalic acid (HMDB00426), D-Xylono-15-lactone (HMDB11676), Methyl 3-methyl-1-butenyl disulfide (HMDB38890)
186.1124	57.5	2.365	1.413	Pseudoecgonine (HMDB06348), Ecgonine (HMDB06548)
112.9556	22.4	2.346	1.117	11-Dichloroethylene epoxide (HMDB60333), 22-Dichloroacetaldehyde (HMDB60357), Chloroacetyl chloride (HMDB60452)
353.1564	384.2	2.336	1.141	Coriandrone D (HMDB29972)
287.1002	77.8	2.322	1.686	34-Dihydrodiol (HMDB13895), Phenytoin dihydrodiol (HMDB60866)
583.4102	567.2	2.292	0.894	(3S3R5R6R)-78-Didehydro-36-epoxy-56-dihydro-betabeta-carotene-35-diol (HMDB37794)
265.1184	94.7	2.285	1.619	di-Hydroxymelatonin (HMDB61136), Acetyl-N-formyl-5-methoxykynurenamine (HMDB04259), Alpha-N-Phenylacetyl-L-glutamine (HMDB06344)
239.2370	566.1	2.270	0.899	Butyl dodecanoate (HMDB32065), Trimethyltridecanoic acid (HMDB02396), Hexadecanoate (n-C16:0) (HMDB60083), Dodecyl 2-methylpropanoate (HMDB36210), Ethyl tetradecanoate (HMDB34153), Palmitic acid (HMDB00220), Hexyl decanoate (HMDB32324), Isopalmitic acid (HMDB31068), Dodecyl butyrate (HMDB32249), Octyl octanoate (HMDB33166) [all M+H-H2O adducts]
239.2370	566.1	2.270	0.899	Hexadecenal (HMDB60482), 3-Methylcyclopentadecanone (HMDB34181), ()-2-Dodecylcyclobutanone (HMDB37544)
497.3064	487.7	2.262	0.709	(3b16b20R)-Pregn-5-ene-31620-triol 3-glucoside (HMDB41331), 3-alpha20-alpha-Dihydroxy-5-beta-pregnane 3-glucuronide (HMDB10352), Pregnanediol-3-glucuronide (HMDB10318)
176.1030	56.8	2.250	1.295	Citrulline (HMDB00904), Argininic acid (HMDB03148)
1140.5300	489.6	2.213	0.803	Iodipamide (HMDB15581)
226.9516	532.9	2.205	0.620	25-Dichloro-4-oxohex-2-enedioate (HMDB60363)
780.5544	449.1	2.199	1.608	PC(18:1(11Z)18:4(6Z9Z12Z15Z)) (HMDB08075), PC(18:2(9Z12Z)18:3(6Z9Z12Z)) (HMDB08140), PC(16:1(9Z)20:4(5Z8Z11Z14Z)) (HMDB08015), PC(18:2(9Z12Z)18:3(9Z12Z15Z)) (HMDB08141), PC(14:1(9Z)22:4(7Z10Z13Z16Z)) (HMDB07922), PC(18:3(6Z9Z12Z)18:2(9Z12Z)) (HMDB08171), PC(14:022:5(7Z10Z13Z16Z19Z)) (HMDB07891), PC(14:022:5(4Z7Z10Z13Z16Z)) (HMDB07890), PC(22:5(4Z7Z10Z13Z16Z)14:0) (HMDB08656), PC(22:4(7Z10Z13Z16Z)14:1(9Z)) (HMDB08624), PC(16:020:5(5Z8Z11Z14Z17Z)) (HMDB07984), PC(22:5(7Z10Z13Z16Z19Z)14:0) (HMDB08689), PC(18:1(9Z)18:4(6Z9Z12Z15Z)) (HMDB08108), PC(18:4(6Z9Z12Z15Z)18:1(11Z)) (HMDB08235), PC(16:1(9Z)20:4(8Z11Z14Z17Z)) (HMDB08016), PC(20:4(5Z8Z11Z14Z)16:1(9Z)) (HMDB08430), PC(18:4(6Z9Z12Z15Z)18:1(9Z)) (HMDB08236), PC(20:4(8Z11Z14Z17Z)16:1(9Z)) (HMDB08463), PC(18:3(9Z12Z15Z)18:2(9Z12Z)) (HMDB08204), PC(20:5(5Z8Z11Z14Z17Z)16:0) (HMDB08495)
267.0596	57.8	2.193	1.265	Methoxybrassinin (HMDB33351), 4-Methoxybrassinin (HMDB40790)

579.2576	534.9	2.165	0.666	Withaperuvin H (HMDB34061)
153.0659	63.4	2.129	1.875	N1-Methyl-4-pyridone-3-carboxamide (HMDB04194), N1-Methyl-2-pyridone-5-carboxamide (HMDB04193)
236.1298	567.7	2.127	0.880	Pandamarilactam 3x (HMDB33610)
288.1035	77.2	2.126	1.530	34-Dihydrodiol (HMDB13895) [M+H_[+1]], Phenytoin dihydrodiol (HMDB60866) [M+H_[+1]]
145.0490	216.4	2.122	0.506	Dimethyl fumarate (HMDB31257), 3-Methylglutaconic acid (HMDB00522), 3-Hydroxyadipic acid 36-lactone (HMDB29171), Maleic acid homopolymer (HMDB36232), Ethyl hydrogen fumarate (HMDB40207), (E)-2-Methylglutaconic acid (HMDB02266), 3-Hexenedioic acid (HMDB00393), trans-2-Hexenedioic acid (HMDB13311)
539.2106	417.4	2.119	1.100	Citrusin A (HMDB39230), Asticolorin A (HMDB30133), Diosbulbinoside F (HMDB36783)
330.2272	29.5	2.119	0.669	6-Keto-decanoylcarnitine (HMDB13202)
273.2216	348.7	2.089	2.011	5alpha-Androst-16-en-3-one (HMDB34406), 5a-Androst-3-en-17-one (HMDB06046)
257.2476	567.5	2.089	0.858	Butyl dodecanoate (HMDB32065), Palmitic acid (HMDB00220), Hexadecanoate (n-C16:0) (HMDB60083), Octyl octanoate (HMDB33166), Dodecyl 2-methylpropanoate (HMDB36210), Ethyl tetradecanoate (HMDB34153), Trimethyltridecanoic acid (HMDB02396), Isopalmitic acid (HMDB31068), Dodecyl butyrate (HMDB32249), Hexyl decanoate (HMDB32324)
304.1755	290.1	2.058	0.490	Pimelylcarnitine (HMDB13328)

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