

Study	N	M	Cohort	Modality	Initial Metric	Method	AD dementia			MCI			CN			Established Biomarkers	Other	CA			
							n	m	age	sd	n	m	age	sd	n				m	age	sd
Poulakis et al. 2018	627	-	ANM	sMRI, T1, 3.0T	brain volume - 162 ROIs Freesurfer	Random forest clustering	299	-	64 to 84	-	-	-	-	328	165	74.9	3.4	-	<i>APOE</i>	global cognition, dementia screen, memory, visuospatial, executive function, language	
			ADNI	sMRI, T1, 3.0T																	
ten Kate et al. 2018	640		ADCd	sMRI, T1, 3.0T	brain volume - 1024 equally-sized ROIs	non-negative matrix factorization	299	150	67	8	160	344	72	8	-	-	-	-	CSF Aβ42 or PET amyloid, CSF t-tau, CSF p-tau	<i>APOE</i> , WMH	memory, language, visuospatial, attention / executive function
			ADCv				181	86	66	7					-	-	-	-			
	670		ADNI	sMRI, T1, 1.5, 3.0T			227	128	74	8	443				-	-	-	-			
Tam et al. 2018	605		ADNI1	sMRI, T1, 1.5T, 3.0T	grey matter density images, VBM	hierarchical agglomerative cluster analysis	165	80	75.4	7.5	235	139	74, 74.3	7.1, 7.6	205	99	76.1	5	CSF Aβ42, CSF t-tau, CSF p-tau	<i>APOE</i>	global cognition, memory, executive function, language, visuospatial
	512		ADNI2				89	48	74.4	7.8	235	122	70.8, 72.1	7.1, 7.3	188	86	72.8	6.1			
Dong et al. 2017	844		ADNI1, ADNI - GO/2	sMRI, T1, 1.5T, 3.0T	brain volume - 80 ROIs, RAVENS	CHIMERA clustering	314	-	-	-	530	-	-	-	399	-	-	-	CSF Aβ42, CSF t-tau, CSF p-tau	<i>APOE</i> , WMH	-
Hwang et al. 2016	77	43	ADNI2	sMRI, T1, 3.0T	cortical thickness, CIVET	hierarchical agglomerative cluster analysis	77	43	-	-	-	-	-	-	-	-	-	-	-	-	-
Malpas 2016	369	187	ADNI	sMRI, T1	cortical thickness, Freesurfer	model-based clustering (MClust)	250*	-	-	-	-	-	-	-	119	-	-	-	-	-	global cognition
Park et al. 2017	545	208	SMC	sMRI, T1, 3.0T	cortical thickness, Freesurfer	Louvain method based clustering	225	76	70.4	9	-	-	-	-	320	132	70	7.9	-	<i>APOE</i>	global cognition, dementia screen, episodic memory, executive function, verbal fluency, speed, semantic memory

	289	148	ADNI	sMRI, T1, 1.5T			131	74	74.1	7.4	-	-	-	-	158	74	76.2	5.4			
Varol et al. 2017	300	151	ADNI	sMRI, T1, 1.5T	brain volume - 153 ROIs, RAVENS	HYDRA classification & clustering	123	61	74.7	7.39	-	-	-	-	177	90	75.9	5.18	CSF A $\beta$ 42, CSF t-tau, CSF p-tau	<i>APOE</i> , GWAS SNPs	global cognition
Dong et al. 2016	390		ADNI	sMRI, T1, 1.5T	brain volume - 80 ROIs, RAVENS	CHIMERA clustering	177	-	-	-	-	-	-	-	213	-	-	-	-	<i>APOE</i>	-
Zhang et al. 2016	810		ADNI	sMRI, T1, 1.5T	grey matter density images, VBM	bayesian model	188	-	-	-	394	-	-	-	228	-	-	-	CSF A $\beta$ 42	<i>APOE</i> , education	global cognition, memory, executive function
Noh et al. 2014	224	72	SMC	sMRI, T1, 3.0T	cortical thickness, Freesurfer?	hierarchical agglomerative cluster analysis, Principle Component Analysis	152	51	71.8	8.9	-	-	-	-	72	21	71.3	5.76	CSF A $\beta$ 42, CSF t-tau, CSF p-tau, PET (AV45, FDG)	<i>APOE</i>	attention, executive, language, memory, visuospatial
Orban et al 2017	130	48	MTL - ADNI2	fMRI	rsfMRI networks, NIAK	hierarchical agglomerative cluster analysis	65	24	72.7	7.9	65	24	72.7	7.9	65	24	72.6	7.3	-	clinical symptoms	global cognition, memory, language, executive function
	231	59	PREVENT - AD				-	-	-	-	-	-	-	-	231	59	64.1	5.7	CSF A $\beta$ 42, CSF t-tau, CSF p-tau	<i>APOE</i>	

**Table S1:** Characteristics of neuroimaging studies reporting data-driven subtypes. Age is provided as a mean, except for Poulakis et al., where age range is provided. Abbreviations in alphabetical order: AND, AddNeuroMed; APOE, apolipoprotein E; AV45, PET ligand florbetapir; CA, cognitive assessment; CSF, cerebrospinal fluid; FDG, fludeoxyglucose; fMRI, functional magnetic resonance imaging; GWAS, genome-wide association study; M, total number of males in study; m, number of males; N, total number of individuals in study; n, number of individuals; PET, positron emission tomography; p-tau, phosphorylated tau protein; ROI, region of interest; sMRI, structural magnetic resonance imaging; t-tau, total tau protein; T, magnet strength in tesla; VBM, voxel based morphometry.

Study	N	M	Sample	Metabolites	AUC	Method	AD/dementia				MCI				CN		Other notes	CA		
							n	m	age	sd	n	m	age	sd	n	m			age	sd
<i>Metabolite Panels</i>																				
Wang et al. 2014	172	74	Plasma	differential metabolites: CN vs AD (31), CN vs aMCI (40)	aMCI vs CN = 0.998 ; AD vs CN = 1.000	UPLC time of flight MS & GS time of flight MS followed by PCA, PLS-DA & OPLS-DA	57	24	74.2	9.1	58	25	71.7	10.4	57	25	75.5	10.2	-	-
Liang et al. 2016	1243	-	Serum	sphinganine 1 phosphate, 7 ketocholesterol, 3 methoxytyrosine, deoxyribose 5 phosphate, D phenyllactic acid, lysoPC(15:0), L phenylalanine, ornithine, L glutamic acid	sphinganine 1 phosphate + 7 ketocholesterol = 0.90	FUPLC MS followed by PCA and OPLS-DA	660	328	78.6	5.7	583	289	78.9	4.9	-	-	-	-	-	-
Liang et al. 2015	474	-	Saliva	sphinganine 1 phosphate, ornithine, phenyllactic acid, inosine, 3 dehydrocarnitine, and hypoxanthine	sphinganine 1 phosphate, ornithine & phenyllactic acid > 0.8	FUPLC MS followed by PCA, PLS-DA, and OPLS-DA	-	-	-	-	-	-	-	-	218	-	-	-	-	-
Czech et al. 2012	130	59	CSF	343 altered metabolites	Highest discriminative AUC: 5 metabolites (uridine, cortisol, cysteine, serine, phenylalanine) = 0.845	GS MS LC MS/MS, Solid phase extraction LC MS/MS followed by OPLS-DA	79	35	69.7	10	-	-	-	-	51	24	63.1	7.7	-	global cognition, ADAS Cog
Figueira et al. 2016	139	46	Saliva	44 identified metabolite	No AUC reported (acetic acid, histamine, propionatedimethyl sulfone, glycerol, taurine, succinate)	NMR spectroscopy followed by PCA and OPLS-DA	45	14	75.3	5.5	-	-	-	-	94	32	75.4	5.4	AD / dementia group included VaD	-

Mapstone et al. 2017	224	86	Plasma	12 differential metabolites: aspartate, hydroxy hexadecadienylcarnitine [C16:2-OH], 3 hydroxy palmitoleylcarnitine [C16:1-OH], lyso PC a C28:1, arginine, valerylcarnitine [C5], lyso PC a C17:0, asparagine, citrulline, nitrotyrosine, PC aa C38:5, histamine	SN vs CN = 0.89; aMCI vs AD = 1.0; preclinical AD vs CN = 0.97	LC/MS followed by LASSO	74	20	81.9	4.4	-	-	-	-	109	46	82.5	3.6	superior memory performance group: n = 41, m = 20, age = 83.2, sd = 3.4	-
<i>Metabolomics Pathways and Networks</i>																				
Trushina et al. 2013	45	33	Plasma, CSF	342 Plasma, 351 CSF	N/A	LC/MS-based non-targeted metabolomics followed by univariate statistical analysis	15	12	82.7	4.2	15	11	80.4	4.2	15	10	78.6	3.5	-	-
Orešič et al. 2011	226	85	Serum	139 molecular lipids, 544 small polar metabolites	N/A	global lipidomics, based on UPLC MS Platform for global profiling of small polar metabolites, based on comprehensive two-dimensional GS coupled to time-of-flight MS	37	17	75	4	143	47	~72	~6	46	21	71	6	-	-
Gonzalez - Dominquez et al. 2015	44	17	Serum	23 altered metabolites	N/A	GS MS	23	8	79.2	5.9	-	-	-	-	21	9	72.1	5.4	medium age reported	-
Grahman et al. 2015	72	~35	Plasma	22 altered biochemical pathways	N/A	MS, multivariate stats & pathway enrichment analysis	19	~9	-	-	16	8	-	-	37	~18	-	-	-	-
de Leeuw et al. 2017	248	129	CSF	-53 amine compounds, 22 organic acid compounds, 120 lipid compounds, 40 oxidative stress compounds. -26 differentially expressed metabolites. -Identified networks: tryosine, glycylglycine, glutamine, lysophosphatic acid C18:2, and platelet activating factor C16:0	N/A	UPLC-tandem MC, nested linear models, logisitic regression, and network extraction	127	64	65.1	9.1	-	-	-	-	121	65	62.7	8	Also examined APOE ε4- and ε4+ differences	-

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Table S2: Characteristics of metabolomics studies included in review. Abbreviation: AUC, area under the curve; CA, Cognitive Assessment; FUPLC, faster ultra-performance liquid chromatography; GS, gas chromatography; LC, liquid chromatography; NMR, Nuclear magnetic resonance; MS, mass spectrometry; OPLS-DA, orthogonal projections to latent structures-discriminant analysis; PCA, principle component analysis; PLS-DA, partial least-squares-discrimination analysis; UPLC, ultra-performance liquid chromatography

Last author, Year	Biofluid in paper	Count - for Figure 2	Metabolism Category - info from HMDB or KEGG or PubMed databases	KEGG COMPOUND ID	HMDB ID	HMDB Database				LINK (HMDB or Other)	
						Metabolite (HMDB common name)	SUPER CLASS	SUB CLASS	BIOLOGICAL PROCESS (Biochemical pathway or other)		BIOSPECIMEN (literature)
Wang et al., 2014	Plasma	1 plasma	nucleotide metabolism	C00178	HMDB0000262	thymine	Organoheterocyclic compounds	Pyrimidines and pyrimidine derivatives	<i>Biochemical pathway:</i> Pyrimidine Metabolism, MNGIE (Mitochondrial Neuroglycogen Intestinal Encephalopathy)	blood, csf, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000262">http://www.hmdb.ca/metabolites/HMDB0000262</a>
Wang et al., 2014	Plasma	1 plasma	lipid metabolism	NA	HMDB0000560	5,8-tetradecadienoic acid (Goshuyic acid)	Lipids and lipid-like molecules	Fatty acids and conjugates	<i>Biochemical pathway:</i> Lipid metabolism pathway	urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000560">http://www.hmdb.ca/metabolites/HMDB0000560</a>
Wang et al., 2014	Plasma	1 plasma	amino acid metabolism	C01026	HMDB0000092	N,N-dimethylglycine (dimethylglycine)	organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> betaine metabolism, glycine and serine metabolism, methionine metabolism, sarcosine oncometabolite pathway	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000092">http://www.hmdb.ca/metabolites/HMDB0000092</a>
Wang et al., 2014	Plasma	1 plasma	lipid metabolism	C00219	HMDB0001043	arachidonic acid	Lipids and lipid-like molecules	Fatty acids and conjugates	<i>Biochemical pathway:</i> Acetaminophen Action Pathway, Acetylsalicylic Acid Action Pathway, Alpha Linolenic Acid and Linoleic Acid Metabolism, Antipyrine Action Pathway, Antrafenine Action Pathway and plus	blood, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001043">http://www.hmdb.ca/metabolites/HMDB0001043</a>
Wang et al., 2014	Plasma	3 (2 plasma, 1 serum)	amino acid metabolism	C00064	HMDB0000641	glutamine (L-Glutamine)	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amino Sugar Metabolism, Ammonia Recycling, Aspartate Metabolism, Azathioprine Action Pathway, Glutamate Metabolism and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000641">http://www.hmdb.ca/metabolites/HMDB0000641</a>
Wang et al., 2014	Plasma	2 (1 plasma, 1 serum)	amino acid metabolism	C00025	HMDB0000148	glutamic acid (L-Glutamic acid)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Acetaminophen Action Pathway, Acetylsalicylic Acid Action Pathway, Alanine Metabolism, Amino Sugar Metabolism, Ammonia Recycling and plus	blood, cellular cytoplasm, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000148">http://www.hmdb.ca/metabolites/HMDB0000148</a>
Wang et al., 2014	Plasma	1 plasma	amino acid metabolism	C00956	HMDB0000510	2-aminoadipic acid (Aminoadipic acid)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> lysine degradation, pyridoxine dependency with seizures	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000510">http://www.hmdb.ca/metabolites/HMDB0000510</a>
Wang et al., 2015	Plasma	1 plasma	nucleotide metabolism	C02961	HMDB0000089	cytidine	Nucleosides, nucleotides, and analogues	NA	<i>Biochemical pathway:</i> MNGIE, pyrimidine metabolism	blood, breast milk, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000089">http://www.hmdb.ca/metabolites/HMDB0000089</a>
Mapstone et al., 2017	Plasma	2 (1 plasma, 1 serum)	amino acid metabolism	C00152	HMDB0000168	asparagine (L-Asparagine)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amikacin Action Pathway, Ammonia Recycling, Adhekan Action Pathway, Aspartate Metabolism, Azithromycin Action Pathway and plus	blood, breast milk, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000168">http://www.hmdb.ca/metabolites/HMDB0000168</a>
Mapstone et al., 2017	Plasma	1 plasma	lipid metabolism	C04230	HMDB0012108	lysoPC (17:0)	Lipids and lipid-like molecules	Glycerophosphocholines	<i>Biochemical pathway:</i> Glycerophospholipid metabolism, Lipid metabolism pathway	blood, feces, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0012108">http://www.hmdb.ca/metabolites/HMDB0012108</a>
Mapstone et al., 2017	Plasma	1 plasma	amino acid metabolism	NA	HMDB0001904	nitrotyrosine (3-Nitrotyrosine)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Pathologic process:</i> Oxidative stress	blood, csf, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001904">http://www.hmdb.ca/metabolites/HMDB0001904</a>
Mapstone et al., 2017	Plasma	1 plasma	lipid metabolism	NA	HMDB0013128	valerylcarnitine	lipid and lipid-like molecules	fatty acid esters	<i>Biochemical pathway:</i> Lipid metabolism pathway	blood, CSF, feces, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0013128">http://www.hmdb.ca/metabolites/HMDB0013128</a>
Mapstone et al., 2017	Plasma	2 (2 serum)	amino acid metabolism	C00062	HMDB0000517	arginine (L-arginine)	organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> lysinuric protein intolerance, arginine and proline metabolism, aspartate metabolism, glycine and serine metabolism, hypoaecylaspartia, transcriptoptranslaion, urea cycle	blood, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000517">http://www.hmdb.ca/metabolites/HMDB0000517</a>
Mapstone et al., 2017	Plasma	2 (1 serum, 1 saliva)	amino acid metabolism	C00388	HMDB0000870	histamine	organic nitrogen compounds	amines	<i>Biochemical pathway:</i> Acrivastine H1-Antihistamine Action, Alcafladine H1-Antihistamine Action, Alimemazine H1-Antihistamine Action, Antazoline H1-Antihistamine Action, Astemizole H1-Antihistamine Action and plus	blood, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000870">http://www.hmdb.ca/metabolites/HMDB0000870</a>
Mapstone et al., 2017	Plasma	2 (1 plasma, 1 serum)	amino acid metabolism	C00049	HMDB0000191	aspartate (L-aspartic acid)	organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Ammonia Recycling, Arginine and Proline Metabolism, Aspartate Metabolism, Azathioprine Action Pathway, Beta-Alanine Metabolism	blood, CSF, breast milk, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000191">http://www.hmdb.ca/metabolites/HMDB0000191</a>
Mapstone et al., 2017	Plasma	1 plasma	amino acid metabolism	C00327	HMDB0000904	citrulline	organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Arginine and Proline Metabolism, Aspartate Metabolism, Hypoaecylaspartia, urea cycle	blood, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000904">http://www.hmdb.ca/metabolites/HMDB0000904</a>
Mapstone et al., 2017	Plasma	1 plasma	lipid metabolism	NA	NA	Hydroxyheptadecadienylcarnitine (C16:2-OH)	NA	NA	NA	NA	<a href="http://www.lipidhome.co.uk/lipids/simple/carnitin/index.htm">http://www.lipidhome.co.uk/lipids/simple/carnitin/index.htm</a>
Mapstone et al., 2017	Plasma	1 plasma	lipid metabolism	NA	NA	3-Hydroxypalmitoleylcarnitine (C16:1-OH)	NA	NA	NA	NA	<a href="http://www.lipidhome.co.uk/lipids/simple/carnitin/index.htm">http://www.lipidhome.co.uk/lipids/simple/carnitin/index.htm</a>
Mapstone et al., 2017	Plasma	1 plasma	lipid metabolism	NA	HMDB002922	Lyso PC a C28:1 (LysoPC(28:1(SZ)))	Lipids and lipid-like molecules	Glycerophosphocholines	<i>Biochemical pathway:</i> Phospholipid metabolism, Lipid transport, Lipid metabolism, Fatty acid metabolism	Blood, Feces	<a href="http://www.hmdb.ca/metabolites/HMDB002922">http://www.hmdb.ca/metabolites/HMDB002922</a>
Mapstone et al., 2017	Plasma	1 plasma	lipid metabolism	C00157	HMDB08306	PC aa C38:5 (PC(20:1(11Z):18:4(6Z):9Z,12Z,15Z))	NA	NA	<i>Biochemical pathway:</i> phosphatidylcholine biosynthesis, phosphatidylethanolamine biosynthesis, Glycerophospholipid metabolism, Lipid metabolism pathway	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB008306">http://www.hmdb.ca/metabolites/HMDB008306</a>
Liang et al., 2016	Serum	3 (2 serum, 1 CSF)	amino acid metabolism	C00079	HMDB0000159	L-phenylalanine	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Phenylalanine and Tyrosine Metabolism, Transcription/Translation	blood, breastmilk, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000159">http://www.hmdb.ca/metabolites/HMDB0000159</a>
Liang et al., 2016	Serum	1 serum	lipid metabolism	NA	HMDB0000501	7-ketocholesterol	Lipids and lipid-like molecules	Cholestanes steroids	<i>Biochemical pathway:</i> Lipid metabolism pathway	blood, csf	<a href="http://www.hmdb.ca/metabolites/HMDB0000501">http://www.hmdb.ca/metabolites/HMDB0000501</a>
Liang et al., 2016	Serum	1 serum	amino acid metabolism	NA	HMDB0001434	3-methoxytyrosine	Organic acids and derivatives	Amino acids, peptides, and analogues	NA	blood, csf, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001434">http://www.hmdb.ca/metabolites/HMDB0001434</a>
Liang et al., 2016	Serum	1 serum	carbohydrate metabolism (not added)	C00673	HMDB0001031	deoxyribose-5-phosphate	Organic oxygen compounds	Carbohydrates and carbohydrate conjugates	<i>Biochemical pathway:</i> Pentose Phosphate Pathway	NA	<a href="http://www.hmdb.ca/metabolites/HMDB0001031">http://www.hmdb.ca/metabolites/HMDB0001031</a>
Liang et al., 2016	Serum	1 serum	lipid metabolism	C04230	HMDB0010381	lysoPC (15:0)	Lipids and lipid-like molecules	Glycerophosphocholines	<i>Biochemical pathway:</i> Glycerophospholipid metabolism, Lipid metabolism pathway	blood	<a href="http://www.hmdb.ca/metabolites/HMDB0010381">http://www.hmdb.ca/metabolites/HMDB0010381</a>
Liang et al., 2016	Serum	already counted	amino acid metabolism	C00025	HMDB0000148	L-glutamic acid	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Acetaminophen Action Pathway, Acetylsalicylic Acid Action Pathway, Alanine Metabolism, Amino Sugar Metabolism, Ammonia Recycling and plus	blood, cellular cytoplasm, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000148">http://www.hmdb.ca/metabolites/HMDB0000148</a>
Liang et al., 2016	Serum	2 (isurum, 1 saliva)	lipid metabolism	C01120	HMDB0001383	sphinganine-1-phosphate	Lipids and lipid-like molecules	Phosphosphingolipids	<i>Biochemical pathway:</i> Globoid Cell Leukodystrophy, Metachromatic Leukodystrophy (MLD), Sphingolipid Metabolism, Lipid metabolism pathway	blood	<a href="http://www.hmdb.ca/metabolites/HMDB0001383">http://www.hmdb.ca/metabolites/HMDB0001383</a>
Liang et al., 2016	Serum	4 (2 serum, 1 plasma, 1 saliva)	amino acid metabolism	C00077	HMDB0000214	ornithine	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Lysinuric protein intolerance, Arginine and Proline Metabolism, Glycine and Serine Metabolism, Spermidine and Spermine Biosynthesis, urea cycle	blood, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000214">http://www.hmdb.ca/metabolites/HMDB0000214</a>
Liang et al., 2016	Serum	2 (1 serum, 1 saliva)	amino acid metabolism	C01479	HMDB0000779	p-phenyllactic acid (phenyllactic acid)	Phenylpropanoids and polyketides	NA	NA	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000779">http://www.hmdb.ca/metabolites/HMDB0000779</a>
Liang et al., 2015	Saliva	already counted	lipid metabolism	C01120	HMDB0001383	sphinganine-1-phosphate	Lipids and lipid-like molecules	Phosphosphingolipids	<i>Biochemical pathway:</i> Globoid Cell Leukodystrophy, Metachromatic Leukodystrophy (MLD), Sphingolipid Metabolism, Lipid metabolism pathway	blood	<a href="http://www.hmdb.ca/metabolites/HMDB0001383">http://www.hmdb.ca/metabolites/HMDB0001383</a>
Liang et al., 2015	Saliva	already counted	amino acid metabolism	C00077	HMDB0000214	ornithine	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Lysinuric protein intolerance, Arginine and Proline Metabolism, Glycine and Serine Metabolism, Spermidine and Spermine Biosynthesis, urea cycle	blood, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000214">http://www.hmdb.ca/metabolites/HMDB0000214</a>
Liang et al., 2015	Saliva	already counted	amino acid metabolism	C01479	HMDB0000779	phenyllactic acid	Phenylpropanoids and polyketides	NA	NA	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000779">http://www.hmdb.ca/metabolites/HMDB0000779</a>
Liang et al., 2015	Saliva	1 saliva	nucleotide metabolism	C00262	HMDB0000157	hypoxanthine	Organoheterocyclic compounds	Purines and purine derivatives	<i>Biochemical pathway:</i> Azathioprine Action Pathway, Mercaptopurine Action Pathway, Purine Metabolism, Thioguanine Action Pathway	breast milk, cellular cytoplasm, csf, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000157">http://www.hmdb.ca/metabolites/HMDB0000157</a>
Liang et al., 2015	Saliva	1 saliva	nucleotide metabolism	C00294	HMDB0000195	inosine	Nucleosides, nucleotides, and analogues	NA	<i>Biochemical pathway:</i> Azathioprine Action Pathway, Mercaptopurine Action Pathway, Purine Metabolism, Thioguanine Action Pathway	blood, cellular cytoplasm, csf, feces, pericardial effusion, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000195">http://www.hmdb.ca/metabolites/HMDB0000195</a>
Liang et al., 2015	Saliva	1 saliva	lipid metabolism	NA	HMDB0012154	3-dehydrocarnitine	Organic acids and derivatives	Short-chain keto acids and derivatives	NA	feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0012154">http://www.hmdb.ca/metabolites/HMDB0012154</a>
Figueira et al., 2016	Saliva	1 serum	lipid, amino acid and carbohydrate metabolism	C00033	HMDB0000042	acetic acid	organic acids and derivatives	carboxylic acids	<i>Biochemical pathway:</i> Amino Sugar Metabolism, Aspartate Metabolism, Disulfiram Action Pathway, Ethanol Degradation, Fatty Acid Biosynthesis and plus	blood, breast milk, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000042">http://www.hmdb.ca/metabolites/HMDB0000042</a>

Figueira et al., 2016	Saliva	already counted	amino acid metabolism	<a href="#">C00388</a>	HMDB0000870	histamine	organic nitrogen compounds	amines	<i>Biochemical pathway:</i> Acrivastine H1-Antihistamine Action, Alcaftadine H1-Antihistamine Action, Alimemazine H1-Antihistamine Action, Amazoline H1-Antihistamine Action, Astemizole H1-Antihistamine Action and plus	blood, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000870">http://www.hmdb.ca/metabolites/HMDB0000870</a>
Figueira et al., 2016	Saliva	1 serum	carbohydrate metabolism (not added)	<a href="#">C00163</a>	HMDB0000237	propionate (propionic acid)	organic acids and derivatives	carboxylic acids	<i>Biochemical pathway:</i> Propanoate Metabolism, Vitamin K Metabolism	urine, feces, saliva, blood, CSF	<a href="http://www.hmdb.ca/metabolites/HMDB0000237">http://www.hmdb.ca/metabolites/HMDB0000237</a>
Figueira et al., 2016	Saliva	1 serum	energy metabolism (not added)	<a href="#">C11142</a>	HMDB0004983	dimethyl sulfone	organosulfur compounds	sulfones	NA	blood, CSF, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0004983">http://www.hmdb.ca/metabolites/HMDB0004983</a>
Figueira et al., 2016	Saliva	1 serum	lipid metabolism	<a href="#">C00116</a>	HMDB0000131	glycerol	organic oxygen compounds	carb and carb conjugates	<i>Biochemical pathway:</i> D-glyceric aciduria, Galactose metabolism, Glycerolipid metabolism	blood, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000131">http://www.hmdb.ca/metabolites/HMDB0000131</a>
Figueira et al., 2016	Saliva	1 serum	amino acid metabolism	<a href="#">C00245</a>	HMDB0000251	taurine	organic acids and derivatives	organosulfonic acids and derivatives	<i>Biochemical pathway:</i> bile acid biosynthesis, Cerebrotendinous Xanthomatosis (CTX), Congenital Bile Acid Synthesis Defect Type II, Congenital Bile Acid Synthesis Defect Type III, Taurine and hypotaurine metabolism	blood, breast milk, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000251">http://www.hmdb.ca/metabolites/HMDB0000251</a>
Figueira et al., 2016	Saliva	1 serum	amino acid, lipid and energy metabolism	<a href="#">C00042</a>	HMDB0000254	succinate (succinic acid)	organic acids and derivatives	dicarboxylic acids and derivatives	<i>Biochemical pathway:</i> Arginine and Proline Metabolism, Butyrate Metabolism, Carnitine Synthesis, Citric Acid Cycle, Congenital lactic acidosis and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000254">http://www.hmdb.ca/metabolites/HMDB0000254</a>
Czech et al., 2012	CSF	1 CSF	nucleotide metabolism	<a href="#">C00299</a>	HMDB0000296	uridine	Nucleosides, nucleotides, and analogues	na	<i>Biochemical pathway:</i> MNGIE (Mitochondrial Neurogastrointestinal Encephalopathy), Pyrimidine Metabolism	Feces Urine Blood Breast milk Cerebrospinal fluid	<a href="http://www.hmdb.ca/metabolites/HMDB0000296">http://www.hmdb.ca/metabolites/HMDB0000296</a>
Czech et al., 2012	CSF	1 CSF	lipid metabolism pathway	<a href="#">C00735</a>	HMDB0000063	cortisol	lipid and lipid-like molecules	hydrocysteroids	<i>Biochemical pathway:</i> Rheumatoid arthritis, Congenital Lipoid Adrenal Hyperplasia (CLAH) or Lipoid CAH, Corticotropin Activation of Cortisol Production, Steroidogenesis, Lipid metabolism pathway	blood, CSF, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000063">http://www.hmdb.ca/metabolites/HMDB0000063</a>
Czech et al., 2012	CSF	1 CSF	amino acid metabolism	<a href="#">C00097</a>	HMDB0000574	cysteine (L-Cysteine)	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amiloride Action Pathway, Bendroflumethiazide Action Pathway, Bumetanide Action Pathway, Chlorothalidone Action Pathway, Chlorthalidone Action Pathway and plus	blood, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000574">http://www.hmdb.ca/metabolites/HMDB0000574</a>
Czech et al., 2012	CSF	counted earlier	amino acid metabolism	<a href="#">C00079</a>	HMDB0000159	phenylalanine (L-phenylalanine)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Phenylalanine and Tyrosine Metabolism, Transcription/Translation	blood, breastmilk, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000159">http://www.hmdb.ca/metabolites/HMDB0000159</a>
Czech et al., 2013	CSF	1 CSF	not added	NA	NA	14941096 (unknown)	NA	NA	NA	NA	NA
de Leeuw et al., 2017	Plasma	2 (1 serum and 1 plasma)	amino acid metabolism	<a href="#">C00082</a>	HMDB0000158	L-Tyrosine	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Catecholamine Biosynthesis, Disulfiram Action Pathway, Phenylalanine and Tyrosine Metabolism, Thyroid hormone synthesis, Transcription/Translation, Tyrosine Metabolism	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000158">http://www.hmdb.ca/metabolites/HMDB0000158</a>
de Leeuw et al., 2017	Plasma	1 plasma	amino acid metabolism	<a href="#">C02037</a>	HMDB0011733	glycylglycine (Glycyl-glycine)	Organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Prostate cancer	blood, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0011733">http://www.hmdb.ca/metabolites/HMDB0011733</a>
de Leeuw et al., 2017	Plasma	already counted	amino acid metabolism	<a href="#">C00064</a>	HMDB0000641	glutamine (L-Glutamine)	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amino Sugar Metabolism, Ammonia Recycling, Aspartate Metabolism, Azathioprine Action Pathway, Glutamate Metabolism and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000641">http://www.hmdb.ca/metabolites/HMDB0000641</a>
de Leeuw et al., 2017	Plasma	1 plasma	lipid metabolism	NA	NA	lysophosphatic acid C18:2 or LPA C18:2 (LysaPA(0:0118:2/9Z,12Z))	Lipids and lipid-like molecules	glycerophosphates	NA	feces	<a href="http://www.hmdb.ca/metabolites/HMDB0007852">http://www.hmdb.ca/metabolites/HMDB0007852</a>
de Leeuw et al., 2017	Plasma	1 plasma	lipid metabolism	NA	HMDB0062195	platelet-activating factor C16:0 (2-acetyl-1-alkyl-sn-glycero-3-phosphocholine)	Lipids and lipid-like molecules	glycerophosphocholines	<i>Biochemical pathway:</i> Glycerophospholipid metabolism, Lipid metabolism pathway	blood	<a href="http://www.hmdb.ca/metabolites/HMDB0062195">http://www.hmdb.ca/metabolites/HMDB0062195</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	NA	NA	4-aminobutanol (1-(3-Aminopropyl)-4-aminobutanol)	Organic acids and derivatives	amino acids, peptides, and analogues	NA	NA	<a href="http://www.hmdb.ca/metabolites/HMDB0012135">http://www.hmdb.ca/metabolites/HMDB0012135</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C00300</a>	HMDB0000064	creatine	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Arginine and Proline Metabolism, Glycine and Serine Metabolism	blood, breast milk, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000064">http://www.hmdb.ca/metabolites/HMDB0000064</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C00334</a>	HMDB0000112	GABA (gamma-Aminobutyric acid)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Glutamate Metabolism, Homocarnosinosis	blood, csf, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000112">http://www.hmdb.ca/metabolites/HMDB0000112</a>
Graham et al., 2015	Plasma	already counted	amino acid metabolism	<a href="#">C00062</a>	HMDB0000517	L-arginine	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Lysinuric protein intolerance, Arginine and Proline Metabolism, Aspartate Metabolism, Glycine and Serine Metabolism, Hypocytaspartia, Transcription/Translation, urea cycle	blood, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000517">http://www.hmdb.ca/metabolites/HMDB0000517</a>
Graham et al., 2015	Plasma	already counted	amino acid metabolism	<a href="#">C00077</a>	HMDB0000214	L-ornithine (ornithine)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Lysinuric protein intolerance, Arginine and Proline Metabolism, Glycine and Serine Metabolism, Spermidine and Spermine Biosynthesis, urea cycle	blood, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000214">http://www.hmdb.ca/metabolites/HMDB0000214</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C00170</a>	HMDB0001173	methylthioadenosine (5'-Methylthioadenosine)	Nucleosides, nucleotides, and analogues	5'-deoxy-5'-thionucleosides	<i>Biochemical pathway:</i> Methionine Metabolism, Spermidine and Spermine Biosynthesis	blood, feces, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001173">http://www.hmdb.ca/metabolites/HMDB0001173</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C01029</a>	HMDB0002189	N1 or N8-acetyl-spermidine (N8-Acetylspermidine)	Organic acids and derivatives	Carboximidic acids	NA	blood, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0002189">http://www.hmdb.ca/metabolites/HMDB0002189</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C02714</a>	HMDB0002064	N-acetylputrescine	Organic acids and derivatives	Carboximidic acids	NA	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0002064">http://www.hmdb.ca/metabolites/HMDB0002064</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C02896</a>	HMDB0001414	putrescine	Organic nitrogen compounds	Amines	<i>Biochemical pathway:</i> Pancreatic cancer, Methionine Metabolism, Spermidine and Spermine Biosynthesis	blood, csf, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001414">http://www.hmdb.ca/metabolites/HMDB0001414</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C00315</a>	HMDB0001257	spermidine	Organic nitrogen compounds	Amines	<i>Biochemical pathway:</i> Methionine Metabolism, Spermidine and Spermine Biosynthesis	blood, csf, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001257">http://www.hmdb.ca/metabolites/HMDB0001257</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C00750</a>	HMDB0001256	spermine	Organic nitrogen compounds	Amines	<i>Biochemical pathway:</i> Spermidine and Spermine Biosynthesis	blood, csf, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0001256">http://www.hmdb.ca/metabolites/HMDB0001256</a>
Graham et al., 2015	Plasma	1 plasma	amino acid metabolism	<a href="#">C03413</a>	HMDB0002172	N1, N12-diacetylspermine	Organic acids and derivatives	Carboximidic acids	NA	blood, feces, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0002172">http://www.hmdb.ca/metabolites/HMDB0002172</a> , PubMed: 7775374
Trushina et al., 2013	Plasma & CSF	NA	NA	NA	NA (too many, went with pathways)	NA	NA	NA	NA	NA	NA
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C00026</a>	HMDB0000208	alpha-ketoglutarate (oxoglutaric acid)	organic acids and derivatives	gamma-keto acids and derivatives	<i>Biochemical pathway:</i> Alanine Metabolism, Ammonia Recycling, Arginine and Proline Metabolism, Aspartate Metabolism, Beta-Alanine Metabolism plus	urine, saliva, feces, blood, breast milk, CSF	<a href="http://www.hmdb.ca/metabolites/HMDB0000208">http://www.hmdb.ca/metabolites/HMDB0000208</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	carbohydrate metabolism (not added)	<a href="#">C00311</a>	HMDB0000193	isocitric acid	organic acids and derivatives	tricarboxylic acids and derivatives	<i>Biochemical pathway:</i> Citric Acid Cycle, Congenital lactic acidosis, Glutaminolysis and Cancer, The oncogenic action of 2-hydroxyglutarate, The Oncogenic Action of Fumarate, The Oncogenic Action of Succinate, Warburg effect	blood, cellular cytoplasm, CSF, saliva, semen, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000193">http://www.hmdb.ca/metabolites/HMDB0000193</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	carbohydrate metabolism (not added)	<a href="#">C00031</a>	HMDB0000122	glucose (D-Glucose)	organic oxygen compounds	carb and carb conjugates	<i>Biochemical pathway:</i> congenital disorder of glycosylation CDG-Hd, galactose metabolism, gibberellinamide action pathway, gliclazide action pathway, globoid cell leukodystrophy and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000122">http://www.hmdb.ca/metabolites/HMDB0000122</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	lipid metabolism	<a href="#">C00712</a>	HMDB0000207	oleic acid	lipid and lipid-like molecules	fatty acids and conjugates	<i>Biochemical pathway:</i> Lipid metabolism pathway	blood, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000207">http://www.hmdb.ca/metabolites/HMDB0000207</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	nucleotide metabolism	<a href="#">C00212</a>	HMDB0000050	adenosine	nucleosides, nucleotides, and analogues	N/A	<i>Biochemical pathway:</i> Azathioprine Action Pathway, Betaine Metabolism, Intracellular Signalling Through Adenosine Receptor A2a and Adenosine, Intracellular Signalling Through Adenosine Receptor A2b and Adenosine, Mercaptopurine Action Pathway and plus	blood, breast milk, cellular cytoplasm, CSF, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000050">http://www.hmdb.ca/metabolites/HMDB0000050</a>

Gonzalez-Dominquez et al., 2015	Serum	1 serum	lipid metabolism	<a href="#">C00187</a>	HMDB0000067	cholesterol	lipid and lipid-like molecules	cholesterols steroids	<i>Biochemical pathway:</i> Biochemical pathway: Alendronate Action Pathway, Atorvastatin Action Pathway, bile acid biosynthesis, Cerebrotendinous Xanthomatosis (CTX), Cerivastatin Action Pathway and plus	bile, blood, CSF, feces saliva	<a href="http://www.hmdb.ca/metabolites/HMDB0000067">http://www.hmdb.ca/metabolites/HMDB0000067</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C00086</a>	HMDB0000294	urea	organic acids and derivatives	organic carbonic acids and derivatives	<i>Biochemical pathway:</i> Amiloride Action Pathway, Arginine and Proline Metabolism, Bendroflumethiazide Action Pathway, Bumetanide Action Pathway, Chlorothiazide Action Pathway and plus	blood, breast milk, cellular cytoplasm, CSF, feces, saliva, urine, sweat	<a href="http://www.hmdb.ca/metabolites/HMDB0000294">http://www.hmdb.ca/metabolites/HMDB0000294</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C00183</a>	HMDB0000883	valine (L-Valine)	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amikacin Action Pathway, Arbekacin Action Pathway, Azithromycin Action Pathway, Chloramphenicol Action Pathway, Clarithromycin Action Pathway and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000883">http://www.hmdb.ca/metabolites/HMDB0000883</a>
Gonzalez-Dominquez et al., 2015	Serum	already counted	amino acid metabolism	<a href="#">C00049</a>	HMDB0000191	aspartic acid (L-aspartic acid)	organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Ammonia Recycling, Arginine and Proline Metabolism, Aspartate Metabolism, Azathioprine Action Pathway, Beta-Alanine Metabolism	blood, CSF, breast milk, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000191">http://www.hmdb.ca/metabolites/HMDB0000191</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C01879</a>	HMDB0000267	pyroglutamic acid	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Glutathione Metabolism	saliva, feces, urine, blood, CSF	<a href="http://www.hmdb.ca/metabolites/HMDB0000267">http://www.hmdb.ca/metabolites/HMDB0000267</a>
Gonzalez-Dominquez et al., 2015	Serum	already counted	amino acid metabolism	<a href="#">C00064</a>	HMDB0000641	glutamine (L-Glutamine)	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amino Sugar Metabolism, Ammonia Recycling, Aspartate Metabolism, Azathioprine Action Pathway, Glutamate Metabolism and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000641">http://www.hmdb.ca/metabolites/HMDB0000641</a>
Gonzalez-Dominquez et al., 2015	Serum	already counted	amino acid metabolism	<a href="#">C00079</a>	HMDB0000159	phenylalanine (L-phenylalanine)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Phenylalanine and Tyrosine Metabolism, Transcription/Translation	blood, breastmilk, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000159">http://www.hmdb.ca/metabolites/HMDB0000159</a>
Gonzalez-Dominquez et al., 2015	Serum	already counted	amino acid metabolism	<a href="#">C00152</a>	HMDB0000168	asparagine (L-Asparagine)	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amikacin Action Pathway, Ammonia Recycling, Arbekacin Action Pathway, Aspartate Metabolism, Azithromycin Action Pathway and plus	blood, breast milk, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000168">http://www.hmdb.ca/metabolites/HMDB0000168</a>
Gonzalez-Dominquez et al., 2015	Serum	already counted	amino acid metabolism	<a href="#">C00077</a>	HMDB0000214	ornithine	Organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Lysinuric protein intolerance, Arginine and Proline Metabolism, Glycine and Serine Metabolism, Spermidine and Spermine Biosynthesis, urea cycle	blood, csf, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000214">http://www.hmdb.ca/metabolites/HMDB0000214</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C00408</a>	HMDB0000070	pipelicolic acid	organic acids and derivatives	Amino acids, peptides, and analogues	NA	Amniotic Fluid,blood, CSF, feces, saliva,urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000070">http://www.hmdb.ca/metabolites/HMDB0000070</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C00135</a>	HMDB0000177	histidine (L-Histidine)	organic acids and derivatives	Amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Amikacin Action Pathway, Ammonia Recycling, Arbekacin Action Pathway, Azithromycin Action Pathway, Beta-Alanine Metabolism and plus	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000177">http://www.hmdb.ca/metabolites/HMDB0000177</a>
Gonzalez-Dominquez et al., 2015	Serum	already counted	amino acid metabolism	<a href="#">C00082</a>	HMDB0000158	tyrosine (L-Tyrosine)	organic acids and derivatives	amino acids, peptides, and analogues	<i>Biochemical pathway:</i> Catecholamine Biosynthesis, Disulfiram Action Pathway, Phenylalanine and Tyrosine Metabolism, Thyroid hormone synthesis, Transcription/Translation, Tyrosine Metabolism	blood, breast milk, CSF, feces, saliva, sweat, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000158">http://www.hmdb.ca/metabolites/HMDB0000158</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	nucleotide metabolism	<a href="#">C00266</a>	HMDB0000289	uric acid	Organoheterocyclic compounds	Purines and purine derivatives	<i>Biochemical pathway:</i> Azathioprine Action Pathway, Mercaptopurine Action Pathway, Purine Metabolism, Thioguanine Action Pathway	Amniotic Fluid, Bile, Blood, CSF, Feces, Saliva, Urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000289">http://www.hmdb.ca/metabolites/HMDB0000289</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	lipid metabolism	<a href="#">C00249</a>	HMDB0000220	palmitic acid	Lipids and lipid-like molecules	fatty acids and conjugates	<i>Biochemical pathway:</i> Alendronate Action Pathway, Atorvastatin Action Pathway, bile acid biosynthesis, Cerebrotendinous Xanthomatosis (CTX), Cerivastatin Action Pathway and plus	blood, CSF, Feces, Saliva, Sweat, Urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000220">http://www.hmdb.ca/metabolites/HMDB0000220</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	check	<a href="#">C00525</a>	HMDB0013609	tryptophan (D-Tryptophan)	organoheterocyclic compounds	indolyl carboxylic acids and derivatives	NA	blood, feces	<a href="http://www.hmdb.ca/metabolites/HMDB0013609">http://www.hmdb.ca/metabolites/HMDB0013609</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	lipid metabolism	<a href="#">C01530</a>	HMDB0000827	stearic acid	Lipids and lipid-like molecules	fatty acids and conjugates	<i>Biochemical pathway:</i> Mitochondrial Beta-Oxidation of Long Chain Saturated Fatty Acids, Plasmalogen Synthesis, Lipid metabolism pathway	blood, CSF, feces, saliva,sweat,urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000827">http://www.hmdb.ca/metabolites/HMDB0000827</a>
Gonzalez-Dominquez et al., 2015	Serum	1 serum	amino acid metabolism	<a href="#">C00491</a>	HMDB0000192	cystine (L-Cystine)	organic acids and derivatives	amino acids, peptides, and analogues	NA	blood, CSF, feces, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000192">http://www.hmdb.ca/metabolites/HMDB0000192</a>
Orešič et al. 2011	Serum	1 serum	lipid metabolism	NA	HMDB0000360	2,4-dihydroxybutanoic acid	Organic acids and derivatives	short-chain hydroxy acids and derivatives	NA	blood, CSF, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000360">http://www.hmdb.ca/metabolites/HMDB0000360</a> ; <a href="https://pubchem.ncbi.nlm.nih.gov/compound/2_4-Dihydroxybutanoic_acid#section=Chemical-Co-Occurrences-in-Literature">https://pubchem.ncbi.nlm.nih.gov/compound/2_4-Dihydroxybutanoic_acid#section=Chemical-Co-Occurrences-in-Literature</a>
Orešič et al. 2011	Serum	NA	not added	NA	NA	unidentified carboxylic acid	NA	NA	NA	NA	NA
Orešič et al. 2011	Serum	1 serum	lipid metabolism	<a href="#">C00157</a>	HMDB0000564	PC 16.0/16.0	Lipids and lipid-like molecules	Glycerophosphocholines	<i>Biochemical pathway:</i> phosphatidylcholine biosynthesis, phosphatidylethanolamine biosynthesis, Phospholipid Biosynthesis, Glycerophospholipid metabolism, Lipid metabolism pathway	blood, feces, saliva, urine	<a href="http://www.hmdb.ca/metabolites/HMDB0000564">http://www.hmdb.ca/metabolites/HMDB0000564</a>

**Table S3:** Detailed information on metabolites. We include key metabolites highlighted in the 11 studies reviewed. We queried for specific details on each metabolite listed on three different databases: HMDB, KEGG Pathway, and PubMed.



Gene	Symbol	MAF	AD Pathways	Desiken 2017	Morgan 2017*	Slegers 2015	Escott-Price 2017	Xiao 2015	Adams 2015	Chouraki 2016	Tosto 2017	Martiskainen 2015	Naj 2014	Escott-Price 2015^
<i>Early-onset familial AD</i>														
Amyloid $\beta$ (A4) precursor protein	<i>APP</i>		abnormal A $\beta$ production, clearance & aggregation; amyloid hypothesis (A $\beta$ cascade)											
Presenilin 1	<i>PSEN1</i>		abnormal A $\beta$ production, clearance & aggregation; amyloid hypothesis (A $\beta$ cascade)											
Presenilin 2	<i>PSEN2</i>		abnormal A $\beta$ production, clearance & aggregation; amyloid hypothesis (A $\beta$ cascade)											
<i>Late-onset AD: Common, High Risk</i>														
Apolipoprotein E	<i>APOE</i>	0.12	abnormal A $\beta$ clearance & aggregation; inflammatory response, cholesterol/lipid metabolism	x	x	x		x	x	x	x	x	x	x
<i>Late-onset AD: Rare, High Risk</i>														
Triggering receptor expressed on myeloid cells 2	<i>TREM2</i>	0.002	immune response & inflammation			x								
Phospholipase D 3	<i>PLD3</i>	-	unknown											
<i>Late-onset AD: Common, Low Risk</i>														
ATP-binding cassette, subfamily A (ABC1), member 7	<i>ABCA7</i>	0.16	cholesterol/lipid metabolism, inflammatory response	x		x			x	x	x	x		x
Bridging integrator 1	<i>BIN1</i>	0.37	abnormal A $\beta$ production & clearance; synaptic vesicle endocytosis	x		x			x	x	x	x		x
Cas scaffolding protein family member 4	<i>CASS4</i>	0.08	APP, tau, cytoskeletal function, axonal transport	x		x				x	x	x		
CD2-associated protein	<i>CD2AP</i>	0.26	receptor endocytosis & cytokinesis			x		x	x	x	x	x		x
CD33 molecule	<i>CD33</i>	-	inflammatory response			x					x	x		x
CUGBP, Elav-like family member 1	<i>CELF1</i>	0.31	cytoskeletal function, axonal transport, tau pathology			x			x	x	x	x		
Clusterin	<i>CLU</i>	0.4	abnormal A $\beta$ clearance & aggregation; inflammatory response; cholesterol/lipid metabolism	x		x			x	x	x	x		x
Complement component (3b/4b) receptor 1 (Knops blood group)	<i>CRI</i>	0.19	abnormal A $\beta$ clearance; inflammatory response	x		x			x	x	x	x		x
Desmoglein 2	<i>DSG2</i>	-									x	x		
EPH receptor A1	<i>EPHA1</i>	0.35	inflammatory response			x			x	x	x	x		x
Fermitin family member 2	<i>FERMT2</i>	0.08	tau pathology, angiogenesis	x		x		x	x	x	x	x		
Major histocompatibility complex class II DR beta 5	<i>HLA - DRB1</i>	0.28	immune response, inflammation	x		x				x	x	x		

Complex, class II, DR beta 1 and DR beta 1	<i>HLA - DRB5</i>	-		x	x		x	x	x	
Inositol polyphosphate 5 phosphatase, 145kDa	<i>INPP5D</i>	0.46	immune response & inflammation, APP metabolism; regulation of gene expression; post-translational modification of proteins; microglial & myeloid cell function	x	x		x	x	x	x
Myocyte enhancer factor 2C	<i>MEF2C</i>	0.39	immune response & inflammation; hippocampal synaptic function		x		x	x	x	x
Membrane-spanning 4 domains, subfamily A, member 6A	<i>MS4A6A</i>	0.41	inflammatory response	x	x		x	x	lx	x
Membrane-spanning 4 domains, subfamily A, member 4E	<i>MS4A4E</i>	-	inflammatory response						lx	x
NME/NM23 family member 8	<i>NME8</i>	0.37	cytoskeletal function, axonal transport		x		x	x	x	x
Phosphatidylinositol-binding clathrin assembly protein	<i>PICALM</i>	0.37	abnormal Aβ production & clearance; clathrin-mediated endocytosis; synaptic transmission	x	x			x	x	x
Protein tyrosine kinase 2 beta	<i>PTK2B</i>	0.36	hippocampal synaptic function, cell migration	x	x		x	x	x	x
Sortilin-related receptor, L (DLR class) A repeats containing	<i>SORL1</i>	0.04	endocytosis & cargo sorting (trafficking and metabolism of APP), lipid transport	x	x	x	x	x	x	x
Solute carrier family 24 (sodium/potassium/calcium exchanger), member 4	<i>SLC24A4</i>	0.21	possible cardiovascular risk	x	x		x	x	x	x
Triggering receptor expressed on myeloid cells L2	<i>TREML2</i>	-	unknown, protective							
Zinc finger, CW type with PWWP domain 1	<i>ZCWPW1</i>	0.29	epigenetic regulation	x	x		x	x	x	

**Table S4:** Key AD risk genes and major AD-related pathway(s) associated with each genes. Listed are the 3 early-onset familial AD genes; high-risk common and rare late-onset AD genes; and 24 key GWAS identified, low-risk, late-onset AD genes. Studies are listed in the order of appearance in the section entitled "Polygenic Risk Score Approach". An "x" indicates if the PRS includes one of the 24 key GWAS identified, low-risk, late-onset AD genes. \* indicates that the PRS was comprised of 87,605 SNPs, which included APOE. ^ indicates that the PRS was comprised of 6,928,531 SNPs, which included APOE. Studies used for the compilation of the genes in the table are as follows: Bertram and Tanzi, 2012; Gómez-Tortosa et al., 2018; Guerreiro, Brás, & Hardy, 2012; Harold et al., 2009; Hollingworth et al., 2011; Kunkle et al., 2018; Lambert et al., 2013; Medway & Morgan, 2014; Reitz, 2015. Abbreviations: AD = Alzheimer's Disease. MAF = minor allele frequency.

Study	N	M	Cohort(s)	# of SNPs (P, nP)	Method (P, nP)	AD-dementia				MCI				HC SD	Other Biomarkers	CA				
						N	M	Age	SD	N	M	Age	SD							
Desikan et al, 2017	54162	-	IGAP	31 (P)	hazard ratios (P)	17008	6293	74.7	8	-	-	-	-	37154	15976	68.6	8.5	-	-	
	15795	-	ADGC1			6409	2500	74.7	7.7	-	-	-	-	9386	3848	76.4	8.1	-	-	
	17956	-	ADGC2			6984	2961	73.6	7.3	-	-	-	-	10972	4312	75.7	8.6	-	-	
	3321	-	NIA-ADC			x	-	-	-	-	-	-	-	-	-	-	-	-	postmortem brain: tau, Aβ	-
	692	-	ADNI1			x	-	-	-	-	x	-	-	x	-	-	-	-	CSF: Aβ42; t-tau, structural MRI volumes	yes
Morgan et al, 2017	93	-	GERAD1	87605 (P)	weighted (P) (b)	93	36	-	-	-	-	-	-	-	-	-	-	plasma inflammatory markers	-	
Sleegers et al, 2015	2451*	-	Flanders - Belgian AD	22 (P)	additive vs weighted (P)	1328 (878 PRS)	491	Onset 74.4	8.9	-	-	-	-	1123 (661 PRS)	494	64.9	13.7	CSF: Aβ42; t- & p-tau	-	
Escott-Price et al, 2017	1594	-	IGAP subset	23 (P)	weighted & normalized (P)	1011	-	-	-	-	-	-	-	583	-	-	-	postmortem confirmed	-	
Xiao et al, 2015	1280	-	Chinese Han	6 (P)		459	228	71.2	9.6	-	-	-	-	751	354	72.7	5.9	-	-	
Adams et al, 2015	3605	1548	Rotterdam	19 (P)	weighted (P)	156	-	-	-	360	-	-	-	x	-	-	-	-	yes	
Chouraki et al, 2016	19687	-	IGAP (cohorts included: 3C, ACT, AGES, CHS, FHS, ROSMAP, Rotterdam, WHICAP)	19 (P)	log transformed odds ratio (P)	2782	-	>65	-	-	-	-	-	16905	-	>65	-	-	-	
Tosto et al, 2017	4792	1818	NIA-LOAD	21 (P)	weighted (P)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	3324	1136	EFIGA (replication)		weighted (P)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Martiskainen et al, 2015	1591	575	Finnish-AD	22 (P)	log transformed odds ration (P)	890	294	Onset 69.8	8.2	-	-	-	-	701	281	Exam 69.1	6.2	CSF: Aβ42, t- & p-tau	-	
	59	17	Kuopio University Hospital			59	17	79.1 - 81.3	7 - 11.1	-	-	-	-	-	-	-	-	temporal cortex Aβ42; γ-secretase	-	
Naj et al, 2014	9162	3682	ADGC	10 (P)	unweighted (P)	9162	3682	Onset 74.3	7.6	-	-	-	-	-	-	-	-	-	-	
Escott-Price et al, 2015	10454	-	GERAD (test sample)	6928531 (P)	weighted & normalized (P)	3177	-	-	-	-	-	-	-	7277	-	-	-	-	-	
Karch et al, 2016	150	103	GSE15745	21 (nP)	NA	-	-	-	-	-	-	-	-	150	103	45.8	-	brain tissue	-	
	364	-	GSE15222			176	88	84	-	-	-	-	-	188	103	81	-	-	-	
	47	-	GSE5281			33	15	79.9	-	-	-	-	-	14	10	79.8	-	-	-	
	134	-	UKBEC			-	-	-	-	-	-	-	-	134	-	-	-	-	-	
	74046	-	IGAP LOAD GWAS			x	-	-	-	-	-	-	-	x	-	-	-	-	-	
56260 (a)	-	ADGC			x	-	-	-	-	-	-	-	x	-	-	-	-	-	-	

Rosenthal et al, 2014	NA	NA	NA	44 (nP)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Raj et al, 2012	-	-	ADGC; GERAD+	11 (nP)	protein network integrated haplotype score	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ebbert et al, 2014	2419	1013	Cache County Memory Study	10 (P, nP)	weighted	326	119	80.2	7.2	-	-	-	-	2093	894	74.3	6.7	-	-
Patel et al, 2016	30,717	-	ENIGMA2 consortium ADNII	24 (nP)	stratified false discovery rate	-	-	-	-	-	-	-	-	-	-	-	-	-	sMRI brain volumes
	757					x	-	-	-	x	-	-	-	x	-	-	-	-	-
Huang et al, 2018	-	-	-	335 (nP)	support vector machine	-	-	-	-	-	-	-	-	-	-	-	-	-	-

**Table S5:** Studies listed in the order of appearance in the sections entitled "Polygenic Risk Score Approach" and "Mechanism-based Interaction and Network Approaches". \* indicates that sample demographic statistics is based on larger sample; (a) Information provided in Naj et al., 2011; (b) Information provided in Escott-Price et al. 2015. x indicates that a specific cohort was used, but detailed composition of cohorts was not provided. Abbreviations: 3C, Three City study; ACT, Adult Changes in Thought; ADGC, Alzheimer's disease genetics consortium; ADNI, Alzheimer's disease neuroimaging initiative; AGES, Age, Gene/Environment Susceptibility; CA, cognitive assessment; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; GERAD, Genetic and Environmental Risk for Alzheimer's disease; GSE15745, dataset from Johns Hopkins University and Miami Brain Bank; GSE15222, dataset from 20 National Alzheimer's Coordinating Center brain banks and the Miami Brain Bank; GSE5281, dataset from Washington University, Duke University and Sun Health Research Institute; IGAP, International genomics of Alzheimer's project; LOAD, Late onset Alzheimer's disease; NA, not applicable; NACC, National Alzheimer's Coordinating Center; NIA-ADC, National institute of aging Alzheimer's disease centers; nP, not used for PRS construction; P, used for PRS construction; ROSMAP, Religious Order Study/Memory and Aging Project; WHICAP, Washington Heights-Inwood Community Aging Project; UKBEC, United Kingdom Brain Expression Consortium

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