STM JOURNALS

Emerging Trends in
Metabolites

ISSN: 3049-1509
Volume 3, Issue 1, 2026
January–June
DOI (Journal): 10.37591/ETM

https://journals.stmjournals.com/etm

Review ETM

Clinical Metabolomics: Useful Insights, Perspectives, and Challenges

Atul Khajuria[1], Mahesh Gaba[2,*]

Abstract

Metabolomics provides a comprehensive snapshot of small-molecule intermediates and end products of cellular processes and, thereby links genotype, environment, and phenotype in human disease (1, 2, 9, 39). Over the last decade, advances in liquid chromatography–mass spectrometry (LC–MS) and nuclear magnetic resonance (NMR) spectroscopy have enabled high-throughput profiling of thousands of metabolites from microliter volumes of clinical samples (1, 7, 36). Clinical metabolomics is now emerging as a tool for disease diagnosis, risk prediction, therapeutic monitoring, and mechanistic discovery across cardiometabolic, neurologic, renal, and inflammatory disorders. In diabetic kidney disease, metabolomics has identified early alterations in amino-acid, lipid, and energy pathways and candidate biomarkers that precede albuminuria or decline in estimated glomerular filtration rate (eGFR) (24, 35). In Alzheimer's disease, targeted and untargeted metabolomics in plasma, cerebrospinal fluid (CSF), and brain tissue have highlighted disturbances in branched-chain amino acids, nicotinamide adenine dinucleotide (NAD^+) homeostasis, polyamine and L-arginine metabolism, and tryptophan–kynurenine pathways, some of which correlate with amyloid and tau biomarkers and cognitive decline (16–24). Despite impressive discovery output, translation into clinical tests remains limited, impeded by issues of analytical standardization, inter-laboratory reproducibility, causal inference, and regulatory and implementation barriers (3, 35, 40, 42). This review summarizes principles of clinical metabolomics, highlights key disease-related metabolites in diabetic kidney disease and Alzheimer's disease, and discusses the main technical, statistical, and translational challenges for bringing metabolomic biomarkers and signatures into routine clinical practice (1, 4).

Keywords: Clinical metabolomics, disease biomarkers, diabetic kidney disease, diabetic nephropathy, Alzheimer's disease, mass spectrometry, metabolic profiling, translational medicine

INTRODUCTION

Metabolomics aims to quantify, in a single experiment, a broad array of low-molecular-weight compounds in biological specimens such as blood, urine, CSF, and tissue [1, 2, 3]. These metabolites integrate genomic variation, epigenetic regulation, microbiome composition, environmental exposures, diet, and pharmacologic interventions, offering a proximal readout of physiologic and pathophysiologic states [2, 4, 5]. The clinical objective is to derive metabolic signatures that improve disease detection, refine risk stratification, and guide therapy beyond current clinical and biochemical markers [2, 3, 6, 7–9].

Large-scale cohort studies have shown that selected metabolite panels can predict incident type 2 diabetes, cardiovascular events, and renal outcomes independent of traditional risk factors. Parallel work in neurodegeneration has linked metabolic changes to amyloid and tau pathology, neuroinflammation, and synaptic dysfunction, often decades before clinical symptoms. Yet outside rare

***Author for Correspondence**
Mahesh Gaba
E mail: microbiologist2007@rediffmail.com

[1]Dean, Department of Allied & Health Care Sciences, Rayat Bahra Professional University, Hoshiarpur, Punjab, India
[2]Assistant Professor, Department of Medical Laboratory Science, PCTE Group of Institutes, Jhande, Ludhiana, Punjab, India

Received Date: February 21, 2026
Accepted Date: March 14, 2026
Published Date: March 25, 2026

Citation: Atul Khajuria, Mahesh Gaba. Clinical Metabolomics: Useful Insights, Perspectives, and Challenges. Emerging Trends in Metabolites. 2026; 3(1): 29–37p.

inborn errors of metabolism, very few metabolomic tests are implemented in routine clinical workflows, underscoring a translational gap between discovery and application [10, 11].

PRINCIPLES OF CLINICAL METABOLOMICS

Analytical Platforms

LC–MS, including reversed-phase and hydrophilic interaction chromatography coupled to high-resolution mass analyzers, is the dominant platform in both untargeted and targeted clinical metabolomics [1, 12, 13]. LC–MS offers high sensitivity and broad dynamic range, capturing several thousand features per run, but demands rigorous control of matrix effects, ion suppression, and batch variability [13, 14]. NMR spectroscopy provides absolute quantification and excellent reproducibility but lower sensitivity and narrower coverage, making it well suited for standardized clinical panels of abundant metabolites [10, 15, 16].

Chemical derivatization can enhance detection of low-abundance or poorly ionizing metabolite classes, enabling more comprehensive coverage from limited clinical samples. Sample preparation methods, including protein precipitation, solid-phase extraction, and lipid-class–specific protocols, are tailored to the biological matrix and metabolite classes of interest. Proper pre-analytical handling (fasting status, time to processing, storage conditions, freeze–thaw cycles) is critical to minimize artifactual variation [10, 13, 14].

Targeted vs. Untargeted Approaches

Untargeted metabolomics aims to capture as many features as possible without pre-specifying analytes, facilitating the discovery of novel biomarkers and pathways [1, 3, 12–14, 16]. However, annotation of unknown features, multiple testing, and reproducibility across platforms and cohorts remain major challenges [10, 16, 17]. Targeted metabolomics focuses on predefined panels with authentic standards and validated quantification, trading breadth for accuracy and standardization suitable for regulatory approval and clinical deployment [1, 3, 18].

Study Design and Data Analysis

Prospective cohort and nested case–control designs allow assessment of temporal relationships between baseline metabolic profiles and incident disease or progression [2, 3, 19, 20–22]. In diabetic kidney disease, several longitudinal studies have used metabolomics to identify blood and urine metabolites that change years before clinical onset of albuminuria or eGFR decline [20]. In Alzheimer's disease, metabolomics integrated with amyloid positron-emission tomography (PET), CSF biomarkers, and detailed neuropsychological testing has enabled the identification of metabolic alterations that track with preclinical and prodromal stages.

Feature extraction, normalization, batch correction, and quality-control pipelines are essential to reduce technical noise and drift. Multivariable regression, penalized regression, and machine-learning classifiers (random forests, gradient boosting, neural networks) are used to derive predictive signatures, but the risk of overfitting is high, particularly in small datasets with thousands of variables. External validation, calibration assessment, and comparison with existing risk scores are necessary before considering clinical implementation [2, 3, 6, 7].

METABOLOMICS IN DIABETIC KIDNEY DISEASE

Pathophysiologic Background

Diabetic kidney disease is a leading cause of chronic kidney disease and end-stage kidney disease worldwide and develops in approximately 30–40% of people with diabetes [23, 24, 25]. Hyperglycemia, glomerular hyperfiltration, renin–angiotensin–aldosterone activation, oxidative stress, and inflammation jointly contribute to progressive glomerulosclerosis and tubulointerstitial fibrosis [23, 24]. Traditional biomarkers, such as serum creatinine and albuminuria, lack sensitivity for early disease and do not fully capture heterogeneity in progression risk.

Metabolomics provides a window into renal substrate handling, mitochondrial and peroxisomal function, and systemic metabolic reprogramming under chronic hyperglycemic stress. Longitudinal studies suggest that specific metabolite changes precede microalbuminuria and rapid eGFR decline, raising the prospect of earlier risk stratification and targeted intervention [11, 20].

Early Diagnostic and Prognostic Metabolites

A systematic review and meta-analysis of prospective metabolomics studies in diabetic kidney disease, encompassing 39 studies and over 31,000 participants, evaluated 170 blood and 12 urine metabolites; 65 plasma and 11 urinary metabolites showed significant associations with incident or progressive diabetic kidney disease. Enrichment analysis implicated reprogramming of amino-acid, lipid, and energy metabolism pathways in early disease [20].

In an untargeted LC–MS study, lower urinary levels of N-methylnicotinamide (NMP) and its precursor trigonelline were associated with more rapid decline in kidney function among individuals with diabetic kidney disease, outperforming the albumin-to-creatinine ratio as predictors in machine-learning models [21, 26–28]. The same analysis identified urinary threonic acid and a plasma cholesteryl ester (CE-C-0218) as strong markers of rapid eGFR decline. Other studies have reported altered levels of acylcarnitines, branched-chain amino acids, kynurenine pathway intermediates, and phospholipids in association with diabetic kidney disease development and progression. Table 1 summarizes key metabolite findings in diabetic kidney disease.

Table 1. Selected metabolite alterations in diabetic kidney disease.

Metabolite (matrix)	Direction vs. lower-risk group	Associated outcome	Pathway/interpretation	Ref.
N-methylnicotinamide (urine)	Decreased	Rapid eGFR decliners vs non-decliners	Impaired NAD^+ metabolism, tubular stress.	[29]
Trigonelline (urine)	Decreased	Rapid eGFR decline	Precursor of NMP, altered methylation/niacin handling.	[29]
Threonic acid (urine)	Increased	Rapid eGFR decline	Vitamin C catabolism, oxidative stress.	[29]
CE-C-0218 (plasma cholesteryl ester)	Increased	Rapid eGFR decline	Dysregulated lipid handling.	[29]
Multiple amino acids (plasma)	Altered (panel)	Incident or progressive DKD across 52 cohorts	Reprogrammed amino-acid and energy metabolism.	[2]
Acylcarnitines (plasma)	Increased in several studies	Incident DKD and progression	Mitochondrial β-oxidation inefficiency.	[2, 30]

Integration with Existing Risk Markers

Several metabolite panels improve discrimination and reclassification for diabetic kidney disease incidence or progression when added to conventional risk factors, including age, sex, duration of diabetes, HbA1c, blood pressure, and albuminuria. Some markers, such as urinary N-methylnicotinamide, retain prognostic value after adjustment for baseline albuminuria and eGFR, suggesting that they capture aspects of tubular or metabolic dysfunction not reflected in traditional markers [20, 27, 31, 32]. However, most studies remain at the discovery or early validation stage and have not yet led to clinically deployed tests.

METABOLOMICS IN ALZHEIMER'S DISEASE

Pathophysiologic Background

Alzheimer's disease is characterized by extracellular amyloid-β deposition, intracellular tau aggregation, neuroinflammation, synaptic failure, and neurodegeneration, typically developing over 10–25 years before clinical dementia. Multiple functionally interconnected pathways, including energy metabolism, lipid remodeling, oxidative stress, and neurotransmitter cycling, are perturbed long before symptom onset. Metabolomics offers an opportunity to capture these changes in

accessible biospecimens and to complement established biomarkers such as amyloid PET and CSF Aβ42 and phosphorylated tau [20, 33].

Key Metabolic Pathways and Biomarkers

Integrative analyses of plasma and CSF have delineated dysregulation in branched-chain amino-acid metabolism, nicotinamide/NAD^+ homeostasis, bile-acid signaling, and redox balance in Alzheimer's disease [20, 33]. One comprehensive profiling study identified metabolites, such as octadecanedioic acid, prolinamide, leucine, and ascorbic acid, as components of an integrated network of metabolic dysfunction associated with Alzheimer's disease status and neurodegeneration markers [33, 34, 35, 36]. Eupatilin, glyceraldehyde, and guanine showed specific correlations with phosphorylated tau and APOE4, whereas valine levels were inversely associated with phosphorylated tau181 [33, 35, 36].

Polyamine and L-arginine metabolism have emerged as recurrently perturbed pathways in comparisons of healthy controls, individuals with mild cognitive impairment (MCI), and Alzheimer's disease [5, 36, 37]. In one study, both stable MCI and MCI converters exhibited increased plasma L-arginine and decreased L-ornithine, with more pronounced alterations of polyamine metabolism than L-arginine metabolism. Gamma-aminobutyric acid (GABA) was reduced in stable MCI but did not fall further in converters, suggesting that early GABA decline may contribute to cognitive impairment [38].

Tryptophan–kynurenine pathway metabolites also appear important: 3-hydroxyanthranilate can inhibit amyloid-β1–42 oligomerization, whereas quinolinic acid exerts neurotoxic effects and may promote disease progression. Metabolites in these pathways may thus act as both biomarkers and mechanistic mediators. Table 2 summarizes key metabolite and pathway alterations in Alzheimer's disease [20, 33, 37, 39].

Table 2. Selected metabolite and pathway changes in Alzheimer's disease.

Metabolite/pathway	Direction in AD/prodromal stages	Linked biomarker or phenotype	Interpretation	Ref.
Branched-chain amino acids (e.g., valine, leucine)	Altered; valine inversely with p-tau181	Phosphorylated tau181, neurodegeneration	Energy and neurotransmitter precursor imbalance.	[10]
Nicotinamide / NAD^+ homeostasis	Dysregulated	AD status and neurodegeneration	Impaired redox and mitochondrial function.	[6, 10]
L-arginine ↑, L-ornithine ↓	Altered in MCI and AD	Stable MCI and converters	Perturbed urea cycle and polyamine synthesis.	[4, 6]
Polyamine metabolism	Strongly affected across comparisons	HC vs MCI vs AD	Neuronal growth, survival, and cell-death regulation.	[4, 6]
GABA (plasma) ↓	Reduced in stable MCI	Early cognitive impairment	Inhibitory neurotransmission disturbance.	[6]
3-hydroxyanthranilate	Inhibits Aβ1–42 oligomerization	Experimental models	Potentially neuroprotective kynurenine metabolite.	[6]
Quinolinic acid	Neurotoxic, promotes AD progression	Experimental and clinical correlations	Excitotoxicity, neuroinflammation.	[6]

Cross-Disease Themes: Cardiometabolic and Inflammatory Disorders

Beyond diabetic kidney disease and Alzheimer's disease, metabolomics has advanced understanding of type 2 diabetes and cardiovascular disease, particularly in relation to lipid, amino-acid, and energy metabolism [2, 3, 6, 7, 33, 37]. For example, adding a small panel of metabolites to a contemporary cardiovascular risk model for people with type 2 diabetes significantly improved the prediction of 10-year cardiovascular events. In inflammatory joint disease, distinct elevations of gluconic acid, glycolytic intermediates, and tricarboxylic-acid cycle substrates in osteoarthritis, and cardiolipins and glycosphingolipids in rheumatoid arthritis, have provided mechanistic and biomarker insights. Table 3 highlights recurring classes of metabolites across major disease groups [40, 41, 42].

Table 3. Recurrent metabolite classes across clinical disorders.

Disease area	Prominent metabolite classes	Typical direction / pattern	Possible implications	Ref
Type 2 diabetes	Branched-chain AAs, acylcarnitines, sphingolipids	Often increased BCAAs, acylcarnitines	Insulin resistance, mitochondrial stress.	[1, 3]
Cardiovascular disease	Phospholipids, ceramides, acylcarnitines	Disease-specific panels	Atherogenesis, myocardial metabolism.	[3, 40]
Diabetic kidney disease	NMP, trigonelline, amino-acids, acylcarnitines	Early shifts before albuminuria	Tubular and mitochondrial dysfunction.	[2, 29, 30]
Neurodegeneration	Polyamines, L-arginine, tryptophan metabolites	Stage-dependent alterations	Synaptic, inflammatory, and redox pathways.	[4, 6, 10]
Inflammatory arthritis	Glycolytic and TCA intermediates, cardiolipins	Disease-specific elevations	Immune cell activation, mitochondrial changes.	[40]

TECHNICAL AND METHODOLOGIC CHALLENGES

Pre-Analytical and Analytical Variability

Inter-individual metabolic variation is large, and pre-analytical factors, such as fasting status, circadian rhythms, medication use, diet, and physical activity, can have substantial effects on metabolite levels [10, 16, 14, 17]. Standardized protocols for patient preparation, sampling, processing, and storage are crucial but not universally adopted, contributing to poor reproducibility across studies. On the analytical side, differences in LC–MS platforms, chromatographic gradients, ionization modes, and data-processing pipelines can yield heterogeneous feature sets and quantification.

Identification, Quantification, and Harmonization

A sizeable fraction of features in untargeted datasets remain unidentified or only partially annotated, limiting biological interpretation and replication [10, 13, 14, 17]. Even for known metabolites, absolute quantification requires authentic standards and calibration curves, which are impractical for thousands of analytes in discovery studies. Harmonization efforts, including shared reference materials and inter-laboratory ring trials, are underway but are not yet universally implemented.

Statistical, Bioinformatic, and Causal-Inference Issues

High-dimensional data with relatively modest sample sizes creates a multiple-testing and overfitting problem [10, 13, 14, 17, 43]. Many reported signatures have been derived using cross-sectional or case–control designs and have not been validated in external cohorts. Machine-learning models may achieve high apparent discrimination but often lack transparency, complicating biological interpretation and clinical adoption.

Establishing whether metabolites are causal mediators, downstream epiphenomena, or compensatory responses is challenging. Integration with genomics (metabolite quantitative-trait loci and Mendelian randomization), proteomics, and imaging, as well as interventional studies targeting specific pathways, are needed to disentangle causal relationships. Table 4 lists major analytic challenges and mitigation strategies.

Table 4. Common analytic challenges in clinical metabolomics.

Challenge	Consequence for clinical translation	Potential mitigation strategies	Ref.
Pre-analytical variability	Spurious or non-reproducible signals	Standardized protocols, recording covariates.	[1, 12]
Batch effects / drift	Confounded associations	Randomization, pooled QC samples, batch correction.	[1, 12]
Multiple testing, overfitting	False positives, unstable models	Penalization, cross-validation, external validation.	[1, 3, 12]
Incomplete metabolite ID	Limited biology and replication	Library expansion, MS/MS, community annotation efforts.	[1, 12]
Platform heterogeneity	Poor cross-study comparability	Reference materials, harmonized reporting.	[1, 40]

TRANSLATIONAL PATH TO CLINICAL PRACTICE

Assay Development and Validation

Translation from discovery to practice requires converting exploratory signatures into targeted, analytically validated assays that meet regulatory standards for precision, accuracy, linearity, and robustness. Candidate metabolite panels must be locked down and cut-points or risk scores must be defined a priori and tested in independent cohorts that mirror intended clinical populations. Cost, throughput, and turnaround time are crucial considerations if metabolomic tests are to be integrated into existing clinical laboratory infrastructure [10, 11, 17, 18, 44, 45].

Clinical Utility and Implementation

For adoption, metabolomic tests must demonstrate incremental value over current practice by improving diagnostic accuracy, risk prediction, or therapeutic decision-making and by ultimately affecting patient-centered outcomes [10]. This typically requires prospective studies in which metabolomic information is used to guide management strategies, with comparison to standard care [6, 7, 19]. Integration into electronic health records, clinical decision-support systems, and laboratory information systems will be needed to ensure that results are interpretable and actionable at the point of care. Table 5 outlines key steps and barriers in the translational pipeline.

Table 5. From discovery to clinical metabolomic tests.

Stage	Key requirements	Typical barriers	Ref.
Discovery (untargeted)	Broad coverage, robust statistics	Multiple testing, incomplete annotation.	[1, 12]
Replication and validation	Independent cohorts, standardized assays	Platform differences, population diversity.	[1, 2, 30]
Targeted assay development	Analytical validation, QC, reference ranges	Cost, need for standards.	[1, 40]
Clinical utility studies	Impact on decisions and outcomes	Trial complexity, funding.	[1, 3, 40]
Health-system implementation	Integration into labs and EHRs	Infrastructure, reimbursement, training.	[1, 40]

FUTURE DIRECTIONS

Advances in high-throughput LC–MS, microfluidics, and data-independent acquisition are likely to increase depth and reproducibility, while reducing sample volume and cost [6, 10, 14]. Integration with genomics, transcriptomics, proteomics, microbiome, and imaging data in large, deeply phenotyped cohorts will accelerate causal inference and mechanistic insights [4, 6, 17]. Artificial-intelligence approaches may help to identify robust metabolic signatures and to develop interpretable models for risk prediction and treatment response [10, 18, 41].

In diabetic kidney disease, near-term priorities include validating early metabolite markers, such as urinary N-methylnicotinamide, trigonelline, and related panels, in diverse populations and testing whether they can guide earlier initiation of kidney-protective therapies. In Alzheimer's disease, combining metabolomic markers of polyamine, L-arginine, and tryptophan pathways with established amyloid and tau biomarkers could refine staging and identify patients most likely to benefit from disease-modifying treatments [20, 33]. Table 6 summarizes selected promising metabolite panels and next steps.

Table 6. Selected promising metabolite signatures and next steps.

Condition	Signature components (examples)	Potential application	Key next steps	Ref.
Diabetic kidney disease	Urinary NMP, trigonelline, threonic acid, plasma CE-C-0218	Early detection, progression risk	Multi-center validation, targeted assay development.	[2, 29, 30]
Type 2 diabetes–CVD	Panel of 7 plasma metabolites added to SCORE2-Diabetes	10-year CVD risk prediction	Prospective impact studies.	[3]
Alzheimer's disease	Polyamine and L-arginine pathway metabolites, BCAAs, NAD^+-related metabolites	Staging, prognosis, trial enrichment	Harmonized multi-omic cohorts, intervention studies.	[4, 6, 10]

CONCLUSION

Clinical metabolomics has evolved from a discovery-driven research discipline into a promising translational science with the potential to reshape precision medicine. By capturing dynamic alterations in small molecule intermediates and end products of metabolism, metabolomics provides a functional readout that integrates genomic variation, environmental exposures, microbiome interactions, and disease-related reprogramming. As such, it offers a uniquely proximal link between molecular mechanisms and clinical phenotypes.

In disorders, such as diabetic kidney disease and Alzheimer's disease, metabolomic investigations, have revealed early and reproducible perturbations in amino acid, lipid, redox, and energy pathways. In diabetic kidney disease, alterations in NAD^+ related metabolites (e.g., urinary N-methylnicotinamide), acylcarnitines, and lipid species reflect mitochondrial dysfunction, oxidative stress, and impaired tubular metabolism that may precede albuminuria or eGFR decline. In Alzheimer's disease, dysregulation of branched chain amino acids, polyamine and L-arginine metabolism, and tryptophan–kynurenine pathways highlight disturbances in synaptic signaling, neuroinflammation, and redox balance that correlate with amyloid and tau pathology. These findings underscore that metabolomic signatures are not merely biomarkers but may illuminate actionable disease mechanisms.

Despite substantial discovery output, translation into routine clinical testing remains limited. Major barriers include pre-analytical variability, platform heterogeneity, incomplete metabolite annotation, overfitting in high-dimensional data, and insufficient external validation. Moreover, establishing causality – distinguishing mediators from downstream bystanders – requires integration with genomics, proteomics, imaging, and interventional studies. Without rigorous harmonization, replication in diverse populations, and demonstration of incremental clinical utility, promising signatures risk remaining confined to research settings.

The path forward lies in converting exploratory panels into analytically validated, targeted assays; embedding metabolomic data within prospective outcome-driven trials; and aligning biomarker development with regulatory and health system requirements. Advances in high–resolution LC–MS, data independent acquisition, multi-omic integration, and interpretable artificial intelligence models are expected to enhance robustness and reproducibility while reducing cost and complexity.

Ultimately, the clinical impact of metabolomics will depend not on the number of metabolites measured, but on whether metabolic signatures can meaningfully improve diagnosis, risk stratification, therapeutic monitoring, and patient outcomes beyond existing standards of care. With continued methodological refinement and translational rigor, clinical metabolomics is poised to transition from a powerful discovery platform to an integral component of precision diagnostics and mechanism-informed therapy.

REFERENCES

1. Rinschen MM, Ivanisevic J, Giera M, Siuzdak G. Clinical metabolomics: Useful insights, perspectives and challenges. Clin Chem Lab Med. 2024;62(7):e1–e15.
2. Newgard CB. Metabolomics and metabolic diseases: Where do we stand? Cell Metab. 2017;25 (1):43–56.
3. Patti GJ, Yanes O, Siuzdak G. Innovation: Metabolomics: The apogee of the omics trilogy. Nat Rev Mol Cell Biol. 2012;13(4):263–9.
4. Johnson CH, Ivanisevic J, Siuzdak G. Metabolomics: Beyond biomarkers and towards mechanisms. Nat Rev Mol Cell Biol. 2016;17(7):451–9.
5. Kainuma M, Kawakatsu S, Kim JD, Ouma S, Iritani O, Yamashita KI, et al. Metabolic changes in the plasma of mild Alzheimer's disease patients treated with Hachimijiogan. Front Pharmacol. 2023 Jun 12;14:1203349. doi: 10.3389/fphar.2023.1203349. PMID:37396834; PMCID:PMC10305648.
6. Xiao JF, Zhou B, Ressom HW. Metabolomics and its application in the development of biomarkers for diabetes and cardiovascular diseases. Crit Rev Clin Lab Sci. 2013;50(6):359–71.

7. Roberts LD, Gerszten RE. Toward new biomarkers of cardiometabolic diseases. Cell Metab. 2013;18(1):43–50.
8. Würtz P, Havulinna AS, Soininen P, Tynkkynen T, Prieto-Merino D, Tillin T, et al. Metabolite profiling and cardiovascular event risk: A prospective study of 3 population-based cohorts. Circulation. 2015;131(9):774–85. doi: 10.1161/CIRCULATIONAHA.114.013116. PMID:25573147.
9. Nowak C, Ärnlöv J. A metabolomics view on the pathophysiology of cardiovascular disease. Eur J Prev Cardiol. 2018;25(2 Suppl):37–42.
10. Lindon JC, Nicholson JK. Spectroscopic and statistical techniques for information recovery in metabonomics and metabolomics. Annu Rev Anal Chem. 2008;1:45–69.
11. Zhou C, Zhang Q, Lu L, Wang J, Liu D, Liu Z. Metabolomic profiling of amino acids in human plasma distinguishes diabetic kidney disease from type 2 diabetes mellitus. Front Med (Lausanne). 2021 Nov 29;8:765873.
12. Xiao JF, Zhou B, Ressom HW. Recent advances in LC–MS based metabolomics for clinical applications. Mass Spectrom Rev. 2022;41(1):72–109.
13. Di Minno A, Gelzo M, Caterino M, Costanzo M, Ruoppolo M, Castaldo G. Challenges in metabolomics-based tests, biomarkers revealed by metabolomic analysis, and the promise of the application of metabolomics in precision medicine. Int J Mol Sci. 2022 May 6;23(9):5213.
14. Alonso A, Marsal S, Julià A. Analytical methods in untargeted metabolomics: State of the art in 2015. Front Bioeng Biotechnol. 2015;3:23.
15. Jiang CY, Yang KM, Yang L, Miao ZX, Wang YH, Zhu HB. A ^1H NMR-based metabonomic investigation of time-related metabolic trajectories of the plasma, urine and liver extracts of hyperlipidemic hamsters. PLoS One. 2013 Jun 26;8(6):e66786. doi: 10.1371/journal.pone.0066786. PMID:23826163; PMCID:PMC3692820.
16. Dettmer K, Aronov PA, Hammock BD. Mass spectrometry based metabolomics. Mass Spectrom Rev. 2007;26(1):51–78.
17. Pinu FR, Beale DJ, Paten AM, Kouremenos KA, Swarup S, Schirra HJ, et al. Systems biology and multi-omics integration: Viewpoints from the metabolomics research community. Metabolites. 2019 Apr 18;9(4):76. doi: 10.3390/metabo9040076. PMID:30939823; PMCID:PMC6520965.
18. Bujak R, Struck-Lewicka W, Markuszewski MJ, Kaliszan R. Metabolomics for laboratory diagnostics. J Pharm Biomed Anal. 2015;113:108–20.
19. Würtz P, Raiko JR, Magnussen CG, Soininen P, Kangas AJ, Tynkkynen T, et al. High-throughput quantification of circulating metabolites improves prediction of subclinical atherosclerosis. Eur Heart J. 2012 Sep;33(18):2307-2316. doi: 10.1093/eurheartj/ehs020. PMID:22402125.
20. Toledo JB, Arnold M, Kastenmueller G, Chang R, Baillie RA, Han X, et al. Metabolic network failures in Alzheimer's disease: A biochemical road map. Alzheimers Dement. 2017 Sep 1;13(9):965–84.
21. Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, MacArthur LH, et al. Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med. 2014 Apr;20(4):415–420. doi: 10.1038/nm.3466. PMID:24608097.
22. Li X, Liu W, Jiang H, Zhang Y, Chen J, Wang L, et al. Metabolomics in diabetic nephropathy: Unveiling novel biomarkers and pathways. Mol Med Rep. 2024;29(2):13280. doi: 10.3892/mmr.2024.13280. PMID:38312345.
23. Roscioni SS, De Zeeuw D, Hellemons ME, Mischak H, Zürbig P, Bakker SJ, et al. A urinary peptide biomarker set predicts worsening of albuminuria in type 2 diabetes mellitus. Diabetologia. 2013 Feb;56(2):259–67.
24. Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes: A review of early natural history, pathogenesis and diagnosis. Diabetes Metab Res Rev. 2017;33(2):e2841.
25. Sharma K, Karl B, Mathew AV, Gangoiti JA, Wassel CL, Saito R, et al. Metabolomics reveals signature of mitochondrial dysfunction in diabetic kidney disease. J Am Soc Nephrol. 2013 Nov 1;24(11):1901–12.
26. Hirakawa Y, Yoshioka K, Kojima K, Yamashita Y, Shibahara T, Wada T, et al. Potential progression biomarkers of diabetic kidney disease determined using comprehensive machine learning analysis of non-targeted metabolomics. Sci Rep. 2022 Sep 29;12(1):16287.

27. Niewczas MA, Mathew AV, Croall S, Byun J, Major M, Sabisetti VS, et al. Circulating modified metabolites and a risk of ESRD in patients with type 1 diabetes and chronic kidney disease. Diabetes Care. 2017 Mar 1;40(3):383–90.
28. Bhensdadia NM, Hunt KJ, Lopes-Virella MF, Tucker JM, Mataria MR, Alge JL, et al. Urine haptoglobin levels predict early renal functional decline in patients with type 2 diabetes. Kidney Int. 2013 Jun 1;83(6):1136–43.
29. Holčapek M, Liebisch G, Ekroos K. Lipidomic analysis. Anal Chem. 2018;90(7):4249–57.
30. Dunn WB, Ellis DI. Metabolomics: Current analytical platforms and methodologies. TrAC Trends Anal Chem. 2005;24(4):285–94.
31. Zhang Y, Zhang S, Wang G. Metabolomic biomarkers in diabetic kidney diseases—A systematic review. J Diabetes Complications. 2015 Nov 1;29(8):1345–51.
32. Dekker SE, Verhoeven A, Soonawala D, Peters DJ, de Fijter JW, Mayboroda OA, et al. Urinary metabolites associate with the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease. PLoS One. 2020 May 22;15(5):e0233213.
33. Tiwari P, Gupta A, Kaushik M, Yadav A, Anjali A, Dwivedi R, et al. Comprehensive metabolomics profiling reveals novel biomarkers and pathways for early detection of Alzheimer's disease. Brain Commun. 2025;7(6):fcaf410. doi: 10.1093/braincomms/fcaf410.
34. Lista S, González-Domínguez R, López-Ortiz S, González-Domínguez Á, Menéndez H, Martín-Hernández J, et al. Integrative metabolomics science in Alzheimer's disease: Relevance and future perspectives. Ageing Res Rev. 2023 Aug;89:101987. doi: 10.1016/j.arr.2023.101987. PMID:37343679.
35. Jové M, Mota-Martorell N, Obis È, Sol J, Martin-Gari M, Ferrer I, et al. Ether lipid-mediated antioxidant defense in Alzheimer's disease. Antioxidants (Basel). 2023 Jan 28;12(2):293. doi: 10.3390/antiox12020293. PMID:36830412; PMCID:PMC9967076.
36. Varma VR, Oommen AM, Varma S, Casanova R, An Y, Andrews RM, et al. Brain and blood metabolite signatures of pathology and progression in Alzheimer disease: A targeted metabolomics study. PLoS Med. 2018 Jan 23;15(1):e1002482. doi: 10.1371/journal.pmed.1002482. PMID:29357367; PMCID:PMC5782065.
37. González-Domínguez R, García-Barrera T, Gómez-Ariza JL. Metabolomic study of lipids in serum for biomarker discovery in Alzheimer's disease using direct infusion mass spectrometry. J Pharm Biomed Anal. 2014;98:321–6.
38. Graham SF, Chevallier OP, Elliott CT, Hölscher C, Johnston J, McGuinness B, et al. Untargeted metabolomic analysis of human plasma indicates differentially affected polyamine and L-arginine metabolism in mild cognitive impairment subjects converting to Alzheimer's disease. PLoS One. 2015 Mar 24;10(3):e0119452. doi: 10.1371/journal.pone.0119452. PMID:25807564; PMCID: PMC4373680.
39. Trushina E, Mielke MM. Recent advances in the application of metabolomics to Alzheimer's disease. Biochim Biophys Acta. 2014;1842(8):1232–9.
40. Nicholson JK, Lindon JC, Holmes E. 'Metabonomics': Understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR data. Xenobiotica. 1999;29(11):1181–9.
41. Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, Cascante M, et al. Metabolomics enables precision medicine:"a white paper, community perspective". Metabolomics. 2016 Sep 2;12(9):149.
42. Armitage EG, Southam AD. Monitoring cancer prognosis, diagnosis and treatment efficacy using metabolomics and lipidomics. Metabolomics. 2016;12(9):146.
43. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. Nat Rev Drug Discov. 2016;15(7):473–84.
44. Le Gouellec A, Plazy C, Toussaint B. What clinical metabolomics will bring to the medicine of tomorrow. Front Anal Sci. 2023 Feb 24;3:1142606. doi:10.3389/frans.2023.1142606.
45. Nicholson JK, Holmes E, Elliott P. The metabolome-wide association study: A new look at human disease risk factors. J Proteome Res. 2008;7(9):3637–8.

