

Metabonomics and its Potential Application in Clinic Diagnosis and Therapy

Chunlei Xie^{1,†}, Congcong Tang^{1,†}, Qi Tang¹, Faqing Tang^{1,*}

Received 19 July 2026

Revised 2 September 2026

Accepted 24 September 2026

Published 30 September 2026



ISSN 2760-1757 (Online)
ISSN 2760-3288 (Print)

© 2026 The Author(s)
Published by Jandoo Press Co., Ltd.

This article is licensed under the terms and conditions of the Creative Commons Attribution (CC BY) license:
<http://creativecommons.org/licenses/by/4.0/>

Abstract: Metabolomics is a new-generation omics technology emerging after genomics, transcriptomics, and proteomics. It focuses on all small-molecule metabolites with molecular weights below 1 kDa within biological systems, providing a direct reflection of the terminal phenotypic changes in the physiological and pathological states of organisms. With the continuous iteration of detection platforms such as mass spectrometry and nuclear magnetic resonance, both untargeted and targeted metabolomics have been widely used to screen disease-specific metabolic biomarkers and construct non-invasive, and precise disease diagnostic models. This article summarized the main technical platforms and data analysis workflows of metabolomics, consolidated diagnostic applications of metabolomics in the fields including malignant tumors, metabolic diseases, neurological disorders, and autoimmune diseases, while discussing current bottlenecks in sample standardization, biomarker validation, and metabolic-disease causal analysis. Additionally, the article also explored the development prospects of artificial intelligence combined with spatial metabolomics in clinical precision diagnostics, it provides a reference for the translation of metabolomics from basic research to clinical diagnosis.

Keywords: Metabolomics; Biomarkers; Mass spectrometry; Disease diagnosis; Precision medicine; Non-invasive testing

Introduction

The occurrence and progression of diseases are accompanied by disruptions in cellular signaling pathways, alterations in enzyme activity, and reprogramming of metabolic networks, ultimately reflected in changes in the concentration and composition of small-molecule metabolites in body fluids and tissues [1,2,3]. The genome and transcriptome reveal the underlying risks of disease onset, while the metabolome directly reflects the current functional state of the organism, being more closely aligned with clinical phenotypes [2]. Traditional clinical diagnostics often rely on imaging, pathological biopsies, and a limited number of protein biomarkers, which present limitations such as delayed detection, high invasiveness, and low early detection rates [4].

In 1999, Nicholson first proposed the concept of metabolomics, which analyzed the overall metabolic response of the body to pathological stimuli through multivari-

ate statistical analysis of biological spectra [5]. Different from targeted detection of a single indicator, metabolomics achieves global scanning of metabolic fingerprints, screening a set of characteristic metabolite combinations to construct a diagnostic model, significantly improving identification efficiency [6]. In recent years, technologies such as liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry, and high-resolution mass spectrometry imaging have rapidly developed [7]. Combined with machine learning algorithms, metabolomics has become a cutting-edge direction for early disease screening, differential diagnosis, and prognosis evaluation [8].

In recent, a great progress has been harvested in metabolomics. With the continuous expansion of research fields and the development of techniques, many new terms and concepts have emerged, such as metabolite target analysis, metabolic profiling analysis, metabolomics, and metabolic fingerprint analysis [6]. The two mainstream fields of

¹ Department of Clinical Laboratory, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University and Hunan Cancer Hospital, Changsha 410013, China.

[†] These authors contributed equally to this work.

^{*} Corresponding author. Email: tangfq@hnca.org.cn

metabolomics have emerged, namely metabolomics and metabonomics. It is generally believed that metabolomics exists within cells and is a collection of all relatively low molecular weight metabolites necessary for cell growth and function, involved in cellular metabolic activities. Metabonomics is a study of the dynamic changes in the quality and quantity of metabolites produced by pathological and physiological stimuli or gene modifications in living organisms [9]. The former generally focuses on cells as the research object, while the latter pays more attention to animal fluids and tissues; Another approach is that metagenomics mainly refers to the use of nuclear magnetic resonance to analyze the metabolic processes of animal bodies, while the analytical techniques of metagenomics mainly rely on GC/MS [9]. At present, domestic metabolomics researchers have basically reached a consensus to use the term metagenomics to refer to "metabolomics". Metabolomics has been widely applied in various fields of life sciences, especially in disease diagnosis and treatment testing, where significant progress has been made. The article briefly introduces the emergence, development, and technical methods used in metabolomics, this article provides a systematic overview of its progress in disease diagnosis research.

Metabolomics Analysis Techniques

The classic metabolomics research process includes four steps: sample collection, preprocessing, data collection, and data analysis and interpretation. The research platform mainly consists of an analysis technology platform and a data analysis platform.

2.1 Analysis techniques include compound separation techniques, detection and identification techniques. It is usually divided into chromatography (LC), capillary electrophoresis (CE), etc. Detection and identification techniques typically include mass spectrometry (general mass spectrometry, time-of-flight mass spectrometry), spectroscopy (infrared, ultraviolet, fluorescence), nuclear magnetic resonance, and electrochemistry [10]. The different combinations of separation technology and detection and identification technology constitute various metabolomics analysis techniques. Metabolomics analysis techniques can also be divided into three categories based on main detection methods, namely, spectrum based, mass spectrometry based, and Nuclear magnetic resonance (NMR) based metabolomics analysis. The characteristics of mass spectrometry are universality, high sensitivity, and specificity. NMR technology, especially ^1H -NMR, has become the most important analytical tool due to its universality for hydrogen containing metabolites [11]. Liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry can analyze a wide range of metabolic components and have become important tools in metabolomics research and analysis.

2.2 Data analysis techniques are unsupervised methods, supervised methods, and system identification based on the-

ory. Unsupervised methods include cluster analysis (CA), principal component analysis (PCA), and self-organizing maps (SOMs); Supervision methods include Discriminant Function Analysis (DFA), Nonlinear Regression, Feedforward Neural Networks, Genetic Algorithms, Support Vector Machines, Genetic Programming, and Functional Analysis by Co Responses in Yeast (FANCY); System identification methods include chemical kinetics, metabolic control analysis, and nonlinear dynamics. Among them, the simplest and most commonly used effective pattern recognition method is principal component analysis (PCA). The characteristic of PCA is to concentrate information scattered on a set of variables onto a few comprehensive indicators, namely principal components (PC), and use these principal components to describe the internal structure of the dataset, which actually plays a role in data dimensionality reduction [12]

Technical Platforms and Research Strategies of Metabolomics

The process of metabolomics includes sample collection and preprocessing, instrument detection, spectrum preprocessing, qualitative and quantitative analysis of metabolites, multivariate statistical analysis, differential metabolite screening, pathway enrichment, and biomarker validation [13]. According to research strategies, it can be divided into two categories: untargeted metabolomics and targeted metabolomics.

Mass spectrometry detection platform

Liquid chromatography-high-resolution mass spectrometry (LC-HR-MS) is currently the most mainstream platform, suitable for polar and moderately polar metabolites such as amino acids, organic acids, lipids, and bile acids [14]. Gas chromatography-mass spectrometry (GC-MS) is suitable for volatile, thermally stable small molecules, sugars, short chain fatty acids, etc [15]. Mass spectrometry has the advantages of high sensitivity and wide coverage of metabolites. Matrix assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI, spatial metabolomics) can preserve tissue spatial location information, in situ depict the distribution of metabolites in the lesion area, distinguish tumor infiltration boundaries from surrounding normal tissues, and demonstrate great potential in surgical pathological diagnosis [16].

Nuclear Magnetic Resonance (NMR)

^1H -NMR does not require complex sample preprocessing and can non destructively detect samples with excellent reproducibility of results; The disadvantage is that it has low sensitivity and is suitable for screening high abundance metabolites [11]. It is mostly used for initial screening of metabolic fingerprints and batch detection of large-scale queue samples.

Data analysis methods

After peak alignment, denoising, and normalization of the raw mass spectrometry data, unsupervised principal component analysis (PCA) is used to observe the overall separation trend between groups [17]. Supervised orthogonal partial least squares discriminant analysis (OPLS-DA) is used to identify the differentially-expressed metabolites with the greatest contribution [18]. Univariate statistics was combined to screen metabolites with $P < 0.05$ and significant difference multiples, conducting KEGG pathway enrichment analysis to explore perturbed metabolic pathways. Machine learning algorithms such as random forest and LASSO regression are used to screen the optimal combination of biomarkers, construct diagnostic models, and evaluate the diagnostic performance of the model based on the AUC value of the ROC curve [19].

Application of Metabolomics in Disease Diagnosis

Metabolomics has developed rapidly in applications. It has been widely applied in the research fields including botany, toxicology, clinical diagnosis, drug development, and nutritional science [20,21].

Metabolic disorders

Type 2 diabetes, nonalcoholic fatty liver, and metabolic syndrome have abnormal branched chain amino acids, acyl carnitine, and trimethylamine N-oxide (TMAO). Elevated levels of plasma valine, leucine, and isoleucine are closely related to insulin resistance [22]. Metabonomics can not only distinguish healthy people from people with diabetes, but also identify people with pre diabetes, so as to realize risk early warning [22]. At the same time, distinguishing between simple fatty liver and fatty hepatitis can compensate for the weakness of imaging in determining liver tissue inflammation and damage [20].

Diabetes is a typical metabolic disorder. Traditional diagnostic tests include blood glucose measurement, urine glucose measurement, and oral glucose tolerance test. But due to individual differences and other factors, the false positive rate of glucose tests is relatively high. Fatty acids are considered to be an important sign of abnormal lipid metabolism in diabetes patients. Jun Yang et al. [23] used capillary gas chromatography combined with data model analysis to analyze the serum fatty acids of the patients with type II diabetes and healthy people in the control group. The serum lipid metabolism spectrum of patients with type II diabetes was obtained, this lipid metabolism spectrum made the difference from the patients and the control group clear, and it improved the sensitivity and specificity of the test. Chang Wang et al. [24] used the LC/MS method in combination with multivariate statistical analysis to detect phospholipids in plasma samples of type II diabetes and healthy people, obtained phospholipid metabolic profiles for identifying type II diabetes patients, and searched for biomarkers of type II di-

abetes. The analysis method of high-performance liquid chromatography combined with mass spectrometry had improved the selectivity and sensitivity of detection.

Michael et al. [25] believed that horses generally have hyperinsulinemia and a higher probability of developing diseases related to insulin resistance. In this study, horses was used as animal models to conduct oral glucose tolerance tests, colorimetric analysis was applied to detect glucose levels in blood, ELISA was used to detect insulin levels in blood, and $^1\text{H-NMR}$ based metabolomics was applied to analyze normal or abnormal metabolic changes caused by glucose stimulation in plasma samples [A10]. The results showed that compared with traditional detection methods, the metabolomics method based on $^1\text{H-NMR}$ can accurately reflect changes in metabolic processes. Combined with statistical analysis tools, disease-related metabolic markers were identified, and this method has high sensitivity and accuracy [26,11].

Diabetes can lead to multi system damage, such as chronic progressive diseases of kidney, cardiovascular system, nervous system, and eventually lead to dysfunction and even failure. Diabetes nephropathy is the most serious complication of type I diabetes. The clinical diagnosis of diabetes nephropathy is mainly based on 24-hour urinary albumin excretion rate, and the results are often not ideal. Pasi Soninen et al. [27] used $^1\text{H-NMR}$ metabonomics method in combination with statistical model to analyze lipoprotein lipids and low molecular weight metabolites in the serum of type I diabetes patients. The results showed that the sensitivity, specificity, positive predictive value and negative predictive value were higher than the results of routine clinical biochemical analysis. They believed that $^1\text{H-NMR}$ metabonomics analysis results can clearly describe the metabolic characteristics of type I diabetes and provide a new detection method for the diagnosis of diabetes nephropathy.

Tumors

The occurrence and development of tumors inevitably cause changes in the body's metabolism, and nucleosides. A class of metabolites have great potential to become biomarkers of tumors [28,29]. At present, a large amount of research is devoted to using metabolomics methods to search for meaningful tumor specific marker metabolites or metabolic profiles, and to establish diagnostic models for different tumors [30,31]. Jun Yang et al. [32] analyzed 15 nucleosides in urine samples of liver cancer patients using HPLC based metabolomics technology. Significant differences were found in the concentrations of 15 nucleosides in the urine of liver cancer patients and healthy individuals. Compared with AFP detection results, metabolomics has a higher positive rate, avoiding the possibility of false positives of AFP in patients with cirrhosis and chronic hepatitis, and effectively distinguishing liver cancer patients from patients with hepatitis and cirrhosis. Metabolomics analysis of nucleosides in urine has good specificity and sensitivity for the diagnosis of liver cancer.

Xu GW et al. [33] used capillary electrophoresis (CE) and PCA to process data, and conducted a classification study on 68 cancer patients and 54 healthy individuals. They obtained a recognition rate of 72%. By using artificial neural network software to process data, the recognition rate of tumor patients can reach 83%.

Shen P et al. [34] used a metabolomic pattern feature method based on optimal feature combination and BP neural network to screen a group of metabolites that can reflect the metabolic characteristics of breast cancer from urine HPLC analysis data. They identified metabolomic structure using LC/MS/MS technology. The results showed that there were significantly different metabolites in the urine of breast cancer patients, namely, nucleoside whey, adenosine 1-formylate, S-adenosyl-L-methionine and N-formylated guanosine. Taking metabolomic pattern as the characteristic variable of diagnosis mode, the accuracy rate of diagnosis of breast cancer is more than 90%.

Cervical cancer is the most common malignant tumor in gynecology, and the conventional diagnostic methods are CT, magnetic resonance imaging, and positron emission tomography. 75% of patients are diagnosed in the advanced stage, and the 5-year survival rate is only 15% -20% [35]. Therefore, early diagnosis and prediction of recurrence have important clinical significance. Odunsi et al. [36] used 1H-NMR metabolomics to analyze the serum of cervical cancer patients, and they obtained that the detection rate of cervical cancer reached 97.4%. 1H-NMR metabolomics provides a new method for early diagnosis of cervical cancer.

In early diagnosis of malignant tumors, tumor cells undergo the Wallerian effect, with abnormal activation of glycolysis, reprogramming of glutamine metabolism, upregulation of lipid synthesis, and characteristic shifts in blood and urine metabolic profiles. Multiple serum metabolomics studies have confirmed that combined metabolic markers can significantly improve the detection rate of early gastric cancer, colorectal cancer, and lung cancer compared to traditional single tumor markers (CEA, AFP).

Patients with IDH mutations in acute myeloid leukemia have significantly elevated serum levels of 2-hydroxyglutarate (2-HG), which can serve as a diagnostic biomarker for classification. Using plasma metabolism fingerprints to construct a machine learning diagnostic model, the AUC of some queues can reach 0.90 or above. Metabolome liquid biopsy based on body fluids has non-invasive advantages and is expected to be used for large-scale early screening of high-risk populations [1]. However, most biomarkers still lack multi center large sample validation [37].

Cardiovascular diseases

Brindle et al. [38] established a rapid and non-invasive method for diagnosing coronary artery disease using a 1H-NMR based metabolomics approach. In this study, metabolomics analysis was conducted on the serum and plasma of patients with different types of coronary artery disease, combined with pattern recognition techniques such

as PCA, SIMCA, PLS-DA, OSC-PLS, etc., to establish a large-scale NMR database. They achieved discrimination of cardiovascular disease and its severity with a sensitivity and specificity of 90%.

Kazuki et al. [39] used a metabolomics method based on 1H-NMR to analyze the metabolites in the urine of mice with hereditary hypertension, in this study the mice with hereditary hypertension served as a experimental model and the mice with normal blood pressure as a health control group. The results showed that the levels of taurine and creatine in the urine of the experimental group mice were higher than those in the control group, but the levels of some unknown metabolites were lower than those in the control group. This provides an ideal model for further studying the pathophysiological processes of primary hypertension.

Post transplant monitoring

The success of transplantation surgery is related to many factors, including surgical complications, postoperative infections, acute rejection, and so on. Therefore, the success of transplantation surgery is closely related to postoperative monitoring and timely changes in treatment plans. The existing postoperative observation indicators for kidney transplantation include serum creatinine levels, total urine output, body temperature, blood pressure, and blood glucose, but these indicators often lack specificity, sensitivity, and accuracy and cannot provide accurate and timely evidence for clinical intervention. Serkova et al. [40] used mice as a model to study renal ischemia-reperfusion injury and found that the levels of citrate, lactate, and acetate in the urine of mice were elevated, as well as the levels of uracil and TMAO in the blood. There are also studies on the toxicity of immunosuppressive drugs, evaluation of organ function, and determination of organ damage, which have applied metabolomics analysis methods [41].

Natalie et al. [42] used 1H-NMR metabolomics and PCA methods to continuously monitor metabolites in the blood of the same patient who underwent two consecutive liver transplant surgeries (the first surgery failed and the second surgery was successful). A total of 48 metabolites were detected, of which 6 were correlated with transplant failure and appeared within 2 hours after surgery. Due to the current lack of laboratory evidence that can provide early warning of transplant failure, this experiment has great potential for diagnosing early liver transplant failure.

Other diseases

Bacterial meningitis is an acute attack that requires accurate and timely differential diagnosis from viral meningitis and other causes of acute meningitis [43]. In clinical practice, the conventional detection method is cerebrospinal fluid culture, but this method is very time-consuming. Rapid screening methods such as cerebrospinal fluid white blood cell count, protein detection, glucose detection, and Gram staining are not ideal due to lack of specificity or sensitivity. Muireann Coen et al. [44] used 1H-NMR metabolomics combined with PCA to analyze cerebrospinal fluid samples from

patients with bacterial, fungal, and viral meningitis and a normal control group. This method can distinguish bacterial meningitis from viral meningitis and from the control group, and can also be applied to monitor treatment efficacy.

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is currently diagnosed based on clinical phenotypes observed through imaging, endoscopy, and histopathological techniques, which can be harmful [45]. Julian et al. [46] used ¹H-NMR metabolomics combined with multi parameter pattern confirmation technology to analyze the components of fecal extracts from patients with CD and UC. Compared with the control group, the levels of acetate, methylamine, and trimethylamine in the fecal extracts of both groups of patients decreased, while the content of certain amino acids increased. However, there were significant differences in metabolites between the CD group and the control group, indicating that the inflammatory response caused by CD is more widespread and severe when compared to UC, possibly involving the entire intestine.

In neurological disorders, Alzheimer's disease [47], stroke [48], and depression [49] have peripheral blood metabolic disorders. Changes in plasma sphingolipids and tryptophan metabolism pathways are significantly associated with cognitive decline. Metabolomics can assist in distinguishing vascular dementia from Alzheimer's disease. Metabolomics can construct a serum metabolic profile for refractory depression [50], providing a basis for objective biological classification of mental disorders and breaking the current situation where mental disorders mainly rely on scales for diagnosis [49].

In autoimmunity and kidney disease, there are specific differential metabolites in the extracellular vesicles of lupus nephritis patients' urine [51,52], which can achieve non-invasive differentiation between simple systemic lupus erythematosus and lupus kidney injury. The serum lipid metabolism profile of rheumatoid arthritis patients is significantly altered, which is used to distinguish early arthritis from joint pain and achieve early intervention [53]. Metabolomics is also used to evaluate the progression of chronic kidney disease and search for metabolic markers that can warn of renal function deterioration [54].

Clinical Application Challenges

Despite the fruitful achievements in basic researches, metabolomics currently faces great challenges in clinical translation, and there are still multiple obstacles to conventional clinical testing [55,56]. (1) Lack of standardization in sample and testing processes: Fasting state of blood collection, storage temperature, freeze-thaw cycles, and types of anticoagulants can all alter metabolite concentrations. Different laboratory instrument models, chromatographic conditions, and pre-treatment schemes result in poor reproducibility of biomarkers obtained from screening the same disease. At present, there is no unified standard for clinical metabolomics testing. (2) Insufficient biomarker validation:

The vast majority of diagnostic models are based on single center small sample queues, lacking independent external validation from multiple centers. The differential metabolites obtained from partial screening are only secondary metabolic changes of the disease, not disease-specific biomarkers. (3) Difficulties in analyzing the causal relationship between metabolites and diseases: Metabolic disturbances can be both the cause and the result of pathological changes, making it difficult to distinguish between driving factors and accompanying biomarkers. (4) High detection cost and high threshold for data analysis: High resolution mass spectrometry equipment is expensive, and data analysis relies on bioinformatics professionals, making it difficult to popularize in primary hospitals. (5) Individual confounding factors such as age, gender, diet, gut microbiota, and drug intervention can all reshape the human metabolic profile and interfere with the accuracy of diagnostic models.

Conclusion

Metabolomics can capture the global changes of small molecule metabolites in human body under disease conditions, breaking through the limitations of traditional single indicator diagnosis. Metabolomics has a great early diagnostic potential in the fields including tumors, metabolic diseases, and neurological disorders. There are still challenges in this field such as lack of standardization and insufficient verification of biomarkers. With the standardization of detection technology, the advancement of multi center clinical validation, and the iteration of artificial intelligence algorithms, metabolomics is expected to become a new generation of non-invasive and accurate diagnostic tools, promoting the clinical diagnosis and treatment mode from late stage treatment to early warning and intervention, and assisting the implementation of precision medicine.

Prospect

Metabolomics analyzes the composition of body fluids and uses quantitative methods to compare and analyze disease groups and normal groups, obtaining special metabolic products induced by diseases, biomarkers, which helps to understand the metabolic mechanism of human body during pathological process and assists in clinical diagnosis and treatment [56]. Compared with traditional disease diagnosis methods in clinical practice, metabolomics embodies many advantages: small sample size, non-invasive, fast, strong specificity, high sensitivity, and the potential to find biological indicators specific to disease diagnosis. The future direction should include: 1) establishing standardized procedures, building a multi center large-scale population metabolome reference database, establishing metabolic baselines for different age groups in healthy populations, and correcting confounding variables such as diet and microbiota; 2) Multi omics integration, combining metabolomics with genome, transcriptome, and microbiome analysis, to decipher the complete pathway of disease from

gene variation to metabolic disturbance, and screen for biomarkers with both specificity and causal significance; 3) Space metabolomics and single-cell metabolomics continue to develop, analyzing metabolic heterogeneity within tissue microenvironments, delving into local metabolic changes in lesions from macroscopic metabolic characteristics of body fluids, and assisting in precise pathological diagnosis; 4) Artificial intelligence deeply empowers the metabolome, develops automated spectrum recognition and biomarker screening algorithms, and constructs dynamically updated disease intelligent diagnostic models; Develop low-cost targeted metabolic marker kits to promote the shift from scientific mass spectrometry platforms to clinical routine testing.

With the continuous improvement of research methods and the further advancement of software and hardware technology in analysis systems, it is developing towards integration, automation, and high-throughput. This systematic disease diagnosis technology will further highlight its important significance.

Acknowledgement: We thank the members in Department of Clinical Laboratory of Hunan Cancer Hospital and Xianya Hospital of Central South University for constructive suggestion.

Author contributions: CLX, CCT, and QT prepared literature materials, and wrote the manuscript. FQT supervised the project, and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Data accessibility statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement: Author FQT serves on the editorial board of this journal but had no role in the peer review or decision-making process for this article.

References

- Zhang N, Dong N, Xie AR, et al. Urinary extracellular vesicle metabolomic profiling reveals a distinct molecular signature for the non-invasive diagnosis of lupus nephritis. *Front. Immunol.* 2026; 17.
- You J, Cui XH, Chen YL, et al. Mapping the plasma metabolome to human health and disease in 274,241 adults. *Nat Metab.* 2025;7(11):2366–2384.
- Qiang YX, Wang YX, He XY, et al. Genetic architecture of plasma metabolome in 254,825 individuals. *Nat Commun.* 2025;16(1):8272.
- He SY, Zeng HD, Li BY. Application Progress of Spatially Resolved Metabolomics in Disease Diagnosis Research. *Biotechnology Bulletin.* 2024; 40 (1): 145–159.
- Nicholson JK, Lindon JC, Holmes E. Metabonomics: understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data. *Xenobiot.* 1999;29(1):1812–1189.
- Liu X, Locasale J W. Metabolomics: A primer. *Trends in Biochemical Sciences.* 2017;42(4): 274–284.
- Warwick BD, David IE. Metabolomics: Current analytical platforms and methodologies. *Trends in Analytical Chemistry.* 2000;24(4):285–294.
- Chen YZ, Wang BH, Zhao YZ, et al. Metabolomic machine learning predictor for diagnosis and prognosis of gastric cancer. *Nat Commun.* 2024;15(1):1657.
- Patra S, Dutta D, Calra S, et al. Metabolomics in Endocrinology: The Way Forward. *Indian J Endocrinol Metab.* 2025;29(4):394–401
- Patti G J, Yanes O, Siuzdak G. Innovation: Metabolomics: the apogee of the omics trilogy. *Nature Reviews Molecular Cell Biology.* 2012;13(4):263–269.
- Crook AA, Powers R. Quantitative NMR-Based Biomedical Metabolomics: Current Status and Applications. *Molecules.* 2020;25(21):5128.
- Xu H, Lin HD, Liu CX. Current Status and Prospects of Metabolomics Research. *Acta Pharmaceutica Sinica.* 2005;40(9):769–774.
- Huang Q, Shen X, Li Y, Wu H, et al. A Metabolomics-Driven Integrated Machine Learning Framework for Early Prediction of Recurrent Acute Pancreatitis. *Metabolites.* 2026;16(8):575.
- Chen F, Yeung PS, Wong CV, et al. High-resolution mass spectrometry measurement of N-terminal carbamylated hemoglobin as a potential marker for chronic diseases with elevated blood urea levels. *J Mass Spectrom Adv Clin Lab.* 2025;35:8–13.
- Panighel A, Flamini R. Applications of solid-phase microextraction and gas chromatography/mass spectrometry (SPME-GC/MS) in the study of grape and wine volatile compounds. *Molecules.* 2014;19(12):21291–309.
- Ngai YT, Lau D, Mittal P, et al. Mini Review: Highlight of Recent Advances and Applications of MALDI Mass Spectrometry Imaging in 2024. *Anal Sci Adv.* 2025;6(1):e70016.
- Ma S, Dai Y. Principal component analysis based methods in bioinformatics studies. *Brief Bioinform.* 2011;12(6):714–22.
- Worley B, Powers R. PCA as a practical indicator of OPLS-DA model reliability. *Curr Metabolomics.* Author manuscript. 2016;4(2):97–103.
- An Q, Rahman S, Zhou J, et al. A Comprehensive Review on Machine Learning in Healthcare Industry: Classification, Restrictions, Opportunities and Challenges. *Sensors (Basel).* 2023;23(9):4178.
- Rakusanova S, Cajka T. Metabolomics and Lipidomics for Studying Metabolic Syndrome: Insights into Cardiovascular Diseases, Type 1 & 2 Diabetes, and Metabolic Dysfunction-Associated Steatotic Liver Disease. *Physiol Res.* 2024; 73(S1): S165–S183.
- Yan XZ. Metabolomics technology and its application in the discovery of clinical disease biomarkers. *Journal of Analytical Testing.* 2021;40(05):641–648.
- Xu Z, Zhou Y, Xie R, et al. Metabolomics uncovers the diabetes metabolic network: from pathophysiological mechanisms to clinical applications. *Front Endocrinol (Lausanne).* 2025;16:1624878.
- Yang J, Xu GW, Hong QF, et al. Discrimination of Type 2 diabetic patients from healthy controls by using metabonomics method based on their serum fatty acid profile. *Journal of Chromatography B.* 2004;813:53–58.
- Wang C, Kong HW, Yang J, et al. Plasma Phospholipid Metabolic Profiling and Biomarkers of Type 2 Diabetes Mellitus Based on High-Performance Liquid Chromatography/Electrospray Mass Spectrometry and Multivariate Statistical Analysis. *Anal. Chem.* 2005;77:4108–4110.

25. Michael SH, Sarah LR, István Pelczar. Beyond blood sugar: the potential of NMR-based metabolomics for type 2 human diabetes, and the horse as a possible model. *Anal Bioanal Chem.* 2007; 387:533–537.
26. Ralston SL. Factors affecting tests of glucose and insulin metabolism in horses. In: Reed SR, W Bayley, Sellon D eds. *Equine internal medicine.* Saunders, StLouis. 2004;1600–1605.
27. Ville-Petteri M, Pasi S, Carol F, et al. Diagnosing diabetic nephropathy by ¹H NMR metabolomics of serum. *Magn Reson Mater Phys.* 2006;19:281–296.
28. Wang CH, Zhu YF, Zhou HL et al. Integrated analysis of serum untargeted metabolomics and targeted bile acid metabolomics for identification of diagnostic biomarkers for colorectal cancer. *Nan Fang Yi Ke Da Xue Xue Bao.* 2023 Mar 20;43(3):443–453.
29. Liu WS, Ma JL, Zhang JX, et al. Identification and validation of serum metabolite biomarkers for endometrial cancer diagnosis. *EMBO Molecular Medicine.* 2024; 16: 988–1003.
30. Hu ZP. Opportunities and challenges of using tumor metabolomics for early tumor diagnosis. *Journal of Pharmacy.* 2024;59(3):689–702.
31. Bernhardt VG, Bernhardt KL, Pinto JRT, et al. Metabolomics in cancer detection: A review of techniques, biomarkers, and clinical utility. *Biomedicine (Taipei).* 2025;15(3):1–23.
32. Yang J, Xu GW, Zhen YF, et al. Diagnosis of liver cancer using HPLC-based metabolomics avoiding false-positive result from hepatitis and hepatocirrhosis diseases. *Journal of Chromatography B.* 2004;813(1-2):59–65.
33. Xu GW, Liebich H. Normal and modified nucleosides in urine as potential tumor markers analyzed by micellar electrokinetic capillary chromatography and high performance liquid chromatography. *Am Clin Lab.* 2001;20(1):22–32.
34. Shen P, Kang YF, Cheng YY. Methods for discovering metabolome pattern characteristics of breast cancer and HPLC/MS/MS analysis. *Journal of Chemistry of Colleges and Universities.* 2005;26(10):1798–1802.
35. Greenlee RT, Hill-Harmon MB, Murray T, et al. Cancer statistics. *CA Cancer J Clin.* 2001;51:15–36.
36. Odunsi K, Wollman RM, Ambrosone CB, et al. Detection of epithelial ovarian cancer using ¹H-NMR-based metabolomics. *Int J Cancer.* 2005;113(5):782–788.
37. Liu TQ, Zhong XY. Application of metabolomics in neonatal clinical practice. *Zhongguo Dang Dai Er Ke Za Zhi.* 2019;21(9):942–948.
38. Brindle JT, Antti H, Holmes E, et al. Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using ¹H-NMR-based metabolomics. *Nat Med.* 2002;8(12):1439–1444.
39. Kazuki A, Misako I, Takao H. Investigations into Biochemical Changes of Genetic Hypertensive Rats Using ¹H Nuclear Magnetic Resonance-Based Metabolomics. *Hypertens Res.* 2005;28(5):425–430.
40. Serkova N, Fuller TF, Klawitter J, et al. ¹H-NMR-based metabolic signatures of mild and severe ischemia-reperfusion injury in rat kidney transplants. *Kidney Int.* 2005; 67:1142–1151.
41. David SW. Metabolomics in monitoring kidney transplants. *Current Opinion in Nephrology and Hypertension.* 2006;15:637–642.
42. Natalie JS, Zhang Y, et al. Early Detection of Graft Failure Using the Blood Metabolic Profile of a Liver Recipient. *Transplantation.* 2007;4(83):517–521.
43. Olie SE, Staal SL, Ter Horst L, et al. Diagnostic accuracy of inflammatory markers in adults with suspected central nervous system infections. *J Infect.* 2024;88(3):106117.
44. Muireann Coen, Matthew O'Sullivan, William A. Bubb, et al. Proton Nuclear Magnetic Resonance-Based Metabolomics for Rapid Diagnosis of Meningitis and Ventriculitis. *Clinical Infectious Diseases.* 2005;41:1582–1590.
45. Rasmussen NF, Green A, Allin KH, et al. Clinical procedures used to diagnose inflammatory bowel disease: real-world evidence from a Danish nationwide population-based study. *BMJ Open Gastroenterol.* 2022;9(1):e000958.
46. Julian RM, Elaine H, Fatima K, et al. Rapid and Noninvasive Metabolomic Characterization of Inflammatory Bowel Disease. *Journal of Proteome Research.* 2007;6:546–551.
47. Lista S, González-Domínguez R, López-Ortiz S, et al. Integrative metabolomics science in Alzheimer's disease: Relevance and future perspectives. *Ageing Res Rev.* Author manuscript. 2023;89:101987.
48. Zhao L, Wang C, Peng SJ, et al. Pivotal interplays between fecal metabolome and gut microbiome reveal functional signatures in cerebral ischemic stroke. *Transl Med.* 2022;20(1):459.
49. Huang W, Hong X, Huang C, et al. Precision diagnosis model for treatment-resistant depression integrating serum metabolomics and clinical risk factors. *Front Psychiatry.* 2026; 17:1826019.
50. Shih PB. Metabolomics Biomarkers for Precision Psychiatry. *Adv Exp Med Biol.* Author manuscript. 2019;1161:101–113.
51. Fu Z, Xu X. Lysosomal checkpoints in renal autoimmunity: from antigen processing to metabolic-immune crosstalk. *Front Immunol.* 2026;17:1830023.
52. Heckscher S, Ihlo NA, Schueler J, et al. Metabolomic profiling of renal cyst fluid in advanced ADPKD: insights from dialysis and transplantation cohorts. *Metabolomics.* 2025;21(4):90.
53. Budnick I, Argabright A, Anderson CC, et al. Plasma metabolomics analysis in murine prerenal azotemia reveals changes in energy substrates, amino acid metabolism, and uremic toxins. *Am J Physiol Renal Physiol.* 2026;330(6):F683–F701.
54. Schlosser P, Scherer N, Grundner-Culemann F. Genetic studies of paired metabolomes reveal enzymatic and transport processes at the interface of plasma and urine. *Nat Genet.* 2023; 55(6):995–1008.
55. Shih T, Hodeify R, Kaur J, et al. Machine Learning-Driven Metabolomic Biomarker Discovery in Glioblastoma: Advances, Challenges, and Future Directions. *Int J Mol Sci.* 2026;27(9):3842.
56. Ding L, Zhang M, Fan B, et al. Metabolomics reveals key biomarkers for ischemic stroke: a systematic review of emerging evidence. *Front Neurol.* 2025;16:1630390.