



# Metabolomics Role in Health and Disease: Current Status and Future Directions

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## Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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**Review Article**

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## ABSTRACT

The field of metabolomics involves the high-throughput identification and measurement of all endogenous and exogenous low-molecular-weight (<1kDa) small molecules or metabolites in a biological system by analyzing the metabolome in cells, biofluids, tissues, or organisms. Metabolome-wide association studies (MWAS), metabolic phenotyping, single-cell epidemiologic population studies, precision metabolomics, and in combination with other omics fields like integrative omics, biotechnology, and bioengineering are some of the applications of metabolomics in health and disease scenarios. Metabolomics and its potential to enhance human health, along with its developments and implications for pharmacometabolomics, lifespan, cancer, and the exposome, are the main focus of this review. Metabolomic profiles will facilitate the development and improvement of therapeutic strategies to treat human diseases. Future years will see a rise in the application of metabolomics to drug development, aging, and disease monitoring and diagnosis. Its potential extends to food science, and environmental research. Through clinical metabolomics studies, which may also uncover diagnostic biomarkers that predict disease risk, cardiometabolic disorders can be better understood. Metabolomics is already being applied in biomedical settings to develop drugs by using acylcarnitines, phospholipids, genomes, and branch-chain amino acids that are specific to monitoring the emergence of metabolic diseases such as obesity and diabetes. Indicators derived from metabolomics should be evaluated for therapeutic efficacy and adaptability, and their optimal application in large clinical settings should be the focus of future research.

*Keywords: Metabolomics; health; disease; metabolites; Biomarker.*

## 1. INTRODUCTION

The rapidly developing field of metabolomics aims to accurately identify and measure all endogenous and exogenous low-molecular-weight (<1kDa) small molecules or metabolites in a biological system in a high-throughput way. The proteome, genome, lifestyle, environment, drugs, and underlying disease all have an upstream influence on the composition of these endogenous compounds (Zhou and Zhong, 2022). The study of metabolites, which are tiny chemical entities involved in biological systems' cellular processes, is known as metabolomics. It is used in molecular and personalized healthcare in clinical chemistry, transplant monitoring, newborn screening, pharmacology, and toxicology (Zhou and Zhong, 2022). The development of analytical techniques and bioinformatics has led to the emergence of metabolomics, a state-of-the-art omics technique. In order to identify and describe the metabolome, the metabolomics approach typically uses advanced analytical chemistry tools like nuclear magnetic resonance (NMR) and mass spectrometry (MS) in conjunction with different chromatographic techniques, such as gas chromatography (GC-MS) or liquid chromatography (LC-MS), with an emphasis on molecules smaller than 1500 Da found in cells, organs, tissues, or biofluids (Wishart, 2018; Sun et al., 2019).

The new field of medical genomics offers cutting-edge technological instruments for identifying genetic susceptibilities to diseases. But metabolomics allows us to go further by linking disorders and defects in gene expression to the pathological phenotype. Although the concept of "clinical metabolomics" was first introduced in 2008, the term was first used in the literature in 2009 (Le Gouellec et al., 2023). The goal of clinical metabolomics is to identify metabolic signatures in bodily fluids (plasma, urine, saliva, cerebrospinal fluid, etc.) or tissues that are impacted by genetics, epigenetics, dietary patterns, environmental factors, and behavior in order to evaluate and forecast a subject's health and disease risk (Ceglarek et al., 2009; Mallu et al., 2021). A collection or combinations of impacted metabolites make up metabolic signatures (Wishart, 2018).

Metabolomics' use in both health and disease has grown in importance. Based on a particular metabolic signature, metabolomics makes it possible to identify biomarkers for disease diagnosis, prognosis, and response to treatment (Cheng et al., 2012). The pathophysiology of complex diseases like cancer, neurodegenerative diseases, cardiovascular diseases, and metabolic syndrome can be largely explained by such metabolic profiles (Neergaard et al., 2017; Mallu et al., 2021; Vo and Trinh, 2024). Furthermore, metabolomics is

crucial to precision medicine because it allows for the identification of individual metabolic variations that can support tailored treatment approaches (Beger et al., 2016; Nielsen, 2017). According to that perspective, metabolomics is now a potent addition to personalized medicine, bringing fresh insights into the mechanisms underlying illnesses. Biomarkers are important in healthcare, particularly in diagnosis, prognosis, and treatment monitoring, since they are the quantifiable foundation of biological states and conditions (Califf, 2018). Biomarkers are crucial in diagnostics because they enable early and precise disease diagnosis, frequently before symptoms appear. This is especially true for diseases like cancer, where early intervention greatly enhances results. Particular metabolite profiles, for instance, can help distinguish between disease stages or subtypes in order to improve diagnostic accuracy and support patient stratification (Prat et al., 2021; Deng et al., 2022).

Identifying markers of disease severity or recurrence can help healthcare providers predict disease trajectory and appropriately plan interventions, especially for chronic and complex diseases where metabolic biomarkers may indicate the risk for complications or rapid development of the disease process. Biomarkers help monitor treatments by providing real-time responses in patients, allowing for the examination of efficacy and possible treatment-related side effects, allowing for modifications of therapeutic regimens for maximum efficacy with minimum side effects (Vo and Trinh, 2024).

According to Vargas and Harris (2016), biomarkers play a significant role in advancing precision medicine by facilitating more individualized, proactive, and efficient approaches to healthcare delivery. New technical tools for identifying genetic susceptibilities to diseases have emerged with the recent rise of medical genomics. However, by linking the pathological phenotype to disorders and defects in gene expression, metabolomics allows us to go further. While the concept was first introduced in 2008, the term "clinical metabolomics" was first used in the literature in 2009 (Damiani et al., 2020).

In clinical metabolomics, metabolic signatures in bodily fluids (plasma, urine, saliva, cerebrospinal fluid, etc.) or tissues which are influenced by genetics, epigenetics, dietary patterns, environmental factors, and behavior are identified in order to evaluate and forecast a

subject's health and disease risk (Cheng et al., 2012). A group or combination of metabolites that are impacted make up metabolic signatures. In addition to being studied peripherally, as in biofluids like blood plasma, which contains a variety of metabolites that reflect organ metabolic activity and offer important pathophysiological information, the metabolome can also be studied intracellularly, exposing functional abnormalities at the cellular level (Vo and Trinh, 2024).

Human plasma contains both endogenous and environmental metabolites. A number of factors, including dietary patterns, gut microbiota, and lifestyle choices (such as smoking or physical activity), greatly impact the metabolome's variability, which is partially inherited. Individual metabolic variability is mostly influenced by diet and microbiota, which makes each person's metabolotype distinct (Vo and Trinh, 2024). Nonetheless, a person's metabolotype stays largely constant over time if there are no notable changes in their health.

#### **The analysis of metabolites is predicated on two broad methods:**

1. Targeted metabolomics is the study of identifying a particular group of metabolites.
2. Untargeted metabolomics compares and identifies as many metabolites as possible between samples, including unknown ones, using an objective method. The latter strategy allows for the routine detection of numerous metabolite features peaks that correspond to individual ions with unique mass-to-charge ( $m/z$ ) ratios and retention times (RT) using LC/MS-based techniques (Vo and Trinh, 2024). The particular intended application will determine which of these methods is best.

The general trends of recent discoveries and applications of metabolomics-based biomarkers, as well as their revolutionary effects on personalized medicine and precision health, are summarized in this review. It is becoming more feasible to find disease biomarkers, even for complex conditions like cancer, neurodegenerative diseases, cardiovascular diseases, and metabolic syndrome, thanks to technological advancements and metabolomics analysis capabilities. Although early diagnosis and classification are greatly enhanced by these biomarkers, they also enable a much more nuanced understanding of individual variability in

disease progression and response to treatment. This review's objective is to examine these new metabolomics biomarker discoveries with an emphasis on how they may help with healthcare personalization. The translational development of metabolomics for use in mainstream clinical practice is also covered, with particular emphasis on how metabolomics can transform healthcare from a one-size-fits-all model to a highly individualized one where any health risk can be promptly identified and treatment can be tailored for optimal efficacy. Methods for metabolomics research: There are two main methods for metabolomics research:

1. Mass spectrometry (MS)-based metabolomics.
2. Nuclear magnetic resonance (NMR) spectroscopy.

By combining these methods, metabolome coverage can be improved by addressing many of their individual shortcomings (Wilkins and Trushina, 2018). While NMR is useful for identifying core metabolites in important metabolic pathways, MS-based metabolomics offers a broad metabolite coverage that includes polar metabolites as well as non-polar lipids and is particularly good at detecting low-abundance metabolites (Wilkins and Trushina, 2018). Additionally, NMR allows for the study of a large number of participants due to its low cost, high throughput, and analytical power (Surendran et al., 2022).

Although the discovery of new biomarkers in metabolic pathways has contributed to the pathogenetic understanding of disease pathways, untargeted metabolomics has the potential to identify metabolites that may not be recognized due to their absence from the software library (Odom and Sutton, 2021).

## **2. BIOMARKERS OF METABOLIC AND CARDIOVASCULAR DISEASES USING METABOLOMICS**

### **2.1 Cardiovascular Biomarkers**

The metabolomics of cardiovascular disease have identified lipid biomarkers and other metabolites that describe key pathophysiological characteristics, such as inflammation, oxidative stress, and disrupted lipid metabolism (Upadhyay, 2015; Vona et al., 2019). In addition to helping to track the progression of the disease, these biomarkers have excellent diagnostic and

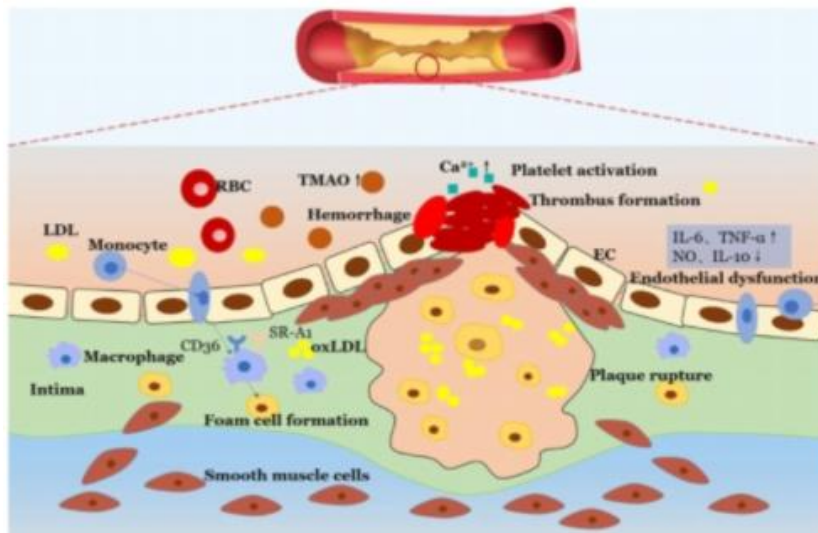
prognostic values for identifying individuals who are at risk of cardiovascular diseases (CVD). By offering details on alterations in lipid metabolism that result in atherosclerosis and CVD, lipid biomarkers play a crucial role in determining the risk of CVD. Higher levels of ceramides have been linked to heart failure and atherosclerosis (Vona et al., 2019), indicating their involvement in inflammatory pathways and cellular apoptosis. More recently, certain lipid metabolites have emerged as novel biomarkers in atherosclerosis. CVD is linked to other non-lipid metabolites, including betaine (Millard et al., 2018), branched-chain amino acids (BCAA) (Doestzada et al., 2022), and trimethylamine N-oxide (TMAO) (Park et al., 2019). As a byproduct of the gut microbiota's metabolism of carnitine and choline, TMAO increases the amount of cholesterol that deposits in arterial walls, increasing the risk of atherosclerosis (Fig. 1) (Zhu et al., 2020).

Cardiovascular problems are linked to elevated BCAA levels, which are known to cause insulin resistance and metabolic syndrome (Lynch and Adams, 2014). Betaine may help prevent heart disease because it is a metabolite that is involved in the metabolism of homocysteine, which is linked to improved endothelial function and decreased inflammation (Zhao et al., 2018). In addition to improving CVD risk prediction, these biomarkers offer potential targets for therapeutic intervention, which aids in the development of more individualized and preventive strategies for cardiovascular health. Clinicians can better risk-stratify patients, track the course of the disease, and improve their treatment plans by characterizing these particular lipid and metabolic biomarkers.

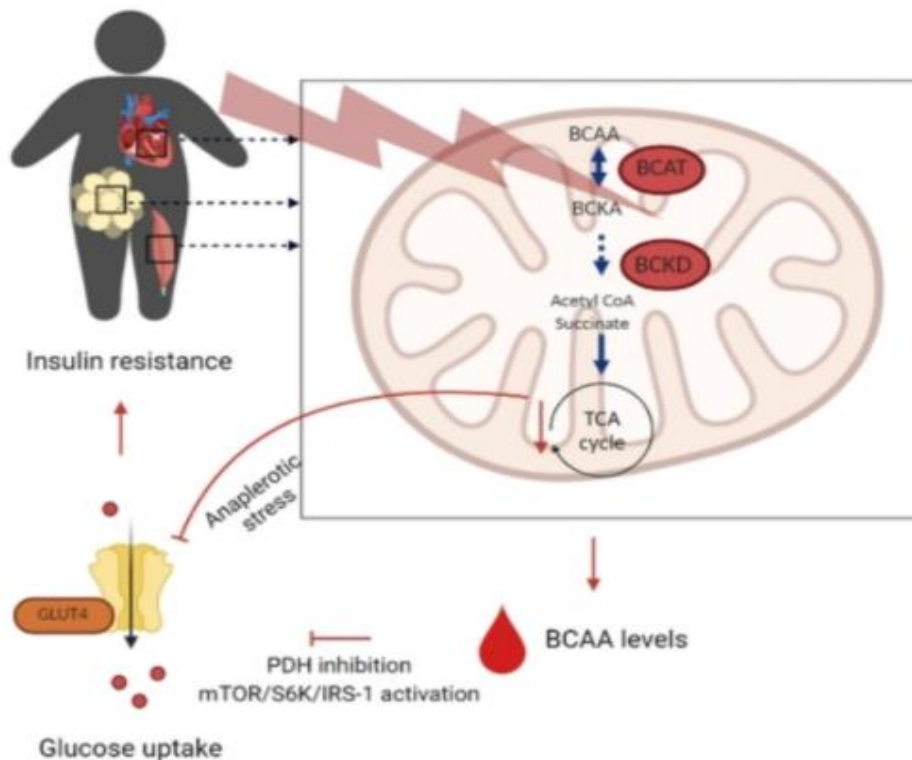
### **2.2 Metabolic Syndrome and Diabetes**

In diabetes and metabolic syndrome, biomarkers based on metabolomics provide information about insulin resistance, obesity, and overall metabolic dysfunction that can be linked to either of these conditions (Park et al., 2015). Indeed, it has been suggested that biomarkers improve metabolic health management by enabling early detection, focused intervention, and therapeutic response monitoring. Insulin resistance and general metabolic dysfunction are modulated by amino acid biomarkers (Gar et al., 2018). High levels of the BCAAs leucine, isoleucine, and valine are frequently linked to insulin resistance and are observed in metabolic syndrome and type 2 diabetes (T2D) (Andersson-Hall et al., 2018). Because

BCAA interferes with insulin signaling, muscle cells are unable to absorb glucose as well as lipids build up (Fig. 2) (Vanweert et al., 2022).



**Fig. 1. TMAO's function in the development and formation of atherosclerotic lesions. High levels of TMAO in the bloodstream are essential for the development of foam cells and endothelial dysfunction; TMAO can stimulate platelets and encourage the formation of thrombi, which increases the risk of rupture of the atherosclerotic plaque Copyright Wiley (2020) (Zhu et al., 2020)**



**Fig. 2. Diagrammatic representation of the processes that connect insulin resistance and BCAA catabolism. GLUT4 glucose transporter type 4, IRS-1 insulin receptor substrate-1, PDH pyruvate dehydrogenase complex, S6K ribosomal S6 kinase, mTOR mammalian target of rapamycin complex, and BCAA branch-chain amino acids. (Vanweert et al., 2022). Copyright Nature Publishing Group (2022)**

A higher risk of type 2 diabetes has also been linked to aromatic amino acids like phenylalanine and tyrosine, which are a sign of impaired amino acid metabolism in obesity and insulin resistance (Luo et al., 2020). Since impaired lipid metabolism is one of the factors contributing to insulin resistance and systemic inflammation, lipid biomarkers are essential in the development of diabetes and metabolic syndrome. High levels of obesity are associated with free fatty acids (FFAs), which exacerbate inflammation and insulin resistance (Marko et al., 2024).

According to Roszczyc-Owsiejczuk et al. (2021), ceramides, a class of sphingolipids, are closely linked to lipid-induced cellular stress and apoptosis and are implicated in insulin resistance. Ceramides are a potential target for therapy because they are predictive of metabolic dysfunction and the onset of type 2 diabetes (Chaurasia et al., 2021). Metabolites of the tricarboxylic and glycolytic acid cycles are examples of additional biomarkers. The end products of glycolysis, lactate and pyruvate, have been found to be elevated in metabolic syndrome, indicating a disruption in the metabolism of glucose (Rabinowitz and Enerbäck, 2020). Insulin resistance-related mitochondrial dysfunction and elevated levels of tricarboxylic acid cycle intermediates, such as citrate and succinate signaling, have been linked to disruptions in energy metabolism in obese individuals (Ives et al., 2020).

Additionally, biomarkers like these are crucial for the early detection of metabolic diseases and have bearing on individualized treatment plans. In addition to identifying individuals at high risk for diabetes and metabolic syndrome, such surveillance of particular metabolic signatures can give clinicians the ability to track the progression of the disease in real time, allowing them to adjust their intervention to maximize metabolic health (Ives et al., 2020).

### **3. METABOLOMICS-BASED BIOMARKERS FOR CANCER**

#### **3.1 Changes in Metabolism in Cancer**

Compared to normal cells, cancer cells exhibit significant metabolic reprogramming that enables them to invade, multiply, and survive quickly (Schiliro and Firestein, 2021). This type of metabolic change has been referred to as the "Warburg effect" (Liberti and Locasale, 2016; DeBerardinis and Chandel, 2020). Even when

oxygen is present, aerobic glycolysis is preferred over oxidative phosphorylation. Due to this process, cancer cells generate massive amounts of lactate, which alters the tumor microenvironment's composition and encourages growth and immune evasion (Beloribi-Djefafia et al., 2016).

Furthermore, in order to maintain high cell division rates, cancer cells exhibit altered lipid metabolism, amino acid dependence (Lieu et al., 2020), and increased nucleotide synthesis (Mullen and Singh, 2023). For identifying specific biomarkers linked to these specific cancer changes in metabolism, metabolomics has proven to be very helpful. According to Danzi et al. (2023), metabolomics profiling of metabolites in blood, tissue, and other biofluids reveals metabolic signatures linked to cancer that can differentiate cancerous cells from healthy cells. Some oncometabolites, like fumarate, succinate, and 2-hydroxyglutarate (2-HG) in gliomas, act as genetic mutations in metabolic enzymes in addition to being biomarkers for particular types of cancer (Sciacovelli and Frezza, 2016; Liu and Yang, 2021).

Potential treatment targets are revealed by these tumor-specific metabolites, which provide insight into tumor metabolism. Additionally, the biomarkers obtained through metabolomics enable the advancement of personalized and precision oncology by facilitating early cancer diagnosis, treatment response, and disease surveillance (Mateo et al., 2022). Through metabolomics, this gives physicians the ability to see how cancer cells alter their metabolic activity in real time as a treatment progresses; as a result, these facts open the door to targeted interventions and individualized therapeutic approaches.

#### **3.2 Important Biomarkers in Cancer**

In cancer diagnosis, prognosis, and treatment targeting, biomarkers particularly oncometabolites are important (Kes et al., 2020). Mostly caused by mutations in metabolic enzymes, oncometabolites are metabolic intermediates that, when present in abnormal amounts, cause neoplastic disease (Yong et al., 2020). In general, these biomarkers are extremely valuable for predicting disease outcomes and treatment response in addition to being used to identify cancers. Mutations in the isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) enzymes in gliomas and acute myeloid leukemia

(AML) (Fig. 1) produce 2-HG, a well-known oncometabolite (Rakheja et al., 2013).

Because 2-HG is a factor that damages cellular differentiation at high levels, which leads to tumorigenesis, high levels of 2-HG function as both a diagnostic and a prognostic biomarker (Wang et al., 2013). For example, Dinardo et al. 2013 emphasize the value of 2-HG in AML for both diagnosis and prognosis (DiNardo et al., 2013). This study showed that IDH1 and IDH2 mutations were linked to significantly elevated serum 2-HG levels, and at a threshold of 700 ng/mL, the diagnostic sensitivity and specificity were high, at 86.9% and 90.7%, respectively. Clinical outcomes were also linked to serum 2-HG levels, with higher levels being associated with a worse prognosis and a greater tumor burden.

The results suggest that 2-HG may be a promising non-invasive biomarker for detecting IDH mutations and tracking the progression of the disease and response to treatment in AML patients. Giving some methodological or standard information about the clinical validation and application of biomarkers would also be pertinent to the research on them. Furthermore, Miller et al. highlight the importance of IDH mutations and their metabolite, 2-HG, in the diagnosis and management of gliomas (Miller et al., 2023). A reliable biomarker for IDH-mutant gliomas, elevated 2-HG levels can be found using non-invasive techniques. Clinically speaking, IDH mutations differ from gliomas with wild-type IDH in that they offer higher survival rates than are otherwise observed. Targeted treatments for these mutations also have the potential to alter the tumor ecosystem in order to enhance therapeutics. These findings demonstrate how crucial IDH mutations are to improving glioma diagnosis and treatment accuracy. According to Dallas Pozza et al. (2020), succinate is another significant biomarker that builds up in some forms of paragangliomas and pheochromocytomas as a result of mutations in the enzyme succinate dehydrogenase (SDH). Similarly, hereditary leiomyomatosis and renal cell carcinoma cause fumarate to build up as a result of mutations in fumarate hydratase (FH) (Trpkov et al., 2016; Wang et al., 2024).

Thus, these metabolites play a role in identifying hereditary cancer syndromes and assessing cancer risks (Collins et al., 2017; Di Gregorio et al., 2021) by acting as "oncometabolites" that drive DNA methylation (Lanzetti, 2024) and hypoxia-like responses (Fandrey et al., 2019).

According to Vo and Trinh (2024), alterations in lipid metabolism metabolites, such as phosphocholine, are also being found to be biomarkers for prostate and breast cancers. Tumor growth is indicated by elevated levels of phosphocholine and other lipid-related metabolites, which can also provide diagnostic details about different cancer subtypes.

In addition to supporting early diagnosis, these important biomarkers also offer valuable insights into tumor behavior and enable personalized prognosis, which leads to targeted therapies. As science continues to advance, the identification of biomarkers and their clinical applications continue to grow. According to Vo and Trinh (2024), these enhance precision oncology and enable therapies that are truly customized to a patient's metabolic profile.

## **4. BIOMARKERS FOR MENTAL HEALTH AND NEURODEGENERATIVE DISEASE**

### **4.1 Neurodegenerative Diseases and Metabolomics**

A powerful tool in the hunt for neurodegenerative diseases is metabolomics, which makes it possible to identify biomarkers connected to the course of the illness and use them for diagnosis and treatment monitoring. In the early stages of detection and differential diagnosis, diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are useful because they exhibit specific metabolic alterations linked to the underlying pathophysiological mechanisms in these conditions (Dubois et al., 2023). Glutamate, myoinositol, and phosphatidylcholine are biomarkers of Alzheimer's disease that are associated with inflammation, oxidative stress, and neuronal damage (Zhang et al., 2023; Revegla et al., 2023; Wang et al., 2024). Low levels of acetyl-L-carnitine are linked to mitochondrial dysfunction and cognitive decline (Pennisi et al., 2020), while elevated myoinositol levels have been linked to amyloid plaque deposition, one of the hallmark events of AD (Voevodskaya et al., 2016). Early intervention may be possible because other lipid-related metabolites, which involve specific phospholipids, are being investigated as biomarkers of the preclinical stages of AD. Dopamine, uric acid, and homovanillic acid are the main metabolomics biomarkers that have been investigated in the context of Parkinson's disease (Kremer et al., 2021). Dopamine depletion brought on by dopaminergic neuron

degeneration is a key component of Parkinson's disease.

Conversely, there is an increase in homovanillic acid, a dopamine metabolite that could indicate the severity of the illness (Kremer et al., 2021). Oxidative stress has been implicated in a higher risk of Parkinson's disease (PD), as evidenced by lower levels of the antioxidant uric acid (Seifar et al., 2022). In ALS, biomarkers like creatine, ascorbate, and different amino acids show abnormalities in energy metabolism, neuroinflammation, and oxidative stress (Kori et al., 2016; Lanznaster et al., 2018). While branched-chain amino acid changes reflect disruptions in the muscle metabolism of these vital nutrients in ALS patients, lower creatine levels signify deficiencies in cellular energy (Parvanovova et al., 2024).

Profiling these biomarkers using metabolomics offers a better understanding of the mechanisms underlying neurodegenerative disease, which may lead to early diagnosis and help distinguish it from other conditions. Additionally, because metabolite levels can be tracked to evaluate treatment effectiveness and select individualized therapeutic approaches in neurodegenerative care, these biomarkers can provide insights into the development of targeted therapies (Parvanovova et al., 2024).

## 4.2 The Biomarkers of Mental Health

The field of mental health research has seen a lot of use of metabolomics, particularly in the hunt for biomarkers linked to a range of psychiatric conditions, such as anxiety, bipolar disorder, schizophrenia, and depression (Abi-Dargham et al., 2023). The examination of neurotransmitter pathways and metabolites associated with the gut-brain axis may yield markers for the biochemical underpinnings of mental health disorders, enabling more precise diagnosis and customized treatment plans. Because they directly affect brain activity and mood regulation, neurotransmitter metabolites are significant in psychiatric disorders. For instance, serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) is the subject of much research in relation to mood disorders (Jayamohananan et al., 2019).

Likewise, dopamine and homovanillic acid dysregulation is associated with schizophrenia and bipolar disorder (Wada et al., 2022), while depression is said to be associated with lower levels of serotonin and its metabolites (Moncrieff et al., 2023). A known inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), has been linked to symptoms of anxiety and depression. Variations in GABA levels reflect shifts in mood

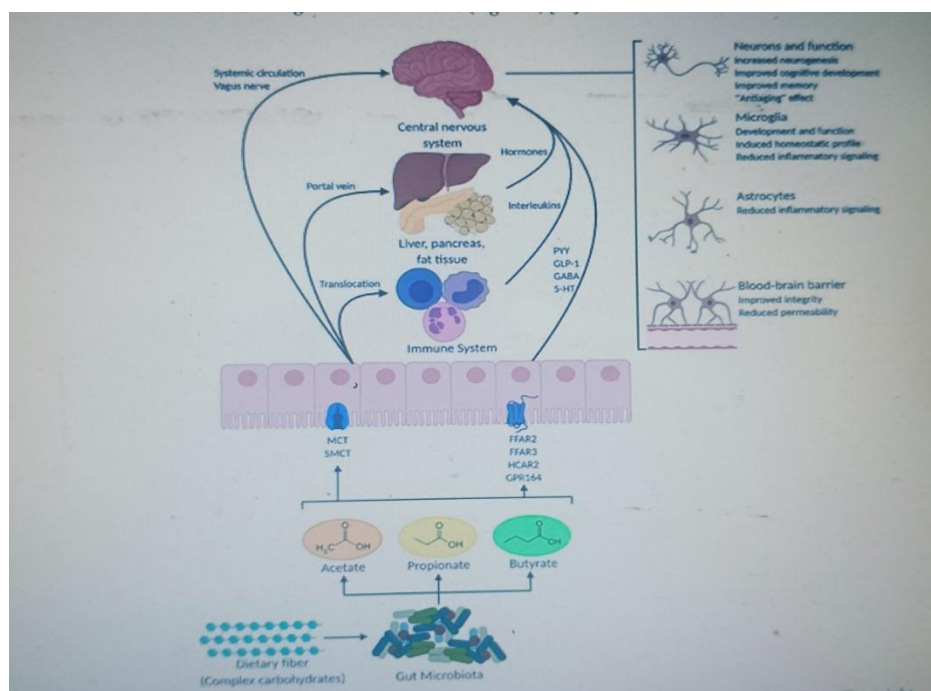


Fig. 3. Potential pathways through which SCFAs influence gut–brain communication. Copyright Frontiers Media SA (2020) (Silva et al., 2020)

regulation and stress modulation (Prévot and Sibille, 2021). Furthermore, metabolites generated by the gut-brain axis are becoming more widely acknowledged for their role in mental health (Góralczyk-Bińkowska et al., 2022).

Intestinal microbiota activity produces short-chain fatty acids (SCFAs), like butyrate and propionate, which impact neuroinflammation, stress reactions, and emotional regulation systems (Fig. 2) (Silva et al., 2020).

Given their role in reducing inflammation and maintaining the integrity of the blood-brain barrier, low levels of SCFAs have been proposed to be linked to anxiety and depression (Silva et al., 2020). Tryptophan and kynurenine, two other gut-derived metabolites, have been linked to mood disorders and schizophrenia and are linked to immunological responses and neurotransmitter synthesis (Marx et al., 2021). Not only can these metabolomic biomarkers reveal the biochemical foundations of psychiatric disorders, but they will also enable a more individualized approach to mental health treatment. Continuous monitoring of these biomarkers would assist medical professionals in streamlining diagnostics, customizing treatments, and probably improving patient outcomes by providing more targeted interventions (Marx et al., 2021).

#### **4.3 Potential Early Diagnosis Biomarkers for Mental Health and Neurodegenerative Diseases**

In the diagnosis and treatment planning of neurological and psychiatric disorders, biomarkers based on metabolomics hold great promise (Török et al., 2020; Mallu et al., 2021). Through the identification of particular metabolic alterations that take place even prior to the manifestation of clinical symptoms, these biomarkers are anticipated to aid in early intervention, improving the prognosis by delaying the course of the disease (Sun et al., 2023).

They are useful for early diagnosis because, for example, a preclinical stage of the disease has been noted in which AD patients exhibit elevated myo-inositol and alterations in phospholipid profiles (Ahanger et al., 2024). If these biomarkers are discovered early, prompt interventions that postpone cognitive decline will be possible. Metabolomics as a foundation for biomarker discovery for the early diagnosis of

psychiatric and neurodegenerative disorders has produced very encouraging results in clinical studies. Alpha-synuclein aggregates and urates have been identified as interesting early indicators of Parkinson's disease (PD) due to their lower levels in CSF (Ganguly et al., 2021). According to Averina et al. (2024), depression and schizophrenia have been linked to alterations in serotonin and dopamine metabolism.

Moreover, increased kynurenic acid levels are associated with oxidative stress and neuroinflammation, providing insight into the early phases of mood disorders and schizophrenia (O'Farrell and Harkin, 2017; Mor, et al., 2021). These gut-brain axis-derived altered SCFAs are emerging as promising biomarkers for mental health conditions, particularly depression (O'Riordan et al., 2022). Furthermore, ALS and MS can be accurately diagnosed early thanks to neurofilament light chain levels in ALS and sphingomyelin reductions in MS (Yang et al., 2022). According to Sacchet et al. (2024), elevated cortisol levels in anxiety disorders raise the risk and help make a diagnosis even before all symptoms appear.

In addition to offering tools for early detection, these biomarkers also enable the application of tailored treatment to enhance prognosis and impede the progression of disease. Early detection of mental health conditions enables physicians to use treatment plans based on individual biochemical profiles that optimize an intervention's efficacy (Sacchet et al., 2024). It is hoped that the use of metabolomics-based biomarkers will eventually lead to a paradigm shift in how doctors choose treatments that are specific to each patient and diagnose illnesses early. This will improve patient outcomes by more effectively managing psychiatric and neurodegenerative conditions (Sacchet et al., 2024).

#### **5. DISEASE AND HEALTH METABOLOMICS**

Applications of metabolomics in health and disease include single-cell, epidemiologic population studies, metabolic phenotyping, metabolome-wide association studies (MWAS), precision metabolomics, and integrative metabolomics, which is the use of metabolomics in conjunction with other omics disciplines (Dalamaga, 2024). Live single-cell mass spectrometry (LSCMS), LC-MS/MS, GC-MS/MS,

and single-cell metabolomics and lipidomics technologies enable high-dimensional characterizations of individual cells, disease heterogeneity and complexity, and the identification, expression, and abundance of disease-associated metabolites and small molecules (Lempesis et al., 2022).

Cell-cell interactions and tumor heterogeneity were discovered through imaging MS analysis of human breast cancer samples at the single-cell level (Lempesis et al., 2022). Metabolomics fingerprinting and footprinting techniques, MWAS, and clinical biomarkers and various metabolotypes of disease severity correlated to exposures (Zhang et al., 2023) and biological outcomes (Sun et al., 2023) have been studied and identified in individuals and populations through metabolomics fingerprinting and footprinting techniques, which will facilitate precision medicine and public healthcare (Guo et al., 2023; Wang et al., 2023; Xu et al., 2023; Ou et al., 2024; Zhou et al., 2024; Xu, *et al.*, 2024).

The transition from genome-wide association studies (GWAS) to metabolome-wide association studies (MWAS) was initially defined in 2008 as "an investigation of the relationships between phenotype variation and disease risk factors through environmental and genomic influences" (Xu et al., 2023; Ou et al., 2024). Exposures to single individual phenotypes and populations, epidemiologic research, disease risk, metabolome-wide association studies, and precision medicine were proposed by Rattray and colleagues (Ou et al., 2024).

## **6. METABOLOMICS AND THE EXPOSOME**

Unique opportunities to identify food ingredients and comprehend their role in the dietary exposome and food quality are provided by metabolomics. Modern metabolomics techniques were employed in a study by Nikou et al. (2020) to find chemical biomarkers relevant to the production process, cultivation methods, and geographic origin of olive oil, a component of the Mediterranean diet that has been described as a nutritious dietary pattern. To examine intact oil and the associated polyphenols of extra virgin olive oils, metabolomic profiling using Flow Injection Analysis-Magnetical Resonance Mass Spectrometry (FIA-MRMS) and the LC-Orbitrap MS platform was employed. The approach may provide a means of combating food fraud and adulteration while also identifying elements of a

nutritious diet. Occupational exposures and patterns, such as shift work, are a significant component of the exposome. In recent years, shift work has been linked to a number of physiological changes and may be related to a number of diseases. Report by Borroni et al. (2023) assessed how night shift work affected the serum metabolome in a group of Italian female nurses who worked nights and female coworkers who did not. They found that there were variations in the levels of taurine, serotonin, aspartic acid, and certain lipids, all of which provide hints about the biological changes brought on by working nights. According to Barupal et al. (2022) Reprocessing metabolomics datasets that have already been published and made publicly available can alter the number of metabolite identifications made and possibly reveal new biomarkers that were overlooked during the initial processing, as the authors of the paper by Barupal et al. (2022) showed. In contrast to the initial data pre-processing method that employed the mass spectrometer manufacturer's software, the authors used MS-Dial, a publicly available program, for data pre-processing and applied less strict data processing thresholds. Different software and even small adjustments to pre-processing parameters can affect the quality and quantity of data reported, as the manuscript illustrated. This presents both opportunities and challenges. Keski-Rahkonen et al. (2021) and Barupal et al. (2022) two additional comments on the manuscript sparked a heated discussion that added to the metabolomics community's broader conversations regarding data pre-processing techniques, software and parameters, reporting standards and formats, and intercomparability among data pre-processing methods.

## **7. FUTURE DIRECTION OF METABOLOMICS**

Metabolomics technology will be integrated with other cutting-edge technologies to guarantee its expansion. MS-based metabolomics will be more precise, and a number of combined techniques, including GC/MS, LC/MS, and others, will provide a strong scientific basis for tackling the challenge of metabolite analysis and metabolic pathway discovery. Extended mass spectrometry holds a prominent position as a vital analytical tool in the field of metabolomics. The growth of this field has provided insight into the etiology of many diseases and assisted in the identification of numerous potential illness biomarkers (Xiong et al., 2020).

Some of the studies that have been assessed include research for recurrence testing, appropriate treatment, medication prognosis and prediction, and early disease diagnosis (Sun et al., 2019). LC, GC, or CE is used in most MS analytical procedures because biological mixtures are very complex. Rapidly growing applications using evolving separation mechanisms and protocols do present both opportunities and challenges, though. With the advent of chromatographic techniques, the capacity to separate metabolites and enhance the number of metabolites identified has surely improved (Li et al., 2017; Zhang et al., 2019).

The inability to analyze and relate the results of the latter studies, which are carried out on comparable or identical samples gathered by multiple research institutions, is a major barrier. This is the biggest obstacle to progress in this field. Other factors, such as sample preparation, sample matrix, and residual effects, can also contribute to data variability. To overcome these challenges, it is essential to switch from calculating relative metabolite concentrations to more accurate absolute concentration measurements, regardless of the analytical platform, approach, and procedure. This approach is important even though MS finds it difficult.

## 8. CONCLUSION

A helpful method for identifying disease-related metabolites in biofluids or tissue as well as for classifying and/or characterizing molecular patterns linked to disease or treatment that are produced from metabolites is mass spectrometry (MS) based metabolomics/lipid omics. We continue to discover new biomarkers in metabolomics that redefine health and disease diagnostic precision and provide insight into the biochemical etiology of a wide range of diseases. This makes metabolomics a potentially useful platform for prognosis, early detection, and the application of tailored treatment plans founded on a thorough comprehension of metabolic changes brought on by illness and environmental influences. The metabolic profiling biomarkers have the potential to improve diagnosis and enable targeted interventions in metabolic syndromes, cancers, cardiovascular diseases, and neurodegenerative disorders. But before the biomarkers can truly reach the clinic, a lot more work needs to be done. To ensure that the biomarkers are accurate and repeatable across a range of populations, considerable attention must

be paid to inter-individual variability, environmental factors, and data complexity in metabolomics. Confounding factor considerations and a strict methodology in biomarker validation with large cohorts are necessary for that. Depending on the features of metabolic profiles, biomarker-focused research and translation to clinical practice are constantly pushing this field away from standard treatment and toward personalized therapies. In order to translate biomarkers from metabolomics into clinical practices for improved patient outcomes and to steer the trajectory of precision medicine, it will be necessary to overcome many of the current obstacles through ongoing research and collaboration among clinicians, researchers, and technologists.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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