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The Role of New-Generation Omics Technologies in Diagnosis, Monitoring, and Development of New Treatment Strategies for Inherited Metabolic Diseases

Olgaç et al. Metabolomics in Inborn Errors of Metabolism

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ABSTRACT
Omics technologies encompass a suite of high-throughput analytical techniques that enable comprehensive investigation of biological systems at the molecular level. A subset of omics technology, metabolomics, focuses on the comprehensive qualitative, quantitative, relational, spatial, and temporal analysis of metabolites under various conditions and states. Rare diseases are conditions that affect a relatively small number of people. Approximately 6,000-8,000 rare diseases have been identified to date. Inborn errors of metabolism (IEMs) represent a significant portion of rare diseases and have a genetic origin. Although IEMs are genetically based, the traditional one-gene-one-disease model is no longer universally accepted for these disorders. Each IEM presents a unique phenotype, necessitating a personalized approach. Therefore, metabolomics—the global study of small molecules, typically between 50 and 1500 Daltons—is expected to contribute significantly to a better understanding of the pathogenesis and pathophysiology of IEMs. This review discusses the current state of knowledge regarding the diagnosis, monitoring, and development of novel therapeutic strategies for patients with IEMs, based on the latest literature.
Keywords: Bioinformatics, Inborn Errors of Metabolism, Metabolomics

INTRODUCTION
"Omics" refers to the comprehensive study of biological systems. Omics technologies are high-throughput analytical techniques that allow for a deep dive into biological systems at the molecular level.[1] By characterizing and quantifying biological molecules on a large scale, omics techniques enable researchers to identify genetic, transcriptional, protein, and metabolic changes associated with various diseases.[2] Omics science encompasses several sub-disciplines, including genomics, transcriptomics, proteomics, metabolomics, lipidomics, epigenetics, glycomics, and metagenomics. These fields offer a holistic view of biological systems, from DNA to metabolites, allowing researchers to investigate complex interactions between biomolecules and drive advancements in fields such as medicine, agriculture, and environmental science.[3,4] For instance, genomic analysis can identify genetic predispositions to diseases, enabling early intervention. Proteomics can reveal abnormal protein patterns, leading to the discovery of new biomarkers for disease diagnosis. Ultimately, omics technologies hold the promise of personalized medicine by tailoring treatments to an individual's unique genetic and molecular profile.[1]
However, metabolomics is at the forefront of omics research most commonly used in medical practice. The metabolome represents the entire collection of small molecules (metabolites) within a biological sample. Metabolomics is the comprehensive study of these metabolites, examining their qualities, quantities, relationships, spatial distribution, and temporal changes under various conditions. In essence, metabolomics provides a snapshot of a cell, tissue, or organism's metabolic activity at a specific moment.[1] While genetic analysis offers insights into an individual's inherent potential, metabolomics complements this by revealing how genetic variations manifest at the phenotypic level. Furthermore, it explores the impact of environmental factors, diet, and lifestyle on metabolic processes, which can significantly influence disease development and progression. By identifying early metabolic changes associated with disease onset, metabolomics facilitates earlier diagnosis and intervention. Combining genetic and metabolomic data allows for the personalization of treatments based on an individual's unique metabolic profile.[5]

The Role of Omics Technologies in Diagnosing Inherited Metabolic Diseases (IMD)
Over the past two decades, the application of omics technologies to rare and IMD has undergone remarkable evolution. Initially, genomic approaches dominated the field, enabling the identification of novel pathogenic variants and expanding the catalog of IMDs through next-generation sequencing.[6] Subsequently, transcriptomics and proteomics facilitated a deeper understanding of dysregulated molecular networks, highlighting the limitations of the traditional "one gene–one disease" model.[4] With the advent of high-resolution mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, metabolomics has emerged as a powerful complement, bridging the gap between genotype and phenotype by capturing the real-time biochemical consequences of genetic defects.[7]
Recent literature emphasizes the advantages of integrated multi-omics approaches in IMD diagnosis and monitoring. For instance, genomics can identify disease-causing mutations, while metabolomics validates their functional impact through altered biochemical signatures.[9] Moreover, multi-omics studies have begun to uncover disease modifiers, reveal compensatory pathways, and identify novel

therapeutic targets, shifting the clinical approach from descriptive diagnostics toward precision medicine.[10] This evolution underscores the critical role of omics technologies in shaping both our understanding and the clinical management of IMDs.

Rare diseases are conditions that are infrequently observed in the general population. Approximately 6,000-8,000 rare diseases have been identified to date.[9] In the United States, a rare disease is defined as a condition that affects fewer than 1 in 200,000 people, while in Europe, it is defined as a condition affecting fewer than 50 in 100,000 people. According to the World Health Organization, a rare disease is considered to be a condition that affects fewer than 65 in 100,000 people.[6]

IMDs are genetic disorders that constitute a significant portion of rare diseases. These are complex medical conditions involving human organ systems and resulting from an enzyme defect in biochemical and metabolic pathways affecting protein, fat, and carbohydrate metabolism, or from impaired organelle function. This basic definition is a dynamic concept that varies as the genetic underpinnings of new diseases are discovered. While the presence of a biomarker was previously a prerequisite for the diagnosis of IMDs, this is no longer the case. On the other hand, the identification of new disease groups related to cellular traffic has highlighted the need for a more holistic approach to the concept of metabolic disease. Another consequence of this holistic approach is the elucidation of the relationships between functional processes within the cell (autophagy, inflammation, oxidative stress, immune dysregulation, energy homeostasis, etc.) and the role of these relationships in determining a patient's diagnosis, treatment, and prognosis. Omics technologies form the foundation of this newly emerging approach and will be the most important component in the medical practice of CMDs in the near future.[8,9]

Rare diseases are those that affect a small portion of the population. IMDs are caused by genetic defects in biochemical pathways. Traditionally categorized into intoxication type, energy metabolism disorders, and complex molecule disorders, metabolic disorders have recently been reclassified by the International Classification of Inherited Metabolic Disorders advisory group, outlining 1450 disorders.[6] While each IMD has a unique phenotype, the previously accepted one-gene-one-disease model is no longer sufficient to clarify their pathogenesis. Metabolomics, the study of small molecules, offers a comprehensive view of metabolic processes and can aid in understanding the pathogenesis and pathophysiology of IMDs.[7]

A deeper understanding of the biochemical and metabolic mechanisms underlying IMDs highlights the value of metabolomics in clinical practice. For example, in phenylketonuria (PKU), deficiency of phenylalanine hydroxylase impairs the conversion of phenylalanine to tyrosine, leading to the toxic accumulation of phenylalanine and the secondary depletion of neurotransmitter precursors. Metabolomics not only detects elevated phenylalanine, but also identifies secondary metabolites such as phenylpyruvic acid and N-acetylphenylalanine, which reflect broader disturbances in amino acid and neurotransmitter metabolism.[11]

Similarly, in maple syrup urine disease, defective activity of the branched-chain α-ketoacid dehydrogenase complex prevents degradation of leucine, isoleucine, and valine. This results in the accumulation of branched-chain amino acids and their corresponding ketoacids, which are neurotoxic. Untargeted metabolomics studies have revealed additional downstream perturbations in energy metabolism, mitochondrial function, and neurotransmitter pathways.[12]

In methylmalonic acidemia (MMA), deficiency of methylmalonyl-CoA mutase or defects in cobalamin metabolism disrupt the breakdown of odd-chain fatty acids and certain amino acids, causing accumulation of methylmalonic acid and propionylcarnitine. These metabolites interfere with the tricarboxylic acid (TCA) cycle, impairing ATP production and promoting mitochondrial dysfunction. Metabolomics has been instrumental in uncovering secondary elevations in acylcarnitines, organic acids, and neuroactive steroids that help explain the neurological and ocular complications of MMA.[13]

In lysosomal storage disorders (LSDs), such as Fabry and Gaucher disease, enzyme deficiencies result in the accumulation of undegraded sphingolipids. Metabolomics approaches have identified disease-specific biomarkers like globotriaosylsphingosine (Lyso-Gb3) in Fabry disease and glucosylsphingosine (Lyso-Gb1) in Gaucher disease. These molecules not only serve as diagnostic and monitoring tools but also provide mechanistic insight into how impaired lysosomal clearance disrupts lipid signaling and inflammatory pathways.[14]

Together, these examples illustrate how metabolomics provides a functional window into the biochemical consequences of specific enzyme deficiencies, linking genotype to phenotype and uncovering potential therapeutic targets.

The lack of specific symptoms, delayed diagnosis, and challenges in traditional diagnostic methods have spurred the integration of omics technologies into the diagnosis and management of IMDs. Omics technologies, such as genomics, transcriptomics, and metabolomics, provide a more holistic view of the disease, allowing for earlier diagnosis and tailored treatment. By identifying the underlying genetic and metabolic alterations, these technologies can help to prevent irreversible complications associated with IMDs.[7]

The clinical relevance of omics technologies extends far beyond basic research, offering direct benefits in the care of patients with IMDs. Metabolomics and other omics approaches enable earlier and more precise diagnosis compared to conventional biochemical methods. Tandem MS-based newborn screening, now standard in many countries, exemplifies how targeted metabolomics can detect dozens of IMDs in a single assay.[14] Furthermore, untargeted metabolomics has identified atypical biochemical signatures that broaden the phenotypic spectrum of known disorders and even reveal novel IMDs.[7]

Once a diagnosis is established, omics approaches facilitate longitudinal monitoring. Targeted metabolite panels, such as phenylalanine in PKU or Lyso-Gb3 in Fabry disease, are widely used to track treatment response and disease burden. Untargeted metabolomics can also capture broader pathway shifts over time, providing early warning of complications or metabolic decompensation.[15]

Omics data support personalized medicine by linking genetic defects to functional biochemical consequences. For instance, metabolomic profiling has demonstrated how amino acid-restricted diets alter tryptophan and tyrosine metabolism in PKU, informing dietary adjustments.[11] Similarly, in serine biosynthesis defects, metabolomics confirmed the biochemical benefit of serine and glycine supplementation, guiding therapy optimization.[10]

Emerging evidence suggests that omics biomarkers can serve as predictors of long-term outcomes. In Fabry disease, plasma Lyso-Gb3 levels correlate with disease severity and risk of organ complications.[12] In MMA, elevations of secondary metabolites such as neurosteroids have been associated with neurological decline, suggesting potential roles as prognostic indicators.[13]

Taken together, these examples underscore that omics technologies are not merely research tools, but practical instruments for clinical decision-making, from diagnosis through lifelong follow-up. As integration with genomic, proteomic, and transcriptomic data continues to advance, omics-based approaches are poised to transform the standard of care for patients with IMDs.

Methods Used in Metabolomics Technologies

Unlike genomics and proteomics, where the building blocks (nucleotides and amino acids) are relatively uniform, the metabolome comprises a diverse array of molecules with vastly different chemical structures. This diversity presents a significant challenge for metabolomic analysis, requiring the use of multiple analytical techniques and instruments. Furthermore, the wide range of metabolite concentrations adds complexity to both qualitative and quantitative analyses.[7]

Metabolomic analyses are broadly categorized into two approaches: targeted and untargeted. Targeted metabolomics focuses on measuring specific metabolites, such as those involved in particular biological pathways or associated with certain diseases. While highly sensitive and specific, this approach is limited to the pre-selected metabolites and cannot be used to discover unknown biomarkers.[16]

In contrast, untargeted metabolomics aims to comprehensively analyze all metabolites within a sample, including those that are yet to be identified. This approach provides valuable complementary information to transcriptomics and proteomics. Although the complete characterization of the metabolome remains a challenge due to the diverse nature and varying concentrations of metabolites, advancements in analytical technologies and expanding databases are continuously improving the sensitivity and specificity of untargeted metabolomics, making it a powerful tool for discovering new biomarkers.[17]

Commonly used techniques for metabolomic analysis include NMR spectroscopy and MS coupled with chromatography (GC-MS and LC-MS). NMR spectroscopy provides valuable information about the structure and dynamics of small molecules without requiring prior separation. However, MS techniques, such as GC-MS and LC-MS, offer significantly higher sensitivity and broader coverage, allowing for more accurate and comprehensive metabolite detection.

The typical metabolomic analysis workflow involves five key steps:

- Sample collection and storage.
- Metabolite isolation.
- Metabolite analysis using appropriate analytical techniques.
- Data filtering and processing.
- Biostatistical analysis.

Blood and urine samples are the most commonly used sources for metabolomic studies due to their easy accessibility. However, various other biological samples, including tissues and other bodily fluids, can also be analyzed.[16]

Omics Technologies in IMD

While metabolomics provides a functional snapshot of the biochemical consequences of genetic defects, the integration of other omics layers — such as genomics, transcriptomics, and proteomics — is essential to achieve a comprehensive understanding of IMDs.

Genomics remains the foundation for identifying causal variants and expanding the catalog of known IMDs. Next-generation sequencing has revealed hundreds of novel pathogenic mutations and has clarified genotype–phenotype correlations in disorders such as mitochondrial diseases and organic acidemias.[6]

Transcriptomics adds a dynamic layer by showing how gene expression changes under disease or treatment conditions. For example, RNA sequencing has uncovered secondary transcriptional dysregulation in LSDs, highlighting pathways involved in inflammation and autophagy that contribute to disease progression.[4]

Proteomics bridges the gap between gene expression and metabolite profiles, offering insights into enzyme abundance, activity, and post-translational modifications. In fatty acid oxidation disorders, proteomic profiling has identified altered mitochondrial protein networks, complementing metabolomic data and revealing novel therapeutic targets.[5]

Multi-omics integration is increasingly applied in IMDs, allowing for cross-validation of findings across molecular layers. A recent study combined genomics, transcriptomics, and metabolomics to demonstrate, the therapeutic effect of sodium phenylbutyrate in combined D,L-2-hydroxyglutaric aciduria, linking metabolite normalization with transcriptional rescue of mitochondrial pathways.[16] Such examples highlight the synergistic power of multi-omics approaches, which not only refine diagnosis but also generate mechanistic insights and guide treatment strategies.

Metabolomics plays a crucial role in diagnosing, monitoring, and managing many IMDs. Newborn screening programs often employ targeted metabolomics, such as measuring blood phenylalanine levels for PKU, using MS. In developed countries, these programs screen for numerous CMDs, including organic acidemias, fatty acid oxidation defects, and even lysosomal storage diseases.[14]

For CMDs requiring dietary restrictions, targeted metabolomics helps assess treatment adherence and effectiveness. It also provides insights into how specific diets impact various metabolic pathways.[11]

Biomarkers identified through metabolomics are valuable tools for diagnosing, monitoring, and predicting treatment responses in CMDs. For example, globotriaosylsphingosine (Lyso-Gb3), a biomarker for Fabry disease, was discovered through metabolomics research. It correlates with disease severity and decreases with effective treatment. Biomarkers can improve patient outcomes by providing crucial information about disease progression, treatment response, and potential complications.

Both targeted and untargeted metabolomics approaches are used to identify biomarkers. While research on untargeted metabolomics in CMDs is ongoing, studies have focused primarily on amino acid metabolism disorders (e.g., PKU, branched-chain amino acid disorders), BH_4 metabolism disorders, and galactosemia.

Untargeted metabolomics studies in PKU have identified potential biomarkers, including phenylpyruvic acid, phenylacetic acid, N-acetylphenylalanine, and N-lactoylphenylalanine. In other studies, metabolomics has revealed changes in indole metabolites in alkaptonuria and tyrosinemia following nitisinone treatment, shedding light on the impact of these metabolites on disease prognosis.[12,15] Gertsman et al.[19] demonstrated a change in indole metabolites following nitisinone treatment in patients with alkaptonuria and tyrosinemia. This research sheds light on the effects of indole metabolites on prognosis in disorders involving tyrosine metabolism. Norman et al.[20] showed, through metabolomic studies, that alternative pathways are activated in patients with hypertyrosinemia to compensate for elevated tyrosine levels. The discovery of these alternative pathways will shed light on new treatment options for patients with hypertyrosinemia. Glinton and colleagues have shown that supplementation with serine and glycine in patients with serine biosynthesis defects balances plasma phospholipid components.[10] In another study conducted in patients with organic aciduria and cobalamin C deficiency, neurosteroids were found to be significantly elevated , and it was suggested that this could shed light on the pathogenesis of accompanying ocular and neurological findings.[13]

Today, targeted metabolomics is used in the routine screening of several CMDs for which specific biomarkers have been identified (Table 1).[21]

Metabolomics research extends beyond diagnosis and monitoring; it holds significant promise for developing novel therapies for IEMs. For example, studies have demonstrated that fibroblast cultures from patients with methylmalonic aciduria exhibit disruptions in the TCA cycle. Notably, treatment with dimethyl oxoglutarate significantly improved these metabolic abnormalities. Similarly, research by Phua et al.[16] showed that sodium phenylbutyrate effectively reduced elevated levels of 2-ketoglutarate and 2-hydroxyglutarate in fibroblast cultures from patients with combined D,L-2-hydroxyglutaric aciduria, suggesting its potential as a therapeutic agent.[16]

The integration of multiple omics approaches — genomics, transcriptomics, proteomics, and metabolomics — offers significant promise for advancing the diagnosis and management of IMDs. Multi-omics approaches provide complementary information at different molecular levels: while genomics identifies pathogenic variants, transcriptomics captures gene expression changes, proteomics reveals alterations in protein abundance and modification, and metabolomics reflects the real-time biochemical consequences of these disturbances.

Applied together, these layers can enhance diagnostic accuracy. For example, genomic sequencing may identify variants of uncertain significance, but metabolomic or proteomic profiling can determine whether such variants cause measurable biochemical or protein-level abnormalities, thereby clarifying pathogenicity.[22] This integration reduces diagnostic uncertainty and supports earlier interventions.

Multi-omics also facilitates personalized medicine by capturing inter-individual variability in disease expression and treatment response. In disorders such as PKU, metabolomics has shown how dietary interventions alter amino acid and neurotransmitter metabolism, while transcriptomic and proteomic studies reveal downstream effects on neuronal and immune pathways.[11] Such combined insights enable tailored treatment plans based not only on genetic diagnosis but also on functional metabolic profiles.

Moreover, multi-omics data can uncover disease modifiers and therapeutic targets. In mitochondrial disorders, integrated omics analyses have identified compensatory pathways that mitigate energy deficits, suggesting novel pharmacological interventions. Similarly, a multi-omics study in combined D,L-2-hydroxyglutaric aciduria demonstrated that sodium phenylbutyrate therapy improved both metabolite profiles and transcriptomic signatures of mitochondrial function, providing mechanistic validation for treatment efficacy.[16]

Ultimately, multi-omics approaches shift the paradigm from descriptive diagnostics toward predictive and precision healthcare in IMDs. By combining molecular signatures across different layers, clinicians will be able to stratify patients more accurately, monitor disease trajectories, and optimize individualized therapy. This integration not only enhances our mechanistic understanding but also translates into tangible clinical benefits for patients with rare metabolic disorders.

CONCLUSION

In conclusion, both targeted and untargeted metabolomics approaches are instrumental in characterizing CMDs, identifying novel biomarkers, and guiding the development of effective diagnostic and monitoring strategies. Furthermore, these studies have shed light on previously unknown metabolites and metabolic pathways, generating valuable hypotheses about disease mechanisms and the impact of treatments. Given the often irreversible consequences of delayed diagnosis and the limited availability of effective treatments for many CMDs, continued investment in metabolomics research is crucial for improving patient outcomes.

Footnotes

Authorship Contributions

Surgical and Medical Practices:
Concept:
Design:
Data Collection or Processing:
Analysis or Interpretation:
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Table 1. Examples of biomarkers used in the diagnosis of several IEMs

IEM type	IEM subtype	Biomarker
Amino acid metabolism disorders	PKU	Phenylalanine (P)
	MSUD	Valine, leucine, isoleucine, allo-isoleucine (P)
	Tyrosinemia	Tyrosine (P) Succinylacetone (B, P, U)
	Homocystinuria	Homoscystine (P)
	MMA	Propionyl carnitine (C3) (B, P) Methylmalonic acid (Urine)
	Propionic acidemia	Propionyl carnitine (C3) (B, P) 3-hydroxy-propionic acid (U)
	Isovaleric acidemia	Isovaleryl carnitine (C5) (B, P) Isovaleric acid (U)
	Non-ketotic hyperglycinemia	Glycine (P, CSF)
Fatty acid oxidation disorders	Medium/short-chain acyl-CoA dehydrogenase deficiency (M/SCHAD)	3-hyroxy isobutyryl carnitine (B, P) (C_4-OH)
	MCAD	Hexanoyl carnitine (C6) Octanoyl carnitine (C8) Decanoyl carnitine (C10:1)
	VLCAD	Myristoyl carnitine (C14:0) Tetradecanoyl carnitine (C14:1) Tetradecadienoyl carnitine (C14:2)
	Biotinidase deficiency Holocarboxylase synthetase deficiency 3-methylcrotonylCoA carboxylase deficiency 3-hydroxy-3-methylcrotonyl-CoA carboxylase deficiency	3-hydroxy isovaleryl carnitine (C5-OH)
Lysosomal storage disease	Gaucher disease	Glycosylsphingosine (P) (Lyso-Gb1) Chitotriosidase (P)
	Fabry disease	Globotriaosylceramide (P) (Lyso-Gb3)
	Pompe disease	Glucotetrasaccharides (Glc4) (U)
	Niemann-Pick type C disease	Lyso-sphingomyeline 509 (P) (Lyso-SM 509)
	Krabbe disease	Galactosylsphingosine/psychosine (P)
	Mucopolysaccharidosis type I (Hurler syndrome)	Dermatan sulfate (U) Heparan sulfate (U)
	Mucopolysaccharidosis type II (Hunter syndrome)	Dermatan sulfate (U) Heparan sulfate (U)
	Mucopolysaccharidosis type III (Sanfilippo type A, B, C, D)	Heparan sulfate (U)
	Mucopolysaccharidosis type IVA (Morquio A syndrome)	Keratan sulfate (U) Kondroitin sulfate (U)
	Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)	Dermatan sulfate (U)
	Mucopolysaccharidosis type VII (Sly syndrome)	Dermatan sulfate (U) Heparan sulfate (U) Kondroitin sulfate (U)
	Niemann – Pick disease type A-B	Lyso-sphingomyelin (Lyso-SM) Lyso-sphingomyelin – 509 (Lyso-SM-509)
	GM1 gangliosidosis	Lyso-monosialogangliosyde (Lyso-GM1)
	GM2 gangliosidoz Tay-Sachs disease	Lyso-monosialogangliosyde Lyso-GM2

	Sandhoff disease	
Peroxisomal diseases	Zellweger spectrum disorders	Phytanic acid (S, P) Pipecolic acid (S, P) Pristanic acid (S, P) Very long chain fatty acids (P)
	Alfa metil KoA racemase deficiency	Phytanic acid (S, P) Pristanic acid (S, P)
	X linked adrenoleukodystrophy	Very long chain fatty acids (P)
	Refsum disease	Phytanic acid (S, P)
IEM: Inborn errors of metabolism, MCAD: Medium-chain acyl-CoA dehydrogenase deficiency, MMA: Methylmalonic acidemia, MSUD: Maple syrup urine disease, PKU: Phenylketonuria, VLCAD: Very long chain acyl-CoA dehydrogenase deficiency		