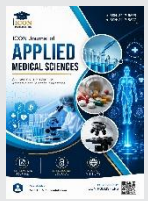

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Advances in Mass Spectrometry for the Diagnosis of Inborn Errors of Metabolism: Recent Developments, Clinical Applications, and Future Perspectives

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Abstract

Inborn errors of metabolism (IEMs) are a heterogeneous category of inherited genetic illnesses caused by abnormalities of enzymes, transport proteins or cofactors involved in metabolic pathways . Although rare individually, together these illnesses are a major source of newborn morbidity and mortality globally. Early identification is needed because timely therapeutic interventions can avert irreversible neurological impairment, organ dysfunction and death. The advent of mass spectrometry (MS) revolutionised the diagnosis of IEMs by enabling quick, sensitive and simultaneous identification of a large number of metabolites from a single biological sample. Tandem mass spectrometry (MS/MS), liquid chromatography–tandem mass spectrometry (LC-MS/MS), gas chromatography–mass spectrometry (GC-MS), high-resolution mass spectrometry (HRMS) and metabolomics-based approaches have made significant contributions to the improvement of newborn screening and confirmatory diagnosis. Recent advances in high throughput analysis, artificial intelligence and integration with genomic technology are improving diagnostic accuracy and broadening the range of treatable illnesses. This review describes recent breakthroughs in mass spectrometry technology, their clinical applications in the diagnosis of IEMs, present obstacles and future opportunities for precision metabolic medicine.

Keywords: *Inborn errors of metabolism; mass spectrometry; tandem mass spectrometry; LC-MS/MS; GC-MS; newborn screening; metabolomics.*

Introduction

Inborn errors of metabolism (IEMs) are a large group of inherited diseases caused by genetic defects in enzymes, transporters, receptors or cofactors that are involved in metabolic pathways. Since Sir Archibald Garrod first described alkaptonuria as a ‘inborn error of metabolism’ in 1908, there have been extraordinary advances in biochemical genetics that have resulted in the identification of over 1700 different metabolic disorders, with new entities in the field being discovered through genomic and metabolomic studies [1,2].

Each individual condition is rare; nonetheless, IEMs as a group impact approximately 1 in 800–2,500 live births globally and are a substantial source of newborn sickness, developmental impairment, and early mortality [3]. The signs and symptoms may be very different, ranging from severe metabolic crises in the newborn era to chronic neurological damage showing later in childhood or adulthood. Common but vague symptoms are poor feeding, recurrent vomiting, seizures, developmental delay, metabolic acidosis, hypoglycaemia, cardiomyopathy, liver failure and unexplained coma [4]. Laboratory diagnosis is crucial.

Traditionally diagnosis was based on laborious biochemical methods such as amino acid chromatography, enzyme assays

and colorimetric methods . These procedures were often time intensive, needed vast amounts of sample and had no multiplexing capability. Mass spectrometry has revolutionised metabolic diagnostics, enabling the simultaneous determination of several metabolites with high analytical sensitivity and specificity [5]. Today, tandem mass spectrometry (MS/MS) is the workhorse of many countries' expanded newborn screening efforts. Modern mass spectrometric methods allow the diagnosis of aminoacid problems, organic acidemias, fatty acid oxidation abnormalities, lysosomal storage illnesses and many other metabolic disorders from one dried blood spot collected shortly after birth [6]. Recent progress in high resolution mass spectrometry, metabolomics, lipidomics, proteomics and computational bioinformatics are continuously enhancing disease detection and biomarker discovery.

This review summarises current achievements in mass spectrometry for diagnosis of IEMs, highlighting the technological developments, clinical applications, limitations and future views.

Inborn Errors in Metabolism: A Summary

Inborn errors of metabolism are hereditary illnesses caused by the disruption of normal metabolic pathways due to deficiency of enzymes, transport proteins or cofactors. These anomalies lead to buildup of toxic metabolites, shortage of key metabolic products or both, resulting in tissue injury and organ malfunction [7].

Most IEMs are inherited in an autosomal recessive pattern, but autosomal dominant, X-linked and mitochondrial inheritance patterns have also been described. Clinical severity is highly variable and is influenced by residual enzyme activity, environmental variables, dietary factors and modifier genes [8].

IEMs usually fall into three broad categories:

Disorders associated with intoxication by accumulation of metabolites (e.g. phenylketonuria, maple syrup urine illness, organic acidemias, and urea cycle disorders).

Disorders of energy metabolism (e.g. fatty acid oxidation disorders, mitochondrial disorders, glycogen storage diseases). Defects in the synthesis or breakdown of complex molecules (e.g. lysosomal storage diseases, peroxisomal diseases, congenital disorders of glycosylation).

Every disease has specific biochemical signatures which can be detected by modern mass spectrometric techniques. Early diagnosis is critical as many IEMs are treatable with dietary restriction, vitamin supplementation, enzyme replacement therapy, substrate reduction therapy, or organ donation if diagnosed before permanent tissue damage occurs [9].

Fundamentals of Mass Spectrometry

Mass spectrometry is an analytical technique that helps to identify molecules by determining their mass-to-charge (m/z) ratios. High sensitivity, specificity, analytical speed and multiplex capabilities have made it a necessity in clinical chemistry [10].

A typical mass spectrometer consists of three main components:

Ion source: Converts the analytes to charged ions. Common ionisation procedures include electrospray ionisation (ESI), atmospheric pressure chemical ionisation (APCI) and matrix-assisted laser desorption ionisation (MALDI).

Mass analyser: Separates ions according to their mass-to-charge ratios. Common analysers are quadrupole, time-of-flight (TOF), orbitrap, ion trap and Fourier-transform ion cyclotron resonance (FT-ICR).

Detector: Detects the number of ions to create a mass spectrum of the molecular makeup of the sample.

Modern tandem mass spectrometry (MS/MS) uses two mass analysers separated by a collision cell. Characteristic product ions are generated by fragmentation of selected precursor ions, greatly improving analytical specificity and allowing structural identification of metabolites [11].

The superior analytical capability of MS permits the simultaneous detection of tens of metabolites from one sample of dried blood spot, plasma, urine or cerebrospinal fluid and is thus ideally suited for newborn screening and confirmatory diagnosis of IEMs.

Mass Spectrometry in the Diagnosis of IEMs: A Historical Perspective

The first clinical use of mass spectrometry was gas chromatography–mass spectrometry (GC-MS) which became the method of reference for identification of urine organic acids in the 1970's and 1980's. GC-MS [12] allowed the diagnosis of several organic acidurias that previously needed multiple independent biochemical procedures.

The introduction of electrospray ionisation in the late 1980s revolutionised the field of biological mass spectrometry by allowing the study of thermally labile proteins without the need for prior derivatisation. This invention gave rise to liquid chromatography-mass spectrometry (LC-MS) and tandem mass spectrometry (MS/MS), and created a new world of therapeutic applications [13].

The 1990s saw a major breakthrough with the introduction of tandem mass spectrometry into newborn screening programmes. While traditional screening procedures were used to detect one problem at a time, MS/MS can identify more than 40 metabolic diseases simultaneously from one dried blood spot. Many national newborn screening programmes now routinely screen for more than 50 inherited metabolic disorders, significantly reducing morbidity and mortality by means of early diagnosis [14].

Recent technological advances, such as high-resolution mass spectrometry, untargeted metabolomics and machine-learning-assisted data interpretation, have further improved the diagnostic potential of mass spectrometry, enabling the identification of novel biomarkers and previously unrecognised metabolic disorders [15].

Newborn Screening using Tandem Mass Spectrometry (MS/MS) One of the major breakthroughs in clinical laboratory medicine is the use of tandem mass spectrometry (MS/MS) in newborn screening. Prior to its implementation, newborn screening programs were dependent on single-analyte assays, such as the bacterial inhibition test utilised by Guthrie for phenylketonuria (PKU), which was only capable of identifying a limited number of metabolic disorders [16]. MS/MS revolutionised screening by enabling the simultaneous detection of several metabolites from a single dried blood spot (DBS) and significantly expanding the number of abnormalities that can be diagnosed during the newborn period. Tandem mass spectrometry is based on two subsequent steps of mass analysis. The precursor ions of the target metabolite are picked in the first quadrupole according to their mass to charge ratio (m/z). These ions are dissociated in a collision cell via collision-induced dissociation resulting in distinctive fragment ions that are analysed by a second mass analyser. This technique greatly enhances the specificity of the analysis by minimising the background interference and enabling the reliable identification of the structurally related metabolites [17].

One of the major advantages of MS/MS is the ability to measure a number of amino acids and acylcarnitines concurrently. These biomarkers enable the early detection of several classes of IEMs, such as:

- Amino acid diseases including phenylketonuria, maple syrup urine illness, homocystinuria and tyrosinemia type I.
- Organic acidemias including methylmalonic acidemia, propionic acidemia, glutaric acidemia type I and isovaleric acidemia.
- Fatty acid oxidation diseases such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, very long chain acyl-CoA dehydrogenase deficit, carnitine transporter deficiency.[18] Some urea cycle diseases through changes in citrulline and arginine concentrations.

The implementation of MS/MS in expanded newborn screening has led to a dramatic improvement of clinical outcome. Metabolic disorders, which previously presented with life-threatening metabolic crises, are now identified prior to the onset of symptoms, allowing for early dietary adjustment, carnitine supplementation, enzyme replacement or cofactor therapy. There are numerous studies showing a decrease in mortality, severe neurological impairment and long-term health expense following the introduction of MS/MS screening [19]. But even with these advantages MS/MS is still primarily a screening tool. Positive results need to be confirmed by further testing e.g. quantitative plasma amino acid analysis, urine organic acid profile, enzymatic assays, molecular genetic testing or further biochemical research. Furthermore, some metabolic illnesses may not have typical metabolite abnormalities in the newborn period, with false-negative results occurring when screening is undertaken too early [20].

Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS)
Clinical metabolomics utilises liquid chromatography-tandem mass spectrometry (LC-MS/MS) as one of the most adaptable systems for analytical applications. Unlike the direct infusion MS/MS, LC-MS/MS also involves chromatographic separation before mass analysis to reduce matrix interference and improve analytical specificity for structurally identical metabolites [21]. In LC-MS/MS, metabolites are initially separated by a chromatographic column according to polarity, molecular size or chemical interactions. Individual substances are then introduced into the mass spectrometer and electrospray ionisation produces charged ions for identification. By combining chromatographic separation with tandem mass analysis, hundreds of metabolites can be quantified simultaneously in a single analytical run.

LC-MS/MS is currently frequently used for the confirmatory diagnosis of several IEMs. Clinical uses include:

- Quantitative amino acid analysis.
- Measurement of acylcarnitine profile.
- Analysis of steroid hormones
- Disorders of purines and pyrimidines.
- Lysosomal storage disorders.
- Congenital diseases of glycosylation.
- Vitamin responsive metabolic disorders.
- Disorders of bile acid synthesis.

LC-MS/MS provides greater analytical sensitivity, wider metabolite coverage, shorter turnaround time and less sample

volume than standard biochemical procedures . Similarly, modern ultra-high performance liquid chromatography (UHPLC)-MS/MS systems improve the chromatographic resolution and cut down the analytical time to less than 10 minutes for numerous specific assays [22]. We also employ LC-MS/MS for multiplex enzyme tests in newborn screening for lysosomal storage diseases, including Pompe disease, Fabry disease, Gaucher disease, Krabbe disease, and mucopolysaccharidosis type I. These assays allow high throughput screening of populations and the enzyme products formed during incubation with synthetic substrates can be simultaneously quantitated [23].

Gas Chromatography-Mass Spectrometry (GC-MS)

Even with the development of newer analytical technologies, gas chromatography–mass spectrometry (GC-MS) remains the reference standard for analysis of urinary organic acids. One of the main groups of IEMs are organic acidurias, characterised by buildup of intermediary metabolites caused by a deficiency in amino acid catabolism or energy metabolism [24]. Organic acids need chemical derivatisation before chromatographic separation by GC-MS to enhance their volatility. Metabolites are introduced into the mass spectrometer after separation and electron impact ionisation induces repeatable fragmentation patterns that allow for compound identification by comparison with spectrum libraries.

GC-MS is the cornerstone of diagnosing conditions such as:

• Methylmalonic acidemias.
• Propionsäuremie.
• Isovaleric acidemia.

Glutaric acidemia type I.

• β-Ketothiolase deficiency.
• Multiple carboxylase deficiency.

Characteristic urine metabolite profiles sometimes confirm the diagnosis even before molecular confirmation is available. GC-MS is also useful for monitoring metabolic control during treatment and for detecting biochemical decompensation during illness episodes [25]. Although GC-MS has good analytical specificity, its routine clinical use is limited by the need for extended sample preparation, metabolite derivatisation, specialised technical competence and relatively long run durations as compared with LC-MS/MS. However, GC-MS is an important tool for the thorough analysis of organic acids in specialised metabolic laboratories [26].

High-Resolution Mass Spectrometer (HRMS)

One of the most important recent advancements in the field of metabolic diagnostics is the use of high resolution mass spectrometry (HRMS). Instruments such as Orbitrap and time-of-flight (TOF) analysers give great mass accuracy (often within a few parts per million (ppm)) that allows the distinction of metabolites with very close molecular masses [27]. Unlike targeted assays, HRMS allows for untargeted metabolomics, enabling the simultaneous detection of thousands of metabolites, even without prior knowledge of their identities. This has revolutionised the study of patients with unexplained metabolic disorders, where the biochemical abnormalities are not detectable by standard screening techniques.

The main advantages of HRMS are:

- Identification of new disease biomarkers.
- Identification of hitherto unknown metabolic diseases.
- Improved resolution of isobaric compounds
- Retrospective analysis on saved datasets without the need to collect repeat samples.
- Simultaneous targeted and non-targeted metabolomics profiling.

Ultra-rare metabolic disorders, mitochondrial diseases, neurotransmitter disorders and deficiencies of intermediate metabolism that result in subtle biochemical anomalies have been particularly well diagnosed with HRMS. HRMS greatly improves the interpretation of variations of unknown significance in conjunction with whole exome or whole genome sequencing, offering functional metabolic data in favour of pathogenicity (28).

Matrix Assisted Laser Desorption Ionisation Time of Flight (MALDI-TOF) Mass Spectrometry Matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) mass spectrometry is commonly used in clinical microbiology for the identification of microbes. Recently, its uses have been explored in metabolic medicine, for example in protein profiling, enzyme activity assays and biomarker discovery [29]. In MALDI-TOF, samples are combined with a matrix and irradiated with a laser, which absorbs energy and causes ionisation with little fragmentation. Then generated ions pass through time-of-flight analyser. The flight time of ions is proportional to their mass-to-charge ratio.

Emerging applications in IEM diagnostics are:

- High throughput enzyme tests for lysosomal storage diseases
- Biomarker discovery for protein.
- Glycoproteomics.
- Characterisation of proteins involved in metabolic pathways.

- Rapid screening for some hereditary enzyme deficits.

Metabolomics and Biomarker Identification

Metabolomics refers to the large-scale qualitative and quantitative examination of small-molecule metabolites in biological materials such as blood, urine, cerebrospinal fluid, tissues and dried blood spots. The advent of high-resolution mass spectrometry (HRMS) has transformed metabolomics into one of the most powerful tools in the investigation of inherited metabolic diseases. Unlike targeted assays that detect predetermined metabolites, untargeted metabolomics captures thousands of endogenous metabolites at the same time, allowing for the identification of new biomarkers and metabolic pathways relevant to the disease [30].

Mass spectrometry-based metabolomics has greatly increased the diagnostic potential of clinical laboratories. Comprehensive metabolomic profiling may be helpful in patients with aberrant biochemical findings or equivocal genetic variations, as it can detect abnormal metabolic signatures that are missed by current neonatal screening approaches [31]. Moreover, metabolomics allows the identification of illness-specific biomarkers that help in diagnosis, disease categorisation, prognosis and therapy monitoring.

Recent developments in liquid chromatography-high resolution mass spectrometry (LC-HRMS) have increased analytical sensitivity and metabolite coverage to detect low abundance molecules previously beyond the boundaries of analysis. The combination of metabolomics with lipidomics, proteomics, transcriptomics and genomes resulted in the emergence of multi-omics techniques that enable a holistic view of disease mechanisms and promote the development of precision medicine [32].

Machine learning methods are being used for the analysis of metabolomic data. Artificial intelligence (AI) allows automatic recognition of complex metabolic patterns, enhances biomarker selection, minimises analytical variability and promotes diagnostic accuracy. It is envisaged that these computational approaches will become a common feature of future metabolic diagnostic laboratories [33].

Clinical Applications of Mass Spectrometry in Selected Inborn Errors of Metabolism

The advent of modern mass spectrometry has revolutionised the diagnosis and clinical management of many hereditary metabolic diseases. One of the first successes was the diagnosis of phenylketonuria (PKU) by quantitative measurement of phenylalanine concentrations. Phenylalanine and tyrosine can be measured simultaneously by tandem mass spectrometry, enhancing diagnostic specificity and minimising false-positive results (34).

Maple syrup urine disease (MSUD) is a disorder characterised by the accumulation of branched-chain amino acids and related ketoacids due to impairment of branched-chain α-ketoacid dehydrogenase. MS/MS quantifies precisely leucine, isoleucine, valine and alloisoleucine, allowing an early diagnosis before catastrophic neurological damage [35]. MS/MS Acylcarnitine profiling has emerged as the diagnostic standard in fatty acid oxidation diseases. One of the most frequent fatty acid oxidation disorders is medium-chain acyl-CoA dehydrogenase (MCAD) impairment, diagnosed by measuring increased octanoylcarnitine (C8). Early diagnosis allows for dietary modification to effectively avert hypoglycemia, sudden mortality and neurological impairment [36].

Organic acidemias such as methylmalonic acidemia and propionic acidemia are first suspected from aberrant acylcarnitine profiles and are then verified by GC-MS analysis of urine organic acids. These additional approaches have good diagnostic accuracy and are useful for monitoring the treatment [37].

Mass spectrometry is also an important diagnostic tool for lysosomal storage disorders, including Pompe disease, Fabry disease, Gaucher disease, Krabbe disease and mucopolysaccharidosis type I. LC-MS/MS multiplex enzyme assays allow simultaneous screening of many lysosomal diseases from a single dried blood spot and are useful for population-wide newborn screening [38].

Similarly, the diagnosis of congenital disorders of glycosylation, peroxisomal disorders, disorders of purine and pyrimidine metabolism and mitochondrial diseases is more and more depending on modern MS platforms for confirming biochemical diagnosis. Metabolomics based on HRMS is especially useful in the diagnosis of ultra-rare metabolic diseases with biochemical anomalies that cannot be detected by traditional focused assays [39].

Advantages of Current Mass Spectrometry

The wide acceptance of mass spectrometry in metabolic medicine reflects its many analytical and therapeutic benefits. Firstly, MS offers increased analytical sensitivity enabling the detection of metabolites at the picomolar, or even femtomolar, level. Such sensitivity is necessary to detect subtle metabolic abnormalities in the neonatal period before clinical presentation [40].

Second, multiplex analysis allows for the simultaneous assessment of dozens to hundreds of metabolites in a single biological specimen. This drastically reduces laboratory turnaround time and increases diagnostic efficiency.

Thirdly, only a tiny volume of sample is necessary. Expanded newborn screening can be performed with a single dried blood spot obtained from a heel prick, which minimises patient discomfort and facilitates specimen delivery from remote healthcare institutions.

Fourth, mass spectrometry offers high analytical specificity through accurate mass determination and characteristic fragmentation patterns, which leads to fewer false positive and false negative results. Finally, current high-resolution sensors allow for retrospective data analysis. When novel disease biomarkers are found, previously collected datasets can be re-examined, and in many situations, the requirement for repeat specimen collection is avoided [41].

Limitations and Difficulties

While mass spectrometry boasts impressive capabilities, there are some constraints which continue to prevent its universal use. The main limitation is the high capital cost of instrumentation. The purchase of LC-MS/MS or HRMS systems is a major financial commitment and these technologies are not accessible in many poor and medium income countries [42]. Maintenance charges are also high. Instruments require regular calibration, preventive maintenance, quality assurance and replacement of consumable parts. Furthermore, operation requires highly qualified laboratory scientists with skills in analytical chemistry, metabolomics and data interpretation. Another problem is standardisation. Differences in analytical procedures, calibrators, quality control materials and reference intervals may affect the comparability of results between laboratories.

False-positive findings represent one of the major problems in neonatal screening. Concentrations of metabolite may be influenced by prematurity, total parenteral nutrition, liver disease, use of medications, and time of specimen collection. Therefore, confirmatory biochemical and molecular studies are required to establish a definitive diagnosis from aberrant screening results [43]. Finally, untargeted metabolomic datasets remain a computational challenge to understand, as thousands of discovered compounds are unidentified. Therefore, the development of metabolite databases and bioinformatics tools is vital.

Future Outlooks

The future of metabolic diagnostics depends strongly on continuing technological improvement in the field of mass spectrometry. As instrument costs continue to fall and analytical workflows become more automated, high-resolution platforms are likely to replace many traditional focused assays [44].

The coupling of mass spectrometry to next generation sequencing (NGS) is one of the most promising developments in the field of precision medicine. An integration of biochemical and genomic analysis increases diagnostic yield by associating metabolic derangements with disease-causing genetic variations.

Artificial intelligence and machine learning are predicted to revolutionise the interpretation of complicated metabolomic data via automated pattern recognition, biomarker development and clinical decision support systems.

Miniaturised and portable mass spectrometers are also being developed. These devices could provide bedside metabolic testing in neonatal critical care units, emergency departments, and resource-poor settings. New fields like single-cell metabolomics, spatial metabolomics and imaging mass spectrometry promise to give us an unprecedented view of cellular metabolism and disease pathogenesis. Such technologies can reveal new therapeutic targets and design personalised treatment strategies for patients with inherited metabolic disorders [45].

Conclusion

Mass spectrometry has revolutionised the diagnosis of inherited metabolic disorders over the last 30 years. Advances in analytical technology, from the advent of tandem mass spectrometry in newborn screening to the advent of high-resolution metabolomics and multi-omics integration, have significantly improved early diagnosis, disease characterisation and patient outcomes. With modern techniques such as MS/MS, LC-MS/MS, GC-MS, HRMS, and MALDI-TOF, metabolic abnormalities can be detected rapidly and sensitively and with high specificity from few biological samples. Their applications are no longer limited to newborn screening, but now include confirmatory diagnosis, treatment monitoring, biomarker research and personalised medicine.

Continuous progress in artificial intelligence, bioinformatics, and integrated multi-omics, albeit challenged by cost, technical skill, and data interpretation, will likely significantly boost diagnosis accuracy and access to these technologies. With the development of precision medicine, mass spectrometry will remain a key player in the diagnosis and therapy of hereditary metabolic illnesses.

References

1. Garrod AE. *Inborn Errors of Metabolism*. London: Henry Frowde; 1909.
2. Saudubray JM, Baumgartner MR, Walter JH, editors. *Inborn Metabolic Diseases: Diagnosis and Treatment*. 7th ed. Cham: Springer; 2022.
3. Blau N, Duran M, Gibson KM, Dionisi-Vici C, editors. *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*. Berlin: Springer; 2022.
4. Wilcken B. Expanded newborn screening: reducing harm, assessing benefit. J Inherit Metab Dis. 2021;44(1):10-18.
5. Millington DS, Kodo N, Norwood DL, Roe CR. Tandem mass spectrometry: a new method for screening newborns for inherited metabolic disease. Clin Chem. 1990;36:1513-1516.
6. Chace DH, Kalas TA, Naylor EW. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem. 2003;49(11):1797-1817.
7. Wilcken B, Wiley V. Newborn screening using tandem mass spectrometry. Clin Chim Acta. 2008;391(1-2):4-11.
8. Rinaldo P, Zafari S, Tortorelli S, Matern D. Making the case for objective performance metrics in newborn screening by tandem mass spectrometry. Ment Retard Dev Disabil Res Rev. 2006;12(4):255-261.
9. Matern D, Tortorelli S, Oglesbee D, Gavrilov D, Rinaldo P. Reduction of the diagnostic odyssey by expanded newborn screening. Clin Chem. 2021;67(3):495-506.
10. Pitt JJ. Principles and applications of tandem mass spectrometry in newborn screening. Clin Biochem Rev. 2010;31(2):57-68.
11. Grebe SKG, Singh RJ. LC-MS/MS in clinical laboratories. Clin Biochem Rev. 2011;32(1):5-31.
12. Want EJ, Wilson ID, Gika H, et al. Global metabolic profiling procedures for biomarker discovery. Nat Protoc. 2013;8:17-32.
13. Johnson DW. Advances in mass spectrometry for clinical diagnostics. Clin Biochem Rev. 2019;40(4):187-202.
14. Ombrone D, Giocaliere E, Forni G, et al. Expanded newborn screening by tandem mass spectrometry. Int J Neonatal Screen. 2022;8:15.
15. Zhang XK, Smon A, Janez A, et al. New developments in newborn screening using tandem mass spectrometry. Int J Neonatal Screen. 2021;7:34.
16. Tan M, et al. Expanded newborn screening and inherited metabolic diseases. Front Pediatr. 2021;9:663326.
17. Ombrone D, Forni G, Malvagia S. Tandem mass spectrometry in inherited metabolic diseases. J Inherit Metab Dis. 2020;43:1028-1040.
18. McHugh DMS, Cameron CA, Abdenur JE, et al. Clinical validation of cutoff target ranges in newborn screening. Genet Med. 2011;13(3):230-254.
19. Therrell BL Jr, Padilla CD. Newborn screening in the genomic era. Semin Perinatol. 2022;46:151559.
20. Loeber JG, Platis D, Zetterström RH, et al. Neonatal screening in Europe revisited. J Inherit Metab Dis. 2021;44:119-132.
21. Ivanovová E, Pisklákova B, Dobešová D, Kvasnička A, Friedecký D. Novel LC-MS tools for diagnosing inborn errors of metabolism. *Microchem J*. 2021;170:106654. doi: 10.1016/j.microc.2021.106654.
22. Gelb MH, Scott CR, Turecek F. Newborn screening for lysosomal storage diseases by tandem mass spectrometry. J Inherit Metab Dis. 2015;38:1021-1032.
23. Millington DS. Mass spectrometry in newborn screening. Mass Spectrom Rev. 2022;41:879-897.
24. Kuhara T. Gas chromatography-mass spectrometry in the diagnosis of organic acidemias. J Chromatogr B. 2005;814:1-11.
25. Sweetman L. Organic acid analysis. In: Blau N, editor. *Laboratory Guide to the Methods in Biochemical Genetics*. Berlin: Springer; 2008.
26. Bonham JR, Downing M. Organic acid analysis in inherited metabolic disease. Ann Clin Biochem. 2019;56:164-178.
27. Wurth R, Turgeon C, Stander Z, Oglesbee D. An evaluation of untargeted metabolomics methods to characterize inborn errors of metabolism. *Mol Genet Metab*. 2024;141(1):108115.
28. Garrett R, Ptolemy AS, Pickett S, Kellogg MD, Peake RWA. Untargeted metabolomics for inborn errors of metabolism: development and evaluation of a sustainable reference material for correcting inter-batch variability. *Clin Chem*. 2024;70(12):1452-1462.
29. Clark AE, Kaleta EJ, Arora A, Wolk DM. Matrix-assisted laser desorption ionization-time of flight mass spectrometry in the clinical microbiology laboratory. Clin Microbiol Rev. 2013;26:547-603.
30. Patti GJ, Yanes O, Siuzdak G. Innovation: metabolomics. Nat Rev Mol Cell Biol. 2012;13:263-269.
31. Fiehn O. Metabolomics by mass spectrometry. Nat Rev Mol Cell Biol. 2002;3:534-541.
32. Psychogios N, Hau DD, Peng J, et al. The human serum metabolome. PLoS One. 2011;6:e16957.
33. Wishart DS. Emerging applications of metabolomics in precision medicine. Nat Rev Drug Discov. 2016;15:473-484.
34. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010;376:1417-1427.
35. Strauss KA, Morton DH. Branched-chain ketoacid dehydrogenase deficiency: maple syrup urine disease. Curr Treat Options Neurol. 2003;5:329-341.
36. Wilcken B, Wiley V, Hammond J, Carpenter K. Screening newborns for MCAD deficiency. N Engl J Med. 2003;348:2304-2312.

37. Saudubray JM, Garcia-Cazorla A. Inborn errors of metabolism overview. Pediatr Clin North Am. 2018;65:179-208.
38. Gelb MH. Newborn screening for lysosomal storage diseases. Int J Neonatal Screen. 2018;4:24.
39. Tang C, Li L, Chen T, Li Y, Zhu B, Zhang Y, Yin Y, Liu X, Huang C, Miao J, Zhu B, Wang X, Zou H, Han L, Feng J, Huang Y. Newborn screening for inborn errors of metabolism by next-generation sequencing combined with tandem mass spectrometry. Int J Neonatal Screen. 2024;10(2):28.
40. Rinaldo P. Newborn screening by tandem mass spectrometry. Clin Chem. 2019;65:161-163.
41. Mansoor S, Qamar R, Azam M. Inborn errors of metabolism: Historical perspectives to contemporary management. Clin Chim Acta. 2024;562:119883. doi: 10.1016/j.cca.2024.119883.
42. Hao L, Liang L, Gu X, Zhou X, Chen T, Xu F, Qian W, Zou H, Han L. Screening of 1.17 million newborns for inborn errors of metabolism using tandem mass spectrometry in Shanghai, China: A 19-year report. Mol Genet Metab. 2024;141(1):108098.
43. Kononets V, Zharmakhanova G, Balmagambetova S, Syrlybayeva L, Berdesheva G, Zhussupova Z, Tautanova A, Kurmambayev Y. Tandem mass spectrometry in screening for inborn errors of metabolism: Comprehensive bibliometric analysis. Front Pediatr. 2025;13:1463294.
44. Nordin FDA, Omar A, Kamarudin B, Abdullah WNHW, Abdul Latiff Z. Whole exome sequencing in energy deficiency inborn errors of metabolism: A systematic review. Mol Genet Metab Rep. 2024;40:101094.
45. Wurth R, Turgeon C, Stander Z, Oglesbee D. From discovery to the clinical laboratory: a methodological appraisal of untargeted metabolomics platforms to characterize inborn errors of metabolism. *J Clin Transl Sci*. 2024;8(S1):144.