Review article:

Diagnostic Advancement in Evaluating Inborn Errors of Metabolism: Past, Present and Future: A systematic review

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Abstract:

Metabolism is a delicately coordinated entity of chemical reactions. Inborn Errors of Metabolism (IEM) are rare congenital disorders that are mainly due to gene defect of enzymes or cofactors participating in a metabolic pathway or the transport of metabolites within a cell or between cells. The development of knowledge in basic sciences together with technology development in medical field has helped to better understand the molecular and biochemical basis of IEM. Environmental factors, ethnicity, race, consanguinity and genetic factors contribute to the increased prevalence of genetic disorders. The analytical methods have evolved over the years from thin layer chromatography (TLC), high performance liquid chromatography (HPLC) to tandem mass spectrometry (TMS) including gas chromatography mass spectrometry (GC/MS). Their applications for 75g of IEM has opened the door for screening of conditions that previously required molecular testing or another methodology that was not practical for population-based screening. Future technologies such as Matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry (MALDI-TOF MS), has the potential for rapid and reliable identification of small metabolites and disease biomarkers in daily clinical laboratories, whereas DNA based screening by DNA microarrays or gene chips will allow much more improved diagnosis.These can be the boon to screening programs which will require excellent detection and follow-up services

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Introduction: Metabolism is a delicately coordinated entity of chemical reactions. For maintenance of tissue, growth and reproduction, the organism through various metabolic processes tries to balance between energy and nutrient intake, consumption and storage. It can be disturbed in either inherited or acquired situations.

Inborn errors of metabolism (IEM) was first described by Sir Archibald Garrod in 1908, during the famous Croonian lectures on the inborn errors of metabolism, i.e., alkap tonuira, cystinuria, albinism and pentosuria.[1] Following this, the world

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of IEMs has been ever expanding, both in terms of diagnosing new affected phenotypes and in their therapeutic measures. They have also been coined different names, e.g., inherited metabolic disorders (IMD), hereditary metabolic disorders (HMD), or congenital metabolic diseases (CMD). Most of them cannot be cured and leads to fatal outcome with episodes of acute metabolic decompensation. Treatment is limited and most often supportive and experimental. Search for new therapeutic approaches is possible by gathering new information about its pathogenesis.[2] IEM are rare congenital disorders that are mainly due to a gene defect of enzymes or cofactors participating in a metabolic pathway or the transport of metabolites within a cell or between cells. This results in either accumulation of substrate, loss of end products, accumulation of normally minor metabolites or secondary metabolic consequences.[3] It can be classified in various forms and one of the ways to classify it is based on its pathophysiology as disorders. According to this, it is classified as (i) Group-I disorders, which gives rise to intoxication, (ii) Group-II disorders, involving energy metabolism, and (iii) Group- III disorders, involving complex molecules.[4] Accumulation of the toxic metabolite, proximal to the metabolic block including aminoacidopathies, organic acidemias, urea cycle disorders, porphyrias, mineral metabolism disorders, sugar intolerances, as well as synthesis defects of neurotransmitters etc. are categorized under first group of disorder. The second group comprises mitochondrial and cytoplasmic energy defects. The last group is the most diverse and includes lysosomal storage disorders, peroxisomal biogenesis disorders, congenital disorders of glycosylation, cholesterol synthesis defects etc.[4] Among the three groups of disorders, the first group of disorders can be diagnosed by simple tests such as blood and urine amino acids, organic acid and acylcarnitine profiling while the second group of disorders are identified by enzyme analysis, tissue biopsies or molecular testing and the third group is diagnosed only by molecular testing methods. Additionally, among the three groups, the disorders of first group can be treated either by specific dietary patterns or medications. Earlier the second and third group of disorders were untreatable but now days therapy is available in some cases.[5-7]

Initially the pathogenesis of IEM was not known. However advancement of technology helped in solving this problem. In 1957, Dorfman and Lorincz first revealed the biochemical basis of mucopolysaccharides by reporting excretion of mucopolysaccharides in the affected patient's urine. Later in 1961, Guthrie developed screening of phenylketonuria using microbiological inhibition assay. The gradual increase of basic knowledge in IEM made it possible to discover over 500 disorders. Advancement in laboratory techniques helped detection of some disorders, even before the presentation of symptoms. Introduction of tandem mass spectrometry (TMS) in 1998 added new approach to screening program. IEM is now a subject of interest for research worldwide and continues to be a scientific challenge to modern medicine.[8-10]

Literature search and review: The literature was reviewed by performing database search such as MEDLINE, EMBASE, Science Direct, Cochrane library and Web of Science, using the keywords – 'Inborn errors of metabolism', 'Inborn metabolic disorder', 'history of IEM', 'diagnostic', 'incidence', 'advancement', 'technology', 'TMS and IEM', Tandem mass spectrometry', 'Gas chromatography-mass spectrometry', 'High performance liquid chromatography', 'screening', 'past', 'present', future', and 'DNA microarrays'. Searches were limited to English language.

Incidence of IEM: Environmental factors, ethnicity, race, consanguinity and genetic factors contribute to the increased prevalence of genetic disorders. This is the reason for such a wide variation of prevalence of IEM from country to country and also within the different regions of a country.[11,12] Individual disorders of IEM are rare but collectively numerous, leading to substantial patient burden[13] with the current incidence of IEMs standing at 1:800 live births. It may present at any age, from infancy to adult and can affect either individual or multiple organs. Depending on the severity of the disorder, they usually affect several organs.[14] Sanderson et al.[15] has reported 1 in 784 live births as an overall incidence of IEM in a five year retrospective study in United Kingdom. Dionisi-Vici et al. from Italy has reported an incidence of 1 in 3,707 live births from their 12 years of study. However using advanced technique such as TMS, reduced the incidence as 1 in 6200.[16] Another study from Canada has reported an overall incidence of 1 in 2500 with disorders of amino acid metabolism, organic acid metabolism, urea cycle disorder, glycogen storage disorder etc. as more prevalent.[17] A study from middle east country like Saudi Arabia has reported a high

incidence of 1 in 666 live births.[18] Another study from the same area reported a prevalence of 1.25% of symptomatic newborn babies were found to be suffering from IEM.[19] Asian and South East Asian countries[20] also reported a varied incidence such as 1 in 4000, 1 in 5,800 in Mainland China[21], 1 in 5882 in Taiwan[22], 1 in 2000 in Korea[23] and 1 in 9330 in Japan.[24] Scarce report is available from India as we still do not have mandatory screening program for IEM in newborns and infants. Only few private hospitals and health centers are providing diagnostic facilities, hence only few Indian studies have addressed the incidence of IEM.[25,26] One study has reported incidence of 1 in 3600[27] and another study by Nagaraja et al.[28] has reported a prevalence rate of 2.3%.

Screening of IEM – Past, Present and Future: The history of screening for IEM started in 1959, when Prof. Guthrie first demonstrated the detection of phenylalanine level in dried blood spot based on bacterial inhibition assay.[29] This technique later came to be known as Guthrie test which was easy, cheap and reliable and followed by mass screening of phenylalanine in children. This mass screening was opposed by medical fraternity at that time. However in 1962, a pilot study was done for screening of phenylketonuria (PKU).[30] In the following years, screening for more conditions such as maple syrup urine disease (MSUD), galactosemia and homocystinuria were started.[31] Later in 1968, the Wilson and Jugner criteria for screening of IEM was framed keeping in view its clinical validility, clinical utility, analytical validity, social and ethical issues to cost effectiveness.[32] Finally in 1975, the United States of America made screening of PKU compulsory for all newborns. The Massachusetts Medical School also started the screening program with addition of more congenital disorders including congenital hypothyroidism, congenital toxoplasmosis, hemoglobinopathies, congenital adrenal hyperplasia, biotinidase deficiency and cystic fibrosis.[31] Soon other countries like Canada, Portugal and Australia started screening of IEM in newborns.[32-34]

In India, the state of Karnataka was the first to start screening of IEM in neonates in 1980 by Appaji Rao and his team. The burden of IEM in neonates was reported to be 0.04% whereas it was 3.2% in high risk population and a bit higher (5.75%) in mentally retarded children.[35,36] Another study from Kerala has reported a high incidence of aminoaciduria, organic aciduria and other IEMs in their studied population which extended over a period of five years.[37] Similar report of high incidence (1 in 1000) has been published from Andhra Pradesh. The common disorders that have been detected were congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) and hyperhomocystinemia[38], using techniques such as chromatography, electrophoresis, ELISA and TMS. Study from North India shows a slightly different incidence from South India. Homocystinuria, alkaptonuria, MSUD and non ketotichyperglycinemia were common in North, whereas homocystinuria, MSUD, PKU, mucopolysaccharidoses were common in South[11,39,40] using advanced techniques such as GCMS and TMS.

Diagnostic advancements: Screening for IEM involves metabolic profiling of blood and urine samples. The analytical methods have evolved over the years from thin layer chromatography (TLC), high performance liquid chromatography (HPLC) to tandem mass spectrometry (TMS) including gas chromatography mass spectrometry (GC/MS).

TLC is one of the oldest techniques introduced which is still in use. It is widely used as it simple to perform, cost effective, rapid and reproducible and requires less space.[41] Stationary phases commonly used for TLC include silica, alumina and cellulose, which are coated onto a backing of aluminium, plastic or glass to provide physical support. It can be used to separate amino acids, organic acids, sugars, phenolic acids, ketoacids, imidazole, steroids, lipids, purine, pyrimidine and related compounds. Hence it is used in detection of aminoacidopathies in IEM cases This technique enabled Kaur et al. to report homocystinuria, MSUD, alkaptonuria, hyperglycinemia, phenylketonuria, cystinuria and general aminoaciduria in high risk infants and children from North India.[42,43] This application has helped in screening more than twenty five different metabolic and transport disorders before the onset of the clinical symptoms. Thus, TLC was and still a useful tool in screening of IEM.[41,44]

HPLC is used to separate compounds on the basis of their chemical characteristics, such as polarity, molecular size and degree of charge in a pH gradient. It helps to quantify the individual components. There are many forms of HPLC—the most common is reverse phase HPLC. The amino acids are derivatized for carrying out HPLC. Earlier researchers used ion exchange chromatography in combination with post column ninhydrin detection, but now day's methods have been simplified with

o-phthalaldehyde (OPA) method.[45] However it can be used for primary amino acids but for a mixture of secondary amino acids, phenylisothiocyanate (PITC) method is used.[46,47] It has helped in detection of homocystinuria, MSUD, tyrosinemia, phenylketonuria, histidinemia, citturullinemia, argininemia and hyperglycinemia.[48] HPLC has also been used by researchers for detection of organic acids such as methyl malonic acid, lactic acid, isovaleric acid, glutaric acid, propionic acid etc. GC/MS is another chromatographic technique used to separate components in physiological samples as well as pharmaceutical, food and forensic samples using gas as the mobile phase (carrier) and a silicon based oil as the stationary phase. It accurately detects the volatile compounds in small samples. It has become one of the commonest methods used by researchers and laboratory personals for identifying organic acid metabolism disorders of IEM.[49]

The TMS technique was introduced by Millington et al. in 1990. Initially it was being used for detection of metabolic disorders such as phenylalanine and tyrosine.[50,51] Now, this technique has gained popularity and it is being used to detect and analyze acyl carnitine profile, amino acids and organic acids simultaneously. Using this technology, one can detect more than 30 different types of IEM. Thus it has helped in screening, diagnosis and treatment[52] and has been accepted in many developed countries leading to significant decrease in morbidity due to IEM.[53,54] The technique has high sensitivity and specificity and comparable to other modern techniques like radio-immunoassay and GC/MS.[55,56]

The introduction of TMS has greatly influenced the screening of IEM, which can detect many treatable and untreatable disorder which might be useful to give therapy as well as guidance to affected families. A study by Wilcken et al.[57], reported a twofold higher prevalence of IEM using TMS as compared to those diagnosed clinically. TMS based screening of IEM in newborns recorded an overall incidence of 1 in 9300 in Japan.[58] Its application to newborn screening has opened the door for screening of conditions that previously required molecular testing or another methodology that was not practical for population-based screening.[59,60]

Future technologies: Advancement in technology will strengthen the diagnostic abilities. New technologies such as Matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry (MALDI-TOF MS), has the potential for rapid and reliable identification of small metabolites and disease biomarkers in daily clinical laboratories, whereas DNA based screening by DNA microarrays or gene chips will allow much more improved diagnosis.[61] Qualitative and quantitative changes in nucleic acid sequences such as mutations, single-nucleotide polymorphisms, insertion/deletion, alternative splicing, copy number variations, gene and allele expression, modifications brought about methylations of DNA, post transcriptional modifications of tRNAs and rRNAs can be done using MALDI-TOF MS.[62] Recently it has been used for screening of IEM in newborns using dried blood spot samples. In a study by Hachani et al.[63], this technique was used to screen sickle cell disease and thalassemia with the primary objective to determine the mass and relative abundance of primary hemoglobin (Hb) α and β subunits and of the HbS subunit, indicative of sickle cell disorder. They reported a decrease in mass of 30 Da in the HbS subunit. They concluded that this involved marked reduction in cost per unit analysis.

DNA microarrays is another future technology which will help to screen IEM in newborns and infants for diseases arising due to mutations in genes.[64]

In conclusion, the upcoming techniques are becoming affordable, simple to handle, provides high throughput and very cost effective with high sensitivity and specificities. These can be the boon to screening programs which will require excellent detection and follow-up services.

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References:

1. Scriver CR. Garrod's Croonian Lectures (1908) and the charter 'Inborn Errors of Metabolism': albinism, alkaptonuria, cystinuria, and pentosuria at age 100 in 2008. J Inherit Metab Dis 2008; 31: 580–98.
2. Maher AD, Zirah SF, Holmes E and Nicholson JK. Experimental and analytical variation in human urine in 1H NMR spectroscopy-based metabolic phenotyping studies. Anal Chem 2007; 79: 5204-11.
3. Sharer JD. An overview of biochemical genetics. CurrProtoc Hum Genet 2011, Chapter 17: Unit 17 .1
4. Saudubray JM, Berghe G van den, Walter JH (eds). Inborn metabolic diseases: diagnosis and treatment, 2012: Springer-Verlag Berlin Heidelberg.
5. Kayton A. Newborn Screening: A Literature Review. Neonatal Network: J Neonatal Nurs 2007; 26(2): 85-95.
6. Saudubray JM, Charpentier C. Clinical phenotypes: Diagnosis/Algorithms. In: Scriver CR, Beaudet AL, Sly W, Valle D. The metabolic and molecular bases of inherited disease, 7th edition. McGraw-Hill; 1995;1995.
7. Saudubray JM, Sedel F and Walter JH. Clinical approach to treatable inborn metabolic diseases: an introduction. J Inherit Metab Dis 2006; 29: 261-74.
8. Schulze A, Lindner M, Kohlmüller D, Olgemöller K, Mayatepek E and Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. Pediatrics 2003; 111(6): 1399-1406.
9. Fang-Hoffmann J, Lindner M, Shahbek N, Barić I, Thani G Al and Hoffmann GF. Metabolic medicine: new developments in diagnosis and treatment of inborn errors of metabolism. World J Pediatr 2006; 2(3): 169-176.
10. Hui J, Kirby DM, David R and Thorburn AB. Decreased activities of mitochondrial respiratory chain complexes in non-mitochondrial respiratory chain diseases. Dev Med Child Neurol 2006; 48: 132-36.
11. Patil VS, Jailkhani R, Trivedi DJ, Kulkarni SP, Sagare AA, Mudaraddi R, et al. Screening for aminoacidurias and organic acidurias in patients with metabolic or neurological manifestations. Biomed Res 2012; 23(2): 253-58.
12. Kaur M, Das GP and Verma IC. Inborn errors of amino acid metabolism in North India. J InherMetab Dis 1994; 17: 230-33.
13. Garg U andDasouki M. Expanded newborn screening of inherited metabolic disorders by tandem mass spectrometry: clinical and laboratory aspects. Clin Biochem. 2006; 39 (4): 315-32.
14. Pampols T. Inherited metabolic rare disease. Adv Exp Med Biol 2010; 686: 397–431.
15. Sanderson S, Green A, Preece MA and Burton H. The incidence of inherited metabolic disorders in the West Midlands, UK. Arch Dis Child 2006; 91(11): 896-99.
16. Dionisi-Vici C, Deodato F, Roschinger W, Rhead W and Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis 2006; 29 (2-3): 383-89.
17. Applegarth DA, Toone JR and Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. Pediatrics 2000; 105 (1): e10.
18. Moammar H, Cheriyan G, Mathew R and Al-Sannaa N. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med 2010; 30 (4): 271-77.
19. Golbahar J, Al-Jishi E a, Altayab DD, Carreon E, Bakhiet M andAlkhayyat H. Selective newborn screening of inborn errors of amino acids, organic acids and fatty acids metabolism in the Kingdom of Bahrain. Mol Genet Metab 2013; 110: 98-101.
20. Han LS, Ye J, Qiu WJ, et al. Selective screening for inborn errors of metabolism on clinical patients using tandem mass spectrometry in China: a four-year report. J Inherit Metab Dis 2007; 30 (4): 507-14.
21. Gu X, Wang Z, Ye J, et al. Newborn screening in China: phenylketonuria, congenital hypothyroidism and expanded screening. Ann Acad Med Singapore 2008; 37 (12 Suppl): 107-110.
22. Niu DM, Chien YH, Chiang CC, et al. Nationwide survey of extended newborn screening by tandem mass spectrometry in Taiwan. J Inherit Metab Dis 2010; 33 (Suppl 2): S295-305.
23. Yoon HR, Lee KR, Kim H, et al. Tandem mass spectrometric analysis for disorders in amino, organic and fatty acid metabolism: two year experience in South Korea. Southeast Asian J Trop Med Public Health 2003; 34 Suppl 3: 115-20.
24. Yamaguchi S. Newborn screening in Japan: restructuring for the new era. Ann Acad Med Singapore 2008a; 37 (12 Suppl): 13-15.
25. Verma IC. Burden of genetic disorders in India. Indian J Pediatr 2000; 67(12): 893-8.
26. Bhatt C, Misra Z and Goyel N. Detection of inherited metabolic diseases in children with mental handicap. Indian J Clin Biochem 2008; 23(1): 10-6.
27. Rama Devi AR, Naushad SM. Newborn screening in India. Indian J Pediatr 2004; 71(2): 157-60.
28. Nagaraja D, Mamatha SN, De T and Christopher R. Screening for inborn errors of metabolism using automated electrospray tandem mass spectrometry: study in high-risk Indian population. Clin Biochem 2010; 43 (6): 581-88.
29. Guthrie R and Susi A. A Simple Phenylalanine Method for Detecting Phenylketonuria in Large Populations of Newborn Infants. Pediatrics 1963; 32: 338-43.
30. Cready MR. Phenylketonuria screening program. N Engl J Med 1963; 269: 52-56.
31. Comeau AM, Larson C and Eaton RB. Integration of new genetic diseases into statewide newborn screening: New England experience. Am J Med Genet C Semin Med Genet 2004; 125C (1): 35-41.
32. Wilson JMG andJungner G. Principles and practice of screening for disease. WHO 1968. Available from: http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf.
33. Therrell BL and Adams J. Newborn screening in North America. J Inherit Metab Dis. 2007; 30 (4): 447-65.

34. Vilarinho L, Rocha H, Sousa C, et al. Four years of expanded newborn screening in Portugal with tandem mass spectrometry. J Inherit Metab Dis 2010; 33 Suppl 3: S133-S138.
35. Kumta NB. Inborn Errors of Metabolism (IEM) - An Indian Perspective. Indian J Pediatr 2005; 72(4): 325-32.
36. Latheef SA. A database for inborn errors of metabolism in the Indian state of Andhra Pradesh. Bioinformation 2010; 4(7): 276-77.
37. Vaidyanathan K, Narayanan MP and Vasudevan DM. Inborn Errors of Metabolism and Brain Involvement – 5 Years Experience from a Tertiary Care Center in South India. 2012, Alina Gonzalez-Quevedo (Ed.), InTech, pp 57-78.
38. Sahai I, Zytkowicz T, Rao Kotthuri S, et al. Neonatal screening for inborn errors of metabolism using tandem mass spectrometry: experience of the pilot study in Andhra Pradesh, India. Indian J Pediatr 2011; 78(8): 953-60.
39. Rao NA, Devi RR, Savithri H, Rao SV andBittles AH. Neonatal screening for amino acidaemias in Karnataka, South India. Clin Genet 1988; 34(1): 60-3.
40. Jailkhani R, Patil VS., Laxman HB, et al. Selective Screening for Inborn Errors of Metabolism In Children: Single Centre Experience From Karnataka. J Clin Diag Res 2008; 2(4): 952-58.
41. Auray-Blais C, Giguère R and Lemieux B. Newborn urine screening programme in the province of Quebec: an update of 30 years' experience. J Inherit Metab Dis 2003; 26(4): 393-402.
42. Reinecke CJ andMienie LJ. Some Inborn Errors of Metabolism at a Local Institute for Mentally Retarded Patients. J InherMetab Dis 1981; 4: 119-20.
43. Kaur M, Kabra M, Das GP, et al. Clinical and biochemical studies in homocystinuria. Indian Pediatr 1995; 32: 1067-75.
44. Auray-Blais C, Cyr D and Drouin R. Quebec neonatal mass urinary screening programme: from micromolecules to macromolecules. J Inherit Metab Dis 2007; 30(4): 515-21.
45. Walker V and Mills G a. Quantitative methods for amino acid analysis in biological fluids. Ann Clin Biochem 1995; 32: 28-57.
46. Tsai V, Marshall JG and Josephson MW. Free Amino Acid Analysis of Untimed and 24-h Urine Samples Compared. Clin Chem 1980; 26(13): 1804-8.
47. Heinrikson RL and Meredith SC. Amino acid analysis by reverse-phase high-performance liquid chromatography: precolumn derivatization with phenylisothiocyanate. Anal Biochem 1984; 136(1):65-74.
48. Babu SVS, Shareef MM, Shetty APK, et al. HPLC method for amino acids profile in biological fluids and inborn metabolic disorders of aminoacidopathies. Indian J Clin Biochem 2002; 17(2): 7-26.
49. Kuhara T, Ohse M, Ohdoi C, et al. Differential diagnosis of homocystinuria by urease treatment, isotope dilution and gas chromatography–mass spectrometry. J Chromatog 2000; 746: 103–14.
50. Millington DS, Kodo N, Norwood DL, et al. Tandem mass spectrometry a new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. J Inherit Metab Dis 1990; 13: 321-324.
51. Naylor EW and Chace DH. Automated tandem mass spectrometry for mass newborn screening for disorders in fatty acid, organic acid, and amino acid metabolism. J Child Neurol 1999; 14 Suppl 1:S4-8.
52. Yoon H, Ryul K, Kang S, et al. Screening of newborns and high-risk group of children for inborn metabolic disorders using tandem mass spectrometry in South Korea: a three-year report. Clin Chim Acta 2005; 354: 167-80.
53. Chace H, Millington DS, Terada N andKahier SG. Rapid Diagnosis of Phenylketonuria by Quantitative Analysis for Phenylalanine and Tyrosine in Neonatal Blood Spots by Tandem Mass Spectrometry. Clin Chem 1993; 39(1): 66-71.
54. Clarke S. Tandem mass spectrometry: The tool of choice for diagnosing inborn errors of metabolism? Br J Biomed Sci 2002; 59: 42-6.
55. Fang-Hoffmann J, Lindner M, Shahbek N, et al. Metabolic medicine: new developments in diagnosis and treatment of inborn errors of metabolism. World J Pediatr 2006; 2(3): 169-76.
56. Han LS, Ye J, Qiu WJ, et al. Selective screening for inborn errors of metabolism on clinical patients using tandem mass spectrometry in China: a four year report. J Inherit Metab Dis 2007; 30: 507-14.
57. Wilcken B, Wiley V, Hammond J, et al. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. N Engl J Med 2003; 348(23): 2304-12.
58. Shigematsu Y, Hirano S, Hata I, Tanaka Y, Sudo M, Sakura N, et al. Newborn mass screening and selective screening using electrospray tandem mass spectrometry in Japan. J Chromatogr B Analyt Technol Biomed Life Sci 2002; 776(1): 39-48.
59. McCandless S. A primer on expanded newborn screening by tandem mass spectrometry. Prim Care Sep 2004; 31(3): 583–604.
60. Riley C. Public Health Follow-up of Abnormal Newborn Screening Results. Epidemiology - Public Health Genetics, School of Public Health and Community Medicine. Seattle, WA, University of Washington. Master of Public Health 2007; 1-104.
61. Ostermann KM, Dieplinger R, Lutsch NM, et al. Matrix-assisted laser desorption/ionization for simultaneous quantitation of (acyl-) carnitines and organic acids in dried blood spots. Rapid Commun Mass Spectrom 2013; 27(13):1497-1504.
62. Gao X, Tan BH, Sugrue RJ, et al. MALDI mass spectrometry for nucleic acid analysis. Top Curr Chem 2013; 331: 55–77.
63. Hachani J, Duban-Deweer S, Pottiez G, et al. MALDI-TOF MS profiling as the first-tier screen for sickle cell disease in neonates: matching throughput to objectives. Proteom Clin Appl 2011; 5: 405–14.
64. Alexander D and van Dyck PC. A vision of the future of newborn screening. Pediatrics 2006; 117: S350-S354.