Newborn Screening for all Identifiable Disorders with Tandem Mass Spectrometry is Cost Effective: Supporting Arguments

Bradford L Therrell Jr,[1] *MS, PhD*, Colleen Buechner,[2] *MS, CGC*

Abstract

Tandem mass spectrometry (MS/MS) has become increasingly popular as the preferred technology for detecting inborn errors of metabolism in newborn screening (NBS) programmes. Its sensitivity and specificity for detecting numerous metabolic conditions is well-documented. As a NBS technology, there are continuing questions about whether MS/MS should be utilised to the fullest when such usage may mean detecting and reporting analytical findings that could lead to differentiating and diagnosing for which treatment efficacy may not yet be proven. As part of a friendly debate to educate conference attendees on both sides of a somewhat controversial issue, 2 papers awere presented giving information supporting or questioning the cost effectiveness of full scan usage and reporting when using MS/MS in NBS. Reported here are some of the supporting arguments.

Ann Acad Med Singapore 2008;37(Suppl 3):32-5

Key words: Cost effectiveness, Newborn screening, Tandem mass spectrometry

Introduction

Tandem mass spectrometry (MS/MS) was first proposed as a possible newborn screening (NBS) technology in the early 1990s.[1] Not only was the feasibility for detecting large numbers of metabolic disorders from NBS dried blood spots recognised, but also that disorders that did not yet have efficacious treatments might be detected in newborns. The relative rarity of metabolic diseases makes defining their natural history a challenge, and NBS for new diseases often uncovers disease variations not previously recognised. Thus, there were also questions about the reliability of detecting some disease markers early in life and how their concentrations (and detectability) might vary over time (from birth to time of specimen collection). On the other hand, NBS is a rare opportunity to increase knowledge about disorders including methods for early detection and treatment/management that can lead to improved outcomes. The net result is a continuing debate about which conditions to include in screening panels, how these policy decisions should be made, and whether such screening is cost effective. [2]

The arguments about MS/MS detectable conditions are particularly complex since the technology allows for multiplex testing (simultaneous detection of large numbers of conditions). In addition to analysing for profiles of detectable ions in the full scan mode, the technology can be restricted to look for specific target ions [commonly referred to as selective reaction monitoring (SRM) or multiple reaction monitoring (MRM)]. Adding to the confusion is the fact that some metabolic disorders may have the same MS/MS detectable markers. This can result in clinically significant disorders other than the primary screening target being revealed during the differential diagnosis of a targeted disorder. Thus, major policy decisions include whether to screen for and report all MS/MS detectable disorders. If all detectable disorders are not included in screening, what should happen if information about non-targeted disorders is obtained incidental to confirming the presence of a targeted disorder?[3]

The question proposed in this debate is whether NBS for *all* detectable conditions using MS/MS is cost effective. The 2 sides of the question can be seen simplistically from 2 comments previously published. Dr. Wilcken, a physician who presents the other side of the cost-effectiveness

[1] Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[2] Project Coordinator, National Newborn Screening and Genetics Resource Center, Austin, TX USA
Address for Correspondence: Professor Bradford L Therrell Jr, National Newborn Screening and Genetics Resource Center, 1912 W Anderson Ln #210, Austin, Texas 78757, USA.
Email: therrell@uthscsa.edu

Disclaimer: Information presented here does not necessarily represent the views of the authors or of the U.S. Health Resources and Services Administration, who provides support funding for the authors.

argument in this journal, has noted that, "The problem of costs and benefits is difficult, and a 'reasonable balance' rather than positive cost/benefit ratio seems desirable."[4] On the other hand, Dr. Howse, a consumer advocate, has stated the position of the March of Dimes that, "… a currently available test should be abandoned for a newer one, if the latter achieves a greater precision and offers a shorter turnaround time, no matter what the cost differential. … The primary consideration should be the health of the infant."[5] So, cost effectiveness appears at the outset to be based on the perspective from which it is viewed – professional or parent. That is, many physicians who must react to screening results by spending time, energy, and resources to try to make an accurate diagnosis may have a different perspective from many parents who may feel entitled to know everything possible about their newborn's health. In this report, we try to focus on the cost effectiveness studies previously reported as one important consideration impacting NBS policy decisions about MS/MS screening.

The economic arguments are challenging and often vary depending on individual perspectives since there are large knowledge gaps in considering rare diseases and subjective considerations must be included. Economic arguments can be used to compare health outcomes, costs of interventions, and averted costs, but they include information that may not be certain. For example, information about disorder prevalence, severity, testing quality (sensitivity and specificity), treatment benefits (decreased mortality and morbidity), and potential harms (recall rate and false positive findings) may be included in costing calculations. Cost-effectiveness usually considers health outcomes in terms of quality adjusted life years (QALYs). That is, a year of life is adjusted for its quality with 1 year of perfect health defined as 1.0 QALY. A year of ill health is discounted based on health outcome projections and experiences. Cost-benefit analyses usually seek to translate health outcomes into money. Economists generally agree that a cost-effective investment exists if the cost for a QALY is $50,000 or less.[6] For a more detailed look at the economic arguments in NBS, readers are referred to published reports by persons with specific health economics expertise.[7,8]

Method

The primary method of obtaining information for this report was through the use of various search engines on the Internet. The terms used included various combinations of 'cost effectiveness,' 'cost benefit,' 'newborn screening,' and 'tandem mass spectrometry.' As articles were located, their references were scanned for additional information. Various parent advocacy organisations were also contacted for stories and information from their members on personal experiences in jurisdictions where MS/MS screening capabilities were not fully utilised and *all* detectable conditions were not included in screening. While many poignant stories were obtained describing adverse affects when MS/MS screening was limited by MRM techniques, these stories were used primarily as illustrative examples during the oral presentation of this report and are not repeated here because of their anecdotal nature and space limitations.

Results

Because NBS using MS/MS technology is relatively new and the economic arguments are complex, published cost studies are limited and do not generally include all detectable conditions. Therefore, the arguments favouring MS/MS full scan screening must be constructed from combinations of individual and multiple cost studies (and their appropriate extrapolations). Because NBS for medium chain acyl-coA-dehydrogenase deficiency (MCADD) has the longest history, several MCADD costing studies exist, some with combinations of other disorders. Early MS/MS cost effectiveness reports date to 2002. In that year, 2 cost studies reported the benefits of MS/MS NBS. The first reviewed the impact of comprehensive MS/MS screening on a large California, USA health maintenance organisation. In the base scenario, the cost for comprehensive MS/MS screening was $5,827/QALY; in the least favourable scenario, it was $11,419/QALY, and in the most favourable scenario, it was $736/QALY. All of these amounts were well within the favourable cost effective range previously noted (≤$50,000). Cost savings occurred primarily in the first years of life due to decreased hospital stays, with lower cost saving in later years as a result of higher follow-up costs due to increased life expectancy. Cost savings were dependent on a low recall rate and subsequent low number of false positive findings.[9]

The other 2002 cost study was conducted in Wisconsin, USA. There, an incremental cost-effectiveness analysis looked at the differences in screening for MCADD alone and in combination with 13 other detectable disorders. Screening for MCADD alone was calculated to cost $41,862/QALY in the worst case scenario and $6,008 in the most realistic case scenario, both illustrating cost effectiveness. The incremental costs of simultaneously detecting the 13 other disorders with MS/MS NBS also gave an acceptable cost effectiveness ratio of $15,252/QALY (assuming that the incremental cost of screening remained under $13.05 per test).[10] A study in Pennsylvania, USA at about the same time also concluded that MCADD screening was cost effective. Their base-case analysis (including start-up costs) over the first 20 years of life, showed a screening cost of $5,600/QALY (95% CI: <0-$17,100/QALY) with cost effectiveness improving to

approximately $100/QALY (95% CI: <0-$6900/QALY) when the life span was expanded to 70 years.[11]

A 2005 Finnish study examining the costs, effects, and ethical consequences for NBS decision making found that MS/MS screening for several metabolic conditions was cost effective when compared to other health interventions already in use (despite the fact that the incidence of PKU is known to be extremely low in Finland. This study of 5 disorders, including 4 detectable by MS/MS [MCADD, long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD), phenylketonuria (PKU) and glutaric aciduria type 1 (GA-1)] found a range of cost effectiveness from €5,500/QALY gained to €25,500/QALY. Calculations and modelling included considerations for adding additional conditions. Avoidance of a single severe handicap as a result of screening was found to decrease the worst case scenario to €18,000, making it cost effective.[12]

In another European study, medical records on all clinically diagnosed MCADD patients in the Netherlands born between 1985 and 2003 were compared to experiences of patients found through NBS. The incremental cost-effectiveness ratio (ICER) was calculated using life years (LYs) as the outcome measure by combining the 2 cohorts in a decision model with second-order Monte Carlo simulation. The resulting ICER was $1653 per LY gained. A sensitivity analysis gave an ICER of $14,839 to $4345 per LY gained. All calculated ICER/LY were well within acceptable range for cost effectiveness.[13]

Perhaps most pertinent to the question at hand is a more recent costs effectiveness study in California, USA. Costs were extrapolated from a NBS pilot program considering *all* identifiable conditions detectable by MS/MS. Cost-effectiveness, benefit/cost, and cost-utility analyses were conducted using a base-case set of assumptions, which were varied to examine more-favourable and less-favourable assumptions. MS/MS screening was estimated to identify 83 affected newborns annually from 540,000 screened and, when all programme costs and savings were calculated, NBS was estimated to save approximately $1.5 million ($3.4 million savings in the best case scenario and $3.8 million additional costs in the worst case scenario) annually. A more rigorous cost effectiveness calculation with sophisticated economic modelling found that NBS with MS/MS was cost effective with a cost of $1,628/QALY in the best case scenario and $14,922/QALY in the worst case scenario.[14]

Discussion

As noted by the American College of Medical Genetics' Expert Group, MS/MS screening for a core set of conditions usually results in screening for a much wider range of conditions since metabolic disease indicators are often not specific to a particular disorder. In the case of the ACMG 'core 29' conditions, several additional conditions, perhaps as many as 8, would likely be detected incidentally as part of the differential diagnosis if MRM screening were used. Further, full scale MS/MS profiling, in addition to being the most efficient use of the screening technology, offers better quality for the MS/MS analytical screening procedure. That is, full scale MS/MS testing allows better detection of spurious signals and/or reagent contaminants. Use of full MS/MS profiles also enhances clinical interpretation by revealing anomalies in associated compounds or internal standards against which excesses or deficiencies can be better interpreted.[3] All of these considerations play a role in cost effectiveness considerations.

Some have argued that increasing the conditions screened by MS/MS increases the psychological stress to parents resulting from increased patient recall to resolve presumptive findings. Indeed, a 2003 study of child outcomes and parental stress in New England, USA found that recall with subsequent false positive findings caused increased parental stress and parent-child dysfunction. This study also confirmed that screening and early diagnosis with MS/MS resulted in fewer and shorter hospitalisations, fewer medical problems, higher developmental scores, and reduced stress to parents in the screened cohort.[15] A separate study in Ohio, USA using questionnaires to assess parent's knowledge about screening, parental stress, and parental attitudes confirmed the New England findings, and also found that the majority of responders favoured expanded testing to greater numbers of conditions even if screening resulted in a recall with subsequent false positive findings.[16]

In conclusion, there is significant cost effectiveness data justifying screening for MCADD. Likewise, there is a growing literature suggesting that MS/MS full scanning techniques used to identify all detectable conditions of clinical significance are also cost effective. As noted by others,[12] a cost effectiveness analysis is only a technical aid that may lead to different screening policy decisions depending on available resources and value judgments. Cost effectiveness is usually not the sole basis for decision-making since the values of individuals, families, healthcare personnel and health decision-makers are different. Ultimately, the decision to screen for all MS/MS detectable conditions or to limit the screening panel must meet both the needs of the professional screening community and families.

Acknowledgement

The authors are supported by a grant from the U.S. Maternal and Child Health Bureau of the U.S. Health Resources and Services Administration (Grant No. U32MC00148).

REFERENCES

1. Millington DS, Kodo N, Norwood DL, Roe CR. Tandem mass spectrometry: a new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. J Inherit Metab Dis 1990;13:321-4.
2. Chace DH, Kalas TA, Naylor EW. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003;49:1797-817.
3. American College of Medical Genetics, Newborn Screening Expert Group: Newborn screening: toward a uniform screening panel and system. Genet Med 2006;8:1S-252S.
4. Wilcken B. Evaluating outcomes of newborn screening programs. Southeast Asian J Trop Med Public Health 2003;34Suppl3:13-8.
5. Howse JL, Katz M. The importance of newborn screening. Pediatrics 2000;106:595.
6. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality adjusted life year: in search of a standard. Med Decis Making 2000;20:332-42.
7. Grosse SD. Does newborn screening save money? The difference between cost-effective and cost-saving interventions. J Pediatr 2005;146: 168-70.
8. Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. Pediatrics 2006;117suppl:S287-S295.
9. Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. Pediatrics 2002;110:781-6.
10. Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. J Pediatr 2002;141:524-31.
11. Venditti LN, Venditti CP, Berry GT, Kaplan PB, Kaye EM, Glick H, et al. Newborn screening by tandem mass spectrometry for medium-chain acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. Pediatrics 2003;112:1005-15.
12. Autti-Rämö I, Mäkelä M, Sintonen H, Koskinen H, Laajalahti L, Halila R, et al. Expanding screening for rare metabolic disease in the newborn: an analysis of costs, effect and ethical consequences for decision-making in Finland. Acta Paediatr 2005;94:1126-36.
13. van der Hilst CS, Derks TG, Reijngoud DJ, Smit GP, TenVergert EM. Cost-effectiveness of neonatal screening for medium chain acyl-CoA dehydrogenase deficiency: the homogeneous population of The Netherlands. J Pediatr 2007;151:115-20,
14. Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. Pediatrics. 2006; 117suppl:S280-S286.
15. Waisbren SE, Albers S, Amato S, Ampola M, Brewster TG, Demmer L, et al. Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress. JAMA 2003;290: 2564-72.
16. Daniels M. Parents' knowledge of and experiences with the Ohio newborn screening program. Proceedings of the 2002 U.S. National Newborn Screening and Genetic Testing Symposium; 2002 November 4-7; Phoenix, Arizona. Washington, D.C.: Association of Public Health Laboratories, 2003:178-86.