Neonatal Screening of Inborn Errors of Metabolism Using Tandem Mass Spectrometry

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practicing medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

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Executive Summary

Objectives and Method

The Medical Advisory Secretariat undertook a review of the evidence on the effectiveness and cost-effectiveness of using tandem mass spectrometer [MS/MS] for the neonatal screening of inborn errors of metabolism [IEM].

The review is based on two systematic reviews commissioned by the National Health Services (United Kingdom) and relevant research literature that was published after the completion of these two systematic reviews. A horizon scanning was conducted to determine the current status of neonatal screening programs in other national and international jurisdictions. The MAS also consulted with stakeholders including the laboratory branch, an expert in IEM at a pediatric hospital, MS/MS experts and a MS/MS manufacturer.

Result

Synthesis of information obtained from the above process showed that:

➤ Ontario is currently screening all newborns for phenylketonuria [PKU] and congenital hypothyroidism [CH] using the Guthrie method on dry blood spots obtained by heel prick before discharge from hospital.

➤ MS/MS can detect 25 IEMs in a single process on the same dry blood spot.

➤ Computer algorithms have been used to automate the MS/MS screening process to provide rapid throughputs of 400 samples or more per day. Screening for additional IEMs using MS/MS does not add significant cost to the program.

➤ MS/MS -based neonatal screening showed sensitivity of 100% and specificity of 83% to 99% depending on the IEM. The specificity of MS/MS in detecting PKU is significantly superior to that of the current Guthrie method and is therefore able to reduce the number of false positive results.

➤ For certain inborn errors of metabolism not currently screened, early detection and simple treatment could avoid early mortality and prevent or reduce mental retardation

➤ Using eligibility criteria recommended by the World Health Organization adapted to Ontario, a rating system was developed and applied to assess the IEMs recommended for inclusion in neonatal screening.

➤ The assessment showed that PKU and CH should continued to be screened. In addition, medium chain acyl-CoA dehydrogenase deficiency [MCADD] and congenital adrenal

hyperplasia [CAH] met most of the criteria for inclusion in a neonatal screening program. MCADD can be screened with PKU by MS/MS while the test for CAH requires a different methodology.

➢ An expanded neonatal program would require an enhanced infrastructure for result interpretation, reporting, care provision and counseling.

➢ Important ethical and societal issues including informed consent need to be addressed.

➢ As of 1998, twenty-six states in the United States were using MS/MS for newborn screening of IEMs. In Canada, British Columbia, Saskatchewan and Nova Scotia use MS/MS for IEM related assays. Manitoba is planning to implement MS/MS -based neonatal screening in 2003.

➢ Among Canadian jurisdictions, British Columbia, Manitoba, Quebec, Nova Scotia and Saskatchewan are screening for more IEMs than Ontario.

I. Objectives

The Medical Advisory Secretariat was asked to review the evidence for an expanded MS/MS - based newborn screening program by conducting a health technology review to determine its effectiveness and cost-effectiveness.

II. BACKGROUND

II -1 Clinical Need

Inborn Errors of Metabolism

An inborn error of metabolism is a permanent and inherited biochemical disorder generally caused by lack of a functional enzyme, transmembrane transporter or similar protein resulting in a blockage of the corresponding metabolic pathway. There may be an accumulation of metabolites prior to the metabolic block and /or deficiency in the ultimate product(s) of the pathway [2]. Detection of IEM through screening is the key to early treatment.

Existing Newborn Screening Program in Ontario

In Ontario, newborn screening for inborn errors of metabolism [IEM] has been applied to the early detection of phenylketonuria [PKU] and congenital hypothyroidism. The cost-effectiveness of this existing screening has been substantiated by international economic analyses that justify the collection of heel prick blood spot testing of all neonates within the first 48-72 hours of birth for the purpose of screening for PKU and congenital hypothyroidism.[Seymour et al, 1997; Dhondt et al, 1991].

Newborn screening in Ontario is performed by provincial laboratories on 130,000 newborn specimens per year using the Guthrie method of bacterial inhibition [Guthrie, 1980] for PKU and an endocrine assay to detect congenital hypothyroidism.

International Neonatal Screening of IEM

The reported incidence of various IEMs currently forming part of one or more newborn IEM screening programs internationally appears in Table 1 [Appendix 1]. Only tests with a sensitivity and specificity >95% as reported in the review by Pollitt et al [1997] are included.

Need for Accurate Simultaneous IEM Testing

Until quite recently, the cost effectiveness of expanding a newborn IEM screening program was limited by the complexities of performing separate assays and the false positive rates for each IEM. In Ontario, for every 10 cases of PKU identified using the existing Guthrie test, 9 are false positives. This results in additional costs and unnecessary distress to parents. There is a need for a technology that can simultaneously screen for multiple IEMs efficiently and accurately. Tandem mass spectrometer has been proposed to be the solution.

II -2   The Technology

Tandem Mass Spectrometry [MS/MS] is an automated technology that allows multiple IEMs to be rapidly detected on a single sample.

MS/MS was introduced in the early 1990s for population-based newborn screening and allows the detection of 25 metabolic disorders in a single process using dried blood spot [DBS] specimens collected by heel prick from newborns.

MS/MS combines two mass spectrometers [MS] linked by a collision cell. A mixture of components is introduced into the first MS through an electrospray ionization device. In the first MS, the compounds are separated according to their mass/charge ratio and the analyte ion of interest is allowed to passed into a collision chamber where the incoming molecules are fragmented into charged molecules of smaller size [daughter ion] through collision with a heavy inert gas [argon]. These smaller daughter ions then pass into the second MS that has been programmed to detect a selected ion. Compounds with similar class will generate at least one similar daughter ion. This permits assignment of a chemical identity to those molecules separated in the first mass spectrometer .
The entire procedure is completed within seconds and in contrast to gas chromatography MS, lengthy procedures are not required to make the compounds volatile.
During analysis of each sample, different daughter ions can be searched sequentially, permitting the identification of many different classes of compounds.

III Literature Review

III -1 Objectives

The objectives of this review were to:

➢ identify the eligibility criteria for including IEMs in a new born screening program;
➢ identify the IEMs that should be included in an expanded newborn screening program based on these eligibility criteria in order to achieve optimal effectiveness and cost-effectiveness.
➢ determine the effectiveness and cost-effectiveness of expanding Ontario's newborn screening program for IEM through the introduction of MS/MS technology;

III -2 Method

The policy of the Medical Advisory Secretariat [MAS] is to, whenever possible, use recent health technology assessments [HTAs] from credible national and international HTA organizations to avoid duplication of effort. This approach includes an analysis of key assumptions made in the HTA and adjustments to economic analyses to ensure their relevance to Ontario.

Search for Systematic Reviews

A preliminary search of the Cochrane database and web sites of members of the International Agency for Health Technology Assessment [INAHTA] including CCOHTA was conducted using the search terms " neonatal screening", " mass screening", "infant – newborn" and "tandem mass spectrometer".

Systematic Reviews of the National Health Service Review and Dissemination HTA Programme [NHS R&D]

Two comprehensive systematic reviews (HTAs) on newborn screening for IEM, commissioned by NHS R&D Health Technology Assessment Program were found. These HTAs were deemed to have been produced by a reputable HTA unit and were therefore accepted as the basis for developing a response to the request for funding MS/MS in Ontario.

The HTA by Seymour et al [0] was conducted through a MEDLINE search from 1966 to June 1996, based on terms "mass screening" and "inborn errors of metabolism." Further searches were carried out for each named IEM plus one of the following terms: mass screening; outcome; incidence; false positive reactions; false negative reactions; costs and cost analysis; sensitivity and specificity. In all, 1,866 citations and abstracts were reviewed. The HTA by Pollitt et al used IEM - specific searches as well as additional search for screening using MS/MS [2]. A total of 1,156 articles were included in the review. Details of the searches are described in the two HTA reports that have been included in the bibliography.

Follow-up review: Update on the NHS R&D HTA on IEM

The NHS R&D HTAs were published in 1997 and included references published up to June 1996. An updated search of MEDLINE and EMBASE was conducted for articles published since June 1996 using the following criteria:

English language articles published between July 1996 to May 2002 which report on one or more of the following aspects of inborn errors of metabolism:

➢ Incidence of specific IEMs.

➢ Course of disease, treatment and effectiveness of early intervention

➢ Method used in screening IEMs

➢ Sensitivity, specificity, positive and negative predictive values of MS/MS and other technologies in the screening of IEMs.

➢ Experience in the implementation of MS/MS screening programs for IEMs.

➢ Cost-effectiveness or cost analysis of using MS/MS in mass screening of IEMs.

➢ Mass screening programs of IEMs in Canadian jurisdictions

➢ Mass screening programs in international jurisdictions

In addition, websites of the guideline clearing houses such as the [American] Agency for Healthcare Research and Quality and websites related to mass neonatal screening programs were also searched. The search yielded 261 articles and 58 met the inclusion criteria. Data in these articles were extracted, categorized and summarized according to IEM.

Data on Economic Analysis

Data on economic analyses were obtained from the systematic review by Pollitt and world literature. Efforts were made to render the data relevant to Ontario

Consultations

The Medical Advisory Secretariat [MAS] consulted with:

➢ An expert in IEM;
➢ MOHLTC staff responsible for the existing IEM laboratory based newborn screening program in Ontario;

➢ Industry representatives to assess the most current versions and costs of MS/MS.

➢ Ministries of Health in Nova Scotia, British Columbia, Saskatchewan and Alberta

IV. Findings

IV-1 Findings of the HTA on New Born Screening of IEM by Seymour et al [0, 3] (Commissioned by the National Health Service Review and Dissemination Program, UK)

The HTA by Seymour assessed each IEM using criteria based on those developed by Wilson and Junger [4]for identifying diseases and their diagnostic tests that would be suitable candidates for neonatal screening. The criteria used in the critical appraisal were:

➢ Clinically and biochemically well-defined disorder;
➢ Known incidence in populations relevant to UK;
➢ Disorder associated with significant morbidity or mortality;
➢ Effective treatment available;
➢ Period before onset during which interventions improve outcome;
➢ Ethical, safe, simple and robust screening test;
➢ Cost-effectiveness of screening.

Principal findings and recommendations made by Seymour et al [0] were:

➢ *Phenylketonuria [PKU] and congenital hypothyroidism* fulfilled all screening criteria and the universal screening of these two IEMs was cost-effective.

The average of reported incidence of PKU [Table 1, Appendix 1] 1:12,000
The average of reported incidence of congenital hypothyroidism [Table 1, Appendix 1] 1:3,500

The conclusion regarding cost-effectiveness is important, since it validates the collection of blood tests for the purposes of newborn screening and supports existing practice that can be used as the basis for expanding the screening program without increasing administrative infrastructure for obtaining blood for these tests. However, this needs to be further explored since the timing of blood collection may significantly influence the test results for other IEMs and the cost-effectiveness of the screening program. For example, blood is presently collected for PKU and congenital hypothyroidism testing before discharge from hospital, which usually occurs within 24 hours of birth. If screening for new IEMs requires sample collection after 24 hours, this would necessitate a change to the current collection process that could result in increased costs to the expanded program.

➢ Seymour et al indicated that a case could be made for screening the following additional IEMs :

Medium-chain acyl CoA dehydrogenase [MCADD]

The average of reported incidence [Table 1, appendix 1] is 1:16,000
Most patients with MCADD are asymptomatic prior to diagnosis, but once manifest, the disease can result in significant morbidity and mortality. The diagnosis is usually only suspected when patients present acutely with hypoglycemia or a Reye-like illness, often precipitated by an infection, at a median age of between 10 and 14 months. Once the diagnosis has been made, metabolic decompensation is associated with a mortality of 20- 25% [0]. Among survivors, 37% have neurodevelopmental problems.

MCADD is readily and cheaply treated, by avoiding fasting, a low fat diet and L-carnitine supplementation [5, 6].

A prevention strategy significantly reduces mortality and neurological handicap. Screening requires MS/MS technology which has a specificity of >99% and sensitivity of >99% for MACDD [7].

Glutaric aciduria type 1[GA I]

The average of reported incidence [Table 1, appendix 1] is 1:91,000
The newborn form of this disease is often fatal during the first few weeks of life. GA I hinders the maturation of the frontotemporal cortex in the second half of gestation leading to frontotemporal atrophy. Injury to the putamen and caudate usually occurs between 6 and 18 months of age and is precipitated by fever or other catabolic states [8]. Infants with GAI are prone to suffer acute subdural hemorrhages. The disease produces severe hypoglycemia, metabolic acidosis, hypotonia and hepatomegaly. Without treatment, more than 90% of affected children will develop severe neurological disabilities.

Recognition of the disorder before the brain has been injured is essential to treatment Screening of this disorder depends on the detection of elevated glutaryl carnitine using MS/MS technology. Treatment includes high-carbohydrate, low protein, low fat and frequent meals with carnitine and riboflavin supplementation.

This IEM is especially relevant to Ontario as there is a much higher incidence of the disease amongst Aboriginal population sub-groups than the average incidence from the world literature.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency

The average of reported incidence [Table 1, appendix 1] is 1: 16,000

Congenital adrenal hyperplasia may lead to life-threatening adrenal crises and/or the incorrect male sex assignment of affected females with ambiguous genitalia. However, most cases of acute adrenal crisis occur within the first week of life and those that develop later tend to be milder. The screening test may therefore only be useful in picking up 20% of total cases that present after the first week. The screening test is performed by the measurement of 17-hydroxyprogesterone in a heel-stick dry blot test. Treatment with lifelong steroid replacement results in disease control [9].

While screening for this abnormality has not been possible with MS/MS, an Australian group is studying whether this technology might lend itself to this application [10]. As of April 2002, however, this application of MS/MS had not been further investigated [Wiley, personal communication, 2002].

Biotinidase deficiency.
The average of reported incidence [Table 1, appendix 1] is 1:84,000
Symptoms include seizures, hypotonia, immune system impairment, rashes, mental retardation, and hair loss. According to Seymour et al, the low incidence is outweighed by the simplicity of the test and the prevention of severe neurological disease with oral biotin supplementation. Screening is performed through enzyme activity and calorimetric determination. This disease can be detected by MS/MS technology though the sensitivity is low compared with enzyme assay.

> *Seymour did not recommend the screening of the following IEMs because they do not meet all of the criteria required to justify a neonatal screening program.*

Galactosaemia.

The average of reported incidence [Table 1, appendix 1] is 1:49,000
Newborn screening for galactosaemia is controversial, because of the low frequency of the disease resulting in an unfavorable cost-benefit ratio; suboptimal screening tests; long-term complications despite early diagnosis and treatment including intellectual impairment, speech disorders, cataracts and hyper/hypogonadism in females.

Galactosemia causes severe symptoms in the newborn period, due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase leading to high concentrations of galactose –1-phosphate which is toxic to several tissues, especially the liver, brain and kidney. Clinical manifestations occur soon after birth and if treatment is not initiated early, death often occurs during the first weeks of life. A galactose –free diet results in rapid regression. However, diagnosis is often delayed.

While newborn screening for galactosaemia is becoming increasingly widespread, Seymour et al pointed out that, despite early treatment, long-term outcome remains poor. According to these authors, galactosemia does not therefore meet the modified criteria of Wilson and Jungner [4] and they did not therefore recommend screening.

Given the overall poor outcomes, despite early diagnosis through screening, some international jurisdictions are now withdrawing galactosemia from their IEM screening programs [Dr. J Clarke, personal communication, June 2002].

The issue of unfavourable cost-benefit should be revisited in light of the recent methodology to detect galactosemia using MS/MS.

Tyrosinaemia Type I

The average reported incidence [Table 1, appendix 1] is 1:122,000.

The incidence of tyrosinaemia type I is variable. In the UK, the incidence reported for Birmingham City is five times higher than the average 1:100,000. In the Saguenay-Lac-St.Jean region of northeastern Quebec in Canada, the disorder is particularly common with an incidence of 1:1,846 [0]. Quebec has been screening for tyrosinaemia since 1971 [0].

Screening for tyrosinaemia type I can be based on the detection of tyrosine concentration in the blood, measurement of succinylacetone, microbiological assay (Guthrie method), fluorometric assay or MS/MS.

Tyrosinaemia type I, a deficiency of fumarylacetoacetase, results in an accumulation of toxic metabolites including succinylacetone. Patients present with liver failure, renal tubular dysfunction and neuropathic crises. It has been reported that about 77% of the children with Tyrosinaemia Type I suffer from an acute form of the disorder, presenting symptoms within weeks of birth. The disease may show a more protracted course resulting in hepatocellular carcinoma in survivors over 2 years of age.

Seymour stated that prognosis of tyrosinaemia Type I is uncertain because the disease may progress despite rigorous dietary restrictions of tyrosine, phenylalanine and often methionine. An international survey showed that even with diet therapy, onset of symptoms before 2 months of age was associated with a 1- year survival probability of 38%. This increased to 96% for those who presented with symptoms after six months.

The long-term effectiveness of two other therapies are still under assessment.
- Liver transplantation before the development of malignancy has the potential to cure the hepatic and neurological components of the disease but not the genetic defect in the kidneys. One-year survival rates of 95% and 4-year survival rate of 88% have been reported. [2].
- Early treatment with enzyme 2-(2-nitro-4-trifluoromethhylbenzoyl)-1, 3-cyclohexanedione [NTBC] is being investigated and showed promising results in improving biochemical parameters. But NTBC offers no cure for patients with hepatoma.

Contrary to Seymour, Pollitt concluded that the long-term outlook for patients with tyrosinaemia type I is improving and recommended early diagnosis through neonatal screening followed by treatment with NTBC regardless of the route of treatment [2].

Maple Syrup Urine Disease [MSUD]

The average of reported incidence [Table 1, appendix I] is 1: 190,000

MSUD is caused by an inherited deficiency of the enzyme branched-chain 2-keto acid dehydrogenase resulting in marked elevation of plasma and urinary concentration of branched –chain ketoacids and branched amino acids.

Acute neonatal onset of MSUD generally presents with symptoms at 4-7 days following birth (possibly before results of screening are available) with rapid progression to severe ketoacidosis, coma and death. Untreated survivors suffer from neurological damage with mental retardation, spasticity and blindness. The disease could present in the intermediate form with delayed and less severe symptoms or in the intermittent form that arises during catabolic stresses.

Management of acute neonatal onset of MSUD includes renal dialysis or haemofiltration to lower metabolite levels. Subsequent treatment involves dietary restriction of branched-chain amino acids. Long - term survival is good but intellectual performance depends on the age at which metabolic control is achieved and the quality of the control. A recent study showed normal IQ in children diagnosed and treated within the first week and those treated later had below normal IQ [2].

Neonatal screening of MSUD is performed in 11 countries and 25 states in the US. Conventional screening method relies on the bacterial inhibition assay of leucine. Tandem MS has been successfully used to screen for MSUD by measuring the leucine and isoleucine: phenylalanine ratio.

MSUD did not meet the criteria for universal screening because Seymour's review found that the dietary treatment is difficult to maintain and does not completely prevent recurrent metabolic crises that remain potentially fatal.

Homocystinuria

The world wide incidence reported is 1:335,000 [Table 1, appendix 1].

Homocystinuria is a multi-organ disease with the most common cause being an inherited deficiency of cystathionine b-synthase activity. Patients with homocystinuria suffered high morbidity including impaired vision, osteoporosis, neurological dysfunction and thromboembolism. Mental retardation and developmental problems are common.

Approximately half of all patients respond to treatment with large doses (250-1200 mg/day) of vitamin B6 (pyridoxine) sometimes in conjunction with folate and vitamin B 12. In the responsive patients, pyridoxine treatment has been shown to prevent thromboembolic events and to reduce the frequency of lens dislocation. A diet restricted in methionine with cystine supplementation is necessary particularly in patients who do not respond to pyridoxine treatment. The use of methyl donors such as betaine is the main treatment for patients who do not tolerate the diet [Dr. Joe Clarke].

Both microbial assay and chromatography methods for screening homocystinuria showed poor sensitivity. MS/MS has been used in a prospective neonatal screening of 173,537 babies with no known false-negative results [0].

➤ Seymour concluded that there was insufficient evidence at the time for the widespread introduction of MS/MS technology into newborn screening programs in the UK but recommended that MS/MS for newborn screening for PKU, MCAD deficiency and GA1 be further evaluated by primary research over 5 years.

IV-2   Findings of HTA on New Born Screening of IEM by Pollitt et al [2] (Commissioned by the National Health Service Review and Dissemination Program, UK)

The HTA by Pollitt et al [1997] took a "causal" approach. For each disease, literature data on incidence, proportion of biochemically defined cases likely to be affected clinically, effectiveness of treatment, overall sensitivity of the screening process, requirement for repeat blood samples and other specific follow-up tests and false positive rate at clinical referral were assessed. Evidence on effectiveness of treatment was graded 1- 4. Pollitt also looked at the screening criteria in the context of whether a disease, though rare, could be incorporated into a MS/MS screening program with little effort and whether the resultant earlier treatment would improve prognosis. Based on this holistic approach, Pollitt et al recommended:

➤ Continuation of the current UK screening programs for cystic fibrosis and Welsh program for Duchenne muscular dystrophy.

➤ No specific screening program be established for galactocemia but secondary screening on samples with increased phenylalanine be performed.

➤ Cystic fibrosis screening be encouraged and monitored.

➤ Galactosaemia, congenital adrenal hyperplasia, Duchenne muscular dystrophy and biotinidase deficiency do not merit high priority as stand alone screening programs. In the case of biotinidase deficiency, the incidence is extremely low in the UK.

➤ A large-scale, three year pilot study of prospective neonatal screening using MS/ MS be initiated with a view to subsequent introduction into general use. The screening should be directed to a limited range of clearly defined diseases with high degree of specificity and satisfactory confirmatory test.

Conditions recommended for general screening in the pilot study include:
PKU, maple syrup urine disease, methylmalonic acidaemia, proprionic acidaemia, isovleric acidaemia, other branch chain disorders, MCADD, very long chain acyl-CoA dehydrogenase deficiency, long chain 3-hydroxyacyl acyl-CoA dehydrogenase deficiency, carnitine parmitoyltransferase deficiency, carnitine transporter defect, glutaryl-CoA dehydrogenase deficiency and glutaric aciduria type II.

➢ The restriction of Tyrosinemia type I, urea cycle defects, biliary atresia/liver disease and homocystine assay for second-line test for cystathionine b-synthase deficiency to specific sites with special interest in these disorders.

IV- 3   Update of NHS R&D HTA on IEM

The main findings obtained through a literature search on newborn screening based on MS/MS from 1997 to January 2002 are summarized below.

Congenital Adrenal Hyperplasia

Van der Kamp [11] reported on a 2-year newborn screening for CAH in the Netherlands in which 176,684 newborns were screened. The study showed an overall prevalence of CAH of 1:11,764. The outcomes of 15 CAH patients identified through screening and started treatment at the median age of 7 days were compared to the outcome of 19 CAH newborns from another area without screening who started treatment at the median age of 14 days. The results showed that the screening avoided severe salt wasting. The specificity of the screening test was 99.76% for the first year and 99.97% for the second. The positive predictive values were 4.5% and 16%. No false-negative cases were detected in the study.

A study compared the incidence and diagnosis of 400,118 unscreened newborns in Arkansas and Oklahoma to 1,613,378 screened newborns in Texas during a five year period [12]. The incidence of classic CH was similar for the two cohorts [1: 17,391 and 1:15,974]. However, the median age of diagnosis was 12 days for the screened cohort compared to 26 days for the unscreened cohort. The study showed that male newborns benefited from the significantly earlier diagnosis, lower morbidity and shorter hospitalization.

According to Honour et al [13], the results of established screening programs suggest that CAH screening is effective in detecting cases not suspected clinically. This report further suggests that procedures for CAH screening should be based on separate flow charts for term and preterm infants to avoid high false positive rates. It also indicates that simultaneous, multiple immunoassay measurements is one approach to reduce costs, particularly when thyroid stimulating hormone is the front line screening test for neonatal congenital hypothyroidism.

MCADD

There is confirmatory evidence that MCADD can be screened using MS/MS and that the false positive and negative rates are acceptable for a population-based screening program. Clayton et al [14] used MS/MS to study 482 neonates, 35 children with proven MCADD and 2168 control children in the UK and concluded that if screening for MCADD is undertaken at 7 – 10 days after birth, the number of false positive and false negative results should be negligible. Because there have been no instance of death or neurological damage after diagnosis of MCADD in this study, Clayton et al indicated a strong case can be made for neonatal screening for MCADD in the UK. This is consistent with the experience at Hospital for

Sick Children in Toronto where there has not been any episodes of severe ancephalopathy after diagnosis [Dr. Joe Clarke].

In another study, forty-one patients diagnosed with MCADD had a median follow-up period of 6.7 years [15]. After diagnosis, two patients were admitted to hospital with severe encephalopathy but there were no additional deaths or appreciable morbidity. Wilson concluded that current management of high carbohydrate intake during periods of infection and anorexia improves outcome, supporting the view that the disorder should be included in newborn screening programs. In Lower Saxony of Germany, where the incidence of MCADD was found to be 1:4,900, significantly higher than the worldwide incidence, efforts were made to obtain DBS for screening after 48 hours in order to obtain a diagnosis within 3-4 days following birth [16].

Despite the above findings, there remains a body of opinion that prospective studies on MCADD need to be performed prior to introducing this as a population-based newborn screening modality [17, 18]. Dezateaux stated that "decisions to start new screening programs should be informed by unbiased estimates of benefits and harms which cannot be derived from observational studies" and recommended that the existing infrastructure for routine IEMs in UK be developed for the purpose of conducting these trials.

Calls for formal prospective studies are likely to be tempered by the study reported by Wilson CJ et al [15] who demonstrated that dietary intervention can significantly alter the clinical course of this disease. This information could pose ethical challenges to a randomized clinical trial with a no-screening control arm.

Irrespective of whether MCADD is subject to further studies, there is increasing interest in introducing this into screening programs. An increasing number of jurisdictions in North America have adopted MCADD as an additional screening test [Dooley, personal communication, June 2002]. In most programs, the screening is performed at 48-72 hours post-partum. If MCADD screening is performed in children >10 weeks of age, free carnitine measurement should also be performed to improve specificity in this sub-set.

Given the high reported incidence of MCADD and the opportunities to modify the severity of disease if detected early, it would be expected that indications for routine screening would be relatively clear cut. Instead, some jurisdictions are still evaluating MCADD screening. Reasons for this are best explained by Leonard and Dezateux [19] who identify the following problems relating to MCADD screening:

➢ Lack of standardization regarding the choice of metabolite, thresholds used to define positive tests and criteria for confirmatory tests make inter-jurisdictional comparisons difficult.

In one study quoted [20] in which explicit diagnostic criteria for re-testing was used, only 12 out of 23 infants with positive screens were found to have MCADD. Most of the infants with false positive screening tests were premature. In the U.S. and Australia studies, the incidence of MCADD was lower than expected.

➢ The impact of screening and treatment on families with true, borderline and false positive diagnosis needs to be taken into account.

➢ There is no systematic follow up reports on long term outcomes in infants detected through screening.

Leonard and Dezateux conclude that it nevertheless seems that with the deployment of MS/MS, screening for MCADD will become inevitable and that "…once again, a screening technology looks to be driven by enthusiasm and opinion rather than by evidence."[19].

Although British Columbia has a MS/MS unit, this province is not offering routine MCADD screening at this time but is using MS/MS for acylcarnitine assay [Dr Vallance, personal communication, June 2002].

Galactosemia

There is now evidence that galactosemia can be screened using MS/MS technology [21]]. The minimal increase in cost for screening galactosemia by MS/MS could impact on any decision whether to add it to the existing newborn screening program if it meets the criteria for screening. However, measurement of galactose –1-phosphate is not being performed at the same time as other tests on MS/MS and therefore represents a slight incremental cost.

While B.C. is screening for galactosemia and has MS/MS, the latter is not being used for this purpose.

Phenylketonuria

In Ontario, for every 10 cases of PKU identified using the existing Guthrie test, approximately 8 to 9 cases are false positives. This causes unnecessary distress to parents. The MS/MS technology allows this high false positive rate to be significantly reduced in part by measuring the PKU:Tyrosine ratio [Dr J Clarke, personal communication, June 2002]

In a study of 40 patients with PKU, Trefz et al showed that in untreated or late treated patients with PKU, the final intelligence is influenced by the time at which dietary treatment started, the intellectual status of the patient, the quality of the treatment and by various genetic factors [22].

Glutaric Aciduria Type I

There is evidence that the substrates toxic to the brain comes from an endogenous source rather than dietary protein. This led to greater emphasis on the role of carnitine supplementation as a means to enhance central nervous system energy supply through the use of alternative pathways [8]. However, the expert consultant cautioned that the treatment of this disease is a major problem, even in infants diagnosed as a result of screening (Expert Consultant)

Congenital Hypothyroidism [CH]

Hsiao et al [23] reported on a study of 82 Taiwanese patients diagnosed before the initiation of a nation-wide screening project. The incidence of CH in Taiwan was estimated to be 1:5,788 live births. The study showed that patients treated before 3 months of age had better intellectual outcomes than patients who began treatment after 3 months. However, 13% of patient treated before 3 months still had mental retardation.

Van Vliet [24] noted that CH has a threshold effect on intelligence of the first generation of children diagnosed through screening. These include lower IQ and DQ [developmental quotient], sensorineural hearing loss, sustained attention problems and various abnormalities in neurophysiological variables. This developmental gap may be closed by treatment with higher initial doses of levothyroxine within two weeks. This treatment did not result in clinical signs of hyperthyroidism.

Similar findings were reported by Rovet et al at the Hospital for Sick Children in Toronto who followed the neuropsychological development of 108 children with CH detected early via newborn screening [25]. The children were tested in three phases until adolescence and compared to those of matched controls (siblings). The results of this study showed that early treated CH markedly improved intellectual outcome with most children functioning well within the normal range. However ability levels of the CH children, particularly in the nonverbal visual-spatial area, were significantly below their siblings, with the difference increasing with age. The same investigators also found that early treated CH is associated with mild delays in reading comprehension and arithmetic at third grad level with catch up by the sixth grade [26]. Correlational analysis suggested that some effects can be improved by better treatment and management approaches whereas others caused by prenatal and perinatal thyroid hormone insufficiency may persist [25].

Homocystinuria

Yap et al reported on a retrospective study of 25 cases of homocystinuria from 19 families in Ireland identified over 25 years [28]. Twenty-one of these patients were identified through a national screening program. Twenty- four of these patients were pyridoxine non-responsive. These patients were started on a low methionine, cystine-enhanced diet supplemented with pyridoxine, vitamin B12 and folate within 6 weeks of birth. The biochemical control of these patients were monitored monthly. When compared to data on untreated homocystinuria, the clinical outcomes of this study suggest that newborn screening, early commencement of dietary treatment and a lifetime median of free homocystine of </=11 u mol/L had significantly reduced the risk of developing complications. The outcomes of the Irish program also suggest that early treatment with good biochemical control seems to prevent mental retardation [29].
In the same study, Naughten [30] concluded that contributing factors to missed cases were early hospital discharge, low protein intake, high blood methionine cut-off concentration and pyridoxine responsiveness.

According to Dr. Joe Clarke, Betaine is a major part of the treatment of older patients with homocytinuria.

VI- 4. Effectiveness of Tandem Mass Spectrometer in the Screening of IEMs

The sensitivity and specificity of screening tests have significant impact on patients and the health care systems. False negatives are more costly because they involve missing potentially detectable disorders and could seriously undermine the screening program. High rate of false positive results would increase the cost of the screening program and place an emotional burden on parents when requested to submit repeat samples.

MS/MS has been shown to provide higher sensitivity and specificity over conventional screening methods and thus has reduced the rate of false positives and the number of repeat samples. In a re-test of stored neonatal blood specimens in California, Chace demonstrated that by measuring both the phenylalanine concentration and the phenylalanine: tyrosine molar ratio, MS/MS was able to identify all infants with true PKU and eliminated 90 of 91 false positive results [31]. The use of phenylalanine: tyrosine ratio for the early detection of PKU was also reported by Levy [52].

Schulze [32] studied the differential diagnosis of different forms of phenylalaninemia in 78 DBS using ESI MS/MS. The results showed that the phenylalanine: tyrosine ratio differentiated between PKU and non-PKU hyperphenylalaninemia.

Green [33] reported that the Birmingham MS/MS screening of PKU yielded 100% sensitivity and 99.9% specificity. Rashed [34] conducted MS/MS screenings with 559 blood spot and 1,151 blood spots (including 147 patients with known metabolic diseases in both studies) from a data bank. The tests showed 100% sensitivity and average cumulative specificity of 83.1%. Johnson et al [35] studied the performance of ESI MS/MS and found no obvious errors in disease identification.

North Carolina, the first state in the USA to perform large scale newborn screening using ESI MS/MS, reported a true incidence of 0.13% and a false positive rate of over 1.9% [36]. A pilot study was conducted in Taiwan to screen 2,100 newborns for 6 amino acid disorders and 9 fatty acid disorders using ESI MS/MS. The study yielded a positive rate of true IEM of 0.09% and a false positive rate of 1.28% [37].

Zythovicz et al [38] reported on the MS/MS-based screening of 160,000 newborns for 23 amino acid, fatty acid and organic disorders. The test identified 22 babies with amino acid disorders and 20 with fatty acid and organic acid disorders. The positive predictive value [PPV] using the flagged amino acids and ratios was 14% and the PPV for all acylcarnitine disorders was 9%. These PPV values were better than the reported values for some other disorders detected by other methods.

One significant benefit of MS/MS is its rapid throughput. Computer aided algorithm has been used to automate the processing of samples and to flag abnormal patterns. In a 1999 study, Rashed reported that 1,000 blood spots were processed over 1,300 minutes by one MS/MS. This involved two technicians preparing batches of 6 microplates each (96 wells in each microplate) in a normal workday [34]. Johnson et al [35] reported throughputs of 400 samples per MS/MS per day.

Ethical issues relating to MS/MS screening for IEM

There is controversy as to whether neonatal screening programs should be mandatory or voluntary. The World Health Organization Guidelines on Ethical Issues in Medical genetics stated that "Newborns should have special protection by providing mandatory screening for disorders, where an early diagnosis and treatment would favorably affect the outcome, as in the case of PKU and CH. Screening should not be mandatory, if the primary purpose is to identify and counsel parents who are carriers prior to their future pregnancies, as in the case of Duchenne muscular dystrophy" [39].

The above issue is closely related to the issue of informed consent for neonatal screening. There are opposing views as to whether informed consent is necessary for neonatal screening for disorders such as PKU and CH in which the benefit of early diagnosis and treatment is well established. Opponent for informed consent expressed concern that consent requirements would undermine the program' cost-effectiveness and that the parents' refusal to screening would pose a risk of harm to the infant. Supporters for consent requirements expressed concerns about potential false positive results and the lingering anxiety and stigmatism that they may produce [40].

Although there is no agreement on consent requirements relating to PKU and CH, there appears to be general acceptance that when a screening program includes disorders for which evidence for effective treatability is incomplete, individual informed consent instead of informed refusal should be obtained [41]. Four states in Bavaria implemented an informed consent protocol for an expanded MS-based new born screening program and reported only 1% definite refusal for screening in the target population despite the written consent requirement [42].

Considerations related to the implementation of MS/MS IEM screening.

While the methodology is simple enough, there are issues that need to be addressed in considering the uptake of MS/MS mass IEM screening, including:

- MS/MS requires new, expanded and expensive resources including MS/MS equipment and expanded information technology support for interpretation, reporting, tracking and outcome [43].
- An MS/MS-based screening program requires expertise and experience in determining appropriate cut-off limits for each IEM tested in order to achieve an acceptable balance between sensitivity and specificity.
- Most IEMs are rare and for which there are no known existing effective treatments.
- The time and process for specimen collection needs to be examined. At present, the newborn screening program is based on a DBS that is obtained prior to discharge from hospital, usually within 24 hours of birth. The sensitivity of MS/MS allows the diagnosis of disorders such as PKU in samples acquired in less than 24 hours. However, in some disorders, slow rise of the marker may result in false negative results. It has been reported that the best time for sample collection for a large number of IEMs appear to be between 48 and 72 hours after birth [44]. This would require specimen collection following discharge from hospital.
- Processes for obtaining informed consent for multiple tests need to be established, including consent to store samples that contain genetic and other information relating to the child.
- An expanded neonatal screening program requires a clinical and supportive infrastructure for pediatric metabolism including trained clinical and laboratory staff. In addition, physicians, nutrition experts and genetic counselors are needed to provide ongoing treatment and care for identified patients and their families [0]. The Oklahoma Genetics Advisory Council identified five essential parts of a new born screening programs including (1) testing of newborns; (2) location & referral of screen-positive infants; (3) diagnosis; (4) management; and (5) Evaluation [45].

- Consideration should be given to the benefits of an integrated approach to an expanded neonatal screening program. The New England Consortium provides an example of a model that integrates newborn screening, metabolic evaluation, primary care and research into a comprehensive and efficient system for the management of patients with inborn metabolic diseases [18].

V. Application of Evidence to Ontario
V-1   Applicability of NHS R&D HTA on IEM to Ontario

While the methodology for developing an HTA has universal acceptance, the application of the HTA to another jurisdiction requires additional analysis if it is being used to further inform policy development. The modified screening criteria of Wilson and Jungner [4] used by Seymour et al [0] therefore need to be further modified for the purposes of policy recommendations in Ontario.

Assumptions made by Seymour et al [0] regarding screening criteria were provided in section IV-1. The following selection criteria for screening need further assessment in relation to their generalisability to Ontario:
Known incidence in populations relevant to United Kingdom

Ontario has a diverse multicultural population. It cannot therefore be assumed that the incidence of all IEMs will be the same as other international jurisdictions. With the exception of PKU and congenital hypothyroidism, the incidence of other IEMs should be known prior to making policy decisions regarding

the expansion of existing newborn screening programs.

Screening policy needs to take into account Ontario's culturally diverse population. For example, while some of the rarer organic acidemias failed to meet the screening criteria in Seymour's review, the incidence of these life-threatening IEMs amongst immigrant populations from the Middle East is high. Whereas previously, Ontario may have needed to conduct case finding in targeted populations, this process would be unnecessary with MS/MS, since MS/MS based analysis does not increase the cost per additional screen.

Effective treatment available

While the modified screening criteria established by Seymour et al [1997] assumed that the absence of treatment for an IEM should preclude its use as a screening test, this assumption might not necessarily apply to Ontario and should be tested through appropriate consultations, focus groups or polling techniques. Ethical and psycho-social issues should be taken into consideration in maintaining provincial funding for this test and may apply to newborn screening.

Cost-effectiveness of screening

While cost-effectiveness is an important consideration when making policy decisions for any screening program, the incremental cost of adding any number of tests to an MS/MS-based screening program could be minimal once a single IEM is being screened. However, the costs of taking samples after hospital discharge and the need for changed procedures need to be taken into account.

V-2   Environmental scan of IEM screening programs in other national and international jurisdictions

National and international IEM screening programs in other jurisdictions are summarized in Table 3a (Appendix 3) and table 3b below.

Loeber et al [46] surveyed 29 programs internationally and reported that all 29 programs screen for PKU and congenital hypothyroidism. The additional IEMs that are most frequently included in screening programs are galactosemia (15), congenital adrenal hyperplasia (15), cystic fibrosis (12), maple syrup urine disease (11) and biotinidase deficiency (11).

While an increasing number of North American jurisdictions are including MCADD in their screening programs [Dooley, personal communication, 2002], the exact numbers are unknown at this time. Most of the literature on MCADD indicated that this should be tested as part of an ongoing evaluation, as is currently occurring in Massachusetts and has been recommended by Seymour et al and Pollitt et al in the United Kingdom.

Two of the additional disorders recommended by Seymour et al to be considered for inclusion in screening programs are biotinidase deficiency and congenital adrenal hyperplasia. These tests were also recommended for screening by the Provincial Advisory Committee (Ontario) in 1991. While the scope of this technology review did not include non-MS/MS related tests, it is important to point out that congenital adrenal hyperplasia has an incidence of 1:22,000 and should be assessed as a possible addition to the newborn IEM screening program.

The other NHS R&D HTA recommendation, glutaric aciduria type I, has not been widely adopted. Manitoba performs screening for glutaric aciduria on the aboriginal populations in Manitoba and Ontario.

Among Canadian jurisdictions, British Columbia, Saskatchewan and Nova Scotia use MS/MS for IEM related assays.

Nova Scotia uses MS/MS for PKU and MCADD screening and has reduced the false- positive reporting on PKU by measuring phenylalanine: tyrosine ratios.

Saskatchewan has been using MS/MS for more than one year to screen for all IEMs that can be detected by MS/MS.

British Columbia has developed MS/MS capacity but is not using it for any screening tests. This province only uses MS/MS for acylcarnitine assays as requested to diagnose MCADD.

In 1998, 26 States in the U.S. were using MS/MS for newborn screening of IEM. One of the largest ongoing evaluation projects for MS/MS based newborn IEM screening is currently underway in California.

The survey by Loeber showed large differences in degree of organization of neonatal screening, turnover times, completeness of coverage and follow-up among jurisdictions [46]. There appears to be no relationship between screening procedures and the degree of legislation or the system of funding. The survey pointed to the importance in quality evaluation of not only the laboratory analysis phase, but also on the pre-analytical phase (e.g., timely sampling and maximum coverage) and the post-analytical phase (follow-up and treatment, evaluation of long-term effects and cost-effectiveness). A periodic epidemiological evaluation and close collaboration between all parties concerned were identified as essential for continuous quality improvement of newborn screening programs.

Table 3b – IEM Screening Programs in Various National and International Jurisdictions

Congenital Abnormality Screened	NHS R&D HTA recomm-endation [0]	USA Number of States Screening [47]	UK [0]	New Zealand	Australia [48]	Recommended by Can. Task Force on Prevent. Health [49]	On	Sk	BC	Ab	Ma	Q	NS
*PKU	X	52	X	X	X	X	X	X	X	X	X	X	X
Congenital hypothyroid	X	52	X	X	X	X	X	X	X	X	X	X	X
Galactosemia	Not recommended	48		X	X			X	X		X		
Biotinidase deficiency	X	22		X				X			X		
Congenital adrenal hyperplasia	X	19		X				X			X		
*Glutaric aciduria Type I	X				X			X			X^		
*MCADD	X	**			X			X					**X**
Hemoglobin-opathies		39				X [sickle cell high risk]							
Cystic fibrosis				X	X								
*Tyrosinaemia Type I		1						X				X	
*Maple syrup urine disease		23						X					
*Homocystinuria		15			X			X					

*Test can be performed by MS/MS [43], [21].
** The states of Massachusetts and Maine introduced MCADD screening as part of a 3 year prospective study [18] and have now formally incorporated it into the newborn screening program. Other States are apparently following suite [Dr. K. Dooley, Nova Scotia, personal communication]

^ Tested only for Aboriginal population, including Aboriginals from Northern Ontario

V-3. Rating of Inborn Errors of Metabolism in Ontario

For the purposes of policy development, the modified criteria for acceptance of a screening program were incorporated into a weighted decision analysis according to:

➢ Known incidence in populations relevant to Ontario/Canada;
➢ Treatment available;
➢ Incremental costs to the existing screening program
➢ Other Canadian, North American and International jurisdictions offering the test

These criteria were weighted as shown in table 4 below.

The following criteria were omitted from the weighting as they apply equally to each test:

Clinically and biochemically well-defined disorder;
Disorder associated with significant morbidity of mortality;
Ethical, safe, simple and robust screening test;
Period before onset during which interventions improve outcome;
Sensitivity and specificity >98%

Table 4 – Weighting of Criteria to Inform Policy Development for Inclusion of Expanded Tests for Ontario's IEM-Based Newborn Screening Program

Criteria	Score Assigned to Each Criteria			
	0	**1**	**2**	**3**
Known incidence (Average across all jurisdictions)	<1:100,000	1:50,000-1:100,000	1:20,000-1:50,000	>1:20,000
Treatment available	No treatment that alters the clinical course of disease	Treatment partially alters outcome	Treatment significantly affects outcomes but not curative	Treatment curative
*Incremental costs to existing screening program	>$500,000	$250,000 -500,000	$125,000 -250,000	<$125,000

*Where incremental costs were based on a common method for testing more that one IEM, the average was assigned to each test, assuming that each test is accepted. Appropriate adjustment to this score needs to be made if one or more of the tests are rejected for screening.

Weights were assigned to modified criteria as shown in table 5 below:

Table 5 – Analysis of Weighted Criteria for Purpose of Policy Development Regarding Appropriateness of Funding IEM

IEM	Known incidence	Treatment available	*Incremental costs to existing screening program	Other jurisdictions offering the test	Total
PKU	3	3	3	3	**12**
Glutaric aciduria	1	1-2	1	3*	**6-7**
Congenital adrenal hyperplasia	3	3	?	2	**>8**
Congenital hypothyroid	3	3	3	3	**12**
Biotinidase deficiency	1	3	?	2	**>6**
Medium-chain acyl CoA dehydrogenase [MCADD]	3	3	1	3	**10**
Galactosemia	1	2	1	3	**7**
Tyrosinemia	0	1	1	2	**5**
Maple syrup urine disease [MSUD]	0	1	1	2	**4**
Homocystinuria	0	1	1	2	**4**

*Test offered to Aboriginal population only – including Northern Ontario

Based on these criteria, the most likely candidates for testing with MS/MS are PKU and MCADD. MS/MS has the added advantage of decreasing the false positive test rate for PKU.

Any attempts to introduce MS/MS should in no way interfere with the idealized screening for PKU and for congenital hypothyroidism. This is especially applicable to considerations relating to the timing of MS/MS testing after birth.

Additional IEMs should be considered for testing with MS/MS for neonates at high risk for certain IEMs

V-4. Implementation Considerations

The following factors should be taken into account if there is a decision to expand neonatal IEM screening:

➢ Informed consent issues must be addressed and the program organized to ensure that this issue is addressed through multiple stakeholder involvement, to represent the public, legal, ethical, health system perspectives.

➢ Processes must be in place to protect privacy of stored specimens according to privacy legislation.

➢ The selection of diseases to be screened for which there are no treatment options needs to be addressed through appropriate consultations and through the informed consent process.

➢ Any new system to capture additional screens must ensure that the current highly efficient and effective system of obtaining blood for PKU and congenital hypothyroid testing is not compromised. Of particular importance is the need to address the added complexity and possible reduced compliance if the blood specimens need to be taken after discharge from hospital to increase sensitivity [decrease false negative results] for the additional tests being considered.

➢ Only tests with a sensitivity and specificity of >98% should be considered, given the low incidence of IEMs and the need to reduce false negative and positive reporting with the attendant stress.

Approach to future evidence on IEM screening

Both UK HTAs pointed to the need for more research in MS/MS screening of IEMs. Some jurisdictions, such as the UK, believe that only randomized controlled trials can overcome the biases inherent in observational studies of screening. Further more, because screening may be associated with unrecognized harms which are difficult to assess within an observational study, a randomized controlled trial is considered the best way to ensure that the potential risks of screening are minimized [17]. The National Screening Committee of the UK formulated a policy that before a screening program can be accepted, there should ideally be evidence from high quality randomized controlled trials. Despite the two HTAs, there is still no consensus in the UK on future action.

Randomized controlled trials in neonatal screening pose certain challenges. Due to the rarity of the IEMs, large and lengthy clinical trials would be required. For example, it was estimated that a randomized controlled trial for the UK to detect a 50% reduction in the primary outcome of death and/or disability from MCADD by age two years would require over 3 million babies, which is the entire UK births for 5 years [Dezateaux, 1998]. Researchers have also expressed ethical concerns about withholding treatment for positive subjects in the control arm because they believe that early treatment would significantly improve the outcome for most diseases detectable by MS/MS. It may also be difficult to obtain informed consent from parents for such trials [33].

As a result, there is no agreement as to what is the best approach to obtain future evidence on neonatal screening using MS/MS technology. In light of the challenges of randomized controlled trials, some jurisdictions have looked to observational studies for evidence. Observational studies can contribute such information as prevalence, test performance and current estimates of sensitivity. Denmark is implementing a large-scale pilot study to evaluate the potential of MS/MS in neonatal screening of IEMs [50]. The study includes the retrospective MS/MS screening of a recent cohort of 10,000 random DBS from the biobank and a two-year prospective study on MS/MS screening of selected IEMs offered as a voluntary adjunct to the existing screening program. The retrospective study will generate decision limits used in the prospective study. At the end of the prospective study, the costs of screening and treatment, true and false positives and negatives rates, and short-term clinical outcomes will be described and compared with the same parameters for patients identified before the screening.

V.   CE

Appendices

Appendix 1: Reported Incidence of Various Inborn Errors of Metabolism

IEM	Seymour et al, 1997 HTA Review [0]	Pollitt RJ et al 1998	Zytkovicz et al, 2001. Samples 1-3 days after birth [38]	Naylor et al, 1996	Seddon et al, 1997 [51]	Wiley et al, 1999 Most samples day 3 after birth [10]	Can. Task Force Prevent. Health, 1994 [49]	Kwon et al, 2000 US [47]	Pollitt RJ et al 1997 [2]	Average
PKU	1:12,000		1:14,000	1:16,000		1:8,000	1:12,000	1:14,000	1:9,000	1:12,000
Glutaric aciduria	1:40,000		0:184,000	1:49,000		1:137,000			1:50,000	1:91,000
Congenital adrenal hyperplasia [CAH]	1:17,000	(AAP) 1:12,000 - 1:15,000						1:20,000	1:11,000 – 1:23,000	1:16,000
Congenital hypothyroidism							1:4,000	1:3,300	1:4,000	1:3,500
Biotinidase deficiency	1:100,000							1:80,000	1:71,000	1:84,000
Medium-chain acyl CoA dehydrogenase [MCAD] deficiency	1:8,000 to 1:15,000	1:22,000	1:18,000	1:13,000	1:13,000	1:70,000			1:13,000	1:16,000
Galactosemia								1:59,000	1:40,000	1:49,000
Tyrosinaemia 1	1:105,000		0:164,000			1:137,000			1:100,000	1:122,000
Maple Syrup Urine Disease [MSUD]	1:185,000		1:257,000			1:137,000			1:224,000	1:190,000
Homocystinuria	1:291,000	1:335,000 world wide (Naughten 1998)	1:206,000 Peterschmitt 1999						1: 58,000 - 1:1 million	1:335,000 Word wide

Appendix 2: Inborn Errors of Metabolism Detectable in Newborns aged 1-5 days by using tandem mass spectrometry[1]

Amino Acid Disorders

Phenylketonuria [PKU]
Maple syrup urine disease
Homocystinuria (cystathione synthase deficiency)
Hypermethioninemia
Citrullinemia
Argininosuccinic aciduria
Tyrosinemia, type I

Organic Acids Disorders

Glutaric acidemia, type I
Proprionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
3-hydroxy-3methyglutaryl CoA lyase deficiency
3-methylcrotonyl CoA carboxylase deficiency

Fatty Acid Disorders

Medium-chain acyl-CoA dehydrogenase deficiency [MCADD]
Very long-chain acyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Multiple acyl-CoA dehydrogenase deficiency
Carnitine palmitoyl transferase deficiency
Carnitine/acylcarnitine translocase defect
Long-chain hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency

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[1] Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns, CDC Recommendations and Reports, April 13, 2001/50(RR03); 1-22

Appendix 3: Screening programs in the various countries per January 01, 1999 [46]

	PKU	CH	Gal	CAH	CF	BDD	MSUD	SCD	HC	DMD	Others	
Argentina	x	x	x	x	x	x	P					PKU - Phenylketonuria
Austria	x	x	x		x	x	x				1	CH – Congenital hypothyroidism
Belarus	x	x		P	P							Gal - Galactosemia
Belgium	x	x	P	x*	x*	x*	x*		x*	x*		CAH – Congenital adrenal hyperplasia
Brazil	x	x	x	x	x	x	x	x	x*		3,4,5	CF – Cystic fibrosis
Bulgaria	x	x										BDD – Biotinidase dehydrogenase deficiency
Czech Rep.	x	x	x*	x*					x*			MSUD – Maple syrup urine disease
Cyprus	x	x							P			SCD – Sickle cell disease
Denmark	x	x		P							3	HC – Homcystinuria
France	x	x		x				x*		P	6	DMD – Duchenne muscular dystrophy
Germany	x	x	x	x	x*	x	x*		x*	P	2	
Greece	x	x	P								5	
Iceland	x	x										
Ireland	x	x	x				x		x			
Italy	x	x	x	x*	x*	x*					5	X= Regular Program;
Japan	x	x	x	x			x		x			P= pilot program
Netherlands	x	x		P								* = not in all parts of the country
New Zealand	x	x	P	P	P	P	P					1 – Argininosuccinate lyase deficiency
Poland	x	x			P							2 – Medium chain acyl-CoA dehydrogenase deficiency
Portugal	x	x	x	x								3 – Congenital toxoplasmosis
Scotland	x	x	x								7	4 – Ghagas' disease
Spain	x	x		x				P			7	5 – Glucose-6-1-phosphate dehydrogenase deficiency
Sweden	x	x	x	x							3,8	6 - Neuroblastoma
Switzerland	x	x	x	x		x						7 – HIV antibody
UK	x	x			x*							8 - Tyrosinemia
US	x	x	x*	x*	P*	x*	x*	x*	x*		2	

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