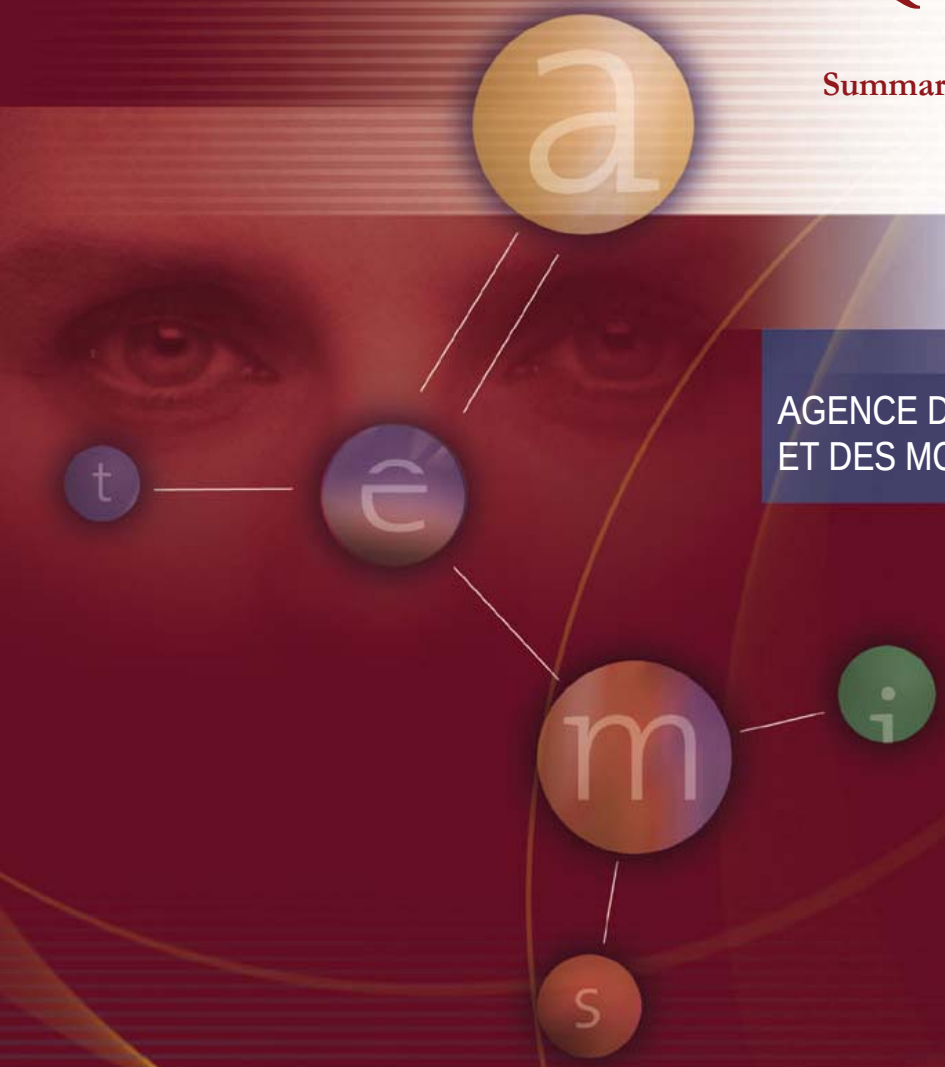
Tandem Mass Spectrometry and Neonatal Blood Screening in Quebec

Summary



AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

Québec

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Summary

Summary report prepared for AETMIS by

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March 2007

Agence d'évaluation des technologies et des modes d'intervention en santé

Québec

This summary was translated from an official French publication of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Both the original summary report, titled *La spectrométrie de masse en tandem et le dépistage néonatal sanguin au Québec : rapport sommaire* and the English summary are available in PDF format on the Agency's Web site.

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How to cite this document:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Tandem Mass Spectrometry and Neonatal Blood Screening in Quebec : Summary. Summary report prepared by Héla Makni, Carole St-Hilaire, Laura Robb, Kathy Larouche and Ingeborg Blancquaert. (AETMIS 07-03). Montréal: AETMIS, 2007.

Legal deposit
Bibliothèque et Archives nationales du Québec, 2007
Library and Archives Canada, 2007
ISBN 978-2-550-48905-4 (printed French edition)
ISBN 978-2-550-49399-0 (PDF) (French edition ISBN 978-2-550-48906-1)

Mission

The mission of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) is to help improve the Québec health-care system. To this end, it advises and supports the Minister of Health and Social Services and decision-makers in the health-care system with regard to the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for the disabled, as well as the methods of providing and organizing services. The assessments examine many different factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic issues.

Note to reader

This brief report is a summary of a technical report prepared at the request of the Ministère de la Santé et des Services sociaux. Both reports stem from the same literature review and include the same sections, although these sections are much more detailed in the technical report, especially with regard to the review on the diseases of interest, the technical aspects of tandem mass spectrometry, and the different issues associated with the use of this technology.

Foreword

Tandem Mass Spectrometry and Neonatal Blood Screening in Quebec

This report was prepared at the request of the Ministère de la Santé et des Services sociaux (MSSS), in the context of scientific debates and pressure in favour of adopting tandem mass spectrometry (MS/MS) for neonatal blood screening of inborn errors of metabolism. MS/MS can be used to simultaneously screen for more than 30 inborn errors of metabolism in a single analytical step with a high throughput. In its request, the MSSS asked AETMIS to evaluate whether it would be pertinent to use MS/MS for neonatal blood screening in Quebec. Once the systematic reviews and the available Quebec data had been analysed, it was agreed that AETMIS would 1) examine the relevance of replacing the current screening methods for phenylketonuria (PKU) and tyrosinemia type 1 (TT1) by MS/MS and of introducing neonatal screening for Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD); and 2) analyze the main ethical, social, economic and organizational issues. The expansion of neonatal screening to other diseases could possibly be the subject of a subsequent report.

Our review confirms the importance of a case-by-case analysis for each inborn error of metabolism. Indeed, the available options depend on the specific characteristics and state of knowledge for each disease, and the applicability of the technological developments to these diseases. Even though there are gaps in the data, current evidence supports the clinical utility of neonatal screening for the three diseases in question. As for the appropriateness of implementing MS/MS-based screening in Quebec, the situation differs according to the disease. For MCADD, MS/MS is the only technology available for neonatal screening, and its performance is one of the best for this particular condition. For PKU, the literature suggests that MS/MS yields fewer false positives than the current technology, but compared to the results observed in Quebec, this advantage would not be substantial. However, if MS/MS were used for MCADD screening, the technology transfer for PKU would avoid a duplication of analytical steps and would be efficient, according to the health economics literature examined. For TT1, MS/MS-based neonatal screening relying on both tyrosine and succinylacetone assays seems promising but needs further validation. Furthermore, the judiciousness of a technology transfer and its optimal timing depend on a number of ethical, social, legal, economic and organizational issues, in addition to the scientific and technical considerations. Therefore, three separate scenarios are proposed for consideration by policy-makers:

1) conducting a pilot study;
2) postponing the introduction of MS/MS until after the necessary validation studies for TT1 screening have been completed; and
3) introducing MS/MS for PKU and MCADD screening, while, either undertaking gradual technology replacement for TT1, or maintaining the current methods until the results of the validation studies are available.

Whichever option is chosen, implementing MS/MS must not be done hastily, since other issues—ethical, economic and organizational—first need to be resolved.

In submitting this report, AETMIS wishes to contribute to decision-making regarding policies governing Quebec's neonatal blood screening program.

Dr. Juan Roberto Iglesias, President and Chief Executive Officer

Acknowledgements

This report was prepared at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) by Dr. **Héla Makni**, M.Sc. (Epidemiology and Biostatistics), **Carole St-Hilaire**, Economist, Ph.D. (Public Health), **Laura Robb**, M.Sc. (Genetic Counselling), **Kathy Larouche**, M.Sc. (Physiology and Endocrinology), and Dr. **Ingeborg Blancquaert**, Pediatrician, Ph.D. (Epidemiology), Coordinator of the Genetics Module and Scientific Advisor, all of whom are research consultants at AETMIS.

AETMIS cordially thanks the external reviewers for their valuable suggestions and their contribution to the overall quality and the rigour of this assessment report:

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The Agency also wishes to express its gratitude to the following experts, whose contribution enriched the contents of this report:

Jean-Marie Lance, M.Sc. (Economics), Senior Scientific Advisor, AETMIS, and **Lee Soderström**, Ph.D. (Economics), Associate Professor, Department of Economics, McGill University, who reviewed the economic section of this report;

Ghislaine Cleret de Langavant, Ph.D. (Bioethics), Research Consultant, AETMIS, who helped draft and revise certain parts of this report;

Dr. **Bridget Wilcken**, Professor, NSW Biochemical Genetics and Newborn Screening Service, Children's Hospital, Westmead, Sydney, Australia, and Dr. **François Rousseau**, Full Professor, Department of Medical Biology, Faculty of Medicine, Université Laval, Quebec City, who kindly provided us with unpublished data;

Pierre Allard and **Raymond Lepage**, Department of Clinical Biochemistry, Centre hospitalier de l'Université de Montréal; **Robert Giguère**, Department of Genetics, Centre hospitalier de l'Université de Sherbrooke; and **Jean Ruel**, laboratory technician for the screening program at the Centre hospitalier universitaire de Québec, who provided us with information on tandem mass spectrometry and other technologies used for neonatal screening of inborn errors of metabolism.

CONFLICT OF INTEREST

None declared.

Summary

In Quebec, three diseases—phenylketonuria (PKU), tyrosinemia type 1 (TT1) and congenital hypothyroidism—are presently screened for in neonates. With the development of tandem mass spectrometry (MS/MS), the scientific community engaged in a debate over the relevance of expanding neonatal screening programs to include a number of inborn errors of amino acid, fatty acid and organic acid metabolism. Pressure in this regard is being exerted by health professionals, patient groups and industry. This technology can be used to selectively screen for specific inborn errors of metabolism or to perform a full scan of the metabolic profiles associated with more than 30 such diseases. Two separate decisional questions need to be addressed: 1) whether MS/MS[1] should replace the technologies currently used for PKU and TT1 screening, and 2) whether neonatal screening should be expanded to other diseases. The second issue requires rigorous evaluation of the clinical utility and relevance of screening for each inborn error of metabolism. According to the literature, the disease that ranks highest as a potential candidate for inclusion in neonatal screening is Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)[2].

The advantages of the MS/MS technology highlighted by its promoters are its ability to screen for a large number of diseases in a single analytical step, its ability to screen for diseases, such as MCADD, that are not detectable by other techniques, the fact that the technology is automated and thus suitable for high throughput and the fact that its performance is better than that of other screening techniques (e.g., fewer false positives for PKU). While recognizing these theoretical advantages, the authors of systematic reviews published thus far have pointed out several significant knowledge gaps which decrease the weight of these assertions. They specifically state that the evaluation of MS/MS performance is mainly based on studies providing results for groups of inborn errors of metabolism and that few studies have evaluated this performance for individual diseases. Given the study designs used, uncertainty persists as to the proportion of false negative results. These estimates depend on the manner in which clinical services are organized for rare metabolic diseases. In addition, for a number of diseases, there is a paucity of epidemiological data, the natural course of the disease is not well known and the clinical benefits of screening have not been clearly demonstrated. Some of these limitations are due to the difficulty in gathering data on rare diseases, for which establishing a clinical diagnosis can be complex.

Given these limitations, the authors of systematic reviews were cautious in their recommendations. The first reviews, which date from 1997, called attention to the technology's potential but did not recommend technology replacement. A number of authors recommended instituting large-scale pilot projects for PKU and MCADD[3] in order to evaluate the performance of MS/MS screening, its efficiency and the impact on health outcomes. A review of the recent literature shows that more studies are presenting MS/MS performance data for the screening of individual diseases. However, no new studies specific to MCADD screening were identified. Even if preliminary data on the impact of early diagnosis and management for MCADD following screening are starting to accumulate, this literature is based on a limited number of cases with insufficient

1. MS/MS can not be used for congenital hypothyroidism screening.

2. PKU and TT1 are inborn errors of amino acid metabolism, while MCADD is a disorder of fatty acid metabolism.

3. One of the two British reports adds glutaric acidemia type I to this list [Seymour *et al.*, 1997].

follow-up and no prospective, controlled studies have been published. The most recent systematic reviews nevertheless tend to recommend the implementation of PKU and MCADD screening programs. These recommendations are supported by the results of several economic modelling exercises suggesting that MS/MS screening is efficient if performed for at least two diseases, including PKU. It seems that these shifting views are not so much due to the accumulation of new knowledge as to the difficulty in implementing the previously recommended pilot projects. The above-mentioned caution, which limits the recommendations to screening for a few diseases, is by no means generalized and a number of non-systematic reviews and publications, based mainly on expert opinions, have come out in favour of technology replacement and expansion of neonatal screening to a wide range of inborn errors of metabolism. These recommendations have led to decisions along these lines in several jurisdictions, but have also prompted a debate over the role of evidence in such decisions.

This report examines the relevance of replacing current technologies by MS/MS for PKU and TT1 screening and of including MCADD in Quebec's neonatal blood screening program. It is based on a review of the literature on the natural course of the three diseases of interest, their epidemiology and the efficacy of therapeutic measures, the performance of MS/MS technology, and cost and efficiency data. A cost analysis and a review of the ethical, psychosocial and organizational issues round out the report. The issue of expanding screening to include other diseases could be considered in a subsequent report, with candidate diseases prioritized according to the available data.

Our review of the evidence on MS/MS performance confirms the reservations expressed in the previous systematic reviews with respect to the quality of available studies. These reservations specifically concern study design, reporting of results, study population selection processes and the lack of standardization with regard to several factors which could affect the quality of MS/MS analyses and to the diagnostic confirmation tests. Most of the available evidence derives from prospective cohort studies carried out in the context of neonatal screening programs because of the difficulty in conducting comparative prospective studies with a suitable control group, as pointed out by several authors. In newborn screening programs, the reference tests to confirm the diagnosis are only performed for patients with a positive MS/MS result. Consequently, the data regarding the proportion of false negatives is of uncertain quality.

Overall, the results of the different studies that were reviewed indicate that the sensitivity, negative predictive value and specificity of MS/MS are high, whether for the neonatal screening of groups of diseases or for the selective screening of PKU, TT1 or MCADD. It is nonetheless possible that the sensitivity and negative predictive value were overestimated because of the quality of the data on false negatives. Furthermore, a considerable variability was observed for positive predictive values, even though there were only minor differences in the prevalence of inborn errors of metabolism between studies. The heterogeneity in the study populations' characteristics, the age of sampling, the choice of metabolic markers, the cut-off values, the protocols for classifying MS/MS results and the diagnostic confirmation tests can influence MS/MS specificity and explain the variability in positive predictive values.

These performance data would not be automatically applicable if different analytical protocols than those used in the reviewed studies were implemented. Even today, the technology is constantly evolving in terms of the analytical procedures. Some of the technological changes on the horizon that could significantly alter MS/MS performance include incorporating the analysis of other metabolites (succinylacetone) into the protocol presently used for TT1 screening and eliminating the derivatization process

from sample preparation. The performance of these new approaches will need to be evaluated rigorously prior to implementation. In addition, the evolving nature of the technology underscores the importance of carefully considering technological options prior to implementation, performing analytical validation following any change to the protocols, and establishing ongoing quality assurance mechanisms.

The decision to include a given disease in a neonatal screening program is based, apart from considerations related to the technology's performance, on the ability to favourably alter prognosis following early detection and intervention. With regards to the clinical utility for patients and their families, neonatal screening is justified for the three diseases of interest, despite gaps in the knowledge base and various issues raised for each disease. Our review confirms the importance of a case-by-case analysis for each disease of interest, since the available options depend on the specific characteristics and state of knowledge for each disease and on the applicability of the technological developments to these diseases.

- For MCADD, neonatal screening can only be carried out with MS/MS, the performance of which is particularly high for this condition. Knowledge of the entire spectrum of clinical forms is limited, especially for the less severe forms, and the variability in phenotypic expression makes it more difficult to compare the prognosis with and without screening and early management. The benefits of early treatment are convincing, however, for the severe end of the spectrum. Periodic reassessment of MCADD screening benefits, through ongoing data collection, will therefore be essential.
- For PKU, the literature suggests that MS/MS yields fewer false positives than the current technology, but compared to the results observed in Quebec, this advantage would not be substantial. According to the health economics literature, technology replacement is efficient if screening is carried out for at least two diseases, including PKU. If MS/MS were used for MCADD screening, the technology transfer for PKU would avoid duplication of analytical steps and would probably be less expensive than continuing with the current analytical method alongside MS/MS.
- For TT1, data supporting the efficacy of NTBC therapy[4] are starting to accumulate, and they corroborate the utility of neonatal screening in Quebec. New approaches to TT1 screening based on assaying both tyrosine and succinylacetone seem promising but need further validation.

The review of the economic literature is aimed at documenting the costs, cost-effectiveness and cost-utility of MS/MS-based neonatal blood screening. This literature is characterized by wide differences in the inborn errors of metabolism considered, as well as by variability in incidence data, in probabilities of neurological disabilities and death in unscreened MCADD children and in the measures of efficacy used[5]. All studies tend to support the efficiency of MS/MS-based screening for several inborn errors of metabolism, especially those that cannot be screened for otherwise, as is the case with MCADD. In fact, all studies show that MS/MS is efficient if at least two diseases are screened for, including PKU. Lastly, it is noteworthy that no economic assessment has specifically examined the efficiency of MS/MS-based screening for TT1.

The economic section of this report also provides budgetary information on certain

4. NTBC [2-(2-nitro-4-triflouromethyl-benzoyl)-cyclohexane-1,3-dione] therapy is available under the name of nitisinone (Orfadin®).

5. Outcomes considered for evaluating efficacy may include medical complications, hospitalizations, care and treatment, moderate or severe neurological disabilities, and prevented deaths.

capital and operating costs relevant to this type of screening. Thus, a budget impact approach was used to estimate the cost of MS/MS-based screening for PKU, TT1 and MCADD. Equivalent annual incremental costs (EAIC) were estimated. These allow the costs for the MS/MS and ancillary equipment, as well as for laboratory facility installation, to be spread out over several years. The EAIC thus represent the annual value of resources used for MS/MS-based neonatal blood screening. The results show that, in the Quebec context, this screening program would cost approximately CA$255,231 annually for a single neonatal screening laboratory. The main expenditures would be for acquisition of the MS/MS and ancillary equipment, and for laboratory technicians. Cost variations according to the equipment lifespan, the type of maintenance plan and the number of full-time equivalent technicians are presented. Lastly, it should be noted that cost estimations do not include expenditures associated with sample collection, interpretation of results, diagnostic confirmation, follow-up of patients and families and database management. These expenditures are assumed to be the same as with current screening methods.

The relevance and optimal timing of implementing MS/MS-based screening in Quebec depend on a number of ethical, social, legal, economic and organizational issues, in addition to scientific and technical considerations. Some of these issues are discussed here, while others are beyond the scope of this report. Three separate scenarios are therefore proposed for consideration by policy-makers:

1) Conducting a pilot study on the screening of these three diseases over several years.
2) Postponing MS/MS implementation until after validation studies for succinylacetone assays have been completed and then implementing a single analytical protocol for neonatal screening of the three diseases.
3) Introducing MS/MS-based screening for PKU and MCADD while, either undertaking gradual technology replacement for TT1, or maintaining the current methods until the results of the validation studies are available.

Each scenario has its pros and cons and entails different repercussions, both in terms of service organization and access to care. The choice between these three options is, of course, based on value judgments, but also depends on more concrete issues. The latter relate to the time required to prepare for technology implementation and to conduct—in Quebec or elsewhere—validation studies of the simplified protocol for TT1 screening, as well as to anticipated difficulties with a phased-in MS/MS implementation. The decision as to the best time to implement MS/MS will involve a trade-off between favouring a rapid access to services and opting to introduce the technology on the basis of data that are scientifically sound and/or applicable to Quebec. More thorough data on the recently developed analytical protocols for TT1 screening could be derived from a validation study and Quebec could be a favourable environment to conduct such a study. As for the advantages of a pilot study, these include gathering epidemiological and genetic data on MCADD and evaluating the costs that are directly applicable in Quebec. Such a pilot project however, is not likely to provide, within a reasonable timeframe, the data required for a definite evaluation of the benefits of MCADD screening in terms of long-term prognosis. It will therefore be essential to periodically reassess the benefits of neonatal MCADD screening.

Whichever option is chosen, implementing MS/MS must not be done hastily, since other issues need to be resolved beforehand. The policy regarding implicit consent for neonatal screening needs to be reviewed, particularly if the decision is taken to add a new disease to the screening program. Indeed, the procedure adopted in Quebec to justify

inclusion of neonatal screening in routine care will pose problems in that event. There needs to be a consensus on practices following detection of non-targeted inborn errors of metabolism and on the protocol for MCADD diagnostic confirmation. A more thorough analysis of the feasibility of implementing MS/MS must also be carried out, taking into consideration, amongst other things, the capital and operating costs for each of the above-mentioned scenarios. At each stage of implementation, organizational issues must be addressed in order to prospectively optimize practices and generate the data needed to monitor program performance and to periodically evaluate the pertinence of choices made.

Lastly, it is worth mentioning the frequently raised concerns about the use of MS/MS technology to scan for complete metabolic profiles detecting more than 30 inborn errors of metabolism. Once the MS/MS technology is implemented, there will be an increased pressure to expand the neonatal screening program to several other inborn errors of metabolism. This pressure will be exerted by health professionals and industry, as well as by parent associations and the general public, who are increasingly informed through Internet. The arguments fuelling this pressure include the minimal costs of adding other inborn errors of metabolism once the technology is in place, the advantage of gathering data for research, the benefits for families and the ability to capitalize on what is considered the main advantage of MS/MS, namely, its capacity to analyze several metabolites simultaneously. Under no circumstances should screening for additional diseases be considered without a prior evaluation of the evidence and criteria that should guide the implementation of population-based screening programs. Finally, several problems discussed in this report, particularly those concerning the provision of information to parents and the availability of an effective network for patient management and follow-up by competent professionals, must necessarily be assessed and solved prior to any expansion of neonatal screening to other inborn errors of metabolism.

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