The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of tandem mass spectrometry (MS/MS) for screening newborns for up to 21 inherited metabolic disorders such as:

- fatty acid beta-oxidation disorders (carnitine transporter defect, carnitine palmitoyl transferase I deficiency, carnitine/acylcarnitine translocase deficiency, carnitine palmitoyl transferase II deficiency, very long-chain acyl-CoA dehydrogenase deficiency, long-chain hydroxyl acyl-CoA dehydrogenase deficiency, medium-chain acyl-CoA dehydrogenase deficiency and glutaric acidemia Type II),
- organic acidemias (HMG-CoA lyase deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, glutaric acidemia type I, isovaleric academia, methylmalonic academia, and propionic acidemia),
- urea cycle disorders (arginemia, arginosuccinic aciduria and citrullinemia), and
- amino acidemias (tyrosinemia Type I, homocystinuria, maple syrup urine disease, phenylketonuria (PKU) and variants).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of newborns.

Setting
The setting was a hospital. The economic study was carried out in Ontario, Canada.

Dates to which data relate
The effectiveness data were derived from studies published between 1981 and 2005. Resource use was mainly based on authors' assumptions and expert opinion. The price year was 2004.

Source of effectiveness data
The clinical data used in the analysis were:

- the incidence of each disease at birth,
- the severity of disease,
the responsiveness to treatment,
accuracy (sensitivity, specificity and positive predictive rates) of screening for all different metabolic disorders, and
mortality.

Modelling
A decision model was constructed to simulate the clinical management of newborns screened for different metabolic
disorders. First, each screening strategy was individually compared with no screening. Then, the model evaluated the
cost-effectiveness of expanding the screening strategy to other diseases (up to 21). All diseases were grouped into three
levels of severity:
neonatal, classical, severe, or early onset forms of the disease;
later onset, chronic, or milder forms of the disease; and
mild variations that would not be detected or treated without newborn screening.

Key assumptions made in the model were reported. All initially positive screening results were confirmed with a second
tandem MS/MS analysis before the patient was contacted. Positive results from MS/MS testing were confirmed with
other technologies before a final diagnosis was made. The authors reported the structure of the decision tree and
described the main pathways. The time horizon of the analysis was not explicitly stated but it might have been lifetime.

Sources searched to identify primary studies
The positive predictive rates came from a pilot study in California. The mortality rates were derived from the 2000
World Health Organization Life Table for Canada. There was little information on the other sources of data. Expert
opinion was often combined with published sources to estimate epidemiological and clinical parameters.

Methods used to judge relevance and validity, and for extracting data
The method used to obtain the clinical data was not reported, thus the primary studies might have been identified
selectively. Data were obtained from Canadian sources, when available.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected number of life-years (LYs) associated with each screening
strategy under examination. The LYs were estimated using the decision model and were discounted at an annual rate of
3%.

Direct costs
The analysis of the costs was restricted to the perspective of the third-party payer. It included the costs of start-up
(equipment, training, analysis software and maintenance), confirmatory tests (tests and counselling), treatment,
hospitalisation, and costs associated with social services and education. The unit costs and the quantities of resources
used were not presented separately. However, annual costs were reported for each category included in the analysis. The
start-up costs were based on an assumed MS/MS throughput per year. The costs of confirmatory tests came from the
Ministry of Health Schedule of Laboratory Fees. Treatment costs came from multiple sources and hospital costs were
derived from Ontario sources. Additional costs associated with social services and education were derived from
published studies. Discounting was relevant, as long-term costs were evaluated, and an annual rate of 3% was used. The
costs were inflated to 2004 values using the Canadian Health Care Price Index.

Statistical analysis of costs
The costs were treated deterministically in the base-case.
Indirect Costs
Productivity costs were not considered.

Currency
Canadian dollars (CAD).

Sensitivity analysis
A univariate sensitivity analysis was performed. This assessed the robustness of the cost-effectiveness ratios to variations in all clinical and economic inputs of the decision model. The sources of the alternative values examined in the sensitivity analysis were not stated. Four pessimistic scenarios were also evaluated in which both the sensitivity and specificity of MS/MS were reduced in combination with increased costs and reduced life expectancy.

Estimated benefits used in the economic analysis
The expected LYs gained with each screening strategy evaluated independently per infant ranged from 0.000000134 with glutaric acidemia Type II to 0.0000965 with medium-chain acyl-CoA dehydrogenase deficiency.

In a cohort of 130,000 babies (estimated annual birth cohort in Ontario), screening for all 21 diseases would result in 32 early diagnoses each year and 107 LYs gained across the whole cohort.

Cost results
The estimated total costs per infant associated with each screening strategy evaluated independently ranged from CAD 17.41 for PKU and its variants to CAD 62.89 for arginosuccinic aciduria.

The costs were mainly related to start-up and base operation costs. Thus, excluding start-up costs, the incremental cost of expanding the screening strategy to another metabolic disorder was very low (less than US$2), except for urea cycle disorders.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative screening strategies.

With respect to no screening, the incremental cost per LY gained ranged from CAD 221,719 with screening for HMG-CoA lyase deficiency to CAD 142,462,687 with screening for medium-chain acyl-CoA dehydrogenase deficiency.

The four most cost-effective diseases to screen for were HMG-CoA lyase deficiency (CAD 221,719), MCADD (CAD 253,161), methylmalonic acidemia (CAD 253,927) and 3-methylcrotonyl-CoA carboxylase deficiency (CAD 266,991), assuming each was screened for independently.

Thus, none of the screening strategies could be considered cost-effective when evaluated individually.

In particular, the incremental cost per LY gained for PKU screening (current strategy) compared with no screening was CAD 5,492,114.

However, the cost-effectiveness of adding additional diseases to a screening programme was much lower. In a scenario in which PKU screening has absorbed all the fixed costs, expanding the screening to a third disease (maple syrup urine disease) cost CAD 15,426 per LY gained.

Adding the seventh disease (glutaric acidemia Type I) to the bundle cost CAD 48,071 per LY gained, while adding the 14th disease (carnitine/acylcarnitine translocase deficiency) cost CAD 95,000 per LY gained. Adding the 15th disease (tyrosinemia Type I) produced instead an incremental cost of CAD 309,409 per LY gained.
Screening a bundle including PKU plus 14 other diseases resulted in an incremental cost of CAD 68,346 per LY gained compared with no screening. This was the most cost-effective screening strategy.

The least cost-effective inborn errors of metabolism to screen for were those that affected the urea cycle (i.e. arginemia, arginosuccinic aciduria, and citrullinemia).

The sensitivity analysis showed that the cost-effectiveness ratios were sensitive to MS/MS specificity. The pessimistic scenarios indicated that reductions in specificity had a significant impact on the cost-effectiveness estimates.

Authors' conclusions
Tandem mass spectrometry (MS/MS) is more cost-effective when screening is performed to screen for bundles of diseases rather than just one disease. However, it is not cost-effective to screen for all diseases (21) that can be screened for using this technology. A screening programme for phenylketonuria (PKU) and 14 other diseases would have an incremental cost per life-year (LY) gained of less than CAD 70,000.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear in that methods of screening for the most relevant inborn errors of metabolism were considered. The strategy currently adopted in Ontario was compared with all possible combinations of additional screening tests. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The approach used to derive the clinical data used in the decision model was not stated. The authors did not report the method and conduct of a review of the literature. Thus, the primary studies might have been identified selectively. The authors did not describe the primary sources in terms of their design and other aspects such as patient populations. Canadian data were used, when possible.

Validity of estimate of measure of benefit
The summary benefit measure was appropriate given the nature of disease. Further, LYS can be compared with the benefits of other health programmes. Discounting was appropriately performed. The impact of the programme on quality of life was not investigated, although this would have been useful. The authors stated that there are several unresolved problems regarding the use of quality-adjusted life-year measurements in infants and children.

Validity of estimate of costs
The analysis of the costs appears to have been consistent with the perspective of a third-party payer. A detailed breakdown of the costs was given for most items, but some costs were presented as macro-categories. Sources of data were reported for all items. Most of the costs came from a large academic hospital. Resource use was based on both published data and authors' opinions. The costs were treated deterministically but the impact of varying some costs was investigated in the sensitivity analysis. The price year was reported, which will help with reflation exercises in other time periods.

Other issues
The authors made some comparisons of their findings with those from other studies that had found screening to be cost-effective, although there was wide variation in the cost-effectiveness ratios. The issue of the generalisability of the study results to other settings was not explicitly addressed, but a sensitivity analysis was carried out. However, the results of the sensitivity analysis were not reported in detail, probably due to the very high number of combination strategies evaluated. In general, the result of the analysis should be considered specific to the study context. However, it is likely that expanding the MS/MS screening programme to several metabolic disorders would prove cost-effective in other locations.
Implications of the study
The study results support the implementation of an MS/MS screening programme for bundles of several diseases.

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