Cost-benefit analysis of universal tandem mass spectrometry for newborn screening
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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) to screen newborn babies for a wide range of inborn errors of metabolism (IEM).

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of newborn infants aged 12 to 144 hours.

Setting
The setting was secondary care. The economic study was carried out in Northern California, USA. The screening tests were performed in regional laboratories, using standardised equipment.

Dates to which data relate
The effectiveness data were derived from studies published from 1999 to 2000, and from direct data for the false-positive:true-positive ratio achieved with the fluorometric method in an HMO in Northern California from 1978 to 2000. The utility data were derived from studies published from 1997 to 1999. The intervention costs were derived from published studies from 1999 to 2001 and from charge data from commercial laboratories. The costs of false-positive test results were based on internal data on existing screening programmes for newborn babies from an HMO in Northern California. The treatment costs for IEM were derived from a published study from 2001, and from internal data from an HMO in Northern California. The price year was not specified.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and authors' assumptions.

Outcomes assessed in the review
The outcomes assessed in the review of effectiveness data were the false-positive and true-positive rates associated with screening for IEM in newborn babies, and the incidence rate of 7 general categories of IEM. The outcome assessed in the review of utility data was the utility in adults with disorders (other than IEM) that cause neurological defects.

Study designs and other criteria for inclusion in the review
Not reported.
Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The review included 8 primary studies.

Methods of combining primary studies
The authors did not report the methods used to combine the primary studies, or the specific results of these studies.

Investigation of differences between primary studies
Not reported.

Results of the review
The authors estimated a false-positive:true-positive ratio of 25:1 associated with screening for maple syrup urine disease (MSUD), medium-chain acyl-CoA dehydrogenase deficiency (MCAD) and other disorders of fatty acid oxidation, glutaric aciduria Type I, methylmalonic or propionic acidemia, urea cycle disorders and homocystinurea. This was based on a range of false-positive rates from 5:1 to 50:1 observed in the primary studies.

The authors stated that they assumed that the false-positive:true-positive ratio associated with screening for phenylketonuria was similar to the 8:1 ratio from published data for the fluorometric method in California. The exact ratio used was unclear, but it can be inferred to be 14:1.

The incidence rates of general categories of IEM were estimated to be 1:20,000 for MSUD and glutaric aciduria Type I, 1:10,000 for MCAD, 1:15,000 for phenylketonuria, 1:50,000 for urea cycle disorders and methylmalonic acidemia, and 1:200,000 for homocystinurea.

Estimates of utility levels with serious neurological defects ranged from 0.15 to 0.30. Early detection of IEM was estimated to result in the addition of between 0.70 and 0.80 QALYs.

Methods used to derive estimates of effectiveness
The authors made assumptions about the annual hospital admission rate associated with early and late detection of IEM, and the effect of early detection of IEM on life expectancy.

Estimates of effectiveness and key assumptions
The authors assumed that the hospital admission rate among patients aged 5 years and younger was 7.5% with early detection of IEM, and 25% with late detection. The corresponding values for patients aged at least 5 years were 3% (early detection) and 9% (late detection), respectively.

The authors assumed that early detection of IEM leads to a 20-year improvement in life expectancy from 45 years (with late detection) to 65 years.
Measure of benefits used in the economic analysis
The main measure of health benefit used was the QALYs. The utility levels were derived from the results of published studies. The methods of valuation used in the primary studies from which the utility estimate was derived were not reported.

Direct costs
The study employed the direct costs to the hospital. These included the laboratory cost of MS/MS, the cost-savings associated with a presymptomatic diagnosis and diagnosis after symptoms manifested, the cost of a false-positive test, the cost of inpatient stay following early and late detection of IEM, and dietary costs for children with IEM. The dietary costs were for disease-specific feeding formula for children aged 0 to 4 years, and a special diet for children aged 5 years and older. The resource quantities were not reported separately from the costs. The cost data were derived from studies published studies between 1999 and 2001, and charge data from commercial laboratories. The costs were discounted at a rate of 3% per annum. The study reported average and incremental costs. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically. This was appropriate for some of the cost estimates (e.g. unit cost of a screening test), but other costs (e.g. length of inpatient stay) typically exhibited high variation both within and between centres. The failure to reflect this variation could reduce the applicability and generalisability of the results.

Indirect Costs
The indirect costs were not included in the analysis. No justification was given for this omission, but it can be inferred that it was due to the study perspective being that of a large HMO rather than societal.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was carried out on the laboratory cost of the screening test, the rate of false-positive test results, and the effects of early detection on mortality and morbidity. The laboratory cost of the screening test was assumed to be $7 in the most favourable scenario and $20 in the least favourable scenario. The increase in life expectancy associated with early detection of IEM, compared with late detection, was assumed to be 25 years in the most favourable scenario and 15 years in the least favourable scenario. The method used to select the ranges explored in the sensitivity analysis was not reported. The ranges used for the rate of false-positive test results and the effect of early detection on morbidity were unclear. The sensitivity analysis explored variability in the data using a multi-way analysis of extremes.

Estimated benefits used in the economic analysis
Early detection of IEM resulted in a gain of 0.0026 QALYs per person in the base-case lifetime analysis, compared with late detection of IEM. This was estimated to be 0.0028 QALYs per person in the most favourable scenario and 0.0024 QALYs per person in the least favourable scenario.

A 3% discount rate was applied to the future health benefits. The utility estimates were based on adult values that were applied over the lifetime of the study population, including childhood. The study considered the costs of false-positive test results as a side effect of screening, but not the effects on life expectancy.

Cost results
The incremental cost (total cost of screening net of savings associated with early detection compared to late detection) of using MS/MS to screen newborn babies was $15.49 per person in the base-case lifetime analysis with a discount rate of 3% per annum.

The net cost of MS/MS screening was $2.23 per person in the most favourable analysis and $27.39 per person in the least favourable analysis.

**Synthesis of costs and benefits**
The incremental cost per QALY for MS/MS screening, compared with no screening, was $5,827 in the base-case lifetime analysis with a 3% discount rate.

The cost/QALY was $736 in the most favourable analysis and $11,419 in the least favourable scenario.

**Authors’ conclusions**
The cost per quality-adjusted life-year (QALY) of tandem mass spectrometry (MS/MS) compared favourably with other screening programmes currently employed in the USA. The authors acknowledged that the set-up costs associated with implementing a MS/MS screening programme might be high.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator was not explicit. However, the costs and benefits of early detection with MS/MS screening were compared to the cost and benefit of late detection. It could therefore be assumed that the comparator was no screening. The comparator of no screening does not reflect current practice in the study setting of Northern California, USA. Current practice involves screening newborn babies for phenylketonuria. The study included the cost saving associated with eliminating the need for the current phenylketonuria testing, but the authors do not appear to have accounted for the effectiveness of the current programme. By including the cost-savings associated with replacing the existing screening programme, but failing to offset the benefits of MS/MS for the number of cases already detected, the results of the study might have overestimated the cost-effectiveness of MS/MS screening.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken to determine the false-positive:true-positive ratio of MS/MS screening for the IEM specified in the study. The authors used data from the available studies selectively. The authors considered the differences in effectiveness between the primary studies. They concluded that the reason most of the published studies reported rates higher than the 14:1 ratio taken directly from the records of an HMO may have been due to a failure to meet three conditions. More specifically, the use of MS/MS to screen for prespecified abnormalities only, the use of MS/MS to screen for only a selection of the full range of diseases it can detect, and the use of a “reasonable”, pre-set cut-off point to determine positive-test results. Thus, the results of this study are only generalisable to situations in which these conditions are met.

**Validity of estimate of measure of benefit**
The study employed utility estimates from adults with neurological impairments. The source of the estimates of life expectancy was unclear. The validity of applying adult health-state valuations to children is uncertain. The authors stated that, due to the rarity of IEM and the rarity of early detection, there is little longitudinal evidence on the effectiveness of early detection. Due to this lack of evidence, the authors acknowledged that some of their estimates made use of expert opinion.

**Validity of estimate of costs**
All the categories of cost relevant to the perspective of a large HMO appear to have been included in the analysis, assuming that the facilities for MS/MS screening were already in place. The authors acknowledged that the set-up costs might be large, so the results of this study will be less applicable to HMOs without the required specialist testing.
facilities. The costs and the quantities were not reported separately. Many of the cost estimates were derived using charge data from a HMO. This means that they incorporated the quantity of resources used and the unspecified price or charge particular to that HMO, which may limit the generalisability of the result. The price year was not reported and the authors did not specify whether any transformation was necessary to ensure that all of the cost data represented the same price year.

Other issues
The authors compared the cost-effectiveness of MS/MS screening with other established screening programmes, but they did not compare it with existing screening programmes for IEM. The results of the study are unlikely to be generalisable outside the USA due to the use of US, HMO-specific cost data. The authors presented their results clearly. However, the generalisability within the USA is unclear due to the lack of clarity over the source and the method used to calculate some of the data needed for the results. The authors performed sensitivity analyses to partly overcome this limitation. The authors’ conclusions reflected the scope of the analysis.

Implications of the study
The authors highlighted the lack of data on the long-term outcomes for children with IEM. This limits the data available for assessing the cost-effectiveness of screening and treatment programmes for these disorders. They also acknowledged that, with the use of special diets and better treatment, the prognosis of IEM has changed over the past two decades. The authors recommended that MS/MS screening be introduced, but only if the facilities are already in place or the cost of establishing such facilities is deemed to be cost-effective.

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