Service provision of complex mutation analysis: a technical and economic appraisal using dystrophin point mutation analysis as an example

Nixon J, Cockburn D, Hopkin J, Seller A, Huson S M

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 dystrophin point mutation analysis (PMA) for the detection of Duchenne muscular dystrophy (DMD). The laboratory based study used reverse transcription-polymerase chain reaction (RT-PCR) and a protein truncation test (PTT).

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
Not reported.

Setting
The practice setting can be categorised as other (i.e. a laboratory). The economic study was carried out in the Oxford Medical Genetics Laboratories, Oxford, UK.

Dates to which data relate
The laboratory work was carried out between 1994 and 1996. It was reported that the costing of the laboratory analysis, which was based on laboratory time and the materials needed for linkage and PMA, was initially carried out in 1997 and subsequently adjusted for material and salary cost inflation. However, the authors did not provide any information on the adjustments.

Source of effectiveness data
The effectiveness data obtained from the laboratory study related to a single study. The assumptions used in the model were based on published data, data from the Oxford DMD register and expert opinion.

Link between effectiveness and cost data
It was unclear whether, or how, the results from the laboratory study were used in the model.

Study sample
Power calculations do not appear to have been carried out. The method of sample selection was not reported. The authors did not justify their choice of sample in terms of the characteristics of the conditions, the technique under investigation, or the generalisability of the findings.
The authors reported that the sample comprised:

12 men affected with DMD who had previous negative analysis for dystrophin mutations (multiplex PCR and pulsed-field gel electrophoresis);

two obligate carrier females from familial pedigrees with an established diagnosis of DMD, with no known dystrophin mutation detectable by pulsed-field gel electrophoresis; and

two mothers of two affected males in whom mutations were found by RT-PCR/PTT (note, mutation-specific carrier testing had shown that both these females carried the mutations detected in their sons).

**Study design**

This study could be described as a cohort study. It took place at a single centre. The study did not involve any degree of follow-up.

**Analysis of effectiveness**

All of the patients included in the study were accounted for in the analysis. The study measured the detection of point mutations.

**Effectiveness results**

Point mutations were detected in 6 of the 12 males. The authors report that four of these mutations were nonsense mutations and two were frameshifting mutations leading to downstream stop codons. Although mutations were not found in the remaining 6 patients, a subsequent analysis undertaken at another centre by RT-PCR/PTT on muscle-derived ribonucleic acid (RNA) revealed point mutations in two of this group of patients.

It was also reported that no unambiguously abnormal bands were seen in the PTT gels of the obligate carriers. PTT reactions were performed on separate RT-PCR products (three for one female and two for the other) in the reactions that had given abnormal results in their sons. In only one of the five reactions did an abnormal PTT band seen in the female correspond to the abnormal band in her affected son.

**Clinical conclusions**

Point mutations were detected in 6 of the 12 males, but in none of the female carriers.

**Modelling**

The model appears to be of a decision tree type. Its purpose was to estimate the costs for those benefits of genetic testing that are readily definable.

**Outcomes assessed in the review**

Not reported.

**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
Not reported.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The authors did not differentiate between those assumptions derived from published data and those formulated as a consequence of expert opinion. Therefore, all assumptions which were referenced are detailed in this section with the others listed in the 'Estimate of Methods of Effectiveness and Assumptions' section.

The assumptions, as detailed by the authors, are as follows.

A high-risk carrier result, whether by LA or PMA, will result in a request for prenatal diagnosis in 85% of pregnancies.

A low-risk carrier result by LA will result in requests for prenatal diagnosis in 10% of cases.

A high-risk prenatal diagnosis result by LA or PMA will lead to termination of pregnancy in 80% of cases, but no terminations will occur after a low-risk result.

There is a 10% recombination rate along the length of the gene.

Methods used to derive estimates of effectiveness
The authors did not differentiate between those assumptions derived from published data and those formulated as a consequence of expert opinion. Therefore, all assumptions that were referenced have been detailed in the 'Results of the Review' section, whilst all others are detailed in the 'Estimate of Methods of Effectiveness and Assumptions' section.

Estimates of effectiveness and key assumptions
The assumptions, as detailed by the authors, were as follows.

The somatic carrier frequency in mothers of isolated affected males is 67%.

The germline carrier frequency for point mutations is the same as that for deletions and duplications, thus the overall carrier frequency in mothers of isolated cases is 73%.

No prenatal diagnosis will be requested by women who have a negative carrier test by PMA (except mothers of affected males).

Mothers of isolated affected males with a negative carrier test will request a prenatal diagnosis in 85% of cases (as they remain at germline mosaicism carrier risk.)
In pedigrees where a point mutation has been detected, subsequent analysis will identify correctly all carriers and affected foetuses.

The LA is informative in all cases.

The mean family size is 2.0 children.

For sporadic pedigrees, the affected male is the first born child in 50% of families and the second born in 50%.

Where the affected was the first born, it was assumed that the diagnosis was made early enough for the mother to have genetic counselling in 50% of cases, and for all other females to have counselling in 100% of cases. This means that, in one in four sporadic pedigrees, the diagnosis was made early enough for the mother to have genetic counselling before completing her family. Thus, on average, 0.25 children were needed to complete the mother’s family after the diagnosis of the affected male was made. For familial pedigrees, the diagnosis was made early enough for the mother to have genetic counselling in all cases. On average, two children would be needed to complete the mother’s family in these pedigrees.

**Measure of benefits used in the economic analysis**

The benefits predicted by the model were the number (per standard family) of prenatal diagnoses, terminations of pregnancy and terminations of pregnancy of unaffected foetuses.

The standard family was defined by the mean number of potentially child-bearing females in 62 pedigrees taken from the Oxford DMD register. It comprised 1.0 mothers, 1.27 sisters and 4.09 others.

**Direct costs**

The resource quantities and the costs were not reported separately. The direct costs of the laboratory were included in the analysis. Details of the individual direct costs were not reported. It was reported that the prices were estimated on the basis of the time taken to carry out given procedures and the salary cost of the person undertaking these tasks. It was also reported that costs were based on routine diagnostic analysis of 10 unrelated families and included repeat analysis in some families for clinical reasons (e.g. the testing of an additional family member). Further, the authors reported that a number of benefits were predicted to accrue from the greater accuracy of PMA (i.e. obviating the need for LA, a decrease in the number of prenatal diagnoses and a decrease in the number of terminations of pregnancy) and these represent cost-savings. Thus, the authors adjusted the measured cost of PMA to account for these potential savings. No further information on the estimation of prices was given.

Although the study took place over 2 years, which would make discounting relevant, it appears that the costing has been undertaken retrospectively using standard resource use and cost parameters. Thus, discounting was not relevant. The study reported the mean costs. The authors reported that the price data were initially for 1997, but that these were then adjusted for material cost and salary inflation. However, details of the adjustment calculations were not reported.

**Statistical analysis of costs**

No statistical analysis of the costs was reported.

**Indirect Costs**

No indirect costs were reported.

**Currency**

US dollars ($). A conversion from UK pounds sterling (£) was carried out using an exchange rate of 1.00 = $1.50.
Sensitivity analyses were performed. The area of uncertainty investigated was the effectiveness of the health technology (i.e. point mutation). The authors reported that the model calculations were performed assuming a range of sensitivities of PMA (50%, 75% and 100%). As only one parameter was varied, one-way simple sensitivity analyses would have been carried out. The rationale used to determine the range used was not reported. No further details were reported.

**Estimated benefits used in the economic analysis**

For all females (LA) the reductions in the number of prenatal diagnoses was 3.88, terminations of pregnancy 0.81, and terminations of unaffected foetuses 0.33.

For all females (PMA; sensitivity 100%), the reduction in the number of prenatal diagnoses was 2.35, terminations of pregnancy 0.45, and terminations of unaffected foetuses 0.00.

Using PMA instead of LA (assuming sensitivity 100%), the reduction in the number of prenatal diagnoses was 1.53, terminations of pregnancy 0.36, and terminations of unaffected foetuses 0.33.

Using PMA instead of LA (assuming sensitivity 75%), the reduction in the number of prenatal diagnoses was 1.15, terminations of pregnancy 0.27, and terminations of unaffected foetuses 0.24.

Using PMA instead of LA (assuming sensitivity 50%), the reduction in the number of prenatal diagnoses was 0.77, terminations of pregnancy 0.18, and terminations of unaffected foetuses 0.16.

**Cost results**

The total laboratory cost associated with LA of one standard family was $355.

The mean laboratory costs of PMA per family analysed were $1,370 (range: 910 - 2,245), of which labour costs made up $760 and material costs were $610.

In families where a mutation was detected, the mean cost of carrier testing (which included the average costs above) was $220 per family (range 140 - 265).

Taking the possible savings arising from PMA into consideration and assuming a sensitivity of 50% for point mutation, the average cost to analyse a standard family was $995 (range: 530 - 1,870).

The mean cost associated with the termination of an affected pregnancy was $1,580 (range: 845 - 2,965), compared with $740 for LA.

The mean cost associated with the prevention of a termination of an unaffected pregnancy by PMA was $6,220 (range: 3,325 - 11,675).

**Synthesis of costs and benefits**

Not applicable.

**Authors' conclusions**

The provision of a routine dystrophin point mutation analysis (PMA) service is both technically and economically viable. Further, the mean cost of PMA to prevent the termination of an unaffected foetus is $6,220.

**CRD COMMENTARY - Selection of comparators**

The choice of the comparator used in the model was not justified explicitly, but it would appear to represent current practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness data came from a single study, the literature and expert opinion.

The study design was a cohort study and there were no alternative patient groups. Further, it was unclear how the study sample, which was very small, was chosen. These factors cast some doubts on the validity of the study findings. The analysis of effectiveness appears to have been handled credibly. The authors did not state that a systematic review of the literature had been undertaken. It is unclear whether the estimates of effectiveness studies were combined, or whether the authors used data from available studies selectively. The authors did not report having considered the impact (if any) of differences between the primary studies when estimating effectiveness. The methods used to derive estimates of effectiveness using expert opinion were not reported.

Validity of estimate of measure of benefit
The measures of benefit were predicted by the model. A justification for the choice of the model outcomes was not given, however, they appear to have been reasonable.

Validity of estimate of costs
It appears that all the categories of cost relevant to the cost perspective have been included in the analysis. Details of the costs included in each category were not reported, nor were details of resource use. The unit costs were not reported separately from the resource quantities. The sources of the prices were not reported. The authors carried out currency conversions. It would appear that the costing was undertaken retrospectively, thus discounting was not relevant. Charges were not used to proxy prices. The date to which the prices referred was not reported.

Other issues
The authors appear to have made appropriate comparisons of their results with findings from other studies. However, the issue of generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively. The authors’ conclusions, as detailed in the abstract, acknowledged the small sample size of the study and detailed model results relating to the effectiveness observed in the study. Thus the authors’ conclusions did reflect the scope of the analysis. In terms of limitations of the study, the authors suggested that the reason for their lower sensitivity (compared with other studies) is probably technical, but it may also reflect some ascertainment bias as successful studies are more likely to be published. The authors also felt that a lack of experience with the technique and the use of lymphocyte- rather than muscle-derived RNA may have been contributory factors.

Implications of the study
The authors suggested that PMA should be carried out in specialist molecular genetic laboratories, preferably using muscle as the source of RNA.

Source of funding
Funded by the Muscular Dystrophy Group (now the Muscular Dystrophy Campaign) and grants from the Oxfordshire Health Authority and the Oxfordshire and Anglia Health Region.

Bibliographic details

PubMedID
12123485

Indexing Status
Subject indexing assigned by NLM
MeSH
Dystrophin /genetics; Female; Genetic Services /economics /standards; Heterozygote Detection; Humans; Male;
Muscular Dystrophy, Duchenne /diagnosis /economics /genetics; Point Mutation; Reverse Transcriptase Polymerase
Chain Reaction /economics; Sequence Analysis, DNA /economics /methods

AccessionNumber
22002001288

Date bibliographic record published
31/08/2005

Date abstract record published
31/08/2005