Fragile-X carrier screening and the prevalence of premutation and full-mutation carriers in Israel


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 a screening programme for fragile-X syndrome, which is caused by an unstable CGG trinucleotide repeat in the FMR1 gene at Xq27. Screening took place at one centre and women applied for testing on their own initiative, or on the advice of their physician, on a self-pay basis. Intermediate alleles (between 51 and 200 repeats) may undergo expansion to the full mutation on transmission from mother to offspring. According to the screening strategy, all women who were found to be carriers of premutation alleles (50 or more repeats) were offered genetic counselling. Information about prenatal diagnosis by amniotic-fluid analysis or chorionic villus sampling was provided to those who were already pregnant at the time of screening and to those who became pregnant following screening.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women of childbearing age (either preconceptional or pregnant) who had no family history of mental retardation.

Setting
The setting was tertiary care. The economic study was carried out at the Rabin Medical Center in Petah Tikva, Israel.

Dates to which data relate
The effectiveness and resource use data were gathered from January 1992 to October 2000 and were obtained from studies published between 1994 and 1999. The price year was likely to have been 1999.

Source of effectiveness data
The effectiveness evidence for the model came from a single study and from completed studies.

Link between effectiveness and cost data
The costing was performed on a sample of pregnant women that was different from that used in the effectiveness study.

Study sample
Power calculations were not necessary. A sample of 14,334 eligible women, who applied for testing on their own initiative or on the advice of their physician, were included in the analysis. A single group of women was considered in
the analysis.

**Study design**
The effectiveness study was based on a long-term observational study of a screening programme (from 1992 to 2000). The length of and loss to follow-up were not reported, but the patients were followed until birth took place (for those who were pregnant) or until genetic counselling was provided (for those who were not pregnant).

**Analysis of effectiveness**
All of the women included in the initial study sample were accounted for in the effectiveness analysis. The primary health outcomes were:

- the number of carriers of an allele with 50 or more repeats, 55 or more repeats, and 200 or more repeats;
- the number of pregnancies and subsequent prenatal diagnosis procedures; and
- the transmission of an allele containing 50 or more repeats.

The analysis was carried out retrospectively on sub-groups of ethnic groups living in Israel.

**Effectiveness results**
There were 207 carriers of an allele with 50 or more repeats. This represented a prevalence of 1:69 (confidence interval, CI: 1:62 - 1:83).

There were 127 carriers of an allele with 55 or more repeats. This represented a prevalence of 1:113 (CI: 1:96 - 1:136).

Full allele mutation (200 or more repeats) was found in 3 women.

There were 193 pregnancies in 173 pregnant women and 177 (91.7%) prenatal diagnosis procedures were performed.

The allele with 50 or more repeats was transmitted in 90 pregnancies (50.8%), of which 5 expanded to the full mutation.

No full mutation was found in any of the foetuses of mothers with less than 70 repeats. There were no statistically significant differences in the diverse ethnic groups considered in the analysis.

**Clinical conclusions**
The observational study indicated that the prevalence of alleles was greater than studies had shown. A cut-off point of 55 (or even 60) repeats can be considered as safe for making a decision about the need for prenatal testing.

**Modelling**
A decision tree model was constructed to estimate the net benefit of the screening programme in comparison with the no screening option. The tree comprised 132 branches, which represented all possible sequences of events. The structure of the tree was not depicted and further details were not provided. The model was populated with data from the current study and from the literature.

**Outcomes assessed in the review**
The outcomes assessed from the literature were the probabilities of:

- the rejection of a screening programme;
not finding the full fragile-X mutation among women who rejected screening;
not being a carrier among women who accepted screening;
the rejection of genetic counselling among carriers;
a foetus that does not have the full fragile-X mutation when the mother is a carrier;
foetal diagnosis being rejected when the mother is a carrier;
finding a normal foetus following foetal diagnosis;
iatrogenic abortion following foetal diagnosis;
finding a somatic chromosome abnormality in the foetus at prenatal diagnosis;
finding a sex chromosome abnormality in the foetus at prenatal diagnosis;
finding the full fragile-X mutation in the foetus at prenatal diagnosis;
a pregnancy termination being rejected where there is a somatic-chromosome abnormality or a sex-chromosome abnormality in the foetus, or where the foetus has the full fragile-X mutation;
a foetus with the full fragile-X mutation being male;
a mentally retarded male (or female) with the full fragile-X mutation;
the pregnancy being a second pregnancy; and
screening being rejected in the second pregnancy where it was rejected in the first pregnancy.

Complementary values will not be reported in this abstract.

Study designs and other criteria for inclusion in the review
A review of the literature was not undertaken. The designs of the primary studies were not reported.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
The probability values used in the decision model were derived from 5 studies.

Methods of combining primary studies
Not stated.
Investigation of differences between primary studies
Not stated.

Results of the review
The probability values were:

0.5 for the rejection of a screening programme;
2,866/2,867 for not finding the full fragile-X mutation among women who rejected screening;
112/113 for not being a carrier among women who accepted screening;
0 for the rejection of genetic counselling among carriers;
0.958 for a foetus that does not have the full fragile-X mutation when the mother is a carrier;
0.5 for foetal diagnosis being rejected when the mother is a carrier;
0.944 for finding a normal foetus following foetal diagnosis;
0.01 for iatrogenic abortion following foetal diagnosis;
0.002 for finding somatic chromosome abnormality in the foetus at prenatal diagnosis;
0.002 for finding a sex-chromosome abnormality in the foetus at prenatal diagnosis;
0.042 for finding the full fragile-X mutation in the foetus at prenatal diagnosis;
0 for a pregnancy being rejected where there is a somatic-chromosome abnormality or sex-chromosome abnormality in the foetus, or where the foetus has the full fragile-X mutation;
0.5 for a foetus with the full fragile-X mutation being male;
1 for a mentally retarded male (0.59 for female) with the full fragile-X mutation;
0.272 that the pregnancy is a second pregnancy;
1 for screening being rejected in the second pregnancy where it was rejected in the first pregnancy.

Measure of benefits used in the economic analysis
The authors calculated the net benefit from screening by calculating the costs saved.

Direct costs
Discounting was relevant since the lifetime costs were estimated, but it was not reported. The unit costs were reported separately from the quantities of resources used for only a few items. The health services in the economic evaluation were programme administration and publicity, blood tests, molecular biology studies, genetic counselling, invasive procedures for prenatal diagnosis, miscarriage after invasive procedures, and patient travel costs. The cost/resource boundary adopted in the study was unclear. The resource use data were estimated from studies published between 1994 and 1999. The costs came from different sources, such as the Israeli Ministry of Health and published studies. The authors estimated the economic benefit of the prevention of the birth of a mentally retarded individual to be the cost of the lifetime care of such a mentally retarded person. This was estimated from a published study. The consumer price index was used to inflate all the costs into a single price year, which was likely to have been 1999.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The authors stated that the loss of work time for attending screening was included in the analysis, but details of the inclusion of the indirect costs were not provided. It was only stated that the indirect costs were estimated from a published study that also provided much of the direct costs and probability data (see Other Publications of Related Interest).

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not carried out.

Estimated benefits used in the economic analysis
The expected net benefit from running the programme was $5,500,000.

Cost results
The lifetime cost of a person with mental retardation was estimated to have been $680,000. This represented the threshold under which the implementation of the screening programme would be considered economically feasible. The analysis showed that the cut-off point at which the lifetime costs of care for a mentally retarded patient under a genetic screening scenario would be lower than those associated with a no screening strategy was $350,000. Thus, the screening programme was efficient relative to a no screening option, because the cut-off point was far below the calculated threshold.

Synthesis of costs and benefits
The costs and benefits were not combined because a net benefit was calculated by valuing the costs saved.

Authors' conclusions
The screening programme for fragile-X syndrome was effective in identifying the carriers of premutation or full-mutation alleles. It was efficient in comparison with a no screening strategy due to the high prevalence in the general population.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was appropriate because a no-screening option was selected, which represented the standard screening strategy currently used in most countries. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used two sources of data. The efficacy of the programme in identifying carriers of premutation or full mutation was estimated from an observational study of a screening programme. The data that were used as probability values in the decision model were estimated from published studies. However, a formal review of the literature was not undertaken. Also, the methods used to ensure the validity of the primary studies and to extract the data were not reported. The estimates were used selectively and the issue of uncertainty in the estimates was not addressed. Thus, it appears difficult to estimate the validity of the analysis.
Validity of estimate of measure of benefit
The authors calculated the net benefit from screening by calculating the costs saved, which is an acceptable measure of benefit from a health service perspective, although this was not explicitly stated.

Validity of estimate of costs
The perspective adopted in the study was unclear because most of the costs may be borne by the Israeli National Health System. It appears that some form of patient co-payment could be considered. The indirect costs were likely to have been included, although the authors did not provide any detail about their calculation. Thus, it could be more appropriate to state that a societal perspective was adopted. The unit costs were provided separately from the quantities of resources used for some items. The source of the cost and resource use data was provided. The price year was likely to have been 1999, although it was not explicitly stated. The main cost analysis was carried out in the appendix. Most of the data used in the economic evaluation were derived from studies conducted in other countries. The use of sensitivity analyses to evaluate the robustness of the conclusions would, therefore, have been interesting.

Other issues
The authors made extensive comparisons of their findings with those from other studies. They described, in depth, the results of the most relevant published articles. Most of the studies found that a screening strategy for fragile-X syndrome was cost-effective. Thus, the conclusions of the current analysis corroborate other studies. However, the authors did not address the issue of the generalisability of the study results to other settings. The lack of sensitivity analyses limits the external validity of the study.

Implications of the study
The authors suggested that screening to identify female carriers of fragile-X syndrome should be carried out on a wide scale. Screening of only those who are mentally retarded or who have learning disabilities may miss a significant number of the full-mutation carriers.

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Other publications of related interest

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