Prenatal screening for cystic fibrosis carriers: an economic evaluation
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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
Prenatal cystic fibrosis carrier screening.

Type of intervention
Screening.

Economic study type
This study included a cost-utility analysis, considered the cost-benefits and savings resulting from a screening programme, and offered some data on patients' willingness to pay for the service. Results were also presented in a cost-effectiveness framework in terms of cost per CF birth voluntarily averted.

Study population
The study population comprised pregnant women who would, potentially, benefit from CF screening.

Setting
The setting was hospital. The study was in set in providers' offices with delivery services in Monroe County, NY, USA.

Dates to which data relate
No dates were given in this paper for either the effectiveness analysis or the resource use data. Costs were estimated in 1996 US dollars.

Source of effectiveness data
The evidence on final outcomes was derived primarily from a single study although the data were supplemented by data on various probabilities from a review of the literature and estimates made by the authors.

Link between effectiveness and cost data
The cost estimates were derived from national samples which were considered by the authors to be more reliable due to regional market effects.

Study sample
The sample consisted of female patients who were of reproductive age, over 18 years old and mostly pregnant (90%). Although the test was designed to be offered to all pregnant women, not all providers routinely undertook this form of screening. Among pregnant women, the acceptance rate for screening was 57%. Among men whose partners were found to be carriers, the acceptance rate was 85%. No power calculations were reported and a larger study sample than the 4,879 women tested would probably have been needed. No data were given on the proportion of women being offered the test who could have been offered it, but in the conclusion the authors comment that 30% of providers
offered screening.

**Study design**
One could describe this study as a non-randomized trial with historical controls since historical data concerning outcomes when no screening programme is in place were implicitly used for comparison. This was a multi-centre study.

**Analysis of effectiveness**
The study was based only on those patients completing the various screening rounds and finally undergoing prenatal diagnosis (via amniocentesis). The primary health outcomes were the determination of carrier status among the parents, the detection of a foetus with cystic fibrosis and the rate of termination of foetuses with cystic fibrosis.

**Effectiveness results**
The probability of a woman choosing to be screened was 0.57. Of the 4,870 women tested, 124 were found to be cystic fibrosis (CF) carriers. Of these 124, 106 partners (85%) were tested. Of these 106 couples, the partner was found to be a carrier in 5 and prenatal diagnosis was chosen by 4 of 5 couples (probability 0.80). Of the 4 couples undergoing prenatal diagnosis, 3 said they would terminate if the foetus was affected (probability 0.75), although, in fact, no foetuses proved to be so affected. Although the effectiveness study found a loss rate from amniocentesis of 20%, this was not used in the calculation as the value was not considered to be representative.

**Clinical conclusions**
CF carrier status for both partners is rare. CF screening enables couples to determine their carrier status such that decisions concerning diagnosis and potential termination decisions can be made. CF screening is undertaken by approximately half the pregnant women who are offered it.

**Modelling**
A base model was used in calculating the results, whereby the values of the input variables were subjected to a sensitivity analysis. Modelling was also employed in estimating benefits in the analysis, by way of a decision tree.

**Outcomes assessed in the review**
Some of the probability estimates used in the economic analysis were derived from sources outside the single study described above, including the probability that the woman or her partner is a carrier, the sensitivity of the screening test and the likelihood that an affected foetus would be replaced.

**Study designs and other criteria for inclusion in the review**
No criteria were given.

**Sources searched to identify primary studies**
No information was given on how the studies were found.

**Criteria used to ensure the validity of primary studies**
No criteria were stated.

**Methods used to judge relevance and validity, and for extracting data**
No methods were stated.
Number of primary studies included
Four published sources were used to supplement the data obtained from the primary study. The authors reviewed studies of prenatal cystic fibrosis in a separate publication, indicated at the references of the current paper.

Methods of combining primary studies
Two of the four studies provided data on the same variable (sensitivity of screening test) but were not combined. Instead the study providing the highest value was used as the upper limit in the sensitivity analysis.

Investigation of differences between primary studies
The reason why these two studies gave different results on the sensitivity of the test was not investigated.

Results of the review
The following probabilities, from the above sources, were used in the base-case scenario: sensitivity of screening test 0.85; probability of woman or partner being a carrier 0.04; replacement of affected foetus 1.0.

Methods used to derive estimates of effectiveness
Several of the values used for inputs in the model were derived from the authors' opinions.

Estimates of effectiveness and key assumptions
No references were given for the probability of repeat prenatal diagnosis or the probability of abortion of a second affected foetus. A value of 25% was chosen, based on Mendelian principles, for the probability that the offspring of two CF carriers will be affected with CF. Assumptions used in the model included:

(1) only pregnant women would be offered screening and early enough that prenatal diagnosis could be carried out;

(2) that women are only offered foetal testing if the partner is also identified as a carrier.

The authors stated that they did not consider the risk of a false-positive result in carrier testing and assumed foetal diagnosis to be 100% accurate. Neither did they consider misidentification or unavailability of the partners.

Measure of benefits used in the economic analysis
The authors used QALYs to measure benefits. Additionally, women were asked about their willingness to pay for carrier testing. Utility weights were derived from teenagers with CF (the parents of younger children were asked to give estimates on behalf of their children) using the time trade-off method. In addition all parents were asked about the effect on their life of having a child with CF. All families with CF children cared for in the CF clinic of the University of Rochester Medical Center were invited to participate. In another part of the study, women were asked what they would be willing to pay for the CF screening test.

Direct costs
The study adopted a societal perspective on costs. Therefore indirect care costs, i.e. the cost of the caregivers' time was included alongside the direct medical costs. Costs were discounted at 3%. Quantities and costs were not measured separately. Estimates of the costs were mostly derived from national sources, notably from the Cystic Fibrosis Foundation and the US Congress Office of Technology Assessment. The authors stated that costs arising from the research alone were not included.

Statistical analysis of costs
No statistical tests were performed on costs.
Indirect Costs
Indirect costs, in terms of time lost from work, were not included. However the cost of the caregivers’ time was included, based on an estimate from the US Congress of Technology Assessment.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were carried out on all costs excluding the indirect-care cost per hour, cost of couple counselling and cost of prenatal diagnosis. In terms of the inputs on the effectiveness side, all were subjected to a sensitivity analysis except the probability that the woman or partner is a carrier and the probability that prenatal diagnosis reveals an affected foetus.

Estimated benefits used in the economic analysis
Assuming that an aborted affected foetus is replaced, screening generates 354 more QALYs per population of 100,000 women offered screening. The side-effects of prenatal diagnosis (which can lead to spontaneous abortion) do not seem to have been considered. The total life-span was considered for the parent and child when calculating QALYs. Expected years of life were not discounted. In the willingness to pay exercise, 77% of women asked would not pay more than $25 and nearly 94% of respondents would pay less than $50. This figure was reported to be similar for women who declined screening.

Cost results
Assuming an affected foetus was not replaced, the total cost of offering screening (including the cost of termination) per 100,000 women offered screening was $11,107,955. Assuming replacement, the cost was $11,140,379. When one subtracts the cost of caring for a child with CF (discounted at 3%), the net screening costs were $2,470,252 without replacement and $2,934,561 with replacement. The costs of care, both direct and indirect, for someone with CF were considered over the entire life-span.

Synthesis of costs and benefits
When screening is offered to 100,000 pregnant women, the cost of screening per CF birth voluntarily averted is $1,322,376 without replacement and $1,396,038 with replacement. When direct and indirect care costs of a child/adult with CF are deducted (discounted at 3%), these figures are $294,078 and $367,740 respectively. Assuming replacement, the cost per QALY as a result of offering testing is $8,290 with a marginal cost per QALY of $8,290 (note: table 1 indicates $290 which the authors, in correspondence received subsequent to this abstract being written, have indicated was a transcription error). Variables reported to have a major effect on the basic conclusions reached by the base-case modelling were the direct cost of care, the cost of offering screening, the sensitivity of the test, the probabilities of choosing screening, of a carrier having her partner tested, of a carrier-couple having prenatal diagnosis and of the couple terminating an affected foetus. Some variables dominated, that is within the range considered in the sensitivity analysis the decision to screen saved money and generated QALYs. This happens if the cost of the laboratory test falls to below $100, if the life expectancy of a CF child increases from 30 to 54 years, or if the discount rate falls from 3% to 0.9%. Offering screening costs money and decreases QALYs if the probability that an affected foetus will be terminated falls to below 0.25.

Authors’ conclusions
The authors concluded that it is possible that the cost of the laboratory test will fall to below $100 which would make screening much more attractive. The authors noted that they did not take into account intangibles such as increased anxiety associated with testing, nor, on the positive side, the fact that the carrier is informed for future pregnancies and may alert relatives to their increased risk. The authors also note that the severity of the disease varies over the lifetime,
which should be adjusted for in the QALYs, and that women found it very difficult to estimate the amount they would be prepared to pay for such a screening test. In conclusion the authors write that the greatest barriers to universal screening were that fewer than one-third of the providers offered screening and that patients were reluctant to accept screening. However, the foremost purpose of parental screening is not to reduce the incidence of genetic disease but to fulfill a couple's reproductive goals.

CRD COMMENTARY - Selection of comparators
The reason for the comparator, i.e. no screening, was clear.

Validity of estimate of measure of benefit
The benefit results would have been more reliable had a comprehensive review of the literature been undertaken in providing data regarding the input variables which could not be obtained from the effectiveness study. More methodological information especially concerning the derivation of the valuation of health states and willingness to pay would have been desirable; and, considering the length of the paper, the could perhaps have been addressed by creating two separate papers. However the authors made their calculations transparent which is an enormous help to others who may wish to insert other probability values, according to their own settings. As the authors themselves admit, intangible costs were not included due to methodological costs in measuring them.

Validity of estimate of costs
The cost data generated by the trial were not considered to be representative, and national data were therefore used instead. The study did not include indirect costs of lost productivity (children and parents) which could have been added into the analysis. However, as with the probabilities on the effectiveness side, all the values used were clearly stated and costs were discounted.

Other issues
As the authors noted, there are still gaps in our knowledge regarding the effect that screening has, most notably with regard to how information on carrier status in the current pregnancy affects future pregnancies.

This was a good and detailed study which admirably attempted to combine many methods of presenting the economic impact of screening into one paper. The authors considered not only the costs and cost savings of such a screening programme, but also combined costs and benefits in terms of a cost-effectiveness study, a cost-utility study and additionally provided data on patients' willingness to pay.

Implications of the study
The authors suggest that their finding of 57% acceptance rate is more reliable than higher rates found in some other studies as it is based on clinical practice. The marginal cost per QALY finding of $8,290 for CF screening compares favourably with that for other widely adopted preventive measures in the USA.

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