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
Cystic fibrosis (CF) carrier screening in the reproductive setting in single-gestation women with identifiable reproductive partners. The 15 strategies considered were categorised according to the sequence (parallel parental sequence or sequential parental sequence), DNA test battery (standard, expanded, or mixed), and additional tests if one and only one parent test proved positive (none, or microvillar intestinal enzyme analysis (MIE)).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
Single-gestation women with no independent reason for undergoing amniocentesis other than the possible results of CF carrier screening, and with identifiable reproductive partners.

Setting
Secondary care. The economic study was carried out in the USA.

Dates to which data relate
Clinical probabilities were obtained from literature published between 1976 and 1993. The date to which the resource use data referred was not specified. Cost data were mainly obtained from reports published in 1992. The price data were inflated to 1995 dollars.

Source of effectiveness data
Effectiveness data were derived from a review of the literature and expert opinion.

Modelling
A decision-analytic model was constructed to estimate the costs and effects associated with each strategy.

Outcomes assessed in the review
The review assessed CF mutation carrier frequency, the detection rate for a six-mutation screen, the detection rate for an 'expanded' mutation screen, sensitivity and specificity of MIE, chance of spontaneous abortion under 16 weeks, and chance of spontaneous abortion attributable to amniocentesis.
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
A total of 12 studies were included.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The results of the review were as follows:

CF mutation carrier frequency was 0.04;
detection rate for a six-mutation screen, 0.85;
detection rate for an 'expanded' mutation screen, 0.90 (range: 0.86-1.0);
sensitivity of MIE, 0.96 and specificity, 0.98;
chance of spontaneous abortion after 16 weeks, 0.025;
chance of spontaneous abortion attributable to amniocentesis, 0.005.

Methods used to derive estimates of effectiveness
Estimates of effectiveness were also derived from consultation with experts in obstetrics, genetics, and prenatal diagnosis.

Estimates of effectiveness and key assumptions
The sensitivity of DNA direct mutation screen was 0.995 and its specificity was 0.999 (range: 0.99-0.9999). The chance of nonpaternity was assumed to be 0.0 (range: 0.0-0.5). It was assumed that parents with a fetus with two CF mutations would terminate the pregnancy.
Measure of benefits used in the economic analysis
The benefit measure was CF births avoided relative to the strategy of no screening in a cohort of 500,000 pregnancies. The number of abortions for unaffected pregnancies due to false-positive results and miscarriages because of complications related to amniocentesis for prenatal diagnosis were also taken into consideration.

Direct costs
Costs were discounted. Resource use data were not reported separately from the costs except for time spent for genetic consulting. Cost items were reported separately. The direct cost analysis covered the costs of six-mutation DNA screen (including the costs of technical and professional personnel, reagents, equipment, royalties, and laboratory), DNA screen (expanded), genetic counsellor's time per hour with benefits, amniocentesis (excludes karyotyping), MIE, miscarriage, mid-trimester abortion, delivery, travel (per office visit), and lifetime medical and nonmedical direct costs of CF. The perspective adopted in the cost analysis was that of the society, the patient, and the payer. The sources of cost data were different health institutions. The estimation of costs from the societal perspective was based on true costs while, for the patient perspective, 20% of medical charges and 100% of non-medical costs were included. Payer costs were assumed to be 80% of charges. The date to which the price data referred was 1995.

Indirect Costs
Costs were discounted. Quantities were not reported separately from the costs. The calculation of indirect costs consisted of the cost of patient time lost from work. The source of cost data was census data. The perspective adopted in the cost analysis was that of society and the patient. 1995 price data were used.

Currency
US dollars ($).

Sensitivity analysis
A series of one-way sensitivity analyses was performed on the costs of standard and expanded test batteries, cost perspective, specificity of the DNA test, chance of nonpaternity, proportion of couples choosing to terminate affected pregnancies, and number of pregnancies. A two-way sensitivity analysis was conducted on the cost and detection rate of the expanded test battery.

Estimated benefits used in the economic analysis
The number of CF births avoided for a cohort of 500,000 pregnancies, relative to a strategy of no screening, ranged from 138 for the strategy consisting of parallel parental sequence with standard battery and no additional test if one and only one parent tests positive, to 189 for the strategy involving parallel parental sequence with expanded battery and an additional test with MIE.

Cost results
The total cost for a cohort of 500,000 pregnancies ranged from $1,530,313,000 for a strategy of no screening to $1,694,522,000 for a strategy involving parallel parental sequence with standard battery and additional test with MIE. The discount rate was 4%.

Synthesis of costs and benefits
The cost per CF birth avoided relative to no screening was used as the measure of cost-effectiveness. The cost-effectiveness ratio ranged from $367,000 per CF birth avoided for the strategy involving sequential parental screening with mixed approach (the first partner was screened with a standard battery, and in the case of positive result, the second partner was screened with an expanded test) and no additional test to $930,000 per CF birth avoided for the strategy involving parallel parental screening with expanded battery and no additional test. The relative rankings of the strategies were generally robust to the changes in the parameters of the model.
Authors' conclusions
The cost-effectiveness of CF carrier screening depends greatly on couples' reproductive plans. CF carrier screening is most cost-effective when it is performed sequentially, when the information is used for more than one pregnancy, and when the intention of the couple is to identify and terminate affected pregnancies.

CRD COMMENTARY - Selection of comparators
The reason for the choice of no screening as the comparator is clear.

Validity of estimate of measure of benefit
The internal validity of the estimates of benefit cannot be objectively assessed due to lack of information regarding the comprehensiveness of the literature review and the quality assessment of the primary studies included in the review.

Validity of estimate of costs
Resource quantities were not reported separately from the costs. Adequate details of methods of cost estimation were given. Costs were reported from three different perspectives: societal (independent of charges), and those of the patient and the payer (using estimates of charges). Cost results may not be generalisable outside the USA.

Other issues
Appropriate comparisons were made with other studies. However, it was reported that the cost-effectiveness results may not be generalisable to a population of African or Asian descent. The authors' conclusion is justified given the uncertainties surrounding the parameters of the model (these were addressed by performing sensitivity analysis). A composite measure of benefit (including abortions for unaffected pregnancies due to false-positive results, and miscarriages because of complications related to amniocentesis for prenatal diagnosis) may have been more appropriate especially with regard to the results of sensitivity analysis on the specificity of the DNA test.

Implications of the study
According to the authors, the study 'conclusions are important for policy considerations regarding population-based screening for CF, and may also have important implications for screening for less common diseases'.

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