The cost-effectiveness of neonatal screening for cystic fibrosis: an analysis of alternative scenarios using a decision model


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
Neonatal screening for cystic fibrosis (CF), added to the existing routine neonatal screening programme for congenital hypothyroidism and phenylketonuria, was examined. The screening programme used two-stage immunoreactive trypsin (IRT) combined with genetic testing.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of newborns.

Setting
The setting was a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published from 1989 to 1997. Some resource use data came from a study published in 1999. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A Markov model was used to assess the lifetime costs and quality of life of screening versus no screening in a hypothetical cohort of newborns. The structure of the model was reported graphically. The cycle length was one year and the time horizon lifetime. All babies were born into the pre-symptomatic health state and then, each year, there was a given probability of moving into the symptomatic disease state, then into the severe irreversible lung disease-state, and finally death. The model excluded those cases diagnosed at or shortly after birth, as these infants would have received the same prognosis and treatment under both strategies. Under the "no screening" strategy, infants would be diagnosed with CF symptomatically (late diagnosis), while under the screening strategy, most CF cases would be detected by screening (early diagnosis). The remainder (false negatives) would experience the disease under late diagnosis assumptions.
**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the CF incidence,
- the rate of CF diagnosed at birth (meconium ileous and family history),
- the sensitivity and specificity of IRT,
- the sensitivity and specificity of DNA testing,
- the percentage of mutations detected with DNA testing,
- the increased annual transition probability of remaining without diagnosis in early-diagnosed cases,
- the utility values associated with specific health states, and
- the hazard rates.

**Study designs and other criteria for inclusion in the review**
It was unclear whether a systematic review of the literature was undertaken to identify the primary estimates. There was limited information on the design and other characteristics of the primary studies.

**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**
Five studies provided the clinical data.

**Methods of combining primary studies**
Each study appears to have provided a series of clinical estimates.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The CF incidence was 0.0004 (range: 0.00067 to 0.00029).

The rate of CF diagnosed at birth was 0.15 (range: 0.10 to 0.40).

The sensitivity of IRT was 0.9 (alternative value 0.99) and the specificity was 0.995 (alternative value 0.999).
The sensitivity of DNA testing was 0.9856 (alternative value 0.9975) and the specificity was 1.0.

The percentage of mutations detected with DNA testing was 0.88 (range: 0.85 to 0.95).

The increased annual transition probability of remaining without diagnosis in early-diagnosed cases was 10% (range: 10 to 40).

The utility values were as follows:

- asymptomatic state (late), 0.95 (alternative value 0.90);
- asymptomatic state (early), 0.95 (alternative value 0.90);
- symptomatic state (force expiratory volume in one second, FEV1=60%, range: 40 to 80), 0.75 (range: 0.65 to 0.90);
- severe irreversible symptoms (FEV1 30%, range: 20 to 40%), 0.68 (range: 0.58 to 0.78).

**Methods used to derive estimates of effectiveness**

The authors made some assumptions to derive the estimates of effectiveness.

**Estimates of effectiveness and key assumptions**

The annual transition probability of remaining pre-symptomatic was 69% for those diagnosed through screening and 59% for those diagnosed symptomatically. Thus, screening led to a delay of the emergence of symptoms of 6 months.

The annual transition probabilities were (for the balanced scenario, "late diagnosis"):

- from asymptomatic to symptomatic, 0.491 per year (with the remainder all staying asymptomatic);
- from symptomatic to severe irreversible lung disease, 0.0064 (increasing exponentially according the accumulated years with symptoms); and
- from severe irreversible lung disease to death, 0.09 (increasing according to the number of years spent in the severe irreversible disease stage).

All people with CF ultimately died of CF-related respiratory symptoms, and all passed through both the symptomatic and severe irreversible lung disease stages before they died.

The sensitivity and specificity of confirmatory sweat tests were both 100%.

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

The main summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated by combining the utility values and life expectancy in the different states of the decision model. The utility values were based on the Quality of Well-Being Scale and were obtained from published studies. Mortality was based on UK age-specific survival data. An annual discount rate of 2% was applied. Diagnosed cases were also combined with the costs.

**Direct costs**

The perspective of a UK Health Authority was chosen for the analysis. The study included screening costs, pre-diagnosis costs and disease-related costs. Screening costs included counselling time required by midwives to obtain consent for testing, IRT test, DNA analysis and sweat chloride test. Other costs related to obtaining the blood spot, as well as feedback of results by health visitors, were not considered as they were already included in the existing neonatal screening programmes for phenylketonuria and congenital hypothyroidism. Time for genetic counselling for carriers...
identified by the screening programme was excluded. Pre-diagnosis costs covered general practitioner visits, outpatient attendances and inpatient admissions. A breakdown of the disease-related costs was not provided. The unit costs were presented separately from the quantities of resources used for some items. The estimation of resource use was based on samples of children with CF at different UK hospitals. Some assumptions were also made. The costs came from typical National Health Service (NHS) sources, such as NHS Trusts and the Government's Expenditures Plans. Discounting was relevant, as the costs were incurred during a long timeframe, and an annual rate of 6% was applied. The price year was 1998.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included.

**Currency**
UK pounds sterling (). 

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were carried out on several model inputs to assess the robustness of the cost-utility ratios to variations in the base-case assumptions. Alternative ranges of values were derived from the literature or were based on authors' opinions.

**Estimated benefits used in the economic analysis**
CF neonatal screening led to an average of 0.36 additional QALYs in comparison with conventional neonatal screening.

**Cost results**
The additional costs associated with neonatal screening for CF over conventional screening were 2,895.

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated to combine the costs and QALYs of the alternative screening strategies.

The incremental cost per QALY gained with neonatal screening for CF over conventional screening was 6,864.

The cost per diagnosed infant was 5,387 (or 1.83 per infant screened), and the cost per case diagnosed clinically was 936.

The sensitivity analysis produced some interesting results. Specifically, a delay in the emergence of symptoms, or an increase in survival of 11 months or more (6 months in the base-case), would produce lower costs and better outcomes than no CF neonatal screening (i.e. a dominant strategy). Further, if pre-diagnosis care of babies diagnosed symptomatically did not involve admission to a hospital, the incremental cost-utility ratio fell to 4,640 (-32%). If annual treatment costs were increased by 20% the cost per QALY gained only increased by 11%. Finally, the incremental cost-utility ratio was 7,474 in the conservative survival scenario (lower life expectancy than in the base-case) and 6,532 in the optimistic survival scenario (higher life expectancy than in the base-case). Changes in utility adjustments did not affect the conclusions of the analysis.

**Authors' conclusions**
Neonatal screening for cystic fibrosis (CF) was an expensive strategy, but was cost-effective from the perspective of the
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear since the new screening strategy was compared with the current neonatal screening option. The current option included screening for congenital hypothyroidism and phenylketonuria. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
Although the effectiveness evidence came from published sources, it was unclear whether the studies were identified from a review of the literature and no information on the conduct and method of a review was provided. Details and other characteristics of the primary studies were also not described, which makes it difficult to assess the validity of the primary data. Some assumptions were also made and their impact on the results of the analysis was tested in the sensitivity analysis.

Validity of estimate of measure of benefit
QALYs were the most appropriate benefit measure because they capture the impact of the intervention on both quality of life and survival, which are relevant dimensions of health for the disease examined in the study. QALYs also have the advantage of being comparable with the benefits of other health care interventions. Discounting was applied. Few details on the sources of the utility adjustments were reported.

Validity of estimate of costs
The choice of categories included in the cost analysis was consistent with the perspective of the study. A detailed breakdown of items was reported for two of the three categories of costs considered in the analysis. The disease costs were presented as macro-categories. The unit costs were presented for many items, but there was little information on resource use and this limits the possibility of replicating the analysis in other settings. The price year was reported, which means that reflation exercises in other time periods should be possible. Neither statistical nor sensitivity analyses of the costs were performed. The cost estimates were specific to the study setting. The authors noted that several costs were difficult to assess and were therefore omitted from the analysis.

Other issues
The authors stated that their findings were quite comparable with those from other recent studies. The issue of the generalisability of the study results to other settings was addressed, although the authors acknowledged that their study focused on the UK setting. The authors noted some limitations of their analysis. For example, the simplification of the natural history of CF and the use of several assumptions. It was also pointed out that CF might manifest in different forms in children, thus caution is required when interpreting the results of the current study. Moreover, the authors stated that an external validation of the long-term economic and clinical consequences of the model was difficult because of the lack of long-term survival data for patients with CF.

Implications of the study
The study results support the implementation of routine neonatal screening for CF. However, the simultaneous implementation of both antenatal and neonatal screening would reduce the potential economic benefits associated with neonatal screening, since a reduction in the birth incidence of CF would reduce the cost-effectiveness of neonatal screening. The authors suggested that future studies should use probabilistic modelling techniques to deal with the issue of uncertainty in some model inputs.

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