The cost-effectiveness of newborn screening for Cystic Fibrosis.

James Jarrett (1), Prof. Miranda Mugford (1), Dr. Erika Sims (1,2), Dr. Richard Iles (1,3)

(1)School of Medicine, Health Policy and Practice
University of East Anglia,
Norwich, NR4 7TJ

(2) Optimum Patient Care Ltd
Unit 4
The Old Winery Business Park
Chapel Street
Cawston
NR10 4FE

(3)Paediatrics Department
Addenbrooke's Hospital
Cambridge CB1 0QQ

Background

Cystic fibrosis (CF) is an inherited disorder that is associated with decreased life expectancy and increased morbidity. The disease affects about 1 in every 2381 live births in the UK (Dodge 2007). Since June 2007, newborn screening (NBS) has been rolled out across the UK as part of the national screening programme.

NBS aims to improve prognosis by early diagnosis and intervention. Several published studies have found at least some clinical benefit for screening for CF in terms of better height/weight z-scores and better pancreatic and nutrition status (Sims et al). While these positive changes in outcome may be important, they are far from certain and the variability of the disease makes it difficult to discern concrete health benefits of screening.

As health resources are limited, it is important to justify interventions not only on clinical benefit, but also on their value for money. In a systematic review of the literature, the authors found five economic evaluations of newborn screening for CF. Four were carried out in the USA and none used any objective measures of health effect. The US studies were also over ten years old, and two of the papers excluded a no-screening alternative, which seems inappropriate due to the uncertainty surrounding the benefits of CF screening. Only one study was found in a UK setting. The authors modelled various scenarios using a markov model to account for disease progression over time. Utility values were derived from the literature. Cost data were gathered from the literature and national sources. Disease-state specific annual costs were taken from a large UK CF unit in 1996. The authors found that NBS for CF produces an incremental cost-effectiveness of £6,864 per QALY gained (price year 1998) (Simpson et al 2005).

While useful, Simpson and colleagues' paper uses limited and relatively old patient-level data to determine disease state costs. As CF care has changed, and the screening programme has been rolled out nationwide, it is important to re-evaluate the intervention as new evidence emerges. This paper uses a probabilistic approach to modelling the cost-effectiveness of newborn screening for CF.

Methods

As CF is a complex disease with high variance in severity, a probabilistic decision model with a Markov process was created in Microsoft Excel. The screening model is based on current UK practice of a two-stage immunoreactive trypsin test (IRT) combined with a genetic test (Figure 1). The model parameters were populated with paediatric CF patient data (N= 361) from the six counties in the eastern region (Bedfordshire, Cambridgeshire, Essex, Hertfordshire, Norfolk and Suffolk), as well as data collected from a systematic review of the literature (Jarrett et al, publication in progress). Table 1 sets out the baseline parameters of the model and the source of the information.

Table 1: Baseline Parameters

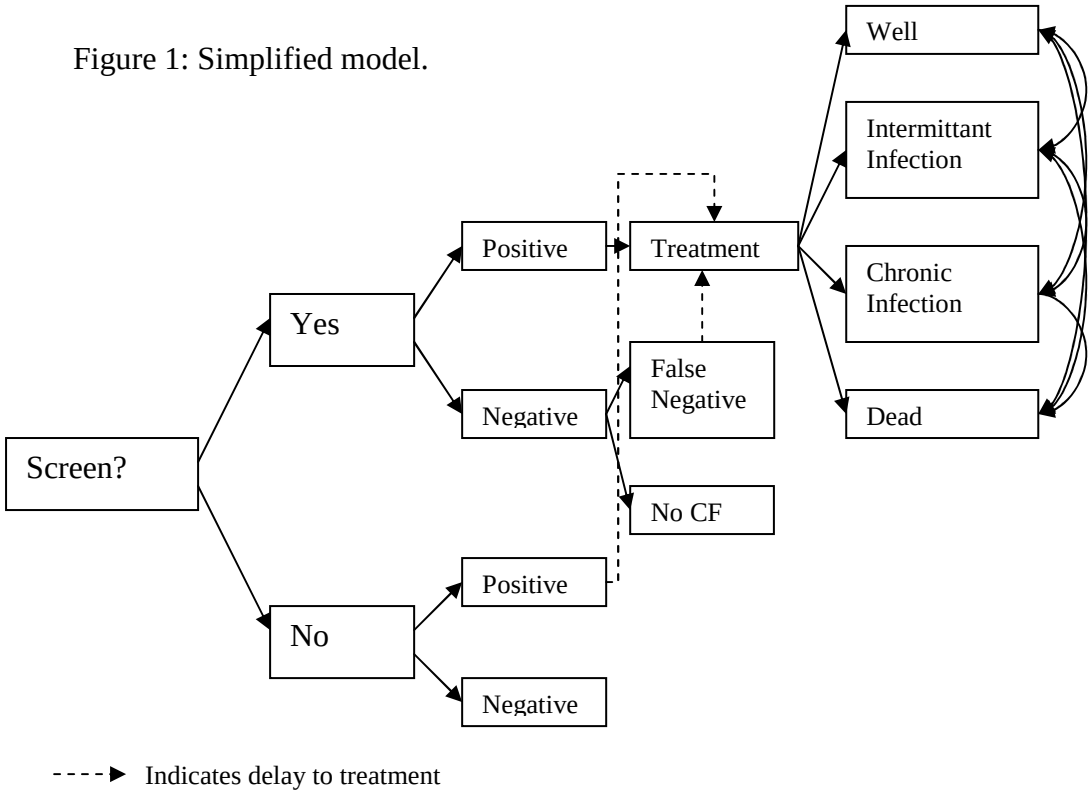
Parameter	Estimate	Source
Incidence of CF	1:2381 live births	Dodge et al (2007)
Incidence of MI/Family history	15%	ERCFD
IRT Sensitivity/Specificity	.99	
DNA Sensitivity/Specificity	1	
Cost Parameter		
Clinical diagnosis		
GP Visit	£18	ERCFD; PSSRU (2006)
Outpatient visit	£152	ERCFD; NHS Tariff (2006)
Inpatient stay	£835	ERCFD; NHS Tariff (2006)
Screening		
Staff time	£0.50	PSSRU (2006)
IRT tests	£0.90	Addenbrooke's Hospital
DNA tests	£0.40	Addenbrooke's Hospital
Sweat test	£0.01	Addenbrooke's Hospital
Treatment		
Cost of well patient	£5,294	Jarrett et al (Forthcoming)
Cost of intermittently infected patient	£7,268	Jarrett et al (Forthcoming)
Cost of chronically infected patient	£18,756	Jarrett et al (Forthcoming)
Cost of Screening	£2	Jarrett et al (Forthcoming)
Cost of Clinical Diagnosis	£1,005	Jarrett et al (Forthcoming)
Utility Parameters		
Well	0.95	Simpson et al (2005)
Intermittent infection	0.75	Simpson et al (2005)
Chronic infection	0.68	Simpson et al (2005)

Disease progression was modelled using a Markov process. Patients were born into a 'well' state, and for each year they are in the model, have a probability of moving into one of two ill states (intermittent infection or chronic infection) or the dead state. Intermittent infection is defined as having 'mild' lung disease typified by having to have IV-antibiotics 1-3 times per year. Chronic infection ('severe' lung disease) is defined as having 4 or more hospitalisations for IV-antibiotics. The probability of moving to the dead state takes into account age and disease related mortality.

The model excludes those babies who were diagnosed at birth, either through family history or they presented with meconium ileus, as these babies would receive the same treatment, regardless of which strategy was used. In the no screening strategy, CF patients would have been identified symptomatically, therefore leading to a late

diagnosis (3 months or more). The screening strategy allows patients to be diagnosed pre-symptomatically and allows treatment to begin immediately. Any false negatives would be detected symptomatically.

Figure 1: Simplified model.



The benefits of the screening strategy were modelled as the difference in timing of first developing symptoms or moving between diseased states between the groups. The probability of remaining in the 'well' stage for those in the screened group was 75%, while those in the no screening strategy had a probability of 60%. This means there was approximately 9 months delay in the emergence of symptoms in the screened strategy.

Transition rates between Markov states were calculated using age-specific mortality rates and hazard rates calculated from Dodge et al (2007). The baseline transition rates are listed in Table 2. The construction of the transition rates meant that most patients followed the 'typical' CF disease path of well-intermittant infection-chronic infection-death. Patients in the intermittent infection and chronic infection status could recover and move 'backwards' into a better state. All patients in the model will eventually end up in the dead state.

Table 2: Baseline Transition Rates

Transition	Baseline Rate
Well – Intermittent	0.04
Well – Chronic	0.01
Well – Death	0.02
Inter – Success	0.01
Intermittent – Chronic	0.04
Intermittent – Death	0.02
Chronic – Well	0.00
Chronic – Intermittent	0.01
Chronic – Death	0.05

Data on effectiveness (lung function and hospitalisations for IV-antibiotics) were drawn from the Eastern Region CF Database. We

did not administer the Cystic Fibrosis Questionnaire (CFQ) for measurement of quality of life analysis due to time and budget constraints. However, previous studies have shown that lung function can be an indicator of quality of life using the quality of well-being scale (Orenstein et al 1989,1990; Simpson et al 2005). However, it is now commonly acknowledged that lung function is not necessarily the best indicator of disease progression (Sims et al 2007). QALYs were estimated by assigning each markov state a utility and multiplying it by the survival time in that state. QALYs were discounted at 3% in the basecase analysis.

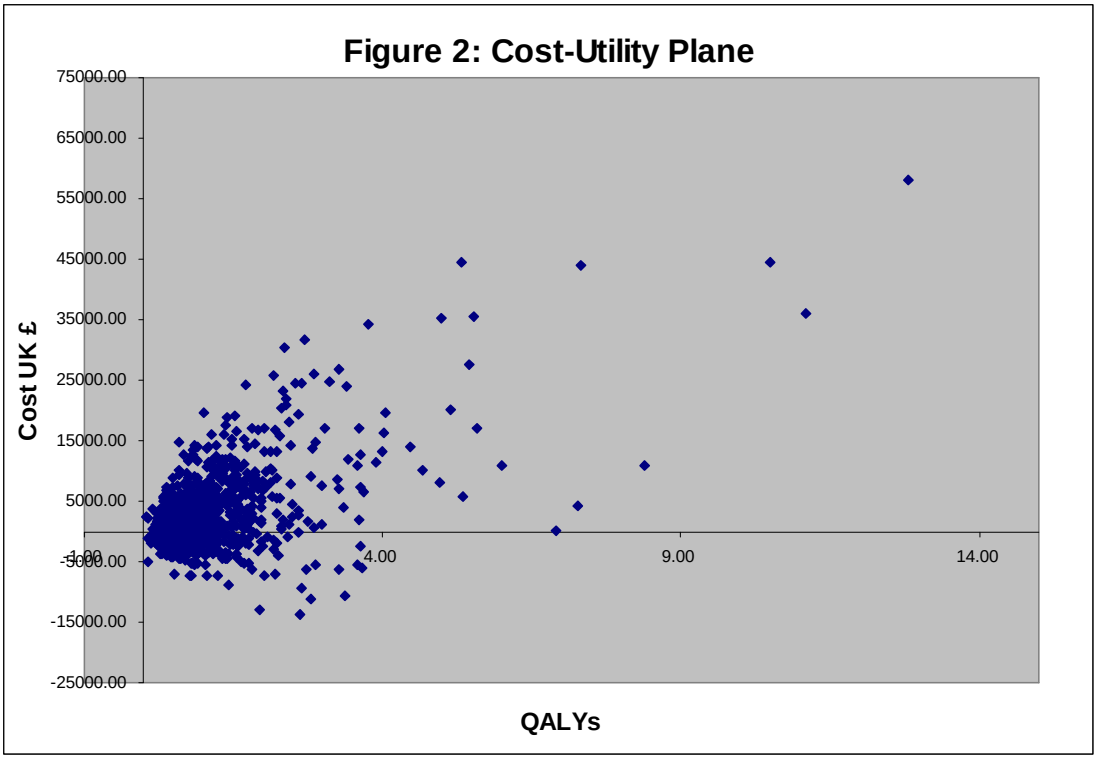
Resource use data was gathered from the Eastern Region CF Database. We assumed that there was 100% uptake on screening. The cost of the two IRT tests, the DNA test and a sweat chloride test as well as time for genetic counselling were included in the model. Other costs, such as obtaining blood spots were assumed to be sunk into the national screening programme. Disease state costs were derived from applying unit cost data gathered from national sources (PSSRU 2006; National Tariffs 2007, British National Formulary for children 2006) to the resource use information gathered from the Eastern Region CF Database. Only CF-related costs were considered. All cost data was adjusted for inflation at 5% with the reference year of 2006. Future costs were discounted at 6%.

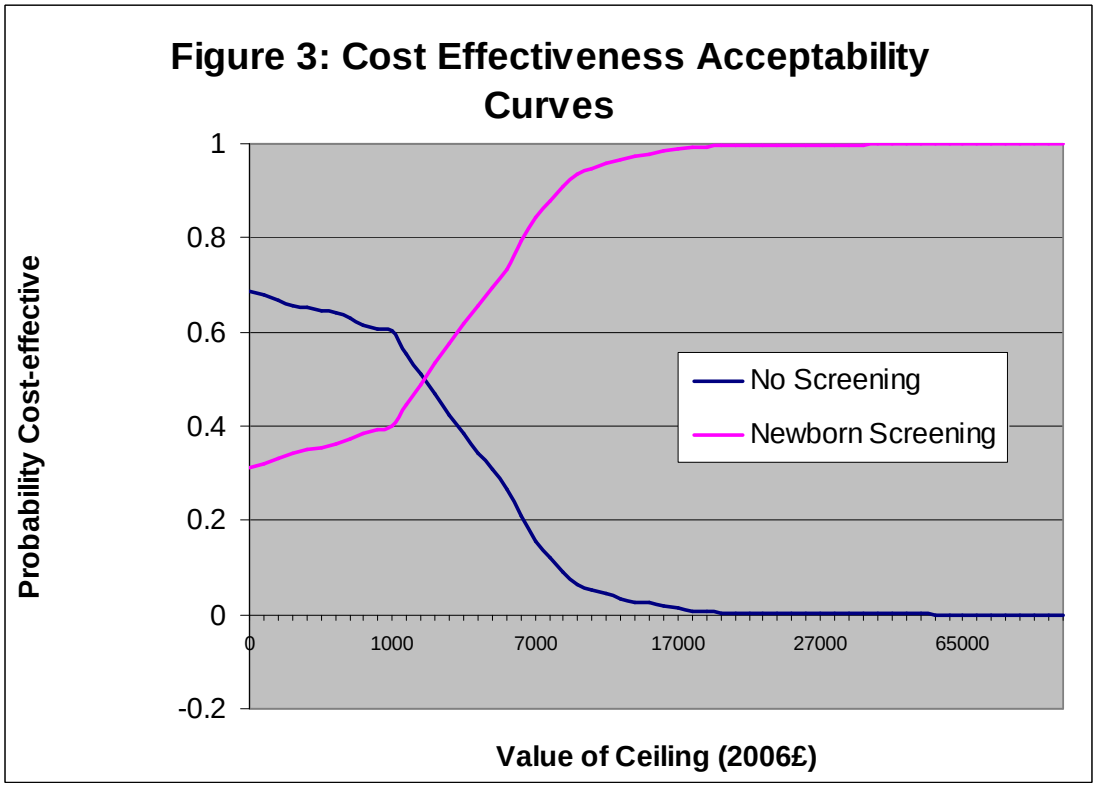
Sensitivity analysis and a value of information analysis will be carried out.

Results

The base estimates yielded a cost per diagnosis of approximately £4309 (£1.81 per screened infant) compared to a cost of £1005 for clinically diagnosed patients. If staff time (to explain test and diagnosis) is assumed to be sunk into the national screening programme, then the cost per diagnosis is £3119 (£1.31 per screened infant). These results differ from the findings of Simpson et al as the price of the tests has decreased slightly, the cost of care and the incidence of CF has increased over time.

On average, newborn screening produced an additional 1.30 QALYs per life with CF at an additional cost of £4024, or £3102 per QALY gained. Figure 2 shows the incremental costs and QALYs from 1000 Monte Carlo simulations. The simulations reveal a fair amount of variation but for a significant amount of simulations, newborn screening was both more effective and less costly than clinically diagnosis. Figure 3 shows the cost-effectiveness acceptability curves. These curves show that for a ceiling threshold of around £2000, newborn screening is a more likely to be a cost-effective strategy than clinical diagnosis.





Discussion

Newborn screening appears to be a relatively more expensive way of diagnosing CF when compared with clinical diagnosis. However, as the cost of treatment increases and the costs of the screening strategy fall, the relative difference is likely to decrease.

To create the model, certain assumptions were made that may limit the study. First, we tried to create a model which would allow for the heterogeneity of CF disease progression by allowing patients to move in and out of various disease states at different times. However, the model was limited to 3 states, which may not adequately reflect the reality of the disease.
We assumed that the benefit of screening was earlier intervention, therefore delaying the onset of symptoms. There is some evidence to support this with regard to nutritional status and height and weight gains (Sims et al 2005; 2007). There is little evidence to support screening results in a better lung function or a delay in bacterial infection. However, data is still being collected for the patients in the region and both of these outcome measures will be looked at when all data is collected.
The use of quality of life estimates from the literature is less than ideal, especially as the chosen measurements are taken from a study on lung function, which we assumed was equivalent to the disease state measurements we used (infection status). Extensive sensitivity analysis is to be done in this area, as the model is likely to be sensitive to changes in quality of life. The CFQ-R measurement tool has been used and validated in the literature, but we did not have adequate time or resources to carry out the questionnaire.

The study is most relevant to a UK context, and has yielded similar results to other studies carried out in the UK (Simpson 2005). Now that national screening has been rolled out nationally, most centres are using the screening protocols tested here. Internationally, various methods are used, but almost all will start with IRT testing and as this accounts for a large part of the cost of screening, alternative methods are unlikely to have a different result.

Further points of discussion:

Inclusion of proportion of costs for the National Screening Programme?

Use of disease-specific QoL measures vs. Quality of Well Being scale?

Model structure? (delay, symptoms, timing)

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