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Cost effectiveness of antenatal screening for cystic fibrosis

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Abstract

***Objective*—To estimate the cost effectiveness of different antenatal screening programmes for cystic fibrosis.**

***Setting*—Antenatal clinics and general practices in the United Kingdom.**

***Design*—Four components of the screening process were identified: information giving, DNA testing, genetic counselling, and prenatal diagnosis. The component costs were derived from the literature and from a pilot screening study in Yorkshire. The cost of a given screening programme was then obtained by summing the components according to the specific screening strategy adopted (sequential and couple), the proportion of carriers detected by the DNA test, and the uptake of screening. Baseline assumptions were made about the proportion with missing information on carrier status from previous pregnancies (20%), the proportion changing partners between pregnancies (20%), and the uptake of prenatal diagnosis (100%). Sensitivity analysis was performed by varying these assumptions.**

***Main outcome measure*—Cost per affected pregnancy detected.**

***Results*—Under the baseline assumptions sequential screening costs between £40 000 and £90 000 per affected pregnancy detected, depending on the carrier detection rate and uptake. Couple screening was more expensive, ranging from £46 000 to £104 000. From the sensitivity analysis a 10% change in the assumed proportion with missing information from a previous pregnancy alters the cost by £4000; a 10% change in the proportion with new partners has a similar effect but only for couple screening; and cost will change directly in proportion to the uptake of prenatal diagnosis.**

***Conclusions*—While economic analysis cannot determine screening policy, the paper provides the NHS with the information on cost effectiveness needed to inform decisions on the introduction of a screening service for cystic fibrosis.**

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Introduction

Cystic fibrosis is the most common recessive condition in the United Kingdom, with a birth prevalence of 1 in 2500,[1] implying a carrier frequency of 1 in 25. Since the discovery of the principal genetic mutations involved,[2-4] antenatal screening has become feasible, and pilot studies show that it is generally acceptable in the United Kingdom.[5-9] Each health authority now needs to decide whether to introduce a service. One consideration will be cost effectiveness, and in this paper we estimate this for different screening strategies and under a range of assumptions.

Methods

The aim was to estimate the cost per affected pregnancy detected. This is dependent on the screening strategy adopted, the proportion of carriers detected by the DNA test, and the uptake rate.

SCREENING STRATEGIES

The aim of screening is to identify women and their partners who are both carriers. There is then a 1 in 4 chance that the infant has cystic fibrosis, and the couple are referred for genetic counselling about having invasive prenatal diagnosis. Those offered screening require basic information about cystic fibrosis, carrier testing, prenatal diagnosis, and consequent options available to them. Carrier couples can be identified by using two different strategies.

Sequential carrier testing is offered to mothers, and a sample is requested from the partner only if the mother is found to be a carrier. Basic information is given initially to all women and subsequently to the partner of each carrier.

Couple carrier testing is offered to couples, and samples are obtained from both parents at the outset. The DNA testing, however, is done exactly as in sequential screening so that only a small percentage of samples from fathers are actually tested. The result is reported as "positive" for carrier couples, otherwise as "negative."[10] This strategy removes the period of anxiety while the partner's result is awaited.

The results of a test in the first pregnancy may suffice for subsequent pregnancies unless the couple cannot remember their carrier status and it is not in the antenatal notes or there is a new partner. In our economic analysis we assume that all women have two pregnancies, the projected average family size in the United Kingdom.[11] In the absence of published data we made the baseline assumptions that carrier couples remember their status but otherwise 20% have missing information and that of the remainder, 20% change

partners. These proportions were each then varied from 10-30% in a sensitivity analysis.

CARRIER DETECTION RATE

The proportion of carriers that can be detected depends on the specific mutations sought and their prevalence among carriers in the population. In the United Kingdom about 70-85% of carriers have the ΔF508 mutation, and the next most common three account for a further 5-10%.[12-16] In this analysis we test for ΔF508 alone in populations where the prevalence of the mutation is 70-85% and use a multimutation test where it is 80-95%. The corresponding proportions of affected pregnancies detected are 49-72% and 64-90%, respectively.

UPTAKE

In the British pilot studies reported so far, the uptake was 78% of the 11 596 women offered screening in Edinburgh,[5,8] 85% of 623 in Manchester (H Harris, personal communication),[6] 67% of 482 in Oxford,[7] and 90% of 2002 in Aberdeen.[9] Uptake was somewhat lower at 62% in our own pilot study of 6071 women in Yorkshire. In our analysis we consider rates of uptake ranging from 55% to 95%.

In the published studies few partners of carrier women refused testing, and we have assumed a 100% uptake. There are too few carrier couples in the published studies to judge how many are likely to refuse prenatal diagnosis. Therefore we made the baseline assumption that uptake is 100% and then examined the effect of reducing this by 10-20% in a sensitivity analysis.

ECONOMIC ANALYSIS

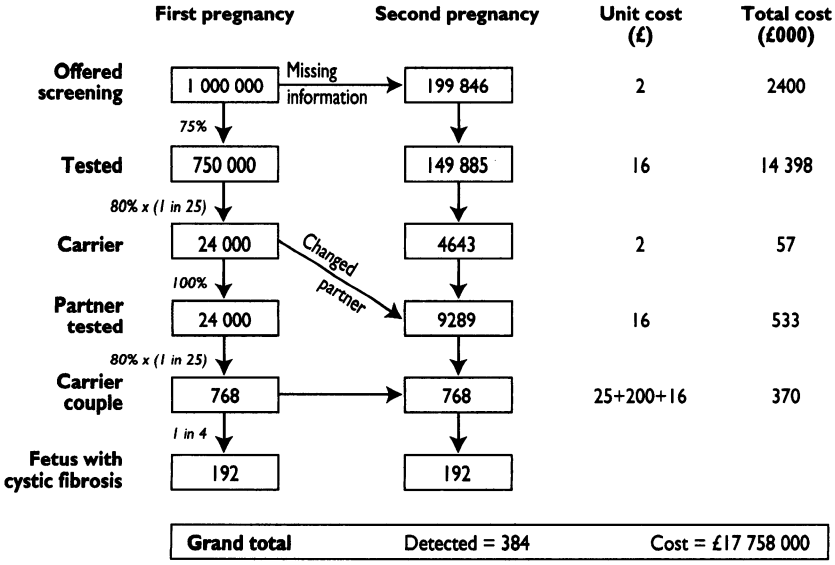
There are four components of the screening process which need to be costed separately—namely, information giving, DNA testing, genetic counselling, and prenatal diagnosis. We did not consider costs consequent on the diagnosis (for example, termination of pregnancy). A reasonable estimate was made for each component cost (at 1995 prices unless otherwise stated).

Information giving—In the Yorkshire pilot study, as in Edinburgh,[5,8] a printed leaflet backed up by a face to face interview with a midwife or general practitioner was found to be adequate. The number of women that can be seen by a given midwife will depend on the length of the interview, interval between interviews, paperwork, and other related duties. We timed the midwife interview for 31 women, and on average it lasted 11 minutes, which is similar to the 10 minutes found for the interviews with general practitioners in Manchester.[6] If we consider all factors together, a half time midwife would suffice for the additional workload in an obstetric unit with 5000 patients annually. This would cost £10 000, or £2 per woman. The cost of printing the leaflet is negligible.

DNA testing—For ΔF508 only a relatively cheap, in house polymerase chain reaction method can be used. This was done in the Yorkshire pilot study, which had average laboratory costs during 1992-4 of £6.70 for consumables, £6.20 for staff, and £3.20 for overheads, bringing the total to £16.10 a specimen, including the cost of technical repeats and controls. As this was a research study licence fees were not paid to patent holders. The additional cost of licences for routine NHS use, however, are likely to be offset by reduced unit cost due to a higher laboratory throughput. Testing in house for multiple mutations would be more costly. At present only one set of commercial reagents is available in the United Kingdom and is fully licensed (Johnson and Johnson Clinical Diagnostics, Amersham). In Aberdeen DNA testing with this during 1993 was costed at £23.17 a specimen[17]; this underestimated distributors' minimum reagent costs, which would increase the overall cost to £33.21. For our principal analyses we have taken £16 as the cost of DNA testing for ΔF508 alone and £33 when multiple mutations are sought. In the long term it is likely that the cost may fall, and a sensitivity analysis is carried out for costs in the range £5-£25.

Genetic counselling—We do not know of any published information on the cost of counselling couples who are carriers of cystic fibrosis. The genetics services of a region with 100 000 births annually would typically need to cope with about 80 carrier couples a year. The additional counselling both before the prenatal diagnosis and when necessary after the result was known would require a genetic nurse specialist for one session. This would cost about £2000, or £25 per couple.

Prenatal diagnosis—The invasive procedure was taken to cost £200, a similar figure to that adopted in recent analyses of screening for Down's syndrome.[18-20] The laboratory costs are the same as for carrier testing; the costs of testing the sample for other fetal disorders such as Down's syndrome are excluded.



Cost of a sequential antenatal screening programme for cystic fibrosis

Results

The figure shows the calculation of the estimated cost of a sequential screening programme directed at a population of 1 000 000 pregnant women. In this example a ΔF508 only test is used; the carrier detection rate is 80% and uptake is 75%. The total cost divided by the number of affected pregnancies detected yields a cost per affected pregnancy detected of £46 000.

Table 1 shows the cost for a sequential strategy with a range of different carrier detection rates and uptakes. Uptake does not have a major impact as it influences only the relatively low cost of information giving (see figure). The carrier detection rate has a much greater effect as the number of affected pregnancies diagnosed is directly proportional to the square of this rate. The rate will be higher if a multimutation test is used, but the cost per affected pregnancy detected will increase substantially. Unless the rate is more than 10% higher the marginal cost will exceed £100 000.

Table 2 gives the estimated cost of a couple screening strategy. This is more expensive than sequential screening by £6000-14 000 because of the need to retest women who have changed partners, the woman's carrier status being unknown if the result from the first pregnancy is reported as negative.

The effect of varying our main assumptions is

examined in table 3. For both the screening strategies the cost increases steadily according to the proportion with missing information. There is a similar rate of increase in costs according to the proportion with new partners but only for couple screening. If the uptake of prenatal diagnosis assumed in the figure is reduced to 90% only 346 affected pregnancies would be detected and the cost would increase from £46 000 to £51 000; thus costs rise directly in proportion to the fall in uptake. The DNA test is by far the largest contributor to cost, and so variations in the unit cost of the test are influential. A reduction will lead to an almost proportionate fall in the cost of detecting an affected pregnancy (table 4).

Table 1—*Sequential screening: cost (£000s) per affected pregnancy detected according to carrier detection rate* and uptake of screening*

Carrier detection rate	Uptake of screening				
	55%	65%	75%	85%	95%
ΔF508 only test:					
70%	63	61	60	59	58
75%	55	53	52	52	51
80%	48	47	46†	45	45
85%	43	42	41	40	40
Multimutation test:					
80%	90	89	88	87	86
85%	80	79	78	77	77
90%	72	70	70	69	69
95%	64	63	63	62	62

*Proportion of carriers detected by DNA test.
†Example illustrated in figure.

Table 2—*Couple screening: cost (£000s) per affected pregnancy detected according to carrier detection rate* and uptake of screening*

Carrier detection rate	Uptake of screening				
	55%	65%	75%	85%	95%
ΔF508 only test:					
70%	73	71	69	68	67
75%	64	62	60	60	59
80%	56	54	53	53	52
85%	50	48	47	47	46
Multimutation test:					
80%	104	103	101	101	100
85%	92	91	90	89	89
90%	83	81	81	80	79
95%	74	73	73	72	71

*Proportion of carriers detected by DNA test.

Table 3—*Cost (£000s) per affected pregnancy detected according to proportion with missing information* and new partners in second pregnancy assumed in analysis†*

Missing information	New partner	Screening strategy	
		Sequential	Couple
10%	10%	42	45
10%	20%	42	49
10%	30%	42	53
20%	10%	46	49
20%	20%	46	53
20%	30%	46	57
30%	10%	49	52
30%	20%	50	57
30%	30%	50	60

*Proportion who do not remember their carrier status in first pregnancy, and it is not in obstetric records.
†Assumed: ΔF508 test only, carrier detection rate is 80%, uptake is 75%.

Table 4—*Cost (£000s) per affected pregnancy detected according to carrier detection rate,* screening strategy, and cost of DNA test†*

Carrier detection rate and screening strategy	Cost of DNA test				
	£5	£10	£15	£20	£25
70%:					
Sequential	25	41	57	72	88
Couple	29	47	66	84	102
75%:					
Sequential	22	36	50	63	77
Couple	25	41	57	73	89
80%:					
Sequential	19	32	44	56	68
Couple	22	36	51	65	79
85%:					
Sequential	17	28	39	50	60
Couple	20	32	45	57	70
90%:					
Sequential	16	25	35	45	54
Couple	18	29	40	51	63
95%:					
Sequential	14	23	32	40	49
Couple	16	26	36	46	56

*Proportion of carriers detected by DNA test.
†Assumed uptake is 75%.

Discussion

We have shown that the cost of detecting a pregnancy affected by cystic fibrosis may range between £40 000 and £104 000 depending on the screening strategy, the proportion of carriers detected by the DNA test, and the uptake. Sensitivity analysis showed that cost was not greatly affected by assumptions relating to the extent to which testing is necessary in subsequent pregnancies. Of more importance was our assumption that all carrier couples accept prenatal diagnosis. In practice some will refuse, and the cost per affected pregnancy detected will increase in direct proportion.

The unit cost of the DNA test was the most important variable. The cost of screening will be lowest in centres where a high detection rate can be achieved with a DNA test for ΔF508 only. The use of a multimutation test may considerably increase the detection rate but at present this will result in an approximate doubling of the cost of detecting an affected pregnancy.

Couple screening is more expensive than sequential screening because the carrier status of individual patients is not reported. This non-disclosure is aimed at avoiding anxiety in couples with a moderately high risk of an affected pregnancy because the mother is a carrier but the partner did not have any of the mutations tested for. Studies of sequential screening, however, have not found anxiety levels in such couples to be increased,[5,9] and one study of couple screening found the non-disclosure to be, of itself, a source of anxiety.[9] A form of couple screening with complete disclosure would be no more costly than sequential screening and avoid some of its anxiety.

Three previous studies have estimated the cost per affected birth avoided by antenatal screening to be about $450 000-860 000 depending on the screening strategy (£284 000-542 000 converted by using purchasing power parity),[21] $326 000 (£205 000),[22] and $1 658 000 (£1 043 000).[23] There are four main reasons why these estimates are much higher than our own. Firstly, the cost of the DNA test was greater: $125 (£79),[21] $72 (£45),[22] and $100 (£62).[23] Secondly, one study assumed that only 30% of affected pregnancies

Key messages

- Antenatal screening for cystic fibrosis costs between £40 000 and £104 000 to detect each affected pregnancy
- Cost effectiveness is highly sensitive to the cost of the DNA test and the proportion of carriers it can detect
- Couple screening is more expensive than a sequential testing strategy
- The estimated lifetime costs of treatment are considerably greater than the costs of screening
- Screening for this disorder is less cost effective than screening for Down's syndrome but not greatly so

detected would be terminated.[23] Thirdly, one study included the indirect costs of travelling for the test and work loss which amounted to one third of the direct costs.[22] Lastly, two studies considered screening in just one pregnancy[21 23]: had we done so the cost would have almost doubled (for example, from £46 000 to £76 000 in the figure).

The method of economic appraisal we have adopted is a cost effectiveness analysis. An alternative approach is cost-benefit analysis, in which the benefits are also measured and valued. For example, the avoidance of treatment costs incurred by an individual patient with cystic fibrosis (estimated in 1990 to be £8000 a year for adults[24]) may be seen as a large benefit. The welfare or utility experienced by a person with cystic fibrosis and their family in not having to care for the affected person, or that gained by an early diagnosis even when it is decided to continue the pregnancy, are more difficult to quantify and are usually ignored. In three such studies of antenatal screening for cystic fibrosis, two concluded that benefits exceed costs provided that (in Israel) only the Ashkenazi Jews are screened[22] or that the cost of the DNA test is under $130 (£82),[25] while the third concluded that under most assumptions costs would exceed benefits.[23]

Another approach to the economic analysis is to value the benefit to couples of knowing their carrier status, whether for its own sake or not,[26] by performing a willingness to pay analysis. This entails asking people how much they would be prepared to pay for the service. The results of a study in Aberdeen suggest that this is about £18-19.[27] This is remarkably close to the actual cost per woman offered screening with ΔF508 only (for example, £18 each or £17 758 000/1 000 000 women in the figure) but only half the cost of using a multimutation test.

The cost of screening for cystic fibrosis is higher than for established services, although not greatly so (for example, about £30 000 for screening maternal serum for Down's syndrome[18-20]). Thus there are no economic grounds for not introducing a service into routine NHS practice, although there may be other social, ethical, and political reasons for not doing so.

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Commentary: Cost effectiveness of antenatal screening for cystic fibrosis

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As a clinical geneticist commenting on this paper I will consider some assumptions made by the authors and the context in which antenatal screening for cystic fibrosis might be carried out.

There are four aspects of this study that raise important questions. The first concerns the provision of information before the test and the influence of this on the uptake of testing. From the reports of (non-pregnant) population screening for cystic fibrosis in Britain, the mode of invitation seems to be a major influence on most people's decisions about testing. For example, uptake after invitation by letter has been about 9-12%; after active opportunistic invitation to an appointment for counselling and testing 25%; and after opportunistic invitation to on the spot testing 66-87%.[1 2] This can be interpreted as the compliance of