Prenatal Screening for Cystic Fibrosis
An Economic Analysis

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Introduction

Cystic fibrosis (CF) is the most common life-shortening genetically transmitted disease in Denmark with a birth prevalence of 1 in 4700 (1), resulting in 12-15 new cases of cystic fibroses annually. Since the discovery of the principal genetic mutations involved antenatal screening has become feasible, and pilot studies of screening programmes have been launched in several countries (2-6) including Denmark. The Danish pilot was initiated in June 1990 and ran over a period of 2 years (6). A total of 7,400 pregnant women were offered a blod test in order to test for CF carrier status. The aim of screening was to identify women and their partner who are both carriers of a CF mutation through sequential carrier testing. If both carry a CF mutation there is a 1 in 4 chance that the infant has cystic fibrosis, and the couple are referred to genetic counselling concerning the decision of having invasive prenatal diagnosis (typically choironic villus sampling). If the infant has cystic fibrosis the parents have the option of aborting the fetus.

The aim of this study is to disclose the societal resource implications of introducing a population wide prenatal screening programme for cystic fibrosis in Denmark. The present analysis is limited to the monetary consequences of introducing a screening programme, where costs of screening are compared to the potential benefits measured in cost savings involved if birth of CF patients are avoided. We will henceforth describe this analysis as a cost benefit analysis, although it suffers from the limitation of excluding intangible costs and benefits. The evaluation is based on the experiences of the Danish pilot project as well as data on the Danish treatment strategy extracted from the patient records of 247 CF patients who are treated at Rigshospitalet in Copenhagen.

Methods

Potential scenarios for the economic evaluation

Evaluating the implications of a prenatal screening programme is a complicated exercise since it involves the question of parental reactions subsequent to the abortion of an affected fetus. Parents may choose to "replace" the aborted fetus with an unaffected fetus. In this case a consequence of screening is not only that a CF patient is avoided, but also that a healthy individual is born instead. Alternatively, parents may choose to have no more children on the grounds that they do not wish to run the risk of going through yet an abortion of an affected fetus. Another important question is how parents react if screening is not offered, and the affected fetus remains undetected. Parents with a CF child may opt for an extra sibling as a form of insurance to themselves and other siblings. In contrast, some parents may have fewer children than initially anticipated, as a consequence of the burden of having an unhealthy child. The pattern of responses are as yet undetermined, and hence an evaluation can only be based on assumptions. If the general patterns is that an extra healthy child is born irrespective of whether the affected fetus is detected and aborted, the effect of a replacement child nulls out when resource implications of introducing a prenatal screening programme is evaluated. However, if parents of CF children generally stick to their original plan of reproduction, a replacement child, and the underlying resource implications, may well be a result of screening.

Yet another vital issue which is important in the context of evaluating prenatal screening, is the notion of unrelated costs and benefits and the extent to which they should be included in economic evaluations when the perspective is societal. The issue is controversial within the field of health economics and involves the question of whether the resource effects of prolonging life should be incorporated into economic

evaluations. Generally, production gains as a result of saving or prolonging life have been included in evaluations, but it may be argued that if benefits associated with additional life-years are considered in economic evaluations, unrelated health care costs and cost of general consumption initiated in these additional years should also be included (7). As a consequence, the benefits associated with aborting an affected fetus not only include the saving of direct health care costs of treating CF, but unrelated costs and production value over lifetime should likewise be incorporated in order to estimate the net effect of avoiding a CF patient/gaining a healthy child.

Further complications arise when production losses/gains are to be estimated since the friction cost method and the human capital represent two opposing methods of estimating production implications(8,9). The major difference between the methods arises when production losses are incurred as a consequence of long term or permanent absence from the labour market. The friction cost method assumes that in the long term no production loss is incurred because there is a pool of unemployed individuals who fill the vacancy, hence production levels remain constant. In contrast, the human capital method assumes that the level of unemployment level is such that production losses will take place if individuals are forced to leave the labour market due to chronic illness or death.

Assumptions regarding replacement child and unrelated effects of added life-years as well as choice of method when estimating production implications creates a series of set-ups which could form the basis for estimating the benefits of avoiding a CF patient. The 5 alternative possible scenarios are listed in table I.

Table I. Possible scenarios for the economic evaluation. A, B, C, D and E represent the net benefits of aborting an affected fetus under various scenarios.

	Unrelated effects excluded. Only direct costs are included.	Unrelated effects included. Human capital method applied when estimating production effects.	Unrelated effects included. Friction cost method applied when estimating production effects.
Replacement child	A(>C)	B (>C)	C
No replacement child	---	D (≈B)	E (<B,D and >A)

Scenario C is likely to represent the most conservative estimate of the benefits of aborting a CF patient, whereas scenarios B and D are likely to be of a similar magnitude and will demonstrate the larger measure of benefits. For a detailed discussion of why this may be so, see the appendix. In the following we will estimate the benefits according to the two extreme scenarios: B and C. In addition, we will focus on scenario A which excludes long term production effects as well as unrelated costs, since it represents the least controversial angle to evaluating the implications of prenatal screening, and includes the fewest points of uncertainty. In addition to presenting scenario A from a societal viewpoint, results will also be presented from the perspective of the health care sector.

Costs and benefits included in the analysis

Costs and benefits incurred by the introduction of screening are listed in table II, which includes direct, indirect and intangible costs and benefits. For ease of presentation we have chosen to define "costs" as those resources/intangibles that are invested in order to obtain the primary goal of the screening programme: abortion of affected fetuses. "Benefits" are defined as the resource effects and intangible implications that are a result of the final outcome. Direct benefits are defined as those cost savings that are made as a consequence of reducing the incidence of cystic fibrosis treatment, whereas indirect benefits include unrelated cost savings and production effects as a consequence of avoiding that an individual with CF is born. In addition, indirect benefits may also incorporate the net present value of a potential replacement child. Included amongst intangible costs and benefits are those effects that cannot be monetarised. These were not included in the analysis, but may be measured through contingent valuation studies, or through measuring quality of life of patients and parents, is is done in Rowley et al (5).

Table II. Costs and benefits of introducing pre-natal screening for cystic fibrosis

Direct costs	Direct benefits
Cost of DNA-tests (women + men) Cost of initial counselling (GP) Cost of genetic counselling Cost of choironic villus sampling Cost of spontaneous/elective abortion [Transport and time costs (production loss)] Cost of diagnotics in connection w. replacement child	Treatment cost savings (visits to clinic, inpatient days) Savings on costs of medication Savings on cost of additional nutrition, washing, telephone calls etc Savings on transport and production loss in connection with monthly visits to the outpatient clinic Savings on equipment in the home.
Indirect costs	**Indirect benefits**
	Savings on unrelated health care costs of CF-patient Savings on unrelated consumption of CF-patient Loss of production capacity of CF patient (-) Increase in production capacity of parents Generated health care costs of replacement child (-) Generated consumption of replacement child (-) Gain of production capacity of replacement child
Intangible costs	**Intangible benefits**
Process utility/disutility: [Creation of potential feelings of regret] [Anxiety before test] [Physical discomfort;screening test, CVS, abortion] [Reassurance after result of test (-)] [Avoidance of regret (-)]	Outcome utility/disutility: [Increase in quality of life of parents] [Loss of quality adjusted life-years of CF patients] [Gain of healthy life-years of replacement child]

Note: [..] signifies that these effects are not included in the analysis; "(-)" denotes that this effect decreases costs or benefits, respectively.

Transport costs as well as production losses associated with having the DNA-test taken were assumed to be zero for female participation, since the blood test is taken during a routine visit at the general practitioners clinic in connection with the pregnancy. These costs will, however be initiated for those men who are tested subsequent to their partner testing positive. Carrier frequency is 1:34.5 in Denmark (1), entailing that in 2.9% of cases, the couple will be offered genetic counselling and the partner will be offered a blood test. Due to the rather limited implications of including time and travel costs for this group, we chose to include only the costs of counselling and DNA test.

Data sources used to estimate implications of screening

According to the experiences of the Danish pilot study on prenatal screening for cystic fibroses one can expect 80% participation in a population wide screening programme in Denmark (6). In the USA participation rates as low as 57% have been reported (5), whereas the United Kingdom have experienced participation rates from 62% to 90% in various pilot projects (10). In the present analysis a participation rate of 80% is assumed in the base case scenario. The effect of a lower participation rate is investigated in a sensitivity analysis. Carrier frequency is 2.9% in a Danish context, but it should be noted that higher frequencies will render the programme more beneficial, and a lower frequency will entail a decrease in net benefits, *ceteris paribus.* A sensitivity analysis will investigate the magnitude of this effect. In Denmark the DNA test will involve testing for ΔF508 and the nordic mutation (394delTT), entailing a sensitivity of approximately 90% (specificity is assumed to be 100%). A further important factor in the effectiveness of a prenatal screening programme is whether the partner is willing to participate if the woman is found to be a carrier. According to the Danish experience in which 172 women were tested positive, all partners chose to have a DNA test (6). However, in other countries lower participation rates amongst partners

have been observed. An American pilot project experienced 85% participation (5), whereas others (2,4) observed participation rates of 97% and 99%. In the present analysis we have chosen to use a conservative estimate of 94%. The percentage of couples where both are carriers who choose to have prenatal diagnostics performed is high. In pilot projects on CF screening only 2 to 5 such couples were identified, and in almost all cases the couples continue with prenatal diagnostics. In all cases affected fetuses were aborted. According to Ginsberg et al (3) the experience from alternative prenatal screening programmes (for Downs Syndrome and Tay-sachs) 97.1% of couples have chosen to have the fetus diagnosed and 92% of affected fetuses were aborted. In this analysis we assume that 100% of couples will choose prenatal diagnostics whereas 95% of the affected fetuses will be aborted. Abortion rates are likely to be culture specific, hence a sensitivity analysis will be performed on this parameter.

If a universal prenatal screening programme is initiated, the DNA test will require a blood sample which will be taken at the general practioners, followed by a DNA analysis which is performed at Statens Serum Institut. In the pilot project the test was analysed at Rigshospitalet, so it is problematic to extrapolate on the cost data from the pilot project. Consequently, there is significant uncertainty surrounding the cost of a DNA analysis, which is further enhanced by uncertainty regarding number of annual tests required and the extent to which economies of scale will reduce cost per test. The base case cost estimate of performing a DNA analysis are thus based on ex ante assumptions which are yet to be verified. Since the DNA-test signifies a major cost component in the cost of screening, sensitivity analysis will thoroughly analyse the implications of varying cost levels.

Cost of treating patients were estimated based on hospital statistics as well as patient records at Rigshospitalet, Copenhagen. A total of 274 patients are presently treated at

this hospital. Activity data on CF patients' inpatient visits and length of stay as well as frequency of outpatient visits were extracted from hospital records. Costs were estimated using hospital tariffs from 1998. Generally, tariffs are not guaranteed to reflect actual costs. However, it was beyond the scope of this analysis to estimate the exact cost involved at the patient level. Cost per average bedday for the relevant hospital units were used in order to estimate the cost per inpatient stay. Average costs per bedday are often critised for not reflecting the large variances in cost per day, since in some units, such as a surgery unit, initial days of stay will involve significantly higher resource consumption than subsequent inpatient days, which may involve little more than hotel costs. As CF patients are generally admitted to medical wards with low cost variance across patient days this is not seen as a major problem. Some patients will be admitted to surgery wards in connection with lung tranplantations, but as Rigshospitalet operates with separate tariffs per operation, in addition to tariffs per bedday, a significant proportion of the cost variance is captured.

From hospital records extraordinary inpatient medication (not included in average bedday prices) were extracted as well as medication administered to patients directly from the outpatient clinic. However, most of the medication that a CF patient receives is given on prescription and handed out at local pharmacies. In order to estimate the magnitude of medication prescription patient files were scrutinised and information was collected on all prescription over the course of a year (1998-1999). Costs of medication were estimated using official prices net of tax.

CF patients receive a monthly allowance from the local government to cover extra expenses on food, laundry, telephone bills etc. These allowances are included in this economic evaluation under the assumption that they reflect true costs and not merely transfer payments.

Travel costs as well as production losses due to CF were estimated based on a questionnaire handed out to 55 patients who visited the outpatient clinic over the summer 1999. CF patients visit the clinic on a monthly basis, hence travel costs and production losses incurred by these visits are of a signficant magnitude. CF patients and parents of CF patiens were asked about the average time spent on these monthly visits. In addition adult CF patients and parents were asked whether they were fully employed, employed part-time (number of hours) or unemployed. It was assumed that if CF patients or parents were part-time or fully employed they would be required to take time off work, since the outpatient clinic is open between 9 am and 3 pm, only. Long term production loss was determined by asking those respondents who were not fully employed, if their job situation is a consequence of cystic fibrosis in the family.

Results

Cost of screening

Cost per DNA test includes materials (DKK 50), royalties (DKK 50), logistics such as information materials, response letters, quality control, transportation of tests etc (DKK 60). Fixed annual costs are: cost of staff (DKK 1,000,000), depreciation and maintenance of equipment (DKK 1,200,000), rent of laboratory space (DKK 150,000). If 56,000 tests are performed annually corresponding to 80% of pregnancies cost per test amount to DKK 200 per test. Since a large proportion of costs are assumed to be fixed costs, number of annual tests performed may have considerable influence on cost per test. If, for example only 10,000 -15,000 test are performed annually cost per test could exceed DKK 400. We do, however, judge that "fixed" costs are variable to some degree in the long run, i.e. the need for equipment would be less at lower producion levels. Hence, we expect that a decrease in the number of women screened from 56,000 to 45,000 at subsequent screening rounds will have no

major effect on the cost per DNA test. Finally, it should be noted that the cost estimate reported here reflects marginal costs per DNA test performed. There may be significant fixed costs involved in maintaining and running a laboratory facility of such a standard that DNA tests of this type can be performed at relatively short notice. Such costs should be incorporated in average cost pricing.

In addition to the costs included above, the general practitioner will spend time on informing and counselling each pregnant woman before the blood sample is taken. The cost is initiated irrespective of whether the women agrees to participate in the screening programme or not. It is judged that on average the general practitioner will spend 5-10 minutes on this initial counselling, equivalating a cost in the range of DKK 100. Further costs incurred by the introduction of screening are genetic counselling (DKK 2,656), prenatal diagnostics (DKK 5,162) and cost of abortion (DKK 1,476). All costs are based on 1998 tariffs. In the case of genetic counselling, the tariff is valid irrespective of whether a couple requires one or more counselling sessions. Cost of abortion is based on the assumption that pregnancies are terminated before gestational age exceeds 12 weeks.

Total screening costs

Cost of screening were estimated based on 70,000 annual pregnancies, a carrier frequency of 0.029 and a sensitivity of the DNA test of 90%. Participation rates were assumed to be 80% amongst the pregnant women and 94% amongst partners. Costs were estimated for the first screening round as well as for the stable scenario in which screening has been introduced for some years (subsequent screening round). In Denmark 1.7 children are born per woman, implying that approximately 70% of annual pregnancies will be first time pregnancies, while the latter 30% will consist of women who will already have been through at least one pregnancy. We assume that in these

cases results of the DNA tests are filed, and available to the general practitioner at subsequent pregnancies. We further assume that partners remain together, making further DNA testing unnecessary.

Total cost of screening as well as screening per aborted affected fetus is presented in table III. Costs are estimated for the initial screening round and subsequent screening rounds, respectively.

Table III. Annual cost of screening and cost per aborted fetus. Estimated for the initial screening round and subsequent rounds

Number of individuals, couples or fetuses initial round/*subsequent rounds*	**Unit cost (DKK)**	**Total cost (DKK)**
Women partipating in programme: 70,000*0.8= 56,000 *Subsequent rounds: 56,000*0,7 =39,200*	DNA test: 200	12,200,000 *7,840,000*
Number of partners tested: 0.029*0.09*56,000*0.94=1374 *Subsequent rounds: 1374*0,7 =962*	DNA test:200	274,800 *192,400*
Cost of DNA-tests *Subsequent rounds:*		12,474,800 *8,032,400*
Women invited to screening: 70,000 *Subsequent rounds: 70,000*0,7*	Counselling at GP: 100	7,000,000 4,900,000
Women referred to genetic counselling: 0.029*0.9*56,000= 1462 *Subsequent rounds: 1462*0,7=1023*	Genetic counselling: 2656	3,883,072 2,717,088
Cost of counselling *Subsequent rounds*		10,883,072 7,617,088
Couples who are offered and accept fetal diagnostics: 1374*0.029*0.9*1=35.9	Fetal diagnostics: 5,162	185,316
Cost of fetal diagnostics[1] *Subsequent rounds*		185,316 185,316
Number of aborted fetuses: 35.9*0.25*0.95 = 8.5	Abortion: 1,476	12,546
Cost of abortion *Subsequent rounds*		12,546 12,546
Total cost per annum[2] ***Subsequent rounds***		**23,555,734** **15,847,350**
Cost per aborted affected fetus ***Subsequent rounds***		**2,771,262** **1,864,594**

[1]Cost of spontaneous abortions as a consequence of fetal diagnotistics are not included in the calculations above, since the resource implications will be minimal.

[2]Costs associated with additional pregnancies and fetal diagnostics in connection with replacement child are ignored here. Approximative cost calculations envisage that inclusion will increase total costs by approximately DKK 60,000 entailing an increase in cost per aborted fetus of DKK 7,060.

Benefits associated with aborting an affected fetus

Cost of medication

Cost of medication of CF patients during inpatient stays and medicine given directly to patients during their visits to the outpatient clinic amounted to 9.4 million DKK in 1998. From patient journals the amount of medication prescribed and distributed via pharmacies was calculated. Based on 230 patient records the annual cost amounted to 19.5 million of which Pancreatic enzymes, Colistin and Pulmozyme accounted for more than 90% of the cost.

Cost of inpatient treatment

From Rigshospitalets registers number of visits to the outpatient clinic, number of beddays spent in the medical ward and number of beddays spent in an intensive ward (typically in connection with a lung transplantation) in the year of 1998 were extracted for different age-groups. Table I in the appendix lists the frequencies as well as total costs for 10-year age-groups. Cost are calculated using the following tariffs: Per bedday in medical ward DKK 3,957, per bedday in intensive ward DKK 8,249, per outpatient visit DKK 1,834 and per lung transplantation DKK 185,000. Total annual cost was estimated at DKK 16,453,200 (medical ward), DKK 288,700 (intensive ward) and DKK 4,526,300 (outpatient visits).

Other costs

Patients and patients' parents receive a monthly subsidy from the local government to cover extra expenditures related to cystic fibroses. A subsidy covers costs of extra nutritional requirements over lifetime, while another subsidy is given to parents of

patients under the age of 18 to cover extra expenses related to washing of clothes, telephone calls etc. Information on the size of these subsidies were listed in patients' record at Rigshospitalet. Assuming that extra washing and telephone bill expenditures do not cease at the age of 18, the subsidy was extrapolated to reflect costs beyond the age of 18. Nutrional requirements vary by the patients' weight and hence by age, whereas other expenditures are assumed constant across age-groups. On average yearly allowances for extra nutrition amounted to DKK 5906 for 0-9 year olds, DKK 7,525 for 10-19 year olds, DKK 8,543 for 20-29 year olds and DKK 7,922 for 30-39 year olds. The parental subsidy does not vary be age and amounts to DKK 6096 across all age-groups.

The treatment of CF patients involves PEP mask treatment as well as daily inhalations of Ventoline, Pulmozyme and/or Colistin. Such treatments require equipment in the patients' home which are distributed and costed by the outpatient clinic. On an annual basis 47 PEP masks (DKK 350) and 34 high flow compressors (DKK 1,750) are handed out in addition to 270 sets of masks, infusers and accompanying hoses at a unit cost of DKK 1500. The total annual cost of home equipment amounts to DKK 480,950 equivalent to DKK 1755 per patient per year.

Visits to the outpatient clinic; transport costs and production losses

A total of 55 CF patients and parents of CF-patients received a questionnaire in which question focused on transport costs and production losses. On most questions there was a 100% response rates, with the exception of the question concerning transport costs, where response rate was 66% only. Since the questionnaires were only handed out to 20% of the patients visiting the outpatient clinic, it was vital to test the representativeness of the sample. A χ^2-test on age-distribution proved no significant differences between expected and observed frequencies. Results are listed in the

appendix in table II. On average each patient made 13.6 visits to the outpatient clinic per year involving transport costs of on average DKK 219 per visit. Annual production losses incurred (by adult CF patients or parents) amounts to DKK 5,967.

Production loss in connection with inpatient stays are not included in the analysis. The reason for this being that most stays in the medical wards are routine admissions for 2 weeks every 3 months with the aim of controlling Pseudomonas infection through treatment with intravenous antibiotics. Since these admissions are frequent and systematic we expect that production loss will be incorporated in the long term production loss which is measured through employment status (see later section).

Overall direct cost of treatment per age-group

All direct costs were calculated per 10-year age group. Direct costs incurred by the health care sector and other sectors are reported separately. Table IV lists results.

Table IV. Average cost per CF patient per year in the respective age-categories. Costs in DKK

	0-9 years	10-19 years	20-29 years	30-39 years
Inpatient stays	299	17,571	99,328	164,804

Outpatient visits	22,423	19,257	13,255	12,541
Medicine	48,727	114,288	178,306	192,456
Medical equipment in the home; masks, pumps etc	1,755	1,755	1,755	1,755
Transport costs	2,977	2,977	2,977	2,977
Costs to the health care sector	76,181	155,848	295,621	374,533
Cost of additional nutrition, washing, telephone calls etc	12,002	13,621	14,639	14,018
Production loss in connection w. outpatient visits	5,967	5,967	5,967	5,967
Costs to other sectors	17,969	19,588	20,606	19,98
Total costs	94,150	175,436	316,227	394,518

Life time costs can be estimated based on the cost estimates listed in table IV. Using a discount rate of 5% the present value of direct life-time costs were calculated assuming a median life-expectancy of30 and 40 years respectively. A societal as well as a health care perspective was chosen. See table V.

Table V. Present value of life time costs in 1998 DKK. Discount rate: 5%.

	Societal perspective	Health care sector perspective

Median age: 30 years	2,540,166	2,241,389
Median age: 40 years	3,262,432	2,927,067

Indirect costs and benefits

In the questionnaire which was handed out to 55 CF patients and parents, respondents were asked whether they were full time employed, part time employed or unemployed. They were subsequently asked to qualify whether a reduced number of working hours were a consequence of CF. The results are listed in the appendix, table III.

Those individuals who were working part time due to CF were asked how many hours they worked per week. Assuming that a normal working week constitutes 37 working hours, the number of work hours lost per week were calculated at 117 per week in total (33 hours amongst CF patients and 84 hours amongst parents), corresponding to a total production loss of DKK 711,000 per year. For those who are not in the working force at all as a consequence of CF, the total production loss constitutes DKK 2.7 million (assuming an average gross income of DKK 225.000). The total production loss of DKK 3.4 million is based on 55 individuals (CF patients and parents), resulting in an annual production loss of DKK 62,000 per parent couple/CF patient.

Although the annual loss differs amongst the two groups: DKK 61,000 for parents and DKK 68,000 for CF-patients, we chose for the sake of simplicity to use the average estimate of DKK 62,000 in further calculations. Assuming that parents of CF patients experience production losses over the initial 20 years of a CF patients life corresponding to DKK 62,000, whereafter the CF patient will represent an annual production value of DKK 163,000 (DKK 225,000-DKK 62,000), the net effect on production in present value of a CF patient being born will be DKK -300,000 if a CF patient's median life-expectancy is assumed to be 30 years, whereas the net present value will be approximately zero if life-expectancy is instead 40 years (applying a 5% discount rate).

Data on unrelated costs as well as production capacity across age groups are needed in order to estimate the cost of unrelated health care costs, general consumption and production benefits over life-time for a CF patient and a healthy individual. Danish statistics on income and health care costs across age-groups were available (11, 12). However, it was difficult to find precise statistics on general consumption per individual across age-groups since such statistics are generally calculated per household. Therefore we chose to use American statistics (13) as approximative estimates. American income levels across age-groups are not significantly different from Danish income statistics, hence we assume that consumption will be largely similar. General consumption was estimated to be DKK 78,500 for a 30 year old, rising to DKK 102,700 for a 50 year old, whereafter a decline in consumption occurs such that a 75 year old will consume equivalent to DKK 82,200. All costs were estimated in 1998 DKK.

Below, are presented the net present benefit of avoiding a CF when unrelated costs and benefits are included and a replacement child is assumed (scenarios B and C). The net present value of savings on consumption and productions gains/losses were estimated by including production loss over a CF patient's lifetime as well as the net present value of the additional years of life lived by a healthy replacement child. These benefits were added to the direct cost savings calculated in table V. The net present value of added years of life were estimated assuming a median life-expectancy of a healthy individual of 75 years.

Table VI. Net present value of avoiding a CF patient. All costs in 1998 DKK. Discount rate:5%

Perspective	Benefit element	Median life-expectancy of CF patient: 30 years	Median life-expectancy of CF patient: 40 years
A	**Direct health care cost savings**	**2,241,389**	**2,927.067**
	Total direct cost saving (societal perspective)	**2,540,166**	**3,262,432**

B	Total direct cost savings	2,540,166	3,262,432
	Due to additional life-years being lived by healthy individual:		
	Added unrelated health care costs	-36,895	-24,887
	Added costs of consumption	-373,787	-230,687
	Added production	654,356	341,367
	Added production over CF patients' life-expectancy, when replacement takes place	930,123	1,038,224
	Total benefits	**3,713,963**	**4,386,449**
C	Total direct cost savings	2,540,166	3,262,432
	Due to additional life-years being lived by healthy individual:		
	Added unrelated health care costs	-36,895	-24,887
	Added costs of consumption	-373,787	-230,687
	Added production	0	0
	Added production over CF patients' life-expectancy, when replacement takes place	0	0
	Total benefits	**2,129,484**	**3,006,858**

Screening costs are listed in table III, and reports a cost of DKK 2,771,262 per aborted affected fetus. This cost will at subsequent screening rounds decrease and stabilise at DKK 1,864,594 per aborted affected fetus. Comparing this figure with the estimated benefits in table VI above suggests that introducing a screening programme for cystic

fibrosis will be net cost saving irrespective of the perspective of the analysis, assumptions on replacement children and method of estimating long term production gains/losses. We will below discuss to which extent this result holds if base case assumptions do not hold.

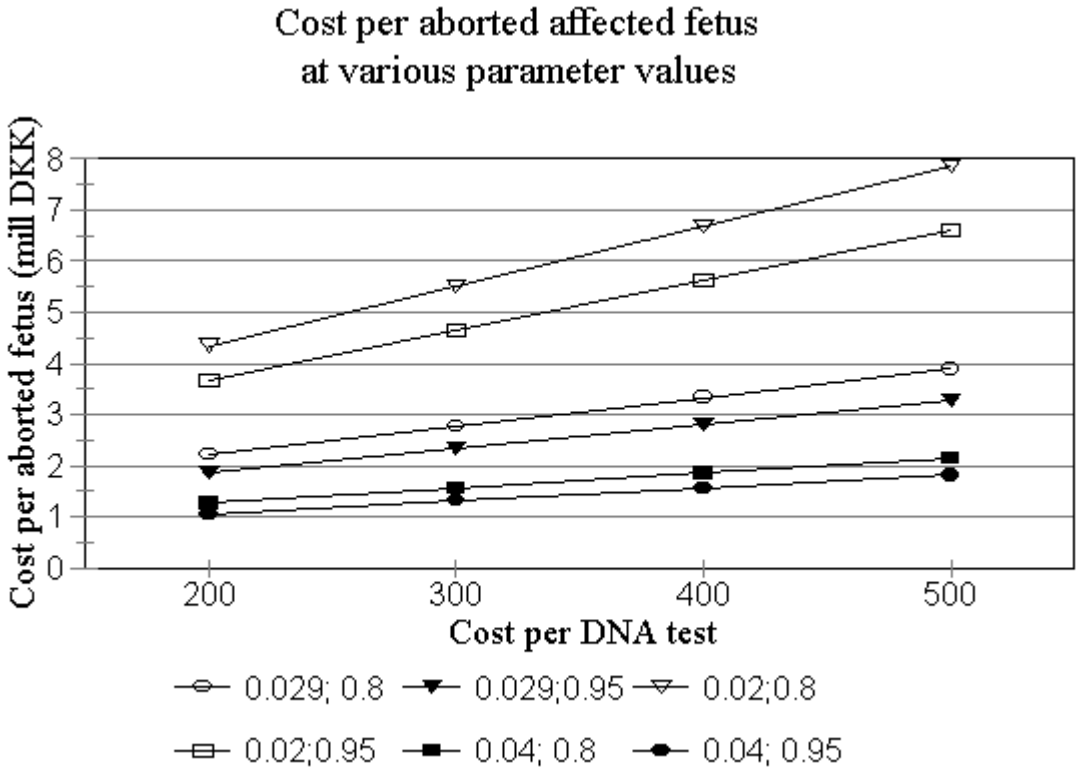
Sensitivity analysis

Altering cost of DNA-test, carrier frequency and abortion rate

Figure 1 illustrates the cost per aborted fetus under various assumptions regarding cost of DNA test, carrier frequency and abortion rate of affected fetuses.

Figure 1

The lines in figure 1 represent the break even points of the cost benefit analysis, where cost per aborted fetus reflects the minimum requirement for cost savings incurred through avoiding a CF case in order for benefits to be at least as great as costs. For each break-even line different assumptions are made on carrier frequency (0.02; 0.029;



0.04), and abortion rates (0.8; 0.95).

Base case assumptions are: cost of DNA-test: 220 DKK, carrier frequency: 0.029 and abortion rate of affected fetuses: 0.95 The cost per aborted affected fetus is under these assumptions DKK 1,959,000 (see table III). If abortion rates were to decrease to 0.8, cost per aborted fetus would increase by 18.8%. If the abortion rate is 0.95 but the DNA cost turns out to be significantly higher than anticipated (DKK 500), cost per aborted fetus will exceed DKK 3 million. If screening for CF were to be introduced in a population with lower carrier frequency prevalence than in the Danish population (1:34.5 or 0.029), f.ex. Finland (1:65 or 0.015), the cost per aborted affected fetus will be significantly increased. This effect will be magnified if abortion is viewed with more skepticisme and/or the country specific cost levels are high.

Altering participation rate, sensitivity of test, cost of genetic counselling

A sensitivity analysis focusing on the effect of women's participation rates shows that a decrease in participation rate from 0.8 to 0.6 would increase cost per aborted fetus by DKK 298,000 when prevalence of CF mutation is 0.029. The increase is less (DKK 177,900) when prevalence is 0.04 and higher (DKK 557,450) when prevalence is 0.02. The sensitivity of the DNA test also influences the cost of detecting a CF fetus. An increase of 1% in sensitivity will decrease cost per aborted fetus by 1.8% irrespective of country specific prevalence and cost of DNA test. Cost of genetic counselling does not have great influence on the overall cost of screening. An increase in cost of genetic counselling of 50% will incur an increase in cost per aborted fetus of 8%.

Discussion

Under base case assumptions, and assuming a median life expectancy of CF patients

of 30 years, this paper concludes that for the initial screening round the cost of preventing a CF case exceeds the avoided life-time costs of a CF patient, if only direct costs are included in the analysis. This conclusion holds irrespective of whether we take a health care sector perspective or a societal perspective. If we estimate long term screening costs per aborted affected fetus, i.e. the cost of subsequent screening rounds, the conclusion reverses. The conclusion is likewise reversed if CF patients' life-expectancy is assumed to be 40 years. If indirect costs and benefits are included in the analysis and production gains/losses estimated by way of the human capital method, benefits of avoiding a CF case increases. If, alternatively, indirect costs and benefits are included and production effects are estimated according to the friction cost method, overall benefits of aborting an affected fetus will decrease, and benefits will only exceed costs as long as median life-expectancy for CF patients is 40 years and/or focus is on long term screening costs per averted CF case.

The evaluation presented here focuses on stepwise/sequential screening rather than couple screening. Miedzybrodzka et al (14) analysed women's preferences with respect to stepwise versus couple screening. A total of 62% preferred stepwise screening whereas only 27% preferred couple screening. These results suggest that the screening mode presented here is likely to be the most popular amongst the target group. The present evaluation is also restricted to analysing the consequences of performing a DNA analysis which detects two mutations only. It would be of potential interest to analyse the full implications, including possible increase in cost of DNA analysis, of extending the sensitivity beyond 90%. An analysis by Asch et al (15) suggests that cost effectiveness may decrease significantly as mutation analysis is expanded.

The results presented in this a nalysis include estimations of savings made on medical expenses if a CF case is avoided. These estimations are based on activity data and

tariffs from the year 1998. To which extent these data can be extrapolated to future time periods is uncertain. More effective and more expensive treatments are expected to surface in the future, perhaps increasing monetary benefits of screening markedly. Moreover, this analysis presented results for a median life-expectancy of 30 years and 40 years, respectively. Today, the median life-expectancy of CF patients is 30 years, but it is expected that those CF patients who are born after 1990 will have a life-expectancy of at least 40 years. This analysis has applied current age-specific medical expenses when estimating the cost of treatment across a life-span of 40 years, but it is likely that those patients who survive beyond the age of 30 years today are special cases which are less expensive to treat. Hence, in the future medical expenses may increase more significantly for the older age-groups than is the case today.

Generally, the direct benefits presented in this analysis are likely to be conservative estimates of future cost savings. It should, however, be noted that as treatment is improved and CF patients' lives are prolonged and quality of life improved, it will become even more important to include intangibles in a full economic evaluation. The cost benefit analysis presented here only includes monetary implications of screening. Consequently, results demonstrating negative net benefits does not necessarily suggest that a prenatal screening programme for CF is not worthwhile. If a definite conclusion is to be reached, it is necessary to elicit stated preferences for such programmes, thereby including intangibles in the evaluation. If, for example, cost per detected CF fetus exceeds benefits of avoiding a CF case by DKK 2 million, a willingness to pay per participating couple only has to exceed DKK 45 for benefits to exceed costs of screening. In comparison, Donaldson et al (17) elicited maximum willingness-to-pay for a CF screening programme and demonstrated that women's average willingness-to-pay was as high as DKK 175.

Validation

A series of other studies have performed economic evaluations of screening for CF. Some evaluations have focused on the cost of screening only, whereas others have compared cost of screening with benefits incurred by a decrease in the prevalence of CF. The latter studies have generally discussed the notion of a replacement child. Garber et al (18) conclude that net benefits will be incurred if the affected fetus is replaced by a healthy child, while a CF screening programme will incur high net costs if the affected fetus is not replaced. This conclusion does not coincide with the conclusions of this paper in which the cost of screening per affected fetus at subsequent screening rounds is lower than incurred benefits irrespective of whether replacement takes place. The reasons are many-fold: Garber et al focus on the economic of the initial screening round rather than subsequent screening rounds. Annual cost of treatment is assumed to be $8000 (in 1985 currency) which is significantly lower than the estimates of this analysis (see table IV). Cost of DNA-test is significantly higher than in the present analysis ($100) and the sensitivity of the test is lower (76%). Indirect effects only encompassed production gains/losses and not unrelated costs of living, which will overestimate the benefits of a replacement child. Ginsberg et al (3) perform a cost benefit analysis very similar to the one presented here, except for the omission of cost of general consumption. They reach the conclusion that if only direct costs are included in the analysis, cost of preventing a CF case will exceed the lifetime costs per case when focus is on the expenses associated with an initial screening round. If, however, benefits of screening also accrue to subsequent pregnancies, the benefit cost ratio will be greater than 1 (1.23). These results coincide with the results of this analysis, the benefit cost ratio being 1.3 when the perspective is societal and only direct costs are included.

Morris et al (19) estimate cost per affected fetus detected at initial screening round to £142,900 (DKK 1.57 million) in 1994 currency. Cost of DNA test was £39 (DKK 430), carrier frequency 0.04 and sensitivity of the test 85%. This cost level would also

be reached by the model applied here under the given assumptions. The results show that a higher carrier frequency in a population allows for higher cost levels of the DNA-test, while still proving a screening programme net beneficial. This is likewise illustrated by Asch et al (15) who assume a carrier frequency of 0.04 and a cost of the DNA-test of $50 (DKK 350) and estimate sequential carrier screening to cost $381,000 (DKK 2.67 million) in 1995 currency per avoided CF case at the initial screening round. Lieu et al (20) estimate the cost per avoided CF fetus at $1.4 million (DKK 9.8 million) in 1993 dollars. Base case assumptions were a carrier frequency of 0.04, test sensitivity of 85%, abortion frequency 30% and cost of DNA test $100. Applying similar assumptions in the present model would reach the exact same results. The high magnitude of this estimate shows the extend to which abortion rate and cost of DNA-test has an effect on overall screening cost per aborted fetus. Other studies (4,6) report that screening for CF is good value for money. These studies do however suffer from lack of documentation for unit costs and omission of discounting future effects.

In Lieu et al (20) life time costs of medical care is estimated at $243,650 (1993 currency, 5% discount rate), corresponding approximately to DKK 1.7 million. This cost estimate is not significantly different from the estimate of the present study. Similarly, direct costs of treatment across age-groups as listed in table IV corresponds very well with the results of a Dutch analysis (21).Haddow et al (16) discuss the overall implications of screening and note that the principal cost savings of avoiding a CF case will result from reduced life-time medical costs directly associated with treatment. They further note that according to estimates by Rowley (5) this cost will amount to at least $600,000 (DKK 4.2 million). Studies by Lieu et al (20), Wildhagen et al (21) and the present study show that the present value of medical costs are more likely to be lower in the range of DKK 2-2.5 million.

Conclusion

The extent to which cost per avoided CF fetus depends on carrier frequency, assumptions on the cost of the DNA-test and abortion rates illustrates that simple comparisons across evaluations are not valid. Hence this analysis has focused on results based on a Danish setting supplemented by a sensitivity analysis which demonstrates the extent to which changes in parameter values influence the break even point in a cost benefit analysis. The analysis further demonstrates that calculated net benefits of avoiding a CF case vary significantly depending on whether and to which extent indirect effects are included in the analysis.

The economic consequences of cystic fibrosis screening were analysed in a Danish setting applying parameter values which are judged relevant in a Danish context. Although initial screening rounds are more costly per affected fetus detected, prenatal screening for cystic fibrosis is net beneficial at subsequent screening rounds irrespective of whether and to which extent indirect costs are included.

References

1. Brandt N.J., Schwartz M., Skovby F., Clausen H. Anlægsbærerscreening for cystisk fibrose. Resultatet af en pilotundersøgelse blandt gravid. Ugeskrift for Læger 1996; **158(33)**:

2. Cuckle H., Quirke P., Sehmi I. et al. Antenatal screening for cystic fibrosis. British Journal of Obstetrics and Gynaecology 1996; **103**: 795-799.

3. Ginsberg G., Blau H., Kerem E. et al. Cost-benefit analysis of a national screening programme for cystic fibrosis in an Israeli population. Health Economics 1994; **3**: 5-23

4. Mennie M.E., Gilfillan A., Compton M. et al. Prenatal screening for cystic

fibrosis. The Lancet 1992; **340**: 214-216.

5. Rowley P.T., Loader S., Kaplan R.M. Prenatal screening for cystic fibrosis carriers: an economic evaluation. Am.J.Hum.Genet 1998; **63**: 1160-1174.

6. Schwartz M., Brandt N.J., Skovby F. Screening for carriers of cystic fibrosis among pregnant women: A pilot study. Eur. Journal of Genet 1993; **1**: 239-244.

7. Meltzer D. Accounting for future costs in medical cost effectiveness analysis. Journal of Health Economics 1997; **16**: 33-64.

8. Koopmanschap M.A.,van Ineveld M. Towards a new approach for estimating indirect costs of disease. Soc. Sci. Med. 1992; **34**: 1005-1010.

9. Johannesson M., Karlsson G. The friction cost method: A comment. Journal of Health Economics 1997; **16**: 249-255.

10. Cuckle H.S., Richardson G.A., Sheldon T.A., Quirke P. Cost effectiveness of antenatal screening for cystic fibrosis. British Medical Journal 1995; 311: 460-4.

11. Sørensen L.H. Det aldersfordelte forbrug af sundhedsydelser. CHS arbejdsnotat 1996:10. CHS Working paper, Odense University. In Danish.

12. Danmarks Statistik: Statistisk Årbog, 1998. Danish Statistics. Yearbook 1998.

13. Bureau of Labour Statistics, 1997: Consumer Expenditure Survey. Intenet adress: http://stats.bls.gov/csxstnd.htm#1997.

14. Miedzybrodzka Z., Semper J., Shackley P. et al. Stepwise or couple antenatal carrier screening for cystic fibrosis? Women's preferences and willingness to pay. Jour.of Med. Genet 1995; 32: 282-283.

15. Asch D.A., Hershey J.C., Dekay M.L. et al. Carrier screening for cystic fibrosis: Costs and clinical outcomes. Medical Decision Making 1998; 18: 202-212.

16. Haddow H.E., Bradley L.A., Palomaki G.E., Doherty R.A. Issues in implementing prenatal screening for cystic fibrosis: results of a working conference. Journal of Medical Screening 1999; 6: 60-66.

17. Donaldson C., Shackley P., Abdalla M., Miedzybrodzka Z. Willingness to pay for antenatal carrier screening for cystic fibrosis. Health Economics 1995; 4: 439-52.

18. Garber A., Fernerty J.P. Costs and benefitss of prenatal screening for cystic fibrosis.. Medical Care 1991; 29(5): 473-86.

19. Morris J.A., Oppenheimer P. Cost comparison of different methods of screening for cystic fibrosis. Journal of Medical Screening 1995; 2: 22-27.

20. Lieu T.A., Watson S.E., Washington A.E. The cost effectiveness of prenatal

screening for cystic fibrosis. Obstetrics and Gynecology 1994; 84(6): 903-912.

21. Wildhagen M.F., Joke B.G.M., Verheil J.G. et al. Cost of care of patients with cystic fibrosis in The Netherlands 1990-91. Thorax 1996; 51: 298-301.

Appendix

The relative size of the alternative benefit measures.

If unrelated effects per life-year are included and the full implications of absence from the labor market are measured using the human capital method, the future net cost savings associated with an aborted affected fetus include savings on health care costs associated with CF, health care costs associated with unrelated ailments over life-time, general consumption over life-time as well as net production value over life-time (including the production capacity of the CF patient as well as the production loss incurred by parents to CF patients). If a replacement child is assumed, the expected net present value of a healthy child should be added to the calculated benefits. Under the assumption that the net present cost to society of an average healthy new-born child does not differ greatly from zero (the plausability is supported by the evidence of Melter - see reference no.7), the difference in benefits alculated in scenarios B and D are likely to be of similar magnitudes. The difference between scenarios C,E and B,D is that long term production losses and gains are assumed to be zero under scenarios C and E. If no replacement child is assumed (scenario E), the net benefit of avoiding an affected fetus will incorporate direct cost saving as well as unrelated cost savings. Hence the potential benefits are greater than in scenario A, which only includes cost savings directly related to CF. Scenario E will however provide lower estimates than in scenario B,D if the net effect of excluding production effects is a decrease in overall benefits. This is the case if the present value of parental production loss exceeds the production value of the adult CF patient. Considering that parents incur potential losses over the initial 16-18 years of a CF patients life time (due to time consuming treatments in the home and outpatient as well as inpatient visits), and CF patients reach a median age of only 30-40 years, this is likely to be the case (it is later demonstrated that net benefits will be negative as long as median survival for a CF patient is ≤ 40). If, however, a replacement child is assumed (scenario C) benefits of screening will be

significantly decreased since savings on costs of care of CF patients are partly offset by the unrelated costs incurred by the healthy replacement child, who will have a normal life-expectancy (>30-40 years). Since unrelated costs by definition are similar for the CF patient and the healthy individual over the CF patient's life-expectancy, the net effect of including unrelated costs will be a reduction in benefits corresponding to the present value of unrelated costs incurred over the additional years lived by the healthy individual. Scenario C will hence produce a net benefit which is less than the direct costs measured in scenario A.

Hence, the expected estimated net present benefits in the different scenarios are expected to rank as follows: C<A<E<B,D where C represents the most conservative estimate of the benefits of aborting an affected fetus and scenarios B and D represent the most optimistic estimate of benefits.

Appendix

Table AI. Number of patients, beddays and calculated cost of treatment for patient in different age categories in the year 1998. Cost in DKK.

Age:	Medical ward	Intensive ward	Outpatient visits
0-9			
patients:	3	0	53
beddays:	4		
cost:	15,828		1,188,432
10-19			
patients:	6	0	84
beddays:	373		
cost:	1,475,961		1,617,588
20-29			
patients:	42	2	88
beddays:	2,136	35	
cost:	8,392,152	288,715	1,166,424
30-39			
patients:	27	0	37
beddays:	1,541		
cost:	6,097,737		464,002
40-49			
patients:	2	0	7
beddays:	62		
cost:	245,334		88,032
50-59			
patients:	1	0	1
beddays:	42		
cost:	166,194		1,834
Total			
patients:	81	2	270
beddays:	4,158	35	
cost:	16,453,206	288,715	4,526,312

Appendix

Table AII. Annual transport and time costs of visits to the outpatient clinic

	Total per year	Average per patient per year
Number of annual visits to the outpatient clinic	747 visits n=55	13.6 annual visits per patient
Transport costs	DKK 110,157 n=37	DKK 2,997 per patient (corresponding to DKK 219 per visit)
Time spent visiting clinic Individuals in the work force only[1]	1,634.5 hours annually n=32	51 working hours per patient Production loss per patient: 51*DKK 117[2]= DKK 5,967

[1] In principle time costs amongst individuals not in the labour force should have been included. However, the difficulties associated with estimating the opportunity cost of housewives and pensionists are wellknown. Hence, we chose to opt for the conservative but theoretically valid estimate.

[2] Average hourly wage in 1998 DKK based on Danish labor statistics (Statistisk Årbog, 1998).

Appendix

Table AIII. Annual production loss due to permanent reduction in working hours

	Working part time due to CF	Not working due to CF	Job situation unaffected by CF	Total
CF-patient	4 (16.7%)	6 (25.0%)	14 (58.3%)	24
Parent	8 (27.6%)	5 (17.2%)	16 (55.2%)	29
Partner[1]	2 (5.6%)	1 (2.8%)	33 (91.6%)	36

[1] CF patients and parents were asked whether partner's jobsituation was affected by CF.CF patients' partners generally remained unaffected.