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Costs, effects, and savings of screening for cystic fibrosis gene carriers

Mark F Wildhagen, Henk B M Hilderink, Jan Gerben Verzijl, Joke B G M Verheij, Loes Kooij, Tjeerd Tijmstra, Leo P ten Kate, J Dik F Habbema

Abstract

Study objective—Evaluating the costs, effects, and savings of several strategies for cystic fibrosis (CF) gene carrier screening.

Design—A general model for evaluating prenatal, preconceptional, school, and neonatal carrier screening was constructed. For prenatal and preconceptional screening, two strategies were evaluated: single entry and double entry two step couple screening. Firstly, the Dutch situation was evaluated prospectively; subsequently the results were generalised to other carrier frequencies.

Setting—Prospective simulation model.

Main results—Of all screening strategies, neonatal carrier screening gives most carrier couples an informed choice concerning reproduction. If the parents of carrier newborns would not be tested however, prenatal screening detects most carrier couples. Prenatal and single entry preconceptional screening programmes have a favourable cost-savings balance in the Netherlands under a wide range of assumptions. For double entry preconceptional screening and neonatal screening, high enough values of uptake of screening, prenatal diagnosis, and induced abortion are necessary. School carrier screening does not have a favourable cost-savings balance.

Conclusions—If a CF screening programme is judged to be useful on individual and social grounds, costs considerations are no obstacle for prenatal and single entry preconceptional screening.

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Cystic fibrosis (CF) is the most frequent serious autosomal recessive disease in white populations. Characteristics of CF are chronic bronchopulmonary infections, pancreatic insufficiency, disturbances of the digestive tract, and high sweat sodium concentration. The disease has a great impact on the length and quality of life and causes a comparatively high medical consumption.^{1,2} Treatment starts from the diagnosis and continues throughout life, and consists of prescribing additional calories, vitamins and pancreas enzymes, and fighting the respiratory infections with antibiotics and intensive physiotherapy.

In 1989, the gene responsible for cystic fibrosis was cloned.^{3–5} Nowadays, more than 600 mutations of this CFTR gene are known

(CF Genetic Analysis Consortium). Of these, the so called $\Delta F508$ mutation, a three base deletion in a part of the gene, is by far the most common in Western Europe, while a limited number of other mutations accounts for more than half of the non- $\Delta F508$ mutated genes.^{6,7} These mutations can be detected by polymerase chain reaction analysis with, apart from laboratory errors, a perfect sensitivity and specificity. This makes it possible to consider introducing a screening programme for carriers of the CF gene, where the primary aim is to detect carrier status and counsel couples whose members are both carrier of a CF gene mutation so that they can make deliberate decisions about reproduction.

Screening for CF gene carriers is under debate in many countries. There are health related, psychosocial, ethical, legal, and economic consequences associated with CF gene carrier screening, as with other genetic screening programmes. In the Netherlands, the Dutch Health Council recently formulated criteria for genetic screening programmes intended to ensure systematic assessment of such programmes before their introduction.⁸ The last criterium states that if the positive consequences clearly outweigh the negative consequences, costs and savings of the screening programme should be calculated and checked in view of a fair distribution of resources within the total area of the health services. We started a prospective evaluation to determine the cost-savings balance of CF screening and related the costs to effect measures. If the economic balance will turn out to be unacceptably unfavourable, CF screening is not warranted anyhow. If, on the other hand, the economic balance is favourable, decision making can concentrate on the crucial non-economic aspects.

Several screening strategies have been suggested^{9–12} and are being or have been analysed in a pilot study.^{13–21} Of these, prenatal, preconceptional, school, and neonatal screening can be considered for general population screening. For the prenatal and preconceptional screening strategies we considered both single entry and double entry two step couple screening (see below). Analogously to Morris and Oppenheimer,²² we did not consider cascade screening (screening of relatives of patients) in this analysis, because the approach is completely different from general population screening. Furthermore, Holloway and Brock²³ have shown that cascade testing is not very effective, as only between 8% and 24% of all carrier couples would be detected if cascade

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testing were restricted to up to the second cousin level.

We calculated the costs, effects, and savings of the screening strategies and compared them with a situation in which there is no CF gene carrier screening. For a one year screening period, we simulated the effects on individuals and couples under certain assumptions concerning reproductive decision making. Although our main analysis uses population genetic figures and cost estimates for the Netherlands, other combinations of assumptions can be analysed as well with our model. In this paper, we will only analyse other carrier frequencies as they may occur in other countries.

Methods

We developed a simulation model for a screening programme for CF gene carriers. We prospectively evaluated four different screening strategies taking the Dutch situation as an example: prenatal screening, preconceptional screening, school screening, and neonatal carrier screening. For each screening strategy we calculated the expected costs, effects, and savings for a one year screening period. CF related costs and savings that occur after that year were taken into account using a five per cent annual discount rate.²⁴

To see by what extent the cost-savings balance depends on our assumptions, we conducted two threshold analyses. In a single-variable threshold analysis, we determined for selected assumptions the maximal or minimal value of that assumption for which savings equal costs. In a multi-variable threshold analysis, we varied these assumptions simultaneously and determined at what percentage change in all assumptions savings equal costs. Furthermore, we examined the influence of the CF gene carrier prevalence on the cost-savings balance. After a brief explanation of the screening strategies, we describe the assumptions and parameters that we used in our analysis.

SCREENING STRATEGIES

Prenatal screening

In the prenatal screening strategy, pregnant women and their partners are screened as early in their pregnancy as possible so that chorion villus sampling may still be possible in case both are carriers. Prenatal screening is the only form of screening in which prevention of pregnancy is not possible. Only for the future children all reproductive options are open. Because almost all women who suspect to be pregnant consult a general practitioner or midwife, it is relatively easy to integrate this form of CF gene screening in the existing health care system. Observed participation rates in the UK range from 62% to 91%.^{18 25-27}

Preconceptional screening

Preconceptional screening concerns couples who consider having a child and want to receive information about their carrier status. The screening result is known before the (potential) reproduction so that all reproduc-

tive options are open to the carrier couples, for example, accepting the risk of giving birth to a CF child, having prenatal diagnosis possibly followed by induced abortion, refraining from having (more) children, adoption, artificial insemination with donor sperm or egg cell donation and pre-implantation diagnosis. For most countries (including the Netherlands) an important obstacle to preconceptional screening is the absence of a preconceptional consultation system. Observed participation rates in the UK range from 4% to 87%, and depend very much on the way people are approached.^{13 14 28}

School screening

In the school screening strategy, acquisition of the testing material (for example, mouth washes) can take place within the school environment. For minimising the time between screening and (potential) reproduction, pupils in the last year of compulsory education (at the age of 16 in the Netherlands) should be offered the test. From a social-genetic perspective, this type of screening also offers a good opportunity for teaching genetics. Good information is important because school screening takes place in a rather unstable stage of life, possibly leading to stigmatisation. Studies in Italy and Canada on thalassaemia and Tay-Sachs disease screening, and for CF carrier screening in Australia and Canada show that school screening is feasible.^{21 29-31} Observed participation rates for screening in high schools range from 42% to 75%.^{21 31}

Neonatal screening

In the neonatal carrier screening strategy, the target population consists of newborn children who are tested in the first months after birth. As almost all newborns are already tested on PKU/CHT by a blood spot, CF gene screening can easily be integrated into the existing screening programme. If a newborn child turns out to be a carrier the target population can be extended to the parents, and if both turn out to be a carrier they can use this information in making further reproductive choices.

However, there are also disadvantages for this strategy. Firstly, screening for curable diseases (PKU/CHT) that have a routine character will be combined with screening for carriership of a (still) incurable disease (CF). Secondly, the information regarding carriership only becomes relevant to the newborn for reproductive decisions after 20 to 30 years. This necessitates considerable efforts for retaining this information that can be helped by, for example, a computer database or an individual health passport.

Single entry versus double entry in prenatal and preconceptional screening

In the school and neonatal screening strategies, single persons are screened. For prenatal screening and preconceptional screening however, we deal with couples and the test can be offered with single or with double entry.^{27 32-34} We assumed that in the single entry two step screening framework (SETS), one partner is

tested initially for carriership of the $\Delta F508$ mutation only. In case he/she is a carrier, the sample of the second partner will be searched for a total of 17 mutations. For the double entry two step screening framework (DETS), we assumed that the mouth wash sample of both partners is initially tested for the $\Delta F508$ mutation and that the sample of the negative partner in case of a positive/negative couple is searched for the other 16 mutations.³² We have assumed that testing material will be directly obtained from both partners, even in the SETS framework. In this way, the partner who is not tested initially does not have to make extra arrangements to be tested in case his/her partner is shown to be a carrier. For the school and neonatal screening programmes, we assumed that for cost considerations the individuals are tested only for the $\Delta F508$ mutation (see also the discussion).

PREVALENCE

The prevalence of CF gene carriers varies between populations; in the Netherlands it is one in 30.³⁵ The $\Delta F508$ mutation is identified in 73.6 per cent of all CF genes and 16 other mutations account for 11.9 per cent.³⁶ It is therefore possible to identify 85.5 per cent of all mutations with a 17 mutations screening test. As a comparison, the prevalences in the United Kingdom and the United States are 1:25 to 1:28, while the $\Delta F508$ mutation accounts for 70–77 per cent of all CF genes and five to 11 other mutations for 15–20 per cent, depending on racial and ethnic background.^{37 38}

In the Netherlands, the presence of autosomal and sex chromosome abnormalities is checked for routinely when chorion villi are analysed for CF. Therefore we took these abnormalities into account, with a prevalence at time of prenatal diagnosis of 1:500 for both autosomal and sex chromosome abnormalities.³⁹

TARGET POPULATIONS

We assumed that the target population of prenatal screening consists of couples who are pregnant with their first child. We used the number of firstborn children, 85 030 in 1995 in the Netherlands,⁴⁰ but corrected for the probability of spontaneous abortion between the time of screening and time of birth (3.5% for low risk pregnancies⁴¹), leading to a target of 88 241 couples (see first line of table 1). For preconceptional screening, the number of firstborn children was corrected with a 10% probability of a couple remaining infertile,⁴² so that the target of preconceptional screening consists of 94 478 couples. The target population of

school screening consists of 183 060 people of 16 years.⁴³ We assumed that 90% of them will form a couple that wants a child, and 10% of these couples remain infertile.⁴⁴ For neonatal screening, the target population consists of all 190 513 children that were born in 1995,⁴⁰ again it is assumed that 90% of them will form a couple that wants a child and that 10% of these remain infertile.⁴⁴

We assumed that in all screening strategies, 84.9% of the people with a firstborn child will have a second child after 2.9 years on average.^{40 44} For computational simplicity, we ignore in our calculations births of children who are thirdborn or more. This assumption will obviously not have effects on the costs per detected carrier couple, but will lead to a conservative estimate of the cost-savings balance.

COVERAGE AND INFORMATION PRESERVATION

As discussed in the description of the strategies, the coverage that may be achieved is probably highest for neonatal screening, somewhat lower for prenatal screening, and again somewhat lower for school screening; we set these values at 95%, 90%,^{18 27} and 85%,⁴⁵ respectively. For preconceptional screening, coverage depends very much on the existence of a preconceptional consultation system and on the way in which people are approached^{13 14}; we took 50% coverage as baseline value.

In the Tay-Sachs disease prevention programme in Montreal, Zeesman *et al*³⁰ found that after eight years 90% of the screened pupils were able to retrieve the test result regarding carriership. Because the time between testing and possible use of the carrier information for school screening is of the same order of magnitude (12 years in our analysis), we took this value for the information retention rate of school screening. For neonatal screening, the time between testing and possible use of the information equals 28 years in our analysis, leading to a lower retention rate. Moreover, carrier status information has to be passed from the parents to the screened child at some time. For these reasons we presumed an information retention rate of 70% for neonatal screening. Furthermore, we assumed that individuals who have not retained their test information will not be retested. We summarise the estimates for coverage and information preservation in the second and third row of table 1.

OTHER ASSUMPTIONS

Furthermore, to assess the consequences of CF gene screening, we had to make a number of assumptions concerning reproduction and use of prenatal diagnosis. In the published pilot carrier screening studies that actually tested persons, 95% of all detected carrier couples opted for prenatal diagnosis and 92% of all affected fetuses were aborted subsequently.^{25-27 46-51} However, these figures were based on very small numbers, and the attenders in these pilot studies might be a selected group that is favourably biased towards screening, prenatal diagnosis, and abortion. Therefore, we decided to take somewhat more conservative estimates and presumed

Table 1 Assumptions that differ between CF gene screening strategies: size of target population, coverage, information preservation, and costs

	Screening strategy			
	Prenatal	Preconceptional	School	Neonatal
Size of target population	88 241	94 478	183 060	190 513
Coverage of screening (%)	90	50	85	95
Information preservation (%)	100	100	90	70
Mass information costs (£)	136 957	228 261	182 609	136 957
Individual information costs (£)	2.37	1.19	0.59	1.19
Organisation costs (£)	9.04	9.04	9.04	0.00

that 15% of the detected carrier couples refrain from having (more) children,⁵² that 85% of the carrier couples make use of prenatal diagnosis, that in 80% of diagnosed affected fetuses parents make the choice for selective abortion, and that prenatal diagnosis carries an attributable risk of iatrogenic abortion of 0.75%.⁵³ Furthermore, we took into account spontaneous abortions. Most of the assumptions were subjected to a sensitivity analysis.

ECONOMIC FACTORS

The costs of screening can be divided in three aspects: the costs of spread of information before the screening—for instance by mass media and leaflets—the costs of the organisation of the screening and the testing itself, and the costs of aftercare. We estimated the costs from a societal point of view: costs are measured by calculating invested manpower and materials with relevant wages and prices. Resulting figures will differ from those obtained when using a purely financial point of view, where commercial prices of, for example, kits are used, including so called transfer payments (for example, profits, margins, tariffs, taxes, royalties).⁵⁴ We regarded as economic savings the precluded lifetime medical costs of patients who will be born less as a result of the screening programme. Because costs of diagnosis and treatment of CF occur at a later point in time than the actual screening, they were recalculated to the (present) value in the year of screening using an annual discount rate of five per cent.²⁴

Costs of information

We divided the information costs into two parts (see table 1): the mass information costs that depend on the target group—for example, costs of mass media campaigns—and the individual information costs that are proportional to the number of individuals or couples—for instance costs of leaflets.

Van der Maas *et al*, studying the costs and effects of mass screening for breast cancer in the Netherlands, obtained £228 261 for the mass information costs and £1.19 for individual information (costs adjusted for inflation between 1990 and 1996).⁵⁵ As we may regard the way of information provision in the preconceptional screening strategy as somewhat analogous to that for the breast cancer screening programme, we took these values as baseline cost estimates for the preconceptional screening programme. Because of its easy integration in the existing health care system, we set the mass information costs for prenatal and neonatal screening lower at 60% of the value for preconceptional screening and we took the school mass information costs at 80% because of the integration in the school setting.

The individual information costs are likely to be highest for prenatal screening because of the direct consequences and emotional sequelae of the test outcome. Therefore we estimated them as twice the costs of individual information for preconceptional screening at £2.37, which is comparable to the costs used by Cuckle *et al*.²⁶ We set the individual information costs lowest

for school screening at 50% of the value of preconceptional screening. The individual information costs to the parents in the neonatal screening strategy were set at the same value as the costs in the preconceptional screening strategy.

Costs of testing

Costs of testing can be subdivided into costs of acquisition of the sample of an individual or couple, shipment of the samples to a laboratory, DNA extraction, DNA analysis, reporting of the results, and costs for the screenee. The so called organisation costs of acquisition, shipment and administration were estimated at £9.04 per couple for prenatal, preconceptional, and school screening. Organisation costs for neonatal screening were ignored because the CF test is assumed to supplement the already existing screening programme for PKU/CHT in the Netherlands; therefore costs of acquisition, shipment, and reporting of the results will not change or change only very slightly if a screening test is added to the PKU/CHT programme. Estimates of the costs of DNA testing for multiple mutations in the United Kingdom range from £30 to £39.^{22 26 56} In our analysis, we took the cost estimate of Cuckle *et al* (£33)²⁶ for the multiple mutations test. The $\Delta F508$ mutation analysis can be performed with a comparatively cheap in house polymerase chain reaction, and is done in much larger quantities than the multiple mutations tests. Therefore we assumed that the cost of DNA testing for the $\Delta F508$ mutation only would cost only a quarter of the multiple mutations test (£8.25). For the costs for the screenee, we took the costs of travelling by public transport and the costs of production loss (one hour for travelling to the screening, waiting time, and the time of screening),⁵⁷ totalling £5.72.

Costs of further diagnosis and treatment

Aftercare consists of counselling carrier couples and positive/negative couples and, depending on the choice of the couple, prenatal diagnosis for detected carrier couples and eventually, depending on the couples decision, abortion of an affected fetus. For counselling we took the costs of a qualified nurse in a clinical genetics centre, assuming that counselling a carrier couple takes one hour²² and counselling a positive/negative couple takes a half hour. At an hourly wage of £16.60 and an overhead percentage of 40%, counselling costs to the clinical genetics centre are £23.24 for a carrier couple and £11.62 for a positive/negative couple. For the carrier couple, we added 15 minutes of waiting time and the costs of public transport to the counselling costs, totalling £9.15 for positive/positive couples and £6.87 for positive/negative couples.⁵⁷ The costs of prenatal diagnosis, selective abortion, early spontaneous abortion, late spontaneous abortion, and iatrogenic abortion were based on Dutch reimbursements between health care providers, government, and insurance companies: £1106.72, £192.51, £60.30, £387.06, and £60.30 respectively.^{58 59}

Table 2 Costs, effects, and savings per year for a CF gene screening programme. See text for further assumptions. Costs and savings are rounded to £1000

	Screening strategy					
	Prenatal		Preconceptional		School	Neonatal
	SETS*	DETS*	SETS*	DETS*		
Costs of information	382 000	382 000	375 000	375 000	261 000	406 000
Costs of testing	2 679 000	3 821 000	1 841 000	2 528 000	2 697 000	1 742 000
Costs of aftercare	146 000	200 000	74 000	107 000	81 000	162 000
Total costs of screening	3 207 000	4 403 000	2 290 000	3 010 000	3 039 000	2 310 000
Detected carrier couples	56	63	33	38	36†	112†
Costs per detected carrier couple	58 000	70 000	69 000	80 000	85 000	21 000
Number of avoided patients	18	21	10	12	8	13‡
Costs per avoided patient	177 000	213 000	223 000	258 000	367 000	178 000
Net economic savings (savings minus costs)	1 397 000	800 000	208 000	-186 000	-1 843 000	-191 000

*SETS=Single Entry Two Step couple screening; DETS=Double Entry Two Step couple screening. †Number of couples whose members both have retained their carrier information until their reproductive period; ‡including seven patients born less because parents are shown to be a carrier couple due to their first carrier child being detected.

Lifetime costs of a CF patient

By means of an examination of the medical records of 81 patients (40 men, 41 women) and a patient questionnaire among 73 patients,² we estimated the age specific cost of illness of a CF patient. We converted this cost of illness into the average lifetime excess costs of care of a CF patient by adjusting for the survival figures of CF patients and discounting at five per cent.¹ The lifetime excess costs of care of a CF patient in the Netherlands were in this way estimated to be £238 634 (corrected for inflation).

Results

Lowest total costs of screening are achieved with single entry preconceptional screening, and with neonatal screening (upper part of table 2). The costs of the other strategies are much higher. The double entry two step (DETS) frameworks for preconceptional and prenatal screening have much higher costs than their single entry counterparts (SETS), because the number of tests performed is almost twice as high.

With regard to the number of detected carrier couples, neonatal screening performs best (112 carrier couples detected). If testing of parents of diagnosed carrier newborns (which is an extra possibility of neonatal screening only) would not be included in the calculations, double entry prenatal screening detects most carrier couples (63 couples). As expected, double entry screening detects more carrier couples than single entry screening (63 compared with 56 couples for prenatal screening). The costs per detected carrier couple are by far lowest for neonatal screening, because its organisation costs are set at zero. The SETS versions of prenatal and preconceptional screening perform much better than the DETS versions, for example, £58 000 and £70 000, respectively for prenatal screening.

When we want to carry the economic analysis of the screening programmes further, we need to calculate the number of patients that are born less as a result of the screening programme (third part of table 2). This number is defined as the number of patients not born because the (would be) parents decide to refrain from having (more) children or to have an induced abortion in case of an affected fetus. In the neonatal screening strategy, some patients are born less because

the first child is detected carrier, and in the follow up his/her parents appear to be a carrier couple and decide to refrain from further children. The DETS framework of prenatal screening results in the highest number (21 patients) of avoided patients. Because we assumed that individuals who have not retained their test information are not retested, school screening does not result in many avoided patients (eight patients). In the neonatal screening strategy, seven patients less are born because the first child is detected carrier. The number of avoided patients in the preconceptional screening strategy is rather small because of its low coverage.

The net economic savings (savings minus costs) are positive for both antenatal screening strategies and the single entry version of preconceptional screening. The costs of double entry preconceptional, school, and neonatal screening are higher than the economic savings, mainly because of the high polymerase chain reaction screening costs, which account for more than 25% of the total costs of these screening programmes. Maximum net economic savings are obtained in the SETS version of prenatal screening (£1.4 million).

THRESHOLD ANALYSIS

We calculated for selected parameters the values for which savings exactly equal costs while keeping all other parameters at their baseline values (table 3). Even if carrier couples never refrain from having more children, prenatal screening and SETS preconceptional screening have a favourable cost-savings balance. The savings of DETS preconceptional screening would be higher than its costs if more than 29% of all carriers would refrain from having children, while an unrealistic 96% of all carriers should refrain to achieve higher savings than costs for neonatal screening. Even if all carrier couples would refrain from having children, costs exceed savings for school screening.

For the prenatal screening programmes, the fraction of the carrier couples that will use prenatal diagnosis can decrease to 74% or less before costs exceed savings, and for SETS preconceptional screening the threshold is 78%. If more than 95% of all carriers would have prenatal diagnosis, even DETS preconceptional screening and neonatal screening would have

higher savings than costs, while costs always exceed savings for school screening, even if all couples will use prenatal diagnosis. The threshold values for the fraction that decides to have an affected fetus aborted are similar to the thresholds for the fraction of the carrier couples that will use prenatal diagnosis, because these two parameters act “multiplicatively” on the number of avoided patients.

Coverage of screening does not influence the cost-savings balance very much because a large part of the costs are so called variable costs that are proportional to coverage. However, savings in the DETS preconceptional screening strategy would be higher than its costs if a coverage higher than 66% is attained. Even if all people would be screened, costs of school and neonatal screening are higher than the savings. Attaining a high enough information preservation is rather important, as the costs exceed savings for SETS preconceptional screening and prenatal screening if many people would forget the test results. If an information preservation of more than 94% would be reached, savings of neonatal screening would be higher than the costs. For school screening and DETS preconceptional screening, costs are always higher than savings.

Because the costs of individual information do not form a large part of total costs, these costs do not influence the cost-savings balance very much: the costs can be more than two times higher before costs exceed savings for the prenatal and preconceptional SETS screening strategies. Even if the costs of individual information would be zero, costs exceed savings for school screening and DETS preconceptional screening.

Costs of testing form a large part of total screening costs, ranging from 24% in antenatal SETS screening to 48% in neonatal screening. For prenatal screening and SETS preconceptional screening, costs will be higher than savings only if the costs of tests rise by more than 37%. However, if the costs of the tests could be lowered by approximately 20% all screening strategies (except school screening) would have a positive costs-savings balance.

KEY POINTS

- Prenatal screening detects more carrier couples and leads to less CF patients than the other screening options.
- Costs of screening are lowest for the preconceptional screening strategy.
- School carrier screening is unlikely to ever satisfy conditions under which costs are less than savings.
- Savings of neonatal carrier screening will exceed its costs only under strict conditions.
- If CF screening is judged to be useful on medical grounds, costs considerations are no obstacle for prenatal screening and for SETS preconceptional screening.

In the multi-variable threshold analysis, we determined by what percentage the parameter values mentioned in the single-variable threshold analysis could deteriorate simultaneously from the baseline values before costs exceed savings (see the last line of table 3). As an increase in the parameter values (except for costs of information and costs of testing) leads to higher savings or lower costs, or both, we decreased these values by a given percentage, while we increased the costs by that same percentage. The conclusion of this multi-variable threshold analysis is that the parameter values for the prenatal screening programmes can deteriorate 4% or more, and the values for SETS preconceptional screening 2%. On the other hand, the parameter values of DETS preconceptional screening and neonatal screening should improve 3% before savings exceed costs, while school screening will never have a favourable costs-savings balance.

OTHER CF GENE CARRIER PREVALENCES

As the CF gene carrier prevalence varies between countries, we calculated the net economic savings for carrier prevalences between one in 35 and one in 25 (fig 1). Using this figure, readers can determine the net

Table 3 Single and multi-variable threshold analyses. The table gives the threshold value for which costs of screening equal savings. Between parentheses: the ratio of threshold to baseline value. Costs and savings are discounted at 5% per year

	Screening strategy					
	Prenatal		Preconceptional		School	Neonatal
	SETS*	DETS*	SETS*	DETS*		
Single variable threshold analysis						
Fraction of the carrier couples that will refrain from having a child (baseline: 15%) (%)	†	†	†	29 (×1.92)	‡	96 (×6.41)
Fraction of the carrier couples that will use prenatal diagnosis (baseline: 85%) (%)	63 (×0.74)	74 (×0.87)	78 (×0.92)	93 (×1.09)	‡	95 (×1.12)
Fraction of the affected fetuses that will be selectively aborted (baseline: 80%) (%)	54 (×0.67)	67 (×0.84)	71 (×0.89)	87 (×1.09)	‡	89 (×1.12)
Coverage of screening (%)	25 (×0.27)	40 (×0.44)	37 (×0.74)	66 (×1.32)	‡	‡
Information preservation (%)	77 (×0.77)	89 (×0.89)	94 (×0.94)	‡	‡	94 (×1.35)
Costs of individual information	£16.74 (×7.05)	£10.60 (×4.46)	£3.19 (×2.68)	‡	‡	£0.30 (×0.25)
Cost of ΔF508 mutations test (baseline: £8.25)	£22.46	£12.76	£11.33	£6.64	‡	£6.82
Cost of multiple mutations test (baseline: £33.00)	£89.86 (×2.72)	£51.03 (×1.55)	£45.33 (×1.37)	£26.55 (×0.80)	‡	£27.29 (×0.83)
Multi-variable threshold analysis (%) §	8	4	2	-3	‡	-3

*SETS=Single Entry Two Step couple screening; DETS=Double Entry Two Step couple screening. †For every value of the parameter, savings exceed costs; ‡for every value of the parameter, costs exceed savings; §all parameter values can simultaneously decrease by this percentage (respective increase for costs of individual information and costs of testing) before costs will exceed savings.

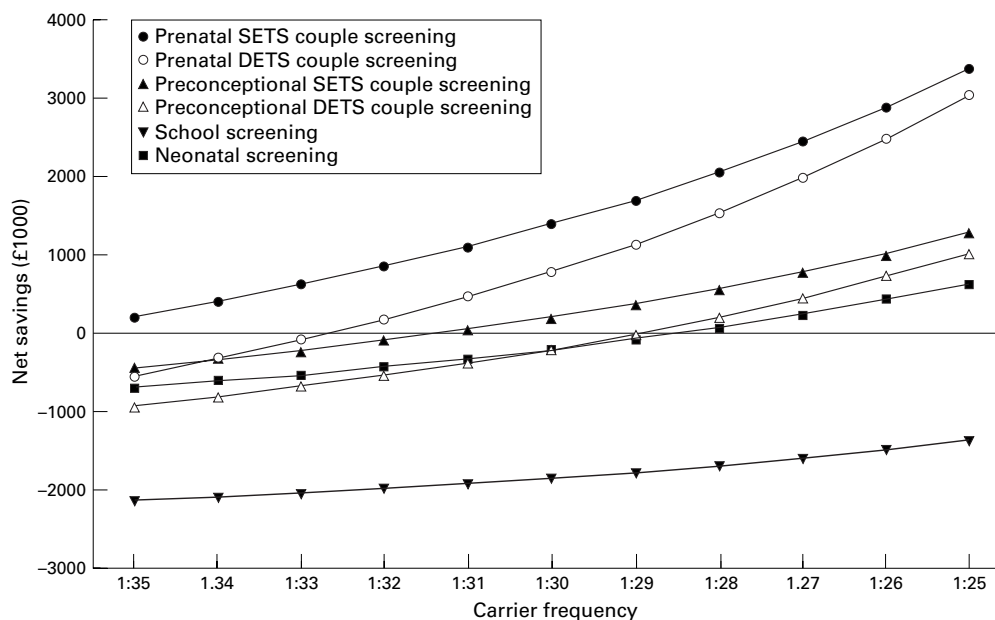


Figure 1 Net economic savings (in £) per year for six CF gene screening strategies for different CF gene frequencies.

economic savings in their country or situation, provided the costs structure is similar to the one we used.

As expected, the cost-savings balance worsens for all strategies if the carrier frequency is lower, but single entry prenatal screening remains the best strategy from a costs point of view. The costs in this strategy will exceed the savings only if the carrier frequency is lower than 1:36. If the carrier frequency is higher than 1:28, both DETS preconceptional screening and neonatal screening will have a favourable cost-savings balance. This means that, other things being equal, prenatal, preconceptional, and neonatal screening would have higher savings than costs in countries (for example, UK and USA) where the CF gene carrier frequency is higher than one in 25. School screening will only have higher savings than costs with a theoretical carrier frequency of 1:18.

Discussion

Using a decision analytic model we found that there are no economic objections against prenatal screening and single entry preconceptional screening for carriers of the CF gene when we take costs of care of CF patients into account. For double entry preconceptional screening, neonatal screening, and school screening, costs are higher than savings. In a sensitivity analysis, this conclusion remained valid for prenatal and single entry preconceptional screening programmes for a wide range of other plausible assumptions. For double entry preconceptional screening and neonatal screening programmes, a favourable cost-savings balance can only be obtained if uptake of screening, prenatal diagnosis or induced abortion would be higher than our assumptions, or if the costs of testing would be lowered by 20%. School screening will never have a favourable cost-savings balance.

We investigated if the poor performance of the neonatal and school screening strategies could be improved upon by testing all persons for 17 CF mutations. In this scenario more carrier couples are detected and more CF patients are avoided than in the baseline scenario, but the increased savings of the avoided patients does not offset the higher costs of screening. Consequently, this scenario has a worse costs-savings balance than the baseline scenario.

Although our model is primarily quantified for the Dutch situation of CF gene screening, it can be adapted for use in other countries or even for other autosomal recessive genetic diseases by changing the relevant parameter values. For example, because the carrier frequency in the United Kingdom is higher (1 in 25) than in the Netherlands,³⁷ screening for CF gene carriers has a better cost-savings balance, provided the costs structure, and especially the relative magnitude of costs and savings, is similar to the Dutch situation. Using the 1 in 25 prevalence of CF gene carriers, we calculated a cost per detected carrier couple of £41 000 for prenatal SETS and £49 000 for DETS. These results are much higher than those of Cuckle *et al.*,²⁶ who calculated a cost per detected carrier couple of £19 250 for sequential prenatal screening (SETS in our notation) and £22 250 for couple screening (almost similar to DETS). An explanation is that they took a 100% uptake of prenatal diagnosis and induced abortion and did not include costs of further diagnosis and treatment. Morris and Oppenheimer²² concluded that sequential prenatal screening costs £36 600 per detected carrier couple and couple screening £35 700. These costs are somewhat lower than ours because we took the costs of further diagnosis and treatment into account.

It should be borne in mind that, even when savings exceed costs, financing a screening

programme for CF gene carriers is not straightforward, because the screening budget has to be made available now, while the savings of the programme will only appear later. Moreover, savings may be realised in different budgets than the costs of screening are made, so that a conflict of interests may arise.

The reader should note that CF is a disease for which advances in medical treatment are or will (probably) be made, for example, lung transplantation and introduction of gene therapy.^{60 61} This progress in treatment will most probably have an impact on the length and quality of the life of a CF patient.⁶² Whether lifetime costs of CF for such a patient will increase or decrease remains to be seen. And when—hopefully—treatment improves the life of CF patients even more, screening for CF gene carriers will be a thing of the past.

This paper focused deliberately on costs aspects. There is much more to be discussed in genetic screening than costs. Economic considerations should not be the primary goal of any screening programme, but a careful costs analysis and a discussion of cost effectiveness and the costs-savings balance as reported in this paper, is an essential part of a full evaluation. Prenatal and single entry preconceptional CF screening have from an economic point of view roughly comparable and reassuring costs prospects. When other aspects are also considered, single entry preconceptional screening, which has a slightly worse cost-savings balance, possibly has to be preferred because with that strategy all reproductive options are still open for a carrier couple. Lack of participation will not be irreparable when prenatal screening is used as a “safety net” for pregnant couples who did not attend the preconceptional screening programme.

Addendum

Readers who would be interested to have an analysis of costs, effects, and savings performed for their specific situation are invited to contact the authors.

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