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Original Article

Cost-effectiveness of newborn screening for cystic fibrosis determined with real-life data

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Abstract

Background: Previous cost-effectiveness studies using data from the literature showed that newborn screening for cystic fibrosis (NBSCF) is a good economic option with positive health effects and longer survival.
Methods: We used primary data to compare cost-effectiveness of four screening strategies for NBSCF, i.e. immunoreactive trypsinogen-testing followed by pancreatitis-associated protein-testing (IRT–PAP), IRT–DNA, IRT–DNA–sequencing, and IRT–PAP–DNA–sequencing, each compared to no-screening. A previously developed decision analysis model for NBSCF was fed with model parameters mainly based on a study evaluating two novel screening strategies among 145,499 newborns in The Netherlands.
Results: The four screening strategies had cost-effectiveness ratios varying from €23,600 to €29,200 per life-year gained. IRT–PAP had the most favourable cost-effectiveness ratio. Additional life-years can be gained by IRT–DNA but against higher costs. When treatment costs reduce with 5% due to early diagnosis, screening will lead to financial savings.
Conclusion: NBSCF is as an economically justifiable public health initiative. Of the four strategies tested IRT–PAP is the most economic and this finding should be included in any decision making model, when considering implementation of newborn screening for CF.

Keywords: Cystic fibrosis; Newborn screening; Cost-effectiveness

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1. Introduction

Cystic fibrosis (CF) is one of the commonest autosomal recessively inherited disorders in Caucasian populations. Early detection of patients with CF by newborn screening aims to start treatment as early as possible to prevent malnutrition and irreversible lung damage.

Previously, we assessed the cost-effectiveness of newborn screening for CF (NBSCF) on a hypothetical birth cohort for different screening strategies based on immunoreactive trypsinogen (IRT) and DNA testing. This study, using a decision analysis model with data from the literature, showed that NBSCF is a good economic option, with positive health effects being expected [1]. Subsequently, in 2008 and 2009 we

Table 1
Model parameters: base-case values and lower and upper values in sensitivity analysis, and distribution for the probabilistic multivariate sensitivity analysis.

Model parameter	Base-case value	Lower value sensitivity analysis	Upper value sensitivity analysis	Distribution
Epidemiology				
Yearly number of neonates born in The Netherlands	185,000			
Participation CF-screening	99.7%	99.5%	99.8%	Triangular
Incidence of CF (classic)	0.021% (1 per 4750)	0.018% (1 per 5500)		Triangular
% newborns with meconium ileus	17%	15%	19%	Triangular
Sensitivity and specificity				
Sensitivity IRT-test (cut-off 60 μg/l)	95.6%	90%	100%	Triangular
Sensitivity PAP-test	95%	90%	100%	Triangular
Sensitivity DNA-test	99%	95%	100%	Binomial
Sensitivity sequencing	100%	97%		Uniform
Specificity IRT-test (cut-off 60 μg/l)	98.99%	98.94%	99.04%	Poisson
Specificity PAP-test	89.99%	88.32%	91.46%	Binomial
Specificity DNA-test	100%			
Specificity sequencing	100%			
Mutations at DNA-test and need for sequencing				
% infants with positive IRT test having 1 mutation at DNA-test	4.6%			
% infants with positive IRT–PAP having 1 mutation at DNA-test	5.4%			
% CF patients with 1 mutation detected by DNA-test	11%	5%	17%	Binomial
Health effects				
CF mortality in childhood (at age of 5 years)	6%	3%	10%	Triangular
Reduction in childhood CF mortality due to screening	25%		50%	Uniform
No of life-years gained per prevented death due to screening (3% discounting)	40 (20.5)	35 (19.4)	45 (21.8)	Triangular
% parents opting for genetic counselling	50%	40%	90%	Triangular
% parents testing carrier status after genetic counselling	80%	50%	90%	Triangular
Costs (€)				
Adding CF screening to newborn screening programme	153,716	100,000	200,000	Triangular
IRT test	2.28			
PAP test	294,413 for a year cohort (155 per test)	200,000		Uniform
DNA test	166 (IRT–DNA–seq) 231 (IRT–PAP–DNA–seq)			
Sequencing	417			
Sweat test	274 (1st test) 206 (repeated test)			
Genetic counselling	515			
Testing for carrier status, per couple	1479			
Clinical diagnosis CF	9986	8000	12,000	Triangular
Lifetime costs of treatment for clinically diagnosed patient	895,291	750,000	1,200,000	Triangular
Number of sweat tests per screen positive child	1.17			
Savings in lifetime costs of treatment due to screening	0%		5%	Uniform
Number of sweat tests for diagnosis of non-CF patients per clinically diagnosed CF patient	100 without screening. With screening: 50% of no without screening	With screening: 10% of no without screening	With screening: 100% of no without screening	Triangular

evaluated pancreatitis-associated protein (PAP)-testing, a new promising second tier after IRT-testing in NBSCF [2] together with another strategy for NBSCF, i.e. IRT–DNA-sequencing (seq) [3] in the CHOPIN study among 145,499 newborns in The Netherlands [4].

The current study assessed the cost-effectiveness of four screening strategies, i.e. IRT–PAP, IRT–DNA, IRT–DNA–seq, and IRT–PAP–DNA–seq compared to a no-screening situation, based on the decision analysis model and real-life data from CHOPIN.

2. Material and methods

We compared lifetime costs and effects of NBSCF with a situation without screening in The Netherlands by using the previously developed decision analysis model, using a societal perspective [1]. All costs and effects were discounted at a rate of 3% to convert future costs and effects to their present value [5]. Model parameters (Table 1) on test results and costs were based on primary data collected in the CHOPIN study [4] and extrapolated to a cohort of 185,000 newborns, the approximate annual number of births in The Netherlands. For other parameters literature review and expert opinions were used.

2.1. Epidemiology

The birth prevalence of CF in The Netherlands is estimated to be 1 in 4750 [6]. With 185,000 newborns, approximately 39 children with CF are born each year. Meconium ileus (MI) is the presenting sign in about 17% of newborns with CF; NBSCF is not needed to detect them. We assumed 6% CF-related mortality in childhood and a life expectancy of 45 years [7–9].

2.2. Newborn screening

The percentage of children participating in newborn screening in The Netherlands was 99.8% in 2008–2009. In CHOPIN, 0.09% refused CF-screening.

Fig. 1 shows the four strategies studied. From CHOPIN these were: 1) IRT–PAP: an IRT-test followed by a PAP-test if positive; 2) IRT–DNA–seq: IRT followed by DNA mutation analysis of 35 frequently occurring *CFTR*-mutations (DNA), followed by sequence analysis of the entire coding sequencing of *CFTR* (seq) of all samples with one *CFTR*-mutation. Post-hoc we evaluated 3) a combination of strategies from CHOPIN (IRT–PAP–DNA–seq): IRT if positive followed by PAP, DNA if PAP was above cut-off, and sequencing if DNA

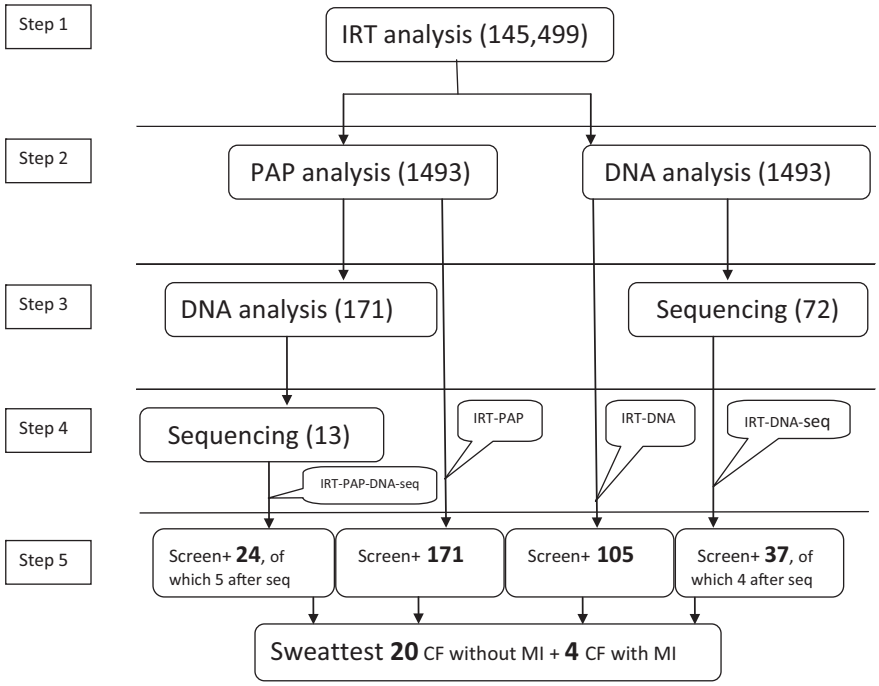

Fig. 1. Flow diagrams for four screening strategies, numbers derived from the CHOPIN study between parentheses. Step 1. All four screening strategies start with IRT-analysis. When the IRT-concentration is below cut-off level (<60 μg/l), the test is negative; when the IRT concentration is elevated (≥60 μg/l) a second step follows. Step 2. This is either a PAP-analysis or a DNA-analysis. When the PAP-concentration is below cut-off level, or when no CF-causing mutation is found in the DNA-analysis the test is negative. The PAP-test is positive if PAP-concentration is above the cut-off level (≥1.6 μg/l if IRT ≥100 μg/l and ≥3.0 μg/l if IRT ≥60 μg/l); and the DNA-analysis is positive in the IRT–DNA strategy when one or two *CFTR*-mutations are found, and in the IRT–DNA–seq strategy when two *CFTR* mutations are found, but when only one mutation is found a third step follows. Step 3. In the IRT–DNA–seq-strategy the test is negative when only one *CFTR* mutation is found after sequencing, and positive when a second *CFTR* mutation is found. In the IRT–PAP–DNA–seq strategy this step, DNA-analysis, follows when both IRT and PAP concentrations are elevated. The test is negative when no *CFTR* mutations are found and positive when two *CFTR* mutations are identified, and when only one *CFTR* mutation is found sequencing follows in step 4. Step 4. Sequencing. The test is negative when after sequencing only one mutation is found, and positive only when a second *CFTR* mutation is found. Step 5. All children that are screen-positive (screen+) are referred for a sweat test. CF diagnosis is confirmed when Cl ≥ 60 mmol/l, excluded when Cl < 30 mmol/l, and equivocal when between 30 and 60 mmol/l.

revealed one *CFTR*-mutation; 4) the most applied strategy worldwide (IRT–DNA): IRT followed by DNA if IRT is above cut-off. In strategies 2 and 3 the screening was only considered positive when two *CFTR*-mutations were identified, but in 4 the screening was considered positive with the identification of one or two pathogenic *CFTR*-mutations [10]. In the post-hoc evaluation of strategy 4 data on sweat tests were lacking when only one DNA-mutation was found. We considered these cases as healthy carriers, and assumed a normal sweat test.

Screen-positive newborns were referred for sweat testing to confirm (Cl ≥60 mmol/l) or exclude CF (Cl <30 mmol/l). After an equivocal sweat test (30–60 mmol/l), the sweat test was repeated. An abnormal or equivocal sweat test in the IRT–PAP-strategy led to DNA-analysis and when one mutation was found to sequencing, in the IRT–DNA-strategy to sequencing if one mutation was found. Children screen-positive with IRT–(PAP)–DNA–seq with a second mutation associated with an unclear phenotype and a normal or equivocal sweat test got a second sweat test [11].

2.3. Specificity and sensitivity

Specificity and sensitivity were determined for each test separately, as the number of tests needed in steps 2 to 5 (Fig. 1) depends on the characteristics of the previous tests.

Our population study was large enough to derive specificity estimates. The specificity of IRT (cut off ≥60 μg/l) was 98.99%. The specificity of PAP (cut off ≥1.6 μg/l if IRT ≥100 μg/l and ≥3.0 μg/l if IRT ≥60 μg/l) was 89.99% (Fig. 1, [4]).

The number of CF patients detected was too small for reliable estimates of sensitivity (Fig. 1). Therefore, we also used data from other studies. The sensitivity of IRT in the French nationwide NBSCF programme among 2.7 million infants was 95.6% at 60 μg/l (95%-CI 93.3–97.1% [12]. In CHOPIN, we found a sensitivity for IRT of 100% (95%-CI 80–100%) [3].

The sensitivity of PAP was 100% in several small studies [2,13], and 84.6% (95% CI 64–95%) in 26 CF-patients without MI [14]. We used 95% as a base-case value. As PAP is preceded by IRT, these base-case values result in a detection rate for IRT/PAP being less than 95%.

The sensitivity of the DNA-test to find at least one mutation in CF-patients was 100% in the 20 CF patients without MI and 98.6% in retrospectively tested dried blood spots of CF (95%-CI 91.6–99.9%) [4]. The sensitivity of sequencing was assumed to be 100%, as all seven samples of CF patients with one mutation at the DNA-test were retrospectively found to have two mutations at sequencing, and earlier studies also found 100% by application of extended gene analysis respectively the Ambry test [3,15]. As certain gene abnormalities are not detected by sequencing, 97% was used in the sensitivity analysis.

2.4. Mutations at DNA-test and need for sequencing

4.6% of 1469 IRT-positive samples of non-CF-patients had one of the 35 *CFTR*-mutations at the DNA-test, and needed sequencing in IRT–DNA–seq to find or exclude a less common *CFTR*-mutation. For IRT–PAP–DNA–seq, 5.4% of 147 IRT- and PAP-positive samples of non-CF-patients needed sequencing [4].

Among the 20 CF patients detected through screening, 17 had 2 *CFTR*-mutations identified by the DNA-test, but in 3 patients (15%, 95%-CI 4–39%) only 1 *CFTR*-mutation was identified initially. Sequencing identified the second mutation. In retrospectively tested dried blood spots of children with CF, sequencing was necessary in 10% (95%-CI 4–19%) [4]. We assumed that in 11% of CF-patients sequencing was necessary to detect the second *CFTR*-mutation.

2.5. Health effects

We assumed a relative reduction of 25% in mortality rates among children with CF diagnosed by NBSCF compared to children with a clinical diagnosis of CF [16,17].

We assumed a gain of 40 life-years per CF death prevented by NBSCF. No gain in life expectancy was assumed for CF patients with MI, as these infants are diagnosed shortly after birth, and therefore do not benefit from NBSCF.

2.6. Costs

Costs are in 2009 Euros. Based on costs of reagents, equipment and technical and administrative personnel the costs of IRT were calculated to be €2.28 per test, assuming that a blood spot has been collected for other newborn screening tests. PAP was performed on 96-wells anti-PAP coated plates once a week (80 samples per plate). The capacity of PAP-testing in the five screening laboratories is therefore more than 20,000/year, while for a population of 185,000 newborns only 1900 tests are needed for IRT–PAP. Yearly costs are therefore almost independent of the number of PAP-tests needed, and are €294,413 for all PAP-tests needed.

The costs of DNA-testing and sequencing were respectively €166 and €417. These costs include the costs of DNA extraction, analysis, laboratory space, equipment, reagents, supplies, licenses, and technical and administrative personnel. As fixed administration and equipment costs need to be distributed among a smaller number of DNA-tests in IRT–PAP–DNA–seq, costs per DNA-test were higher for this strategy (€231).

In the IRT–(PAP)–DNA–seq strategies newborns with one *CFTR*-mutation were healthy carriers and screen-negative (Fig. 1). 87% of Dutch parents wanted to be informed about the carrier result of their child if screening would reveal this [18]. Almost 50% indicated that they want to be tested whether they were a CF-carrier themselves if their child would be a carrier. The percentage of parents accepting genetic counselling for CF is unknown at this moment. After genetic counselling for CF the uptake of genetic testing in other countries varies from 22 to 85% [19–21]. Baseline assumption in the model is that 50% of parents of carriers would accept genetic counselling, and 80% would subsequently be tested. The costs of genetic counselling are €515 per couple and if they decide to be tested for carrier status, the additional costs are €740 per person, both amounts include travel and time (2 h) costs [22].

The costs of integrating NBSCF in the existing NBS programme amount to €153,716 per year.

The costs of a first sweat test amount to €274. These costs consist of referral to a CF-centre (60 min), one outpatient visit to the paediatrician and GP, time of a CF-nurse (90 min), laboratory costs, and travel and time (120 min) costs of both parents [22]. 1.17 sweat tests per screen-positive child were needed on average [4]. The costs of a second or third sweat test were €206 as referral and consultation of the GP were not needed.

Without NBSCF generally several diagnostic tests are performed before the diagnosis CF is made. We assumed an average diagnostic cost of €9986 per patient [1]. In a situation without screening, for each clinical CF patient diagnosed about 100 sweat tests are performed in children without CF [1]. After the introduction of NBSCF, a decreasing number of sweat tests was observed in the UK [23]. The number of sweat tests after the introduction of NBSCF was assumed to eventually be 50% of the number of sweat tests without screening. In a sensitivity analysis also values of 10% and 100% were used.

Yearly costs of care were €34,839 for children up to 18 and €45,564 for adults, based on the present guidelines [24], frequency of complications from the Dutch CF-registry 2007, and 20% overhead costs. They exclude costs of home care, which were added (€5042 [25]) and costs of hospitalisation in case of complications. Estimates based on declarations at health insurance companies are about €10,000 smaller. Lifetime costs of care of a CF-patient are estimated at €895,291 (based on declarations) to €1,154,122 (based on guidelines and data from the Dutch CF-registry, both costs with 3% discounting [5]). We assumed similar lifetime costs of care for patients detected by screening, but also savings of 5% [26]. Costs in life-years gained due to NBSCF were not included in the analysis [5].

2.7. Base-case analysis and sensitivity analysis

Table 1 presents the values of the model parameters used in the base-case model. Lower and upper values of parameters in Table 1 were used in univariate and multivariate sensitivity analyses as described earlier [1]. We performed a probabilistic multivariate sensitivity analysis, with probability distributions for parameters as defined in Table 1. Uniform and triangular distributions varied between the lower and upper value, while for binomial and Poisson distributions these values presented the 95%-confidence interval. Subsequently, 50,000 random

Table 2
Overview of the predicted costs and effects of newborn screening for CF in The Netherlands for a cohort of 185,000 children (3% discounting).

	No screening	IRT–PAP	IRT–DNA–seq	IRT–PAP–DNA–seq	IRT–DNA
Numbers					
Screen-positives		222	53	37	138
Number of CF cases detected, with MI [a]		6	6	6	6
Number of CF cases detected, no MI		29	30	29	30
Number of false-positives excl. equivocal diagnosis detected		182	0	0	88 [b]
Number with equivocal diagnosis detected		4 [c]	17 [d]	3 [d]	14 [d]
Number of carriers detected		0	85	10	88 [b]
Life-years gained		9.0	9.3	8.9	9.3
Costs, k€					
Organisation		154	154	154	154
Screening		714	773	772	735
Diagnosis		78	18	10	45
Genetic counselling for carriers		0	72	9	74
Diagnosis of non-CF patients (sweat test)	883	441	441	441	441
Clinical diagnosis of missed CF cases	322	30	19	34	19
Treatment for patients identified by screening		26,144	27,148	25,791	27,148
Treatment for clinically diagnosed patients	28,872	2728	1724	3081	1724
Total (k€)	30,077	30,289	30,349	30,292	30,340
Additional costs (k€) compared to no screening		213	272	216	263
Costs (€) per life-year gained		23,600	29,200	24,300	28,200
Incremental costs (€) per life-year gained		23,600	NA	NA	147,600 [e]

k€: k€1 = €1000.

NA: not applicable, dominated screening strategy.

[a] Excluded from the analysis.

[b] Only in the IRT–DNA strategy, carriers are false-positives. In this strategy, equivocal diagnosis remains undetected in 3 children with 1 mutation, as sequencing for the second mutation is not performed.

[c] IRT–PAP-positive newborns with equivocal sweat test, who needed further diagnostic tests (DNA-analysis).

[d] Newborns with 2 *CFTR* mutations of which one or both have unclear clinical consequences, and a normal or equivocal sweat test result.

[e] Compared to IRT–PAP.

draws from the distributions were taken for each model parameter, and the resulting cost-effectiveness ratio for these parameter values was calculated. In this way acceptability curves were constructed showing the proportion of random draws for which a screening strategy is optimal as a function of the willingness-to-pay (λ). An intervention is optimal for a particular random draw when it is associated with the maximum net benefit (net benefit: [λ × life-year gained] − cost). Also, information was derived about the influence of individual parameters on the uncertainty in the cost-effectiveness ratio.

3. Results

3.1. Base-case analysis

Table 2 shows the model results of further testing after IRT as a first step in each of the four screening strategies (producing 1899 positive tests). In a situation without screening 32 children with CF without MI were expected to be born annually. IRT–PAP as well as IRT–PAP–DNA–seq would detect 29, and IRT–DNA–seq and IRT–DNA 30. The additional costs of implementing NBSCF ranged from €213,000 to €272,000 per year. IRT–PAP was the cheapest, even though costs of diagnostics of screen-positive children were the highest. The other strategies were more expensive due to higher costs of screening, and the costs of genetic counselling when detecting a carrier.

Compared to a situation without screening, strategies had cost-effectiveness ratios (CER) varying from €23,600 to €29,200 per life-year gained. However, IRT–PAP–DNA–seq was dominated by IRT–PAP, as the latter obtained more effects for lower costs. Also IRT–DNA–seq was dominated, as it resulted in the same number of life-years gained as IRT–DNA, however for higher costs. IRT–PAP had the most favourable CER of €23,600 per life-year gained compared to 'No screening'. Additional life-years could be saved by IRT–DNA.

Table 3
Univariate sensitivity analysis: cost-effectiveness ratios (CER) for lower and upper values of model parameters included in sensitivity analysis.

Model parameter	IRT–PAP		IRT–DNA–seq		IRT–PAP–DNA–seq		IRT–DNA	
	Low	High	Low	High	Low	High	Low	High
Incidence CF	41,300		47,300		42,100		46,200	
% newborns with meconium ileus	20,900	25,900	26,400	31,600	21,600	26,600	25,400	30,600
Participation newborn screening	23,600	23,600	29,100	29,200	24,300	24,300	28,200	28,200
Sensitivity IRT test	27,000	21,200	32,900	26,500	27,700	21,900	31,900	25,600
Sensitivity PAP test	26,700	20,900	BL	BL	27,400	21,500	BL	BL
Sensitivity DNA test	BL	BL	31,500	28,300	26,400	23,500	30,500	27,400
Sensitivity sequencing	BL		29,400		24,500		BL	
Specificity IRT test	24,000	23,300	31,100	27,300	24,500	24,100	30,100	26,400
Specificity PAP test	24,800	22,600	BL	BL	25,000	23,700	BL	BL
% infants with positive IRT test with 1 mutation at DNA-test	BL	BL	26,700	32,300	BL	BL	26,000	31,100
% infants with positive IRT-PAP with 1 mutation at DNA-test	BL	BL	BL	BL	23,500	25,700	BL	BL
% CF patients with 1 mutation detected by DNA-test	BL	BL	29,100	29,300	24,200	24,400	28,100	28,300
CF mortality in childhood	47,200	14,200	58,300	17,500	48,600	14,600	56,400	16,900
Reduction in childhood CF mortality due to screening		11,800		14,600		12,100		14,100
No. of lifeyears gained per prevented death due to screening	25,000	22,300	30,900	27,500	25,700	22,900	29,900	26,600
% parents opting for genetic counselling	BL	BL	27,600	35,300	24,100	25,100	26,600	34,600
% parents testing carrier status after genetic counselling	BL	BL	27,100	29,900	24,000	24,400	26,100	28,900
Costs of adding CF screening to newborn screening programme	17,700	28,800	23,400	34,100	18,200	29,500	22,500	33,200
Costs of PAP test	13,100		BL		13,700		BL	
Costs of clinical diagnosis CF	30,100	17,100	35,600	22,600	30,700	17,800	34,700	21,700
Lifetime costs of treatment for clinically diagnosed patient	BL	BL	BL	BL	BL	BL	BL	BL
Savings in lifetime costs of treatment due to screening		Savings: -k€1095		Savings: -k€1085		Savings: -k€1074		Savings: -k€1094
No. of sweat tests for diagnosis of non-CF patients per clinically diagnosed CF patient	Savings: -k€141	72,700	Savings: -k€81	76,400	Savings: -k€137	74,000	Savings: -k€92	75,500
Baseline	23,600		29,200		24,300		28,200	

CER: costs (€) per life-year gained. When screening resulted in cost savings compared to a situation without screening, CER has no meaning. Instead, cost savings (in k€, i.e. thousands of €) due to screening are presented. In these cases, life-years gained were equal to the values presented in Table 2. BL: results are equal to the results under baseline assumptions (last row).

Relating the additional life-years to the additional costs led to incremental costs of €147,600 per life-year gained for IRT–DNA compared to IRT–PAP.

3.2. Sensitivity analysis

Table 3 shows the results of the univariate sensitivity analyses. Changes in the lifelong costs of clinically diagnosed patients did not affect the CER of screening, when the lifelong costs of patients identified by screening changed accordingly. Assuming that the lifelong costs of treatment of patients detected by screening are 5% lower than the lifelong cost of clinically diagnosed patients, NBSCF would result in both financial savings and years of life gained. Reduction in the yearly number of sweat tests after the introduction of NBSCF also largely affects the costs. With a reduction to 10% of the number of sweat tests before the introduction of screening, NBSCF would result in both financial savings and years of life gained, while CERs are around €75,000 per life-year gained if the number of sweat tests remains equal.

Constructing two sets of extreme parameter values resulting in the least favourable and most favourable cost-effectiveness showed that the CER of adding screening for CF to the Dutch newborn screening programme ranged between €262,000 per life-year gained for IRT–PAP and €305,900 for IRT–DNA–seq in the least favourable situation, to both financial savings (range €2.3 million to 2.4 million) and life-years gained for all strategies (36.0 life-years) in the most favourable situation.

In the probabilistic sensitivity analysis, the uncertainty about whether screening for CF will lead to savings in lifelong costs of treatment determines the variance in the CER most. Other parameters that largely affect cost-effectiveness are lifelong costs of treatment of clinically diagnosed patients, reduction in number of sweat tests with screening, mortality in early childhood due to CF in a situation without screening, reduction in childhood mortality as a result of NBSCF, and cost of clinical diagnosis of CF.

Fig. 2 shows cost-effectiveness acceptability curves for the four newborn screening strategies and the situation of no newborn screening. At all values for willingness-to-pay until €100,000 per life-year gained, the IRT–PAP strategy has a higher probability of being cost-effective than all other strategies.

4. Discussion

The additional costs of implementing NBSCF compared to no screening ranged from €213,000 to €272,000 per year and 8.9 to 9.3 life-years were gained (Table 2). Thus cost-effectiveness ratios (CER) varied from €23,600 to €29,200 per life-year gained, depending on the screening strategy used. IRT–PAP had the most favourable CER of €23,600 per life-year gained. Using screening strategies incorporating DNA led to a gain of additional life-years. The incremental costs of these additional life-years were €147,600 per life-year gained for the IRT–DNA strategy compared to the IRT–PAP strategy. IRT–DNA–seq and IRT–PAP–DNA–seq were dominated by other screening strategies, as they resulted in similar or less life-years saved at comparable or higher costs. Also the acceptability curves show that IRT–PAP has the highest probability of being cost-effective (Fig. 2).

Calculations in our earlier study [1] were based on data derived from the literature. Changed insights of CF incidence, costs of sweat tests and lifetime costs of treatment of CF patients resulted in higher total costs in the situation without screening. Costs per

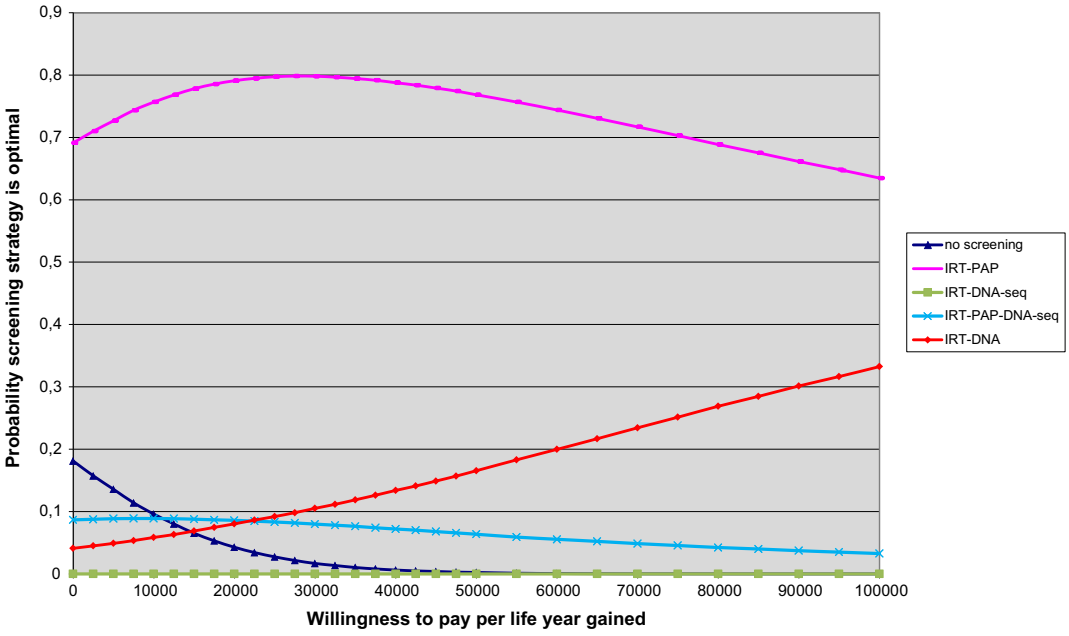

Fig. 2. Cost-effectiveness acceptability curves of the different newborn screening strategies for CF, including no newborn screening.

life-year gained due to NBSCF were smaller in the present study than calculated earlier [1], due to reduced costs of IRT-tests and reduced number of sweat tests needed for non-CF patients after the introduction of screening for CF.

Costs for IRT-DNA were assessed in a decision tree approach at $678,000 ($2010 US) for a cohort of 100,000 children, i.e. around €500,000 [27]. Rescaling our results on costs included by Wells [27] to a cohort of 100,000 results in a comparable figure of €470,000. A more favourable CER of IRT–DNA was observed earlier [9], but we included more cost elements (organisation of CF-screening, genetic counselling) and had higher cost estimates. A recent simulation study also showed that IRT–PAP is the most cost-effective strategy [28].

Some parameters still were assessed on the basis of literature and expert opinions. Sensitivity analyses showed that uncertainty on reduction of lifelong costs of treatment of CF patients detected by screening affected the cost estimates largely (Table 3). The uncertainty about the reduction in the yearly number of sweat tests after the introduction of CF-screening also affects the cost estimates.

Some elements were not incorporated in the CERs [1]. Firstly, we used the number of life-years gained as effect measure, while the preferred outcome measure would have been the number of quality-adjusted life-years gained, but there are insufficient parameters of the effect of NBSCF on the quality of life available [29]. However, it is undisputed that NBSCF leads to improved growth and nutritional status, and solid evidence is arising for a longstanding positive effect on lung function and survival in young adulthood [30]. Our baseline assumption of a 25% reduction in childhood CF mortality by NBSCF may therefore be conservative and cost-effectiveness higher than indicated. Secondly, the costs and effects of changes in reproductive decisions were not included in the CERs.

This comparison of the lifetime costs and effects of CF newborn screening for different protocols in The Netherlands, can be used by health care providers of different countries for decision making. However, the (cost)-effectiveness of every CF screening programme is also dependent on local circumstances, like quality of sample collection and testing (which affect sensitivity and specificity of the screening), diagnostic and treatment possibilities, attitude of the population towards different types of screening and genetic variation. Translation of the current result to other countries should therefore be done carefully.

In The Netherlands, costs are commonly classified as definitely acceptable up to €20,000 per QALY, as acceptable up to €40,000 per QALY. Our results confirm that NBSCF is an economically justifiable public health initiative. Of the four strategies IRT–PAP is the most economic and this finding should be included in any decision making model, when considering implementation of NBSCF. Introduction may even result in cost savings if treatment costs of CF-patients are lower after early detection, or when the number of sweat tests used for diagnosis of children with CF-like complaints decreases due to clinicians' awareness that the incidence of undetected CF is very low in screened birth cohorts.

5. Ethics approval

The Medical Ethical Committee of the Atrium Medical Centre in Heerlen approved the performance of the CHOPIN study according to the Good Clinical Practice guidelines and privacy statements.

Competing interests

None.

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