



Review

Economic evaluation of cystic fibrosis screening: A review of the literature

Muralikrishnan Radhakrishnan^{a,*}, Kees van Gool^a, Jane Hall^a,
Martin Delatycki^{b,c,d}, John Massie^{b,d}

^a Centre for Health Economics Research and Evaluation, University of Technology, Sydney, Australia

^b Royal Children's Hospital, Melbourne, Australia

^c Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Victoria, Australia

^d Department of Paediatrics, University of Melbourne, Australia

Abstract

Objectives: To critically examine the economic evidence regarding cystic fibrosis (CF) carrier screening and to understand issues relating to the transferability of international findings to any national context for policy decisions.

Methods: A systematic literature search identified 14 studies (out of 29 economic studies on CF) focusing on preconception or prenatal screening between 1990 and 2006. These studies were then assessed against international benchmarks on conducting and reporting of economic evaluations, costing methodology used and focusing on the transferability of the evidence to national contexts.

Results: The primary outcome measures varied considerably between studies and there was considerable ambiguity and variation on how costs were estimated. The Incremental Cost Effectiveness Ratio (ICER) and net savings, for preconception and prenatal screening were inconsistent and varied significantly, even after adjusting for timing and exchange rates. Differences in screening participation rates, reproductive choices, test sensitivity, cost of test and lifetime cost of care make up a large part of the ICER variations.

Conclusion: The heterogeneity in study design, model inputs and reporting of economic evaluations of CF carrier screening makes comparability and transferability across countries and even within countries difficult. This reinforces the need to assess any technology within the relevant context, and to not simply generalize from reported studies. In turn, this adds to the complex task of making efficient resource allocation decisions in the area of CF carrier screening. Our evaluation adds weight to the calls for revisiting the way economic studies are conducted and reported.

© 2007 Elsevier Ireland Ltd. All rights reserved.

Keywords: Economic evaluation; Cystic fibrosis; Screening; Costing

* Corresponding author at: Centre for Health Economics Research and Evaluation, University of Technology, City campus, Haymarket, PO Box 123 Broadway, Sydney, NSW 2007, Australia. Tel.: +61 2 9514 4743; fax: +61 2 9514 4730.

E-mail address: murali.kartha@chere.uts.edu.au (M. Radhakrishnan).

Contents

| | |
|--|-----|
| 1. Introduction | 134 |
| 2. Materials and methods | 135 |
| 3. Results | 136 |
| 3.1. Economic evidence on CF carrier screening | 136 |
| 3.2. Examining the sources of variation in economic evidence | 139 |
| 4. Consequence data | 139 |
| 4.1. Probabilities on acceptance/uptake | 139 |
| 4.1.1. Preconceptional screening | 139 |
| 4.1.2. Prenatal screening | 139 |
| 4.2. Foetal diagnosis | 139 |
| 4.3. Reproductive choices | 141 |
| 4.3.1. Preconceptional | 141 |
| 4.3.2. Prenatal | 141 |
| 4.4. Test sensitivity and specificity | 141 |
| 4.4.1. Carrier detection | 141 |
| 4.4.2. Foetal diagnosis | 141 |
| 5. Cost data | 141 |
| 5.1. Pre-screening test costs | 141 |
| 5.2. Cost of screening | 141 |
| 5.3. Costs of post-test stage (after care) | 142 |
| 5.4. Cost of care for CF patients | 142 |
| 6. Review of costing methodology | 143 |
| 7. Discussion | 143 |
| 8. Conclusion | 146 |
| Acknowledgments | 146 |
| References | 146 |

1. Introduction

Cystic fibrosis (CF) is the most common and serious genetic disease in Caucasians [1], with an incidence of 1 in 2500 and carrier frequency of 1 in 25 [2]. Most children with CF can expect to survive into adulthood, with median life expectancy in the late 30s and there is still no cure. The daily therapies are rigorous and there are many years of ill health as the suppurative lung disease progresses to death [2]. Babies with CF are usually detected by newborn screening and most of them to parents with no known family history of CF [3]. Whilst newborn screening facilitates the early diagnosis of CF and genetic counselling for affected families, organisations such as National Institutes of Health [4] and the Joint Committee of the American College of Obstetricians and Gynaecologists and the American College of Medical Genetics [5] recommend that screening tests for gene mutations that cause CF should be offered to all pregnant couples and those planning pregnancy.

Testing prospective parents for CF gene mutations is reliable [6] and can detect over 88% of carriers with a 25 mutation panel [7]. Several screening strategies have been evaluated and reported in the literature. With preconception screening, carrier couples planning children have a range of reproduction options including, refraining from having (more) children, adoption, accepting the risk of giving birth to a child with CF, having prenatal diagnosis possibly followed by termination of an affected foetus and pre-implantation diagnosis. With prenatal screening, pregnant women and their partners are screened as early as possible in their pregnancy. Should both parents be carriers, couples can choose to test the foetus through chorionic villus sampling (CVS) or amniocentesis. If the foetus is affected, parents have the choice of termination.

Screening options can be characterised by [8]:

- Timing (e.g. school-aged, while planning a pregnancy or during pregnancy);

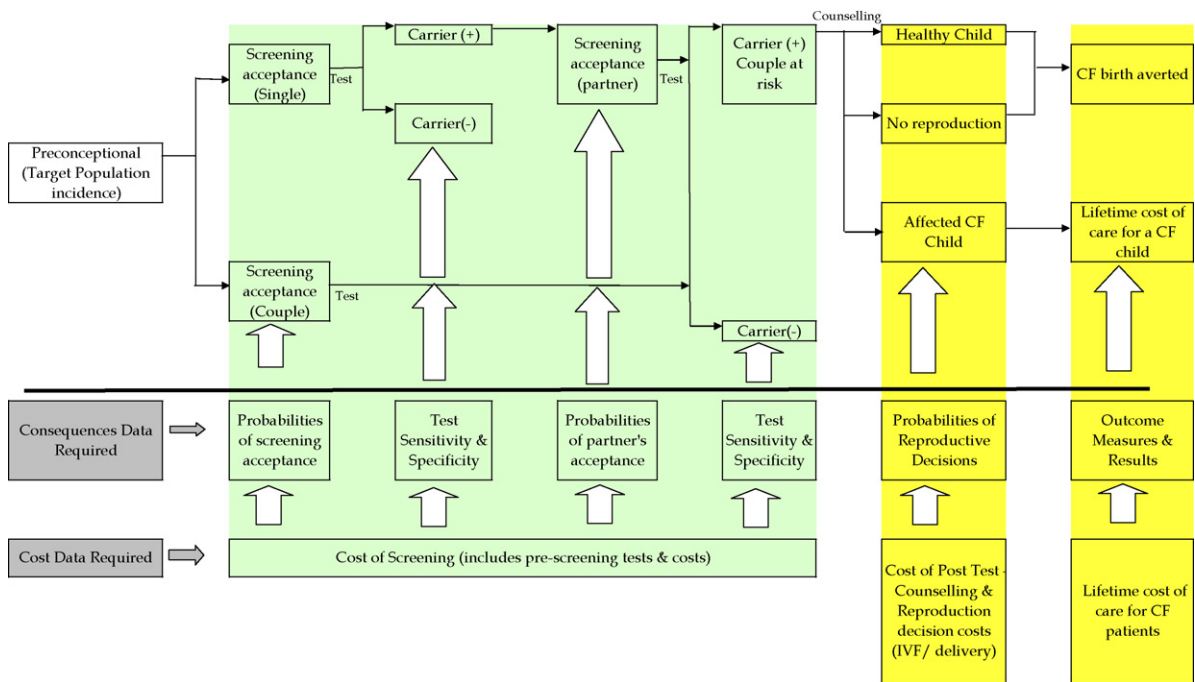


Fig. 1. Decision model of preconceptional screening.

- Model of screening (e.g. stepwise¹ (or sequential), couple² screening or cascade³ screening);
- Place of screening/by whom (e.g. GP, shared care GP, obstetrician, public antenatal clinics, schools, workplace).

A community-based screening program can incur substantial costs but also bring substantial benefits to prospective parents and to the community [9–11]. Therefore, it is important to evaluate the potential costs as well as benefits of proposed CF carrier screening. The aim of this paper is to determine whether the existing economic literature enables us to make evidence-

based recommendations. To do this we will firstly review the economic evidence, based on a systematic review of the peer-reviewed literature published between 1990 and 2006. We will report the findings and examine the consistency of results. Secondly, we evaluate strengths and weaknesses of the available literature, focusing on the transferability of existing evidence, applicability to any national setting which does not have community-based carrier screening for CF. To do this, we developed (using pathways as reported in literature) a generic CF carrier screening decision-analytic framework to identify the data requirements for modelling the costs and outcomes of community based CF screening programs—preconception screening (Fig. 1) and prenatal screening (Fig. 2) compared against no community screening.

2. Materials and methods

A systematic search on economic evaluations for cystic fibrosis was undertaken on the following databases—EMBASE, MEDLINE and the NHS Economic Evaluation DATABASE using keywords; ‘cost,

¹ With stepwise screening, women are offered carrier testing. If found to be a carrier, testing is offered to her partner after genetic counselling. Carriers may suffer anxiety while awaiting their partner’s test result, but are informed of their individual risk status, which may be used to inform relatives or to allow new partners to be tested.

² Couple screening was devised to avoid carrier anxiety if the partner tests negative. With this method, samples are taken from both partners and couples are given a positive result only if both are carriers.

³ Cascade screening is that in which the relatives of CF carriers are sought and tested.

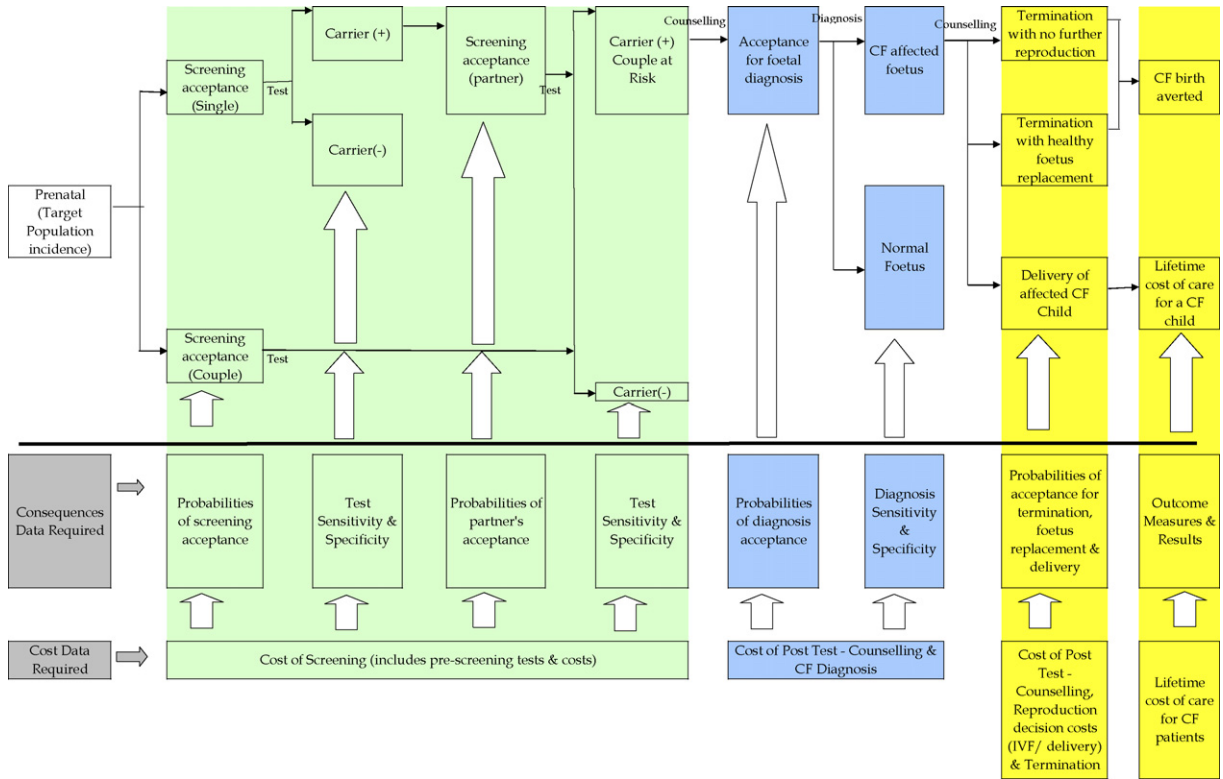


Fig. 2. Decision model of prenatal screening.

cost-effectiveness, cost utility, cost benefit, cystic fibrosis, genetic screening'. Studies that reported empirical evidence in English published between 1990 and 2006 were retrieved and references then hand searched for additional literature. Excluded studies included non-systematic reviews, correspondence, editorials, expert opinions, comments, conference proceedings and non-English language articles. The review described and appraised each study in terms of design, methods, outcomes and costs measures, probabilities reported, key results, assumptions and sensitivity of the model to changes in variables, limitations and conclusions. We then assessed to what extent the information contained in these studies could be used to complete our decision-analytic model. We tested the reproducibility and consistency of this evidence and hence the validity of transferring this information from one setting to another on the basis of standard recommendations [12], including factors identified in recent reports on transferability assessment both generally [13] and

specifically for cystic fibrosis [14]. Additionally, the quality of costing methods were reviewed using the framework suggested in the literature [15].

3. Results

3.1. Economic evidence on CF carrier screening

Searches yielded a total of 200 published articles. After exclusion and hand searches, 29 relevant economic studies were identified for review. Fifteen were from Europe, 12 from North America and 1 each from Australia and Israel. Five were published between 1990 and 1994, 13 between 1995 and 1999 and 11 between 2000 and 2006. Ten reported costs only, 10 reported only cost-effectiveness, 7 reported only cost-benefit (net savings), and 2 used a combined design—cost effectiveness (CEA), cost benefit (CBA) and/or cost utility (CUA). Only 14 studies focussed on preconcep-

Table 1
Overview of published economic evidence on preconception CF carrier screening vs. ‘no screening’

| Reference | Country | Screening strategy | Setting | Outcome measure | Reported result | Converted results (USPPP\$2005) ^a |
|--------------------------------|---------|--------------------|----------------------------|----------------------------------|------------------------|--|
| Wildhagen et al. [17] | NL | Couple | Primary care | Cost per carrier couple detected | UK£80,000 | \$154,788 |
| Morris and Oppenheimer [8] | UK | Couple | Primary care | Cost per carrier couple detected | UK£99,550 ^b | \$210,453 |
| Wildhagen et al. [17] | NL | Individual | School | Cost per carrier couple detected | UK£85,000 | \$164,462 |
| Morris and Oppenheimer [8] | UK | Individual | Workplace | Cost per carrier couple detected | UK£139,600 | \$295,121 |
| Wildhagen et al. [17] | NL | Step wise | Primary care | Cost per carrier couple detected | UK£69,000 | \$33,504 |
| Morris and Oppenheimer [8] | UK | Step wise | Primary care | Cost per carrier couple detected | UK£81200 | \$171,661 |
| Warren et al. [26] | Aus | Individual | School | Cost per carrier detected | A\$5834 | \$4,340 |
| Warren et al. [26] | Aus | Individual | School | Cost per CF birth avoided | A\$530,000 | \$394,307 |
| Weijers-Poppelaars et al. [19] | NL | Step wise | Primary care | Cost per CF birth avoided | US\$438,604 | \$445,933 |
| Weijers-Poppelaars et al. [19] | NL | Step wise | Group counselling | Cost per CF birth avoided | US\$563,316 | \$572,728 |
| Wildhagen et al. [17] | NL | Couple | Primary care | Net savings | No | |
| Wildhagen et al. [17] | NL | Individual | School | Net savings | No | |
| Verheij et al. [18] | NL | Step wise | Community and primary care | Net savings | Yes | |
| Weijers-Poppelaars et al. [19] | NL | Step wise | Group counselling | Net savings | No | |
| Wildhagen et al. [17] | NL | Step wise | Primary care | Net savings | Yes | |
| Weijers-Poppelaars et al. [19] | NL | Step wise | Primary care | Net savings | No | |

^a (Organisation for Economic Co-operation and Development [OECD] rates) with the exception of Ginsberg et al. [22], where Bank of Israel price indexes were used.

^b Midpoint.

tion or prenatal screening. One study published in the observation period used cost data from a 1970 study and so was not included in the review of economic evidence. However, due to methodological relevance, the study was included in the reproducibility and costing methodology assessments [16]. The remaining studies focussed on newborn screening for CF or were not a comparative assessment of cost and outcomes but reported only cost of care of patients with CF. None of the newborn studies were included but the cost of care studies were included in the review to highlight additional evidence on the cost of CF care.

Table 1 provides a summary of the literature on preconception screening versus ‘do nothing’. Most studies report multiple outcome measures and screening interventions and each of these were compared to the ‘do nothing’ base case. For the CEA studies, wide ranging ICER is shown even when comparing studies with identical outcome measures, similar types of interven-

tions, identical base case scenarios and after adjusting for price levels to 2005 levels using national price rise data. All reported currencies were converted to US\$ using purchasing power parity (PPP) exchange rates using OECD tables. The most common outcome measure used were the *cost per carrier couple detected*, followed by *the cost per birth of an individual with CF averted*. One study estimated the *cost per quality adjusted life-year (QALY)*.

Three studies, all set in the Netherlands, examined whether preconception CF carrier screening would result in net savings to society [17–19]. Two of these indicated that step-wise carrier screening may result in net savings [17,18] but one reported a net cost increase to society [19]. These studies consistently took into account the costs and savings to the health system but attempts to measure wider impacts (e.g., social costs, productivity losses, etc.) were not standard. Interestingly, diverse results are reported even with analyses based in the same country.

Table 2
Overview of published economic evidence on *prenatal* CF carrier screening vs. ‘no screening’

| Reference | Country | Screening strategy | Setting | Outcome measure | Reported result | Converted results (USPPP\$2005) ^a |
|------------------------------|----------|--------------------|------------------------------|---|------------------------|--|
| Cuckle et al. [28] | UK | Couple | Clinics and general practice | Cost per affected pregnancy | UK£75,000 ^b | \$158,553 |
| Cuckle et al. [28] | UK | Step wise | Clinics and general practice | Cost per affected pregnancy | UK£65,000 ^b | \$137,413 |
| Lieu et al. [10] | US | Step wise | Not stated | Cost per high-risk pregnancy identified | US\$82,000 | \$110,855 |
| Wildhagen et al. [17] | NL | Couple | Primary care | Cost per carrier couple detected | UK£70,000 | \$134,073 |
| Morris and Oppenheimer [8] | UK | Couple | Hospital | Cost per carrier couple detected | UK£35,700 | \$75,471 |
| Morris and Oppenheimer [8] | UK | Individual | Primary care | Cost per carrier couple detected | UK£40,800 | \$86,253 |
| Wildhagen et al. [17] | NL | Step wise | Primary care | Cost per carrier couple detected | UK£58,000 | \$111,089 |
| Morris and Oppenheimer [8] | UK | Step wise | Primary care | Cost per carrier couple detected | UK£40,900 | \$86,464 |
| Asch et al. [27] | US | Couple | Not stated | Cost per CF birth averted | US\$594,000 | \$739,581 |
| Nielsen and Gyrd-Hansen [20] | Den | Step wise | Primary care | Cost per CF birth averted | DKK2,771,262 | \$386,773 |
| Asch et al. [27] | US | Step wise | Not stated | Cost per CF birth averted | US\$367,000 | \$456,946 |
| Rowley et al. [9] | US | Stepwise | Hospital/clinic | Cost per CF birth averted | US\$1,322,376 | \$1,608,861 |
| Rowley et al. [9] | US | Stepwise | Hospital/clinic | Cost per QALY | US\$8290 | \$10,086 |
| Wildhagen et al. [17] | NL | Couple | Primary care | Net savings | Yes | |
| Wildhagen et al. [17] | NL | Step wise | Primary care | Net savings | Yes | |
| Doyle and Gardner [23] | US (Mex) | Step wise | Not stated | Net savings | No | |
| Nielsen and Gyrd-Hansen [20] | Den | Step wise | Primary care | Net savings | Yes | |
| Lieu et al. [10] | US | Step wise | Not stated | Net savings | No | |
| Vintzileos et al. [21] | US | Step wise | Not stated | Net savings | Yes | |
| Ginsberg et al. [22] | Israel | Step wise | Clinics | Net savings | No ^c | |
| Rowley et al. [9] | US | Step wise | Hospital/clinic | Net savings | No ^c | |

^a (Organisation for Economic Co-operation and Development [OECD] rates) with the exception of Ginsberg et al. [22], where Bank of Israel price indexes were used.

^b Midpoint.

^c There were net savings when the benefits of screening of subsequent pregnancies and productivity changes were taken into account.

Table 2 provides an overview of 10 evaluations of prenatal CF carrier screening. Once again, there was a large variation in the ICER. Similar to the ‘preconception’ studies, the most common outcome measures were *cost per carrier couple detected* and *cost per CF birth averted*. One CUA reported *cost per QALY* [9].

Seven studies reported their outcome as ‘net savings’ by subtracting the cost of screening from the potential health care costs averted through the birth of fewer patients with CF. Three studies reported stepwise screening would result in net savings [17,20,21]

and one study reported net savings for couple screening [17]. Two studies reported additional costs for prenatal carrier screening but in their sensitivity analysis, savings were feasible under a plausible alternative scenario [9,22]. A further two studies reported no net savings [10,23] but one of these was conducted in a Hispanic American population where the incidence of CF carrier status was low compared to the Caucasian American population. Even with the two prenatal stepwise screening studies [20,22] categorized as ‘societal’, one resulted in net savings [20] and the other reported no net savings if benefits of screening subsequent preg-

nancies and productivity changes were not taken into account [22].

Tables 1 and 2 demonstrate that the limited number of studies has delivered wide ranging ICER and inconsistent net savings result, although the majority support the notion that prenatal carrier screening may deliver net savings. What is clear from this overview is that the economic literature offers decision makers limited information and considerable uncertainty over the cost-benefit and cost-effectiveness of such programs. The next section explores the reasons for the variation in ICER results.

3.2. Examining the sources of variation in economic evidence

Table 3 provides an overview of reproducibility for 14 studies on preconception and prenatal programs. All clearly reported the intervention but only five adequately described the comparator although in all cases it could be ascertained that this was ‘no screening’.

Eight indicated the use of a societal perspective and six were from a health sector perspective⁴ for economic evaluation. Eleven used micro-costing, two taking cost data from published literature and two used a macro-costing approach (one in combination with micro-costing). Nine studies used discount rates (3–5%) for discounting future costs (or cost averted). All the studies checked robustness using sensitivity analysis commonly univariate analysis.

The following sections present the results of literature assessment of information contained in these studies to complete the decision-analytic model, using the structure of the diagrams (Figs. 1 and 2).

4. Consequence data

4.1. Probabilities on acceptance/uptake

4.1.1. Preconceptional screening

Reported participation rates for preconception screening ranged from 10% to 100%. Screening strate-

gies such as encouraging patients in GP surgeries, group educational sessions, work place screening, and GP invitations have been reported to result in low uptake rates. Participation rates for school based CF screening programmes show uptake rates of up to 80% amongst the Jewish population but as low as 30% in other groups. A non-economic Australian study reported higher uptake rates in school screening (42–75%) relative to other screening programmes [24].

4.1.2. Prenatal screening

Women’s participation in prenatal screening ranged between 50% and 100%. A high partners’ acceptance rate (85–100%) was used. Widespread variation in participation rates have a large impact on the eventual outcome of the economic study [18]. For example, the cost per QALY of US\$18,628 (20% uptake by pregnant women) reduced to US\$5782 (100% uptake) with even larger variations when uptake by their partners increased from 50% (US\$29,721) to 100% (US\$3693) [9]. The variation in uptake rates is not explained explicitly but may be due to differing approaches to screening, religious beliefs including opposition/reluctance to pregnancy termination, risk perceptions, the presence or absence of a family history of CF, or the actual/perceived risk of negatively impacting on health insurance [25].

4.2. Foetal diagnosis

Once a carrier couple has been identified, they can choose to have a foetal diagnosis via CVS or amniocentesis. For the preconception screening studies, participation rates of 75–85% were used. Sensitivity analysis (range 60–90%) indicated that the probability of foetal diagnosis has a large effect on the cost-savings balance [19]. In the case of prenatal screening, the uptake of foetal diagnosis ranged from 75% to 100%. The ICER was sensitive to the uptake of prenatal diagnosis [9,10,22,23]. For example, the cost per QALY of US\$26,953 with 50% foetal diagnosis, reduced to US\$1955 with 100% prenatal diagnosis. All studies used low rates of miscarriage as a result of foetal diagnosis (CVS: 0.75–1.3% and amniocentesis: 0.5%). Foetal losses are believed to be somewhat higher in the first-trimester for CVS (1:100) compared to Amniocentesis (1:250) [21].

⁴ Societal perspective incorporates some notion of the cost and consequences to patients and the health sector as well wider impacts on the economy as productivity gain or losses. Health Sector perspective measures the costs and consequences incurred through the health care sector as regardless of payers.

Table 3
Reproducibility assessment of preconception and prenatal studies

| Study | Intervention focus | Evaluation type | Well reported intervention | Well reported comparator | Study perspective reported | Model type | Costs included | Costing methods | Discount (%) | | Sensitivity analysis |
|--------------------------------|--------------------------------------|------------------|----------------------------|--------------------------|----------------------------|----------------------|---|-------------------------------|--------------|---------|-----------------------------|
| | | | | | | | | | Cost | Benefit | |
| Weijers-Poppelaars et al. [19] | Preconception | CBA | Yes | No | Societal | Simulation | Information, testing, aftercare and lifetime care | Micro-costing | 4% | 4% | Univariate and multivariate |
| Verheij et al. [18] | Preconception | CBA | Yes | Yes | Societal | Decision analytic | Screening, diagnosis, termination and care | Micro-costing | None | 3% | Univariate |
| Wildhagen et al. [17] | Neonatal, preconception and prenatal | CEA and CBA | Yes | No | Societal | Simulation | Information, testing, diagnosis, lifetime cost of care | Micro costing | 5% | 5% | Univariate and multivariate |
| Nielsen and Gyrd-Hansen [20] | Prenatal | CBA | Yes | No | Societal | Decision analytic | Screening, diagnosis, termination, age specific average costs | Micro-costing | 5% | 5% | Univariate |
| Rowley et al. [9] | Prenatal | CEA, CBA and CUA | Yes | Yes | Societal | Decision analytic | Screening, diagnosis, termination, annual care (direct and indirect) | Micro-costing | 3% | 3% | Univariate |
| Asch et al. [27] | Prenatal | CEA | Yes | No | Societal | Decision analytic | Testing, diagnosis, termination, patient's time and lifetime care (direct and non-medical) | Micro-costing & Macro-costing | None | None | Bivariate |
| Ginsberg et al. [22] | Prenatal | CBA | Yes | No | Societal | Decision analytic | Programme, screening, diagnosis, termination, lifetime care (direct, indirect, parents work loss) | Micro-costing | 5% | 5% | Univariate |
| Garber and Fenerty [16] | Prenatal | CBA | Yes | Yes | Societal | Decision analytic | Testing, diagnosis, termination, lifetime care and earning | Published Est. | 5% | 5% | Univariate |
| Warren et al. [26] | Preconception | CEA | Yes | Yes | Health sector | Decision analytic | Program establishment, overheads and screening | Micro-costing | 5% | 5% | Univariate |
| Morris and Oppenheimer [8] | Preconception and prenatal | CEA | Yes | No | Health sector | Simulation | Screening | Micro-costing | None | None | Univariate |
| Vintzileos et al. [21] | Prenatal | CBA | Yes | Yes | Health sector | Cost-benefit formula | Screening, diagnosis, termination and lifetime care | Macro-costing | None | None | Multivariate |
| Cuckle et al. [28] | Prenatal | CEA | Yes | No | Health sector | Decision analytic | Information, testing, counselling and diagnosis | Micro-costing | None | None | Univariate |
| Doyle and Gardner [23] | Prenatal | CBA | Yes | No | Health sector | Decision analytic | Screening, diagnosis, termination and care | Published Est. | None | None | Univariate and bivariate |
| Lieu et al. [10] | Prenatal | CEA | Yes | Yes | Health sector | Decision analytic | Screening, diagnosis, termination and medical care | Micro-costing | 5% | None | Univariate and bivariate |

4.3. Reproductive choices

4.3.1. Preconceptional

The reviewed studies reported assumptions (based on literature) that 15–25% of carrier couples refrained from having children and assumed that the remaining 75–85% would make use of foetal diagnosis, following conception. Sensitivity analysis (range 10–40%) of CF carrier couples refraining from having children (25% considered in the baseline) does not have a high impact [19]. Further, none of the reviewed studies reported on the use and costs of preimplantation genetic diagnosis. This expensive technology is now widely available and should be part of any future evaluation.

Once a foetus with CF has been identified, parents are faced with a choice of termination. Termination rates used ranged from 80% to 95%. Two studies used a 90–100% interval in their sensitivity analysis but this did not have any impact on the economic results [19]. However, this is a fairly narrow range and a lower pregnancy termination rate may have shifted the result.

4.3.2. Prenatal

Termination of pregnancy ranged from as low as 30% to as high as 100%, with most assuming a rate of 75%. The variations may be culture specific [20]. The 30% rate was taken from empirical surveys of the attitudes of pregnant women and affected families [10]. Reported sensitivity analyses on this did affect economic results. For example, the cost per QALY reduced from US\$23,855 (50% termination rate) to US\$364 (100% termination rate) [9].

4.4. Test sensitivity and specificity

4.4.1. Carrier detection

Although most of the studies have assumed a theoretical specificity value of almost 100% for CF carrier detection, one assumed it to be 99% accounting for misclassification, laboratory contamination and genotyping error [22]. In most, test sensitivity was sourced from published literature and was above 85%. Two used high variations in test sensitivity for various ethnic groups, as low as 30% for Asians, 57% for Hispanics and values of 94% and 97% for native American and Ashkenazi Jews [21,23]. High-test sensitivity provided more cost-effective results. In one analysis the cost per high risk pregnancy identified was \$162,000 at 60% test

sensitivity, reducing to US\$73,000 at 90% sensitivity [10]. Cost per QALY also decreased from US\$16,861 (75% test sensitivity) to US\$4909 (90% test sensitivity) [9].

4.4.2. Foetal diagnosis

Test sensitivity and specificity for foetal diagnosis was assumed as 100% accurate in all studies.

5. Cost data

5.1. Pre-screening test costs

Pre-screening test costs like mass communication varied between studies. Most of the preconception studies included mass communication but used costs from other mass media campaigns such as breast screening awareness and folic acid campaigns [17–19] rather than a specific CF campaign. Only one included data from an actual school-screening program [26]. The mass communication costs were US\$35,205 [26] in school screening and between US\$296,978 to US\$350,318 for general population [18,19]. Only two of the prenatal studies included mass communication costs ranging from US\$39,622 to US\$262,318 [17,22]. No information linked the cost (or intensity) of the mass communication campaign with subsequent participation rates.

All the preconception studies included the cost of personal information (US\$1.77–2.27 per invitation) [17–19]. Only three (out of 10) prenatal studies included this (range US\$1–4.5) [8,17,28]. Only two preconception and three prenatal studies reported a pre-test counselling cost between US\$4–34.5 per person and US\$457.54 per school [10,19,20,22,26].

5.2. Cost of screening

Cost of organisation and acquisition and cost per test was reported in all preconception studies. Cost of test organisation and acquisition is between US\$1.62–17.3 per person [17,19] and US\$1232 per school [26]. It was surprising to note the variation in these costs (with no sources indicated) reported across studies in the same country [17,19]. For the prenatal studies, only two reported these costs (range US\$11–17) [8,17]. Patient costs (like time taken and transport)

were reported by three preconception studies (range US\$3–11) [17,18,26]. Three prenatal studies reported patient costs (range US\$11–42) [17,22,27]. The variations were mainly due to inclusion of different items (such as productivity lost and public transport). All reported the cost per test and ranged from US\$28 to US\$240 [20,18]. The main source of variation was the use of the less expensive single mutation test versus the multiple mutation tests. Results were highly sensitive to the cost of the test [9,10,20,22,28]. An increase from US\$68 to US\$203 resulted in an increase in the cost per high-risk pregnancy identified from US\$52,724 to US\$168,986 [10].

5.3. Costs of post-test stage (after care)

Most studies included cost of counselling for carrier and non-carrier couples. Again, there was wide variation ranging from US\$17 to US\$1189 (carrier couple) and US\$9 to US\$205 (non-carrier couples) [19,22,26]. This is explained by the difference in how the service was provided; for instance the use of a clinical geneticist [19]. Three studies did not include any costs for counselling [20,21,23].

All studies reported the cost of CF foetal diagnosis. The cost ranged from US\$249 to US\$2120 [17,27], based on a variety of sources including the literature, government reimbursements, official hospital tariffs, consultation with administrators, micro-costing, current procedural terminology and trial data. Some used a broader definition of CF diagnosis and included the cost of microvillar intestinal enzyme analysis [27], karyotype cytogenetic testing along with costs of labour, raw materials, depreciation and overheads [22], and ‘packages’—including genetic counselling, DNA testing, karyotype determination and alpha-fetoprotein determination [21]. In preconceptional screening, reproductive decisions was only reflected through carrier parents’ decision to undertake foetal diagnosis. Whilst, the cost ranged from US\$752 to US\$2120 [17–19] and all emanated from the Netherlands using Dutch reimbursement rates, the large variations are unexplained. None conducted sensitivity analysis of the cost of foetal diagnosis.

The cost of reproductive decisions was included in all studies but most restricted this to pregnancy termination. None of the preconception studies included the cost of IVF although one prenatal screening study

included this as a cost in the decision to have a ‘replacement’ child. This cost was estimated to be US\$4696 [9].

Variation in pregnancy termination costs ranged from approximately US\$206 to US\$3486 [20,27]. Estimates were from a variety of sources including literature, government reimbursements, office of technology assessment, official hospital tariffs, consultation with administrators, micro-costing, and from trial data. Some studies included the costs of miscarriage [22,27] and medical care costs after spontaneous abortion, with variation in the first and second trimester [10]. Only one study adjusted medical charges to account for the difference between the fees and opportunity costs [27]. One study conducted a sensitivity analysis on the cost of termination but found that it had very little impact on the ICER [9].

5.4. Cost of care for CF patients

Cost of care for CF patients was estimated in all of the studies where net benefits were estimated. Estimated life time cost ranged from US\$329,388 to US\$1,251,073 [9,10]. Only two studies included estimates of forgone lifetime earnings, which constituted up to 6% of the lifetime costs [20,22]. Studies from the US tended to use the NIH consensus estimate of US\$1,085,700 per patient (US\$800,000 in 1997) [21,23] or the Office of Technology Assessment report estimates, ranging between \$329,388 and \$437,371 [27,29], inflated to the reference year. One US study estimated CF care costs through personal communication with organisations like the CF Foundation [9]. The Dutch studies estimated the life time costs between US\$377,603 and US\$511,768 per patient and were primarily based on reviewing medical records of CF patients (including home care cost data collected with a questionnaire) but did not include indirect costs such as lost earnings [17–19]. The differences were largely driven by the discount rate which ranged from 3% to 5%. A recent cost of illness review for cystic fibrosis reports estimates of US\$227,250–340,875 discounted at 5%, and US\$284,062–568,124 discounted at 3% [14].

These were estimated in several ways. Some varied the cost of care by age with younger patients consuming less than older. Others estimated cost according to disease severity, with annual costs of mild disease around

\$6200–43,300 for severe disease [29]. Cost-of-illness studies have reported age (children versus adults), and disease severity to be the most important determinants of costs of care [14]. Despite this, none of the 14 studies included both factors, though some estimated it separately. Only recent studies have estimated cost using age-severity models, with a mean annual total cost of US\$8459 [30] and lifetime cost for predicted survival age of 32 years of US\$504,833 [31].

Most studies included the cost of hospitalisation, clinic visits, medication and laboratory costs. Hospitalisation and medication formed the major component (40–60%) of medical care cost in most of the studies. Non-hospital costs of care (domestic help, diet, travelling, medication, special facilities) are reported to constitute 50% of total (medical and non-medical) lifetime costs [32]. Recent studies in France have reported that, of the total US\$19,585 per year per patient, outpatient's costs (88%) were higher than inpatient costs (12%). This could be a reflection of the importance of home health care in France, notably for intravenous antibiotic treatments for pulmonary complications [33]. Lifetime costs of care were reported to have an important influence on the economic results [19]. Higher the cost, lower the incremental cost of screening compared with no screening and more net savings of the program.

6. Review of costing methodology

Table 4 provides an overview of the quality of costing methods used. Most indicated the costing perspective but only eight (57%) justified this. Only six (43%) costed all items relevant to the stated perspective. For example, studies in Denmark claim a societal perspective but use Dutch reimbursement rates, which could vary from the actual costs. Only three (21%) showed distinction among long run and short run costs. All studies reported how variable costs were estimated. However, only three (21%) explicitly apportioned human resources and other fixed resources like capital equipment to the cost of CF screening. Ten studies (71%) reported methods for determining the values of resources used. Although 10 (71%) reported the base year for costing, 6 studies neglected to inform readers that costs were not derived in the base year. Further, only six studies (43%) adjusted costs to the base year.

7. Discussion

This overview of the evidence on the costs and consequences of community CF carrier screening has shown widespread variation in the published literature. The ICER varied significantly even after adjusting for evaluation timing and using PPP exchange rates and comparing similar interventions and comparators.

On this basis, it is difficult to make any evidence-based recommendations about whether a CF carrier-screening program should be undertaken on economic grounds. Indeed, this demonstrates that relying on reported studies' conclusions as a basis for determining the efficiency of any new program is inappropriate. Our review was restricted to economic studies, but for some model inputs (such as screening participation rates) it may be more useful take a broader scope of literature.

Cost benefit and cost utility analyses are most useful to decision-makers faced with determining whether to implement a CF carrier-screening program because the outcome measures reported in these studies allows comparison between CF screening programs and other health care programs. The CBA studies reported inconsistent results, largely due to the inclusion and estimate of, potential offsetting 'savings' in health care costs through CF births averted. This approach reduces the value of a CF patient's life to the liability for health care costs. This is also a narrow view of the potential benefits of screening [11], ignoring the value of information that testing offers prospective parents.

The one CUA study [9] found that CF screening represented good value for money when compared to other preventive programs (e.g., newborn phenylketonuria screening, mammography screening). However, to generate a difference in the number of QALYs between the screen and non-screen groups, the study had to assume that each averted CF birth was replaced by a healthy pregnancy. This raises a considerable ethical issue on how we value the life of the unborn child.

The cost-effectiveness studies which reported findings in terms of ICER (e.g. cost per carrier couple identified), provide decision makers with potentially valuable information about the most efficient type of screening program, but not about whether or not a screening program is expected to bring net economic benefits. This is because the outcome measures reported in these studies only allow for explicit

Table 4
Assessment of costing methodology quality

| | Perspective of cost analysis | | | | Methods for determining | | | | | Reporting of data | | |
|--------------------------------|------------------------------|---------------|--|--|-------------------------------|--------------------------------------|---|----------------------------------|---------------------------|-------------------|--------------|-----------------------------|
| | Statement | Justification | Data sufficiency vis-à-vis perspective | Distinction (short and long run costs) | Quantities | | | Values | | Year | Base year | Time periods adjustments |
| | | | | | Resources (variable costs) | Time allocation (human resources) | Allocation (other resources-fixed costs) | Prices, unit costs or charges | Use of other cost data | | | |
| Preconception | | | | | | | | | | | | |
| Wildhagen et al. [17] | Yes | Yes | No | No | Yes | ST | ST | Yes | Yes | No | Yes | Yes |
| Warren et al. [26] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Weijers-Poppelaars et al. [19] | Yes | No | No | No | Yes | No | ST | Yes | Yes | No | No | ST |
| Verheij et al. [18] | Yes | Yes | No | No | Yes | No | ST | ST | Yes | No | No | ST |
| Prenatal | | | | | | | | | | | | |
| Cuckle et al. [28] | Yes | Yes | Yes | No | Yes | ST | No | ST | Yes | No | Yes | No |
| Lieu et al. [10] | Yes | No | No | No | Yes | No | No | ST | Yes | ST | Yes | ST |
| Morris and Oppenheimer [8] | No | No | No | No | Yes | No | No | No | No | No | Yes | No |
| Asch et al. [27] | Yes | Yes | Yes | No | Yes | ST | No | Yes | Yes | ST | Yes | Yes |
| Nielsen and Gyrd-Hansen [20] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Rowley et al. [9] | Yes | Yes | No | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes |
| Doyle and Gardner [23] | Yes | No | Yes | No | Yes | No | No | Yes | No | ST | No | ST |
| Vintzileos et al. [21] | Yes | No | No | No | Yes | No | No | Yes | No | ST | No | ST |
| Ginsberg et al. [22] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Garber and Fenerty [16] | Yes | No | No | No | Yes | No | No | Yes | Yes | Yes | Yes | ST |

ST: Sometimes, which includes “for few items–for many items”, but not full and complete.

comparison with other CF programs and not across other health care programs.

It is inevitable that the ICER will vary from one setting to another. Across countries there are different prices for health care costs. Yet, in examining the studies in more detail we discovered that the variations in ICER are due in large degree to study methods and assumptions and not solely to a difference in cost structures. Some studies limited their cost analysis to the health care system, whereas others took a broader view and included lost productivity. Some studies included discount rates to adjust future costs, others did not. Different discount rates may have a major impact on the ICER of interventions [14]. To a large degree such variations can be taken into account when modelling the cost and consequences of CF screening in local contexts.

However, large parts of the ICER variation were driven by differences in the screening participation rates, the reproductive choices made by prospective parents and sensitivity and specificity of the tests. This indicates the importance of having accurate estimates for the relevant decision making context.

A useful approach would be to gain a better understanding of which model inputs can be used from the international literature, and which ones are likely to vary significantly. Some of the evidence and assumptions found in the literature may be true for most national settings. For example, the low rates of spontaneous miscarriage as a result of foetal diagnosis and the 100% test accuracy for foetal diagnosis are likely to hold true.

With reported high variations in carrier screening test sensitivity for various ethnic groups, the appropriateness of using high-test sensitivity rates in multi-racial populations is debatable. While a 12 mutation panel could detect about 85% of possible severe mutation among those with high risk, e.g. those of Northern European ancestry [2], a large proportion in the multi-racial population could be detected as almost zero risk of CF. Hence, in developing an economic model, we need to be explicit in defining ethnic composition of the screening target group, and take variations in CF carrier incidence and the sensitivity of the screening panel into account.

Generally, a straight transfer of cost data between settings is likely to lead to substantial errors. Price and patterns of care are likely to vary significantly

between countries and thus caution should be exercised in applying international cost data as an input to a local model. Most studies ignored the substantial cost of IVF for those couples who choose to use pre-implantation genetic diagnosis. In some developed countries, this may be a viable option for a large proportion of carrier couples, given the extensive public funding available of such services.

Furthermore, there was considerable ambiguity and variation in the literature on how the various costs, particularly CF care, were derived. There were variations in the costing perspectives, cost items included, the use of average or age-specific, severity specific estimates, and high non-hospital care costs. It shows the importance of not using an “average” cost combining estimates from different studies, especially while extrapolating results to another setting. Instead, a comprehensive costing of age specific, severity-specific medical and non-medical care from a societal perspective should be considered as an input to the model.

Most international papers use the Forced Expiratory Volume (FEV) classification of the American CF Foundation [14]. There is no universal consensus on how to stage CF disease and therefore definitions for disease severity may vary in different countries. Scoring systems that have been developed to monitor the progress of CF have serious limitations [34]. Measures like “pre-symptomatic”, “symptomatic” and “severe irreversible” symptoms without clearly defining the consequences, makes generalization difficult. With such ambiguity in these definitions, using data from the literature reinforces our concern of using cost data from other countries.

The variation in the types of outcome measures used in these studies provides an indication of the complexity of finding the right measure for these economic evaluations [11]. The use of comparators should also be context specific. For example, newborn screening for CF has been irregular elsewhere (like in Colorado, Wisconsin) but Australia and New Zealand do have national new-born screening for CF. This means that CF community screening should be compared to new-born screening rather than comparing to ‘no program at all’ in Australia and New Zealand.

Improving transparency of study results will be beneficial to the transferability of results [13,14]. Taking into account the gaps identified in this review,

future economic evaluations of CF carrier screening should make explicit the decision-analytic path-ways, perspectives, data sources, methods for costing and maintain high levels of transparency of study results for future reproductions in other countries. Indeed, we recommend that health economists and journal editors place greater emphasis on making economic models more widely available to decision-makers. Such an approach will improve quality because there is greater scrutiny of model specification and greater transferability by allowing model inputs to vary in line with the local contexts.

8. Conclusion

This review has identified the gaps and limitations of generalising the existing economic evidence of CF screening. It has highlighted some important weaknesses in generalizing findings and extrapolating economic evidence from one setting to another. At the same time we have attempted to make best use of the existing evidence by highlighting those aspects of the studies that could be transferred to local context and those where new local empirical information would be of most value. To enable greater transparency and generalisability, a greater emphasis on disseminating economic models (rather than just results) is advocated.

Acknowledgments

The paper was written as a part of a CF screening economic evaluation study funded by Cystic Fibrosis Foundation, Australia. A previous draft of the paper was presented at the 28th Australian Health Economics Society Meeting (September 2006), Perth. The authors would like to acknowledge the participants of this conference, Adam Gordois and an anonymous referee for their comments. All remaining errors are the responsibility of the authors.

References

- [1] Welsh M, Ramsey B, Accurso F, Cutting G. Cystic fibrosis (ch. 201). In: Scriver C, Beaudet A, Sly W, Valle D, editors. *The metabolic and molecular bases of inherited disease*. New York: McGraw-Hill; 2001. p. 5121–88.
- [2] Massie RJ, Delatycki M, Bankier A. Screening couples for cystic fibrosis carrier status: why are we waiting? *Med J Aust* 2005;183:501–2.
- [3] Massie RJ, Olsen M, Glazner J, Robertson CF, Francis I. Newborn screening for cystic fibrosis in Victoria: 10 years' experience (1989–1998). *Med J Aust* 2000;172:584–7.
- [4] NIH Consensus Development Panel on Genetic Testing for Cystic Fibrosis. Genetic testing for cystic fibrosis [National Institutes of Health Consensus Development conference on genetic testing for cystic fibrosis]. *Arch Intern Med* 1999;159:1529–39.
- [5] American College of Obstetrics and Gynecology. Genetics ACoM. Preconception and prenatal carrier screening for cystic fibrosis. Clinical and laboratory guidelines. Washington, DC: American College of Obstetricians and Gynecologists; 2001.
- [6] Turner GM. Carrier testing for cystic fibrosis [editorial]. *Med J Aust* 1998;168:375–6.
- [7] Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 Revision of American College of Medical Genetics Mutation Panel. *Genet Med* 2004;6:387–91.
- [8] Morris JK, Oppenheimer PM. Cost comparison of different methods of screening for cystic fibrosis. *J Med Screen* 1995;2:22–7.
- [9] Rowley PT, Loader S, Kaplan RM. Prenatal screening for cystic fibrosis carriers: an economic evaluation. *Am J Hum Genet* 1998;63:1160–74.
- [10] Lieu TA, Watson SE, Washington AE. The cost-effectiveness of prenatal carrier screening for cystic fibrosis. *Obstet Gynecol* 1994;84:903–12.
- [11] Hall J, Viney R, Haas M. Taking a count: The evaluation of genetic testing. *Aust NZ J Public Health* 1998;22:754–8.
- [12] Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 2nd ed. New York: Oxford University Press; 1997.
- [13] Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. *Pharmacoeconomics* 2004;22:857–76.
- [14] Krauth C, Jalilvand N, Welte T, Busse R. Cystic fibrosis: Cost of illness and considerations for the economic evaluation of potential therapies. *Pharmacoeconomics* 2003;21:1001.
- [15] Graves N, Walker D, Raine R, Hutchings A, Roberts JA. Cost data for individual patients included in clinical studies: no amount of statistical analysis can compensate for inadequate costing methods. *Health Econ* 2002;11:735–9.
- [16] Garber AM, Fenerty JP. Costs and benefits of prenatal screening for cystic fibrosis. *Med Care* 1991;29:473–89.
- [17] Wildhagen MF, Hilderink HB, Verzijl JG, Verheij JB, Kooij L, Tijmstra T, et al. Costs, effects, and savings of screening for cystic fibrosis gene carriers. *J Epidemiol Community Health* 1998;52:459–67.
- [18] Verheij JBG, Wildhagen MF, Hofstra RMW, Pals G, Habbema JDF, ten Kate LP. Preconceptional screening of couples for carriers of cystic fibrosis: a prospective evaluation of effects, costs and savings for different mutation detection methods. *Community Genet* 1999;2:74–81.

- [19] Weijers-Poppelaars FA, Wildhagen MF, Henneman L, Cornel MC, Kate LP. Preconception cystic fibrosis carrier screening: costs and consequences. *Genet Test* 2005;9:158–66.
- [20] Nielsen R, Gyrd-Hansen D. Prenatal screening for cystic fibrosis: an economic analysis. *Health Econ* 2002.
- [21] Vintzileos AM, Ananth CV, Smulian JC, Fisher AJ, Day-Salvatore D, Beazoglou T. A cost-effectiveness analysis of prenatal carrier screening for cystic fibrosis. *Obstet Gynecol* 1998;91:529–34.
- [22] Ginsberg G, Blau H, Kerem E, Springer C, Kerem BS, Akstein E, et al. Cost-benefit analysis of a national screening programme for cystic fibrosis in an Israeli population. *Health Econ* 1994;3:5–23.
- [23] Doyle NM, Gardner MO. Prenatal cystic fibrosis screening in mexican americans: an economic analysis. *Am J Obstet Gynecol* 2003;189:769–74.
- [24] Wake SA, Rogers CJ, Colley PW, Hieatt EA, Jenner CF, Turner GM. Cystic fibrosis carrier screening in two new south wales country towns. *Med J Aust* 1996;164:471–4.
- [25] Decruyenaere M, Evers-Kiebooms G, Denayer L, Welkenhuyesen M. Uptake and impact of carrier testing for cystic fibrosis. A review and a theoretical framework about the role of knowledge, health beliefs and coping. *Community Genet* 1998;1:23–35.
- [26] Warren E, Anderson R, Proos AL, Burnett LB, Barlow-Stewart K, Hall J. Cost-effectiveness of a school-based tay-sachs and cystic fibrosis genetic carrier screening program. *Genet Med* 2005;7:484–94.
- [27] Asch DA, Hershey JC, Dekay ML, Pauly MV, Patton JP, Jedrzejewski MK, et al. Carrier screening for cystic fibrosis: costs and clinical outcomes. *Med Decis Making* 1998;18:202–12.
- [28] Cuckle HS, Richardson GA, Sheldon TA, Quirke P. Cost effectiveness of antenatal screening for cystic fibrosis. *BMJ* 1995;311:1460–3.
- [29] Lieu T, Ray G, Farmer G, Shay G. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics* 1999;103:e72.
- [30] Schreyogg J, Hollmeyer H, Bluemel M, Staab DRB. Hospitalisation costs of cystic fibrosis. *Pharmacoeconomics* 2006;24:999–1009.
- [31] Baumann U, Stocklossa C, Greiner W, Graf von der Schulenburg JM, von der Hardt H. Cost of care and clinical condition in paediatric cystic fibrosis patients. *J Cyst Fibros* 2003;2:84–90.
- [32] Wildhagen MF, Verheij JB, Verzijl JG, Gerritsen J, Bakker W, Hilderink HB, et al. The nonhospital costs of care of patients with CF in the Netherlands: results of a questionnaire. *Eur Respir J* 1996;9:2215–9.
- [33] Horvais VST. Cost of home and hospital care for patients with cystic fibrosis followed up in two reference medical centers in france. *Int J Technol Assess Health Care* 2006;22:525–31.
- [34] Hafen GM, Ranganathan SC, Robertson CF, Robinson PJ. Clinical scoring systems in cystic fibrosis. *Pediatr Pulmonol* 2006;41:602–17.