COST EFFECTIVENESS OF NEWBORN SCREENING FOR CYSTIC FIBROSIS: A SIMULATION STUDY

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ABSTRACT

BACKGROUND: Early detection of cystic fibrosis (CF) by newborn screening (NBS) reduces the rate of avoidable complications. NBS protocols vary by jurisdiction and the cost effectiveness of these different protocols is debated.

OBJECTIVE: To compare the cost effectiveness of various CF NBS options.

METHODS: A Markov model was built to simulate the cost effectiveness of various CF-NBS options for a hypothetical CF-NBS program over a 5–year time horizon assuming its integration into an existing universal NBS program. NBS simulated options were based on a combination of tests between the two commonly used immunoreactive trypsinogen (IRT) cutoffs (96th percentile and 99.5th percentile) as first tier tests, and, as a second tier test, either a second IRT, Pancreatic-associated protein (PAP) or CFTR mutation panels. CFTR mutation panels were also considered as an eventual third tier test. Data input parameters used were retrieved from a thorough literature search. Outcomes considered were the direct costs borne by the Quebec public health care system and the number of cases of CF detected through each strategy, including the absence of screening option.

RESULTS: IRT-PAP with an IRT cutoff at the 96th percentile is the most favorable option with a ratio of CAD$ 28,432 per CF case detected. The next most favorable alternative is the IRT1-IRT2 option with an IRT1 cutoff at the 96th percentile. The no-screening option is dominated by all NBS screening protocols considered. Results were robust in sensitivity analyses.

CONCLUSION: This study suggests that NBS for cystic fibrosis is a cost-effective strategy compared to the absence of NBS. The IRT-PAP newborn screening algorithm with an IRT cutoff at the 96th percentile is the most cost effective NBS approach for Quebec.

KEY WORDS: Cystic fibrosis; newborn screening; cost effectiveness; immune-reactive trypsinogen (IRT); pancreatic-associated protein (PAP); CFTR; simulation.

INTRODUCTION

Cystic fibrosis (CF) represents one of the most common and disabling diseases in the Caucasian population[1-2]. In Canada, its incidence is estimated approximately at 1/3600 live births [3] and 1/2500 in the province of Quebec [4].

With the advent of new treatment protocols and nutritional support, most children with CF live to adulthood, with a median age of survival of 48.1 years in Canada [5]. However, age at initial CF diagnosis remains a major problem. Indeed, in the absence of NBS, the median age at initial diagnosis is approximately 7 months while the mean age is 3.8 years, usually following numerous repetitive medical consultations for airway diseases [5-6].

Early detection of CF, i.e. before the appearance of the first symptoms, has a beneficial effect on the evolution of the disease by allowing earlier preventive treatment and follow-up [2, 7-8]. It has been shown that a diagnosis made before 2 months of life is associated with improved nutritional status, better growth, fewer hospitalizations and a decreased rate of complications throughout infancy, childhood, and adolescence, and better cognitive functions [9-11]. Furthermore, early diagnosis and treatment are believed to reduce expenses and parental anxiety associated with failure to thrive and other symptoms[8].

Research has showed the potential benefits of early diagnosis and treatment of CF through NBS. In a retrospective UK cohort, Sims *et al*. (2007) showed that the cost of therapy for patients diagnosed through a NBS program (31 CFTR mutation panel) was significantly lower (60-400%) than the costs of therapy of clinically diagnosed patients of the same age-range. The difference was attributed to lower treatment costs and reduced hospital admissions for invasive therapies. Indirect costs and disruption of family life were also expected to be lower among screened infants.

As a result, NBS for CF has been proposed as a useful approach to improve the quality of life of patients and their family and has been promoted by several Genetic Societies including the American College of Medical Geneticists, the American College of Obstetricians and Gynaecologists [8, 12-13], as well as by the US Center for Disease Control[2]. Since these recommendations, all US States have initiated CF NBS programs. In Canada, as of 2013, five provinces (Alberta, British-Columbia, Manitoba, Ontario and Saskatchewan) have implemented a NBS program for cystic fibrosis. [4-5].

One of the reasons that some jurisdictions in Canada have delayed implementing a screening program is the lack of information regarding the most cost/effective screening strategy amongst the many existing options. Indeed, in spite of the many cost effectiveness studies that have shown that CF NBS is cost effective, no study has compared all together the different screening algorithms that are realistically implementable. Also, no study has tested various immunoreactive trypsinogen (IRT) cutoffs as a first tier test with or without the different CFTR mutation panels commonly used [14-17]. In addition to identifying the optimal screening strategy, our study aims to compare the cost effectiveness of 20 NBS algorithms using two cutoffs (96th percentile and 99.5th percentile) of IRT as first tier, varying the CFTR mutations panels, and comparing these algorithms to the no-screening option.

METHODS

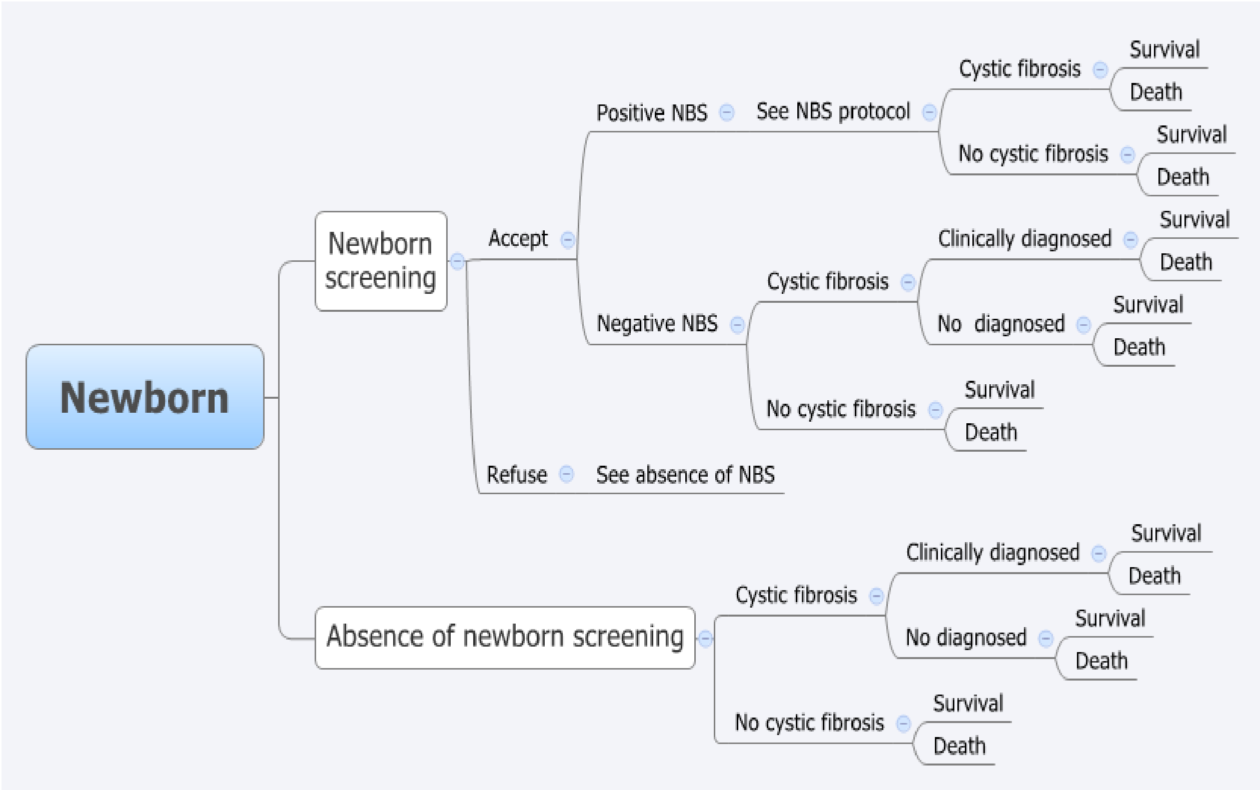
Overview

A Markov decision model was built using the Clumeq supercomputer network-running SCHNAPS platform [18-20] to simulate the cost effectiveness of 20 CF-screening strategies and to compare these strategies to the current situation (absence of universal CF neonatal screening) in the Quebec public health care setting. Comparisons were made for a hypothetical CF NBS program spanning over 5 years and targeting newborns in the province of Quebec [21]. We assumed that this screening program would be integrated into the existing Quebec NBS program [22]. Outcomes considered were the direct costs borne by the Quebec universal health care system and the number of CF cases detected.

Modeling

The simplified model structure is presented in Figure 1. The model, divided into cycles of one year each, has two starting branches: 1) “Absence of NBS strategy “and 2) “NBS strategy”. The model assumed a CF incidence of 1 in 2500 newborns (with 86 000 births, 35 CF cases are expected each year)[4]. The model excludes those diagnosed clinically with a *meconium ileus* (MI) as they would have been diagnosed at birth even in the absence of neonatal screening [16, 23].

Figure 1: Decision model



Under "Absence of NBS", newborns have an annual probability of being diagnosed with CF based on symptoms or a family history. These probabilities were modeled according to data from the Quebec patients of the Canadian cystic fibrosis patient data registry (CPDR)[24]. This population consists of 174 children with CF without MI who were born since the year 2000. The model considered also that 75 (50-100) sweats tests were performed in children without CF for each child with a diagnosed CF[25]. This average estimate is similar to the one observed in Quebec according to data recently published by the Quebec National Institute of Public Health from an analysis of data from laboratories that perform sweat tests [4], and which is around 72 sweat tests per child with CF.

Under "NBS strategy", screening is proposed to all newborns. As we assumed that a screening program would be integrated into the existing neonatal newborn screening program for genetic diseases our model considered a similar screening coverage rate of 99 % of all newborns[22]. Newborns that were not screened because their parents declined screening have the same probability of being diagnosed clinically as those in the "Absence of NBS strategy" option. When parents accept NBS, cases of CF are detected according to the performance of the test used (sensitivity and specificity). The model considered the compliance rate for recall samples if a second IRT is required [16]. We made the assumption that cases of CF would be detected within the first three months in the screening options. For missed cases, we assumed the same probability of being diagnosed clinically as for those in the "Absence of NBS strategy" option.

In addition, we assume that if a child with CF is diagnosed, he is followed in a CF specialized center from that point on. Each year, this child has a probability of developing CF-associated complications that lead to medical visits and hospitalizations. Children with CF who did not yet receive a diagnosis of CF might also experience CF-associated complications but with a higher probability compared to those already diagnosed [9, 26-28]

In all options, there is a probability at the end of each year cycle that the child (with or without CF) has died. Because the survival of children with CF under 5 years of age in Quebec and Canada has been of approximately 100% over the last decade according to the CPDR, we attributed to all children (with or without CF), the same "all-cause death probability", which is an estimate of the average death risk based on age according to data from the Quebec Institute of Statistics. In sensitivity analyses, we used 5-years survival rates of 95% and 98% for children with CF assuming the same death probability each year over the 5 years.

The input parameters are presented in Table 2. They are based on published data, Quebec data extracted from the CPDR as well as on experts' opinion. Parameters were modeled in order to reflect the event probabilities in screened and unscreened children with CF.

Newborn screening options

Screening algorithms are presented in Table 1. For all screening algorithms, the model takes into account the compliance rates at each screening step. For the first tier test (IRT1), the model assumed a coverage rate of 99%, similar to that of the existing Quebec newborn screening program for genetic diseases [22]. The model considers, for all screening algorithms that include the DNA analysis, the probability of accepting genetic counseling as well as the probability of consent to a DNA test[15, 29].

Table 1. Screening protocols

Strategy	Description
IRT_IRT	Newborns with IRT1 above the cutoff used (96^{th} or 99.5^{th}) are recalled for a second IRT. If the second IRT is >70 ng/ml, newborn is referred for sweat test.
IRT_IRT_DNA	Newborns with IRT1 above the cutoff used (96^{th} or 99.5^{th}) are recalled for a second IRT. If the second IRT is >70 ng/ml, newborn is referred for DNA-based CFTR mutation analysis (25- or 43-mutation panel). If one or two mutations are found, newborn is referred for sweat test.
IRT_DNA	DNA CFTR mutation analysis (25- or 43-mutation panel) is done for newborns with IRT1 above the cutoff used (96^{th} or 99.5^{th}). If at least one mutation is found, newborn is referred for sweat test.
IRT_DNA_IRT	DNA CFTR mutation analysis (25- or 43-mutation panel) is done for newborns with IRT1 above the cutoff used (96^{th} or 99.5^{th}). If at least one mutation is found or if no mutations are found but IRT1>99.9^{th} percentile, newborn is referred for sweat test.
IRT_PAP	PAP test is done for newborns with IRT1 above the cutoff used (96^{th} or 99.5^{th}). The result is positive if PAP test is > 1.8 ng/ml if the first IRT is > 96^{th} percentile or 1 ng/ml if the first IRT is > 99.5^{th} percentile. Newborn is then referred for sweat test.
IRT_PAP_DNA	PAP test is done for newborns with IRT1 above the cutoff used (96^{th} or 99.5^{th}). The result is positive if PAP test is > 1.8 ng/ml if the first IRT is > 96^{th} percentile or 1 ng/ml if the first IRT is > 99.5^{th} percentile. Thereafter, DNA CFTR mutation analysis (25- or 43-mutation panel). If at least one mutation is found, newborn is referred for sweat test.

Costs

Direct medical costs that were considered related to the screening and treatment of cases of CF over a 5 year time horizon under the perspective of the Quebec public health care system. The costs of screening included the cost of the tests (IRT, PAP, DNA, and sweat test), genetic counseling for the pre-and post DNA testing options, and the physician fees for the tests' interpretation. The costs of disease management included the cost of medical visits, hospitalizations, laboratory, imaging and electrophysiological tests, medications (antibiotics, corticosteroids, etc.) and special diets (vitamins, pancreatic enzymes, oxygen). Quantification of medical and paramedical services used by CF infants was estimated using data from children with CF without MI included in the CPDR database. Services used before clinical diagnosis of CF were estimated from data of 44 Quebec children diagnosed before 5 years of age and for whom data on services used were available. Quantification of services after clinically diagnosis was estimated using data of 174 Quebec patients of the CPDR born since the year 2000. As NBS for CF is not implemented in the Province, quantification of services used by children diagnosed through NBS was estimated using data from 126 children with CF originating from Alberta, Saskatchewan, British-Columbia and Ontario, provinces that have already implemented the NBS for CF.

All unit prices are Quebec public provincial average prices calculated from governmental databases. The lowest reimbursable price for medications by the provincial public insurance scheme RAMQ (*RAMQ, Manuel des pharmaciens*) [30] and the average price paid by the RAMQ to physicians were considered (*RAMQ, manuel des médecins spécialistes*)[20]. Unit prices for activity centers were calculated using the Quebec financial and operational data base (*SIFO*). This was applied to non-medical services, including ancillary services. Provincial technical units were used for laboratory and imaging tests to calculate their unit prices. All SIFO unit prices were over-headed using the direct approach in order to take into consideration the support activity centers[31]. As the PAP assay is not available in Canada, its cost was estimated from the documentation provided by a scientific adviser from a French biotechnology company (Dynabio), which manufactures and markets the PAP assays.

The fiscal year 2011-2012 was used to calculate all costs. Costs were discounted at a rate of 3%. Detailed estimates of costs used in the model are presented in Table 2.

Table 2.Model input parameters and costs

Parameter		Baseline	Sensitivity analysis	Reference
Number of newborns per year	2011	87 221		[21]
	2012	86 755		
	2013	86 106		
	2014	85 872		
	2015	86 080		
Probability of being clinically diagnosed according to age,%	0-1 year	70.4		[24]
	1-2 year	11.7		
	2-3 year	9.4		
	3-4 year	4.0		
	4-5 year	2.2		
	> 5 year	2.3		
Annual CF incidence		0.0004	0.0006-0.00025	[4]
CF newborns with *meconium ileus*, %		15	10-20	[4]
IRT1 sensitivity (cutoff 96$^{th)}$, %		96.2	92-98	[2, 16-17, 32-33]
IRT1 sensitivity (cutoff 99.5th), %		80	78-85	[16, 33-38]
Sensitivity IRT2,%		92	80-95	[15, 17]
Specificity IRT2,%		94	90-95	
Sensitivity DNA 25-mutation panel,%		97	95-100	[17, 38]

Sensitivity DNA43–mutation panel,%			99	95-100	[38]
Specificity DNA,%			99.99	95-100	[36, 38-39]
Sensitivity PAP,%			85,7	75-95	[40-42]
Specificity PAP			99.991	95-100	
Parents consenting to NBS, %			99	95-100	[22]
Consenting for genetic counseling, %			90	50-100	[15]
Parental consent for DNA testing (conditional to acceptation of genetic counseling),%			50	50-100	[15]
Adherence to second IRT testing (conditional to positive first IRT), %			90	90-100	[16]
NBS	Visits		6	4-8	[24]
	Hospitalization	Probability	0,2	0.1-0.25	
		Number	1.1	1-2.2	
		Length of stay	8	6-10	
Absence of NBS (before diagnosis)	Visits		5	3-7	
	Hospitalization	Probability	0.72	0.51-0.90	
		Number	1.6	1-3.1	
		Length of stay	9.14	5-13	
Absence of NBS (after diagnosis)	Visits		5	3-5	
	Hospitalization	Probability	0.58	0.40-0.70	
		Number	1.3	1-2.6	
		Length of stay	9.35	6-12	
Cost IRT1, CAD$			2.65	1-5	[43]
Cost IRT2, CAD$			20.65	19-23	[43]
Cost DNA multi-mutation analysis, CAD$			315.5	100-500	[43]
Sweat test, CAD$			218.4	150-300	[43]
PAP, CAD$			10	5-15	[44]
Genetic counseling cost, CAD$			124.4	100-200	[20]
CF hospitalization cost, CAD$			1912/day	1200-2700	[45]
Clinic visits cost (including physician fees), CAD$			128.73/visit	100-150	[20, 24]
Lab tests (chest X-ray, pulmonary function test, microbiology, blood/urine tests), CAD$			410.223/visit	350-500	[24, 46]
Outpatient medications (oral and inhaled antibiotics, inhaled and oral corticosteroids, pancreatic enzymes, bronchodilatators, vitamins) + pharmacist fees, CAD$			13740.02/year	10000-20000	[24, 30, 46]
Home IV treatment , CAD$			72.14/day	50-110	[24, 46]
Oxygen therapy, CAD$			74.33/day	50-110	[24, 46]

Sensitivity analyses

Univariate and multi-way sensitivity analyses were performed using the parameters suspected to have an impact on outcomes as detailed in Table 2. One-way sensitivity analyses were performed to evaluate the eventual impact of each single parameter on the results. We tested the minimum and the maximum (from the 95% confidence intervals) value for each of these variables. Subsequently, using Monte Carlo simulations, multi-way probabilistic sensitivity analyses were performed in which all parameters above mentioned were varied concomitantly taking into account their distribution function. We assumed that event probabilities followed a beta distribution, that costs followed a gamma distribution while relative risks were assumed to have a log-normal distribution[47].

Validation

The model and simulation data were validated by three CF experts (PD, LL, and AML). Data produced were then validated by comparison with expected data (such as the number of cases of CF diagnosed according to the algorithm performances, number of expected confirmation tests, mortality rates per age, CF hospitalization rates). For example, for a time horizon of 5 years, our model predicted 174± 2 cases (CI, 95%) of cystic fibrosis for an expected number of cases of CF of 173. For an expected number of clinically diagnosed cases of CF of 154 at the end of year 5, our model predicted 152±2.5 cases of CF.

Ethics Committee

This project was approved by the Research Ethic Committee of Laval University (Approbation no. 2011-135) in order to access the Canadian CF patient registry.

Results

Base case scenario

Baseline results are presented in Table 3. All NBS options are less costly than the absence of NBS. In terms of costs, IRT_PAP and IRT_IRT with an IRT cutoff at the 96th percentile are the less costly options. Options that include a DNA analysis as a second tier test for an IRT cutoff at the 96th percentile are the most expensive options.

In terms of number of cases detected, all screening strategies are more effective than the absence of screening. The most effective options are those that include a DNA test (25- or 43-mutation panels) as a second tier test after a first positive IRT using a cutoff at the 96th percentile. In a time horizon of five years, a NBS program is predicted to detect up to 17 additional cases of CF, i.e. ≈4 cases per year compared to the absence of NBS for a population of 86000 newborns per year. However, even if there is a difference in cases detected by NBS between the different algorithms, we find that, in the end, the difference between these screening options in terms of the total number of cases diagnosed after a 5-year period is small. For example, the IRT^{96}_DNA_25mut strategy detects 17 more cases of CF through NBS than IRT^{96}_IRT, but the difference in total cases of CF diagnosed after a 5-year period between these two strategies is only 4 cases.

In term of cost per case detected, our results show that the absence of NBS is dominated (more expensive and less effective) by all NBS screening options considered. IRT-PAP with an IRT cutoff at the 96^{th} percentile is the most favorable option with a ratio of CAD$ 28,432 per case of CF detected. The next most favorable alternative is the IRT-IRT with an IRT1 cutoff at the 96^{th} percentile.

Table 3. Base case scenario results

Option	Total costs	Total cases detected over 5 years[1]	cost/CF case detected	Cost per additional CF case detected
IRT^{96}_PAP	4 606 040	162	28 432	-
IRT^{96}_IRT	4 705 345	164	28 691	49 653
IRT^{96}_PAP_DNA_43mut	4 757 684	162	29 368	Dominated[2]
IRT^{96}_PAP_DNA_25mut	4 760 827	161	29 570	Dominated
IRT$^{99.5}$_IRT	4 846 455	157	30 869	Dominated
IRT^{96}_IRT_DNA_43mut	4 864 426	164	29 661	Dominated
IRT^{96}_IRT_DNA_25mut	4 916 765	164	29 980	Dominated
IRT$^{99.5}$_DNA_43mut	4 949 418	162	30 551	Dominated
IRT$^{99.5}$_IRT_DNA_43mut	4 967 856	157	31 642	Dominated
IRT$^{99.5}$_DNA_43mut_IRT	4 979 282	162	30 736	Dominated
IRT$^{99.5}$_DNA_25mut_IRT	4 986 294	162	30 779	Dominated
IRT$^{99.5}$_DNA_25mut	5 001 776	162	30 875	Dominated
IRT$^{99.5}$_PAP	5 017 831	155	32 373	Dominated
IRT$^{99.5}$_IRT_DNA_25mut	5 019 528	156	32 176	Dominated
IRT$^{99.5}$_PAP_DNA_43mut	5 083 014	154	33 006	Dominated
IRT$^{99.5}$_PAP_DNA_25mut	5 134 686	154	33 342	Dominated
IRT^{96}_DNA_43mut	7 549 282	169	44 670	406 278
IRT^{96}_DNA_25mut	7 611 016	168	45 303	Dominated
IRT^{96}_DNA_43mut_IRT	7 851 878	169	46 460	Dominated
IRT^{96}_DNA_25mut_IRT	7 858 894	169	46 502	Dominated
Absence of NBS	8 646 422	152	56 884	Dominated

IRT^{96} = IRT above 96th percentile; IRT$^{99.5}$ = IRT above 99.5th percentile

[1] Based on an estimate of 174 children born with CF over the five-year period, excluding those diagnosed clinically with a *meconium ileus*

[2] Dominated strategies are those that were found to be less efficacious and more expensive than another strategy (strict dominance) or to have an incremental cost effectiveness ratio that is greater than that of the next, more effective, and more expensive alternative (extended dominance)

Sensitivity analyses

Results of univariate sensitivity analyses show that our results are robust. The IRT-PAP with IRT1 > 96^{th} percentile remains the most cost effective option with three exceptions. Indeed, when the cost of PAP is set to 15 CAD$ per test or when the sensitivity of PAP is 75%, the most cost effective option becomes IRT^{96}_IRT. When the cost of DNA analysis is set to 100 CAD$, the $IRT^{99.5}$_DNA_43mut is the most cost effective option. In multivariate sensitivity analyses, IRT^{96}_PAP and IRT^{96}_IRT remain the most cost-effective options. The probability of being the most cost effective option is 69.6% for IRT-PAP and 21.7% for IRT-IRT.

Discussion

This study presents the comparison of the expected cost effective of 20 NBS options and the absence of NBS under the perspective of the Quebec health care system. This study was justified on the basis that other modeling approaches [14-17]) have compared either a more limited number of screening algorithms or have tested only one IRT cutoff level and/or a limited CFTR mutation panel and didn't include the PAP testing option.

Our results show that CF NBS dominates the absence of NBS whatever the screening strategies considered. Among the 20 NBS algorithms tested (10 for IRT cutoff of 96th and 10 for 99.5th percentile), the IRT^{96}_PAP strategy is the most cost effective followed by the IRT^{96}_IRT strategy. The cost per additional case of CF detected by the IRT^{96}_IRT strategy compared to the IRT^{96}_PAP strategy is CAD$ 49,653. All other screening strategies are dominated by these two options, as they are more expensive with no or little benefit in term of CF detection. Indeed, at the end of the 5-year period, the total number of children with CF diagnosed in each option is quite similar while the difference in costs is high thereby disadvantaging options that include a DNA analysis as second tier test. These options are also disadvantaged by the inclusion of costs related to carrier identification (genetic counseling and DNA analysis for parents). Finally, because they increase the cost per case detected while not allowing to increase NBS case detection over IRT-IRT and IRT-PAP options, options that include DNA analysis as a 3rd tier test (25 or 43 mutations) seem to be the less favorable options.

However, we recognize the limitation of using available data on the use of PAP. This test has not been used in the Canadian population, including Quebec. There are therefore uncertainties regarding the applicability of data published from European studies to our population. For example, the A455E mutation is more common (around 3%) in Quebec[48] and has been reported as a false negative for PAP results. This might change the cost effectiveness of IRT-PAP and could advantage the IRT-IRT option.

This study has other limitations. The main limitations of such a simulation study are related to the mapping of a complex reality[49-50]. Assumptions and simplifications have to be made for some events for which it is difficult to obtain data. For examples, for cases missed by screening, we assumed the same probability to be diagnosed clinically as for the “absence of screening strategy”. We are aware that this might not completely reflect the reality. For example, if the missed cases by the NBS are more likely to be atypical cases that are difficult to diagnose based on symptoms (pancreatic sufficient or asymptomatic), the estimated costs per case detected might be overestimated. On the opposite, if the majority of missed cases are symptomatic, the estimated costs per case detected might be underestimated. In the same way, our study did not model the cost of management of family "emotional stress" related to the fact that their child was not diagnosed early or was diagnosed as a carrier. The model has not also considered the costs that could be generated by the follow-up of atypical CF case (CF related metabolic syndrome) detected by NBS. The addition of these costs could increase the cost per case detected by NBS. However, as these atypical CF cases are uncommon and occur primarily in NBS algorithms involving DNA detection, we believe that this would not change the ranking order between options.

An additional limitation of this study has to do with the validity of the parameters used in the simulation model. Parameters were retrieved from an extensive literature search and from experts' opinions. Yet, these parameters especially those related to the performances of the NBS tests or the efficacy of NBS may be specific to the populations under study and might not apply totally to our population. However, we believe that we addressed this issue by performing a large set of sensitivity analyses, which showed that our results are robust.

Another limitation is related to the outcome considered for this study. Indeed, we considered as the main outcome the total number of cases of CF detected (i.e. identified through screening or not). This might not be considered as the most relevant outcome. Quality adjusted-life years (QALY) of the children but also of their parents would certainly be more informative, since, especially for chronic diseases, they are considered as the most relevant health outcome in the economic evaluation field. A better survival and a better quality of life in CF patients detected by newborn screening compared with patients detected clinically are expected. However, an evaluation of QALYs could not be performed, as there is no appropriate instrument to measure utility scores in children under 5 years of age[51-52].

A last limitation is related to the use of a single perspective, i.e. the public healthcare perspective. The consideration of the patient/family or societal perspectives could modify the ranking of the options. For example, the addition of the patient/family perspective could disadvantage options that include the second IRT measurement, as an IRT2 measure needs a second blood sample, hence a new contact with the healthcare system.

Despite these limitations, this study suggests that NBS for cystic fibrosis is a cost-effective strategy compared to the absence of NBS in our health care setting. The IRT-PAP newborn screening algorithm with an IRT cutoff at the 96th percentile is the most cost effective algorithm. Results consist exclusively of cost effectiveness considerations. However, several non-economic are taken into consideration when a decision on a NBS program has to be made, such as laws, already existing newborn screening programs, access to genetic counseling, problem of carrier identification, etc. Nevertheless, besides the fact that the IRT-PAP strategy is the most cost effective, it has other advantages compared to other strategies. It is easy to implement because the analysis is done on a single sample and it allows avoiding the ethic difficulty of unwanted carrier's identification. This CF screening strategy should therefore be considered in any NBS screening program.

Finally, our results were produced in the Quebec context (that is characterized by a quasi-exclusive public healthcare system) and remain to be confirmed in other healthcare jurisdictions especially where private insurance plans play a major role.

Author contributions

All authors: Conception, design, acquisition and validation of data

AB, DF: computer simulations
NL, PD, DR, YG, FR, AML, LL, JG: analysis and interpretation of results.
NL: Drafting the article
DR, FR, AML, LL, PD, YG: Critically revising of the article
All authors approved the final version of article.

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Disclosure/Competing interest's declaration

All authors state that they have no conflicts of interest

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Table(s)

Table 1. Screening protocols

Strategy	Description
IRT_IRT	Newborns with IRT1 above the cut-off used (96^{th} or 99.5^{th}) are recalled for a second IRT. If the second IRT is >70 ng/ml, newborn is referred for sweat test.
IRT_IRT_DNA	Newborns with IRT1 above the cut-off used (96^{th} or 99.5^{th}) are recalled for a second IRT. If the second IRT is >70 ng/ml, newborn is referred for DNA-based CFTR mutation analysis (25- or 43-mutation panel). If one or two mutations are found, newborn is referred for sweat test.
IRT_DNA	DNA CFTR mutation analysis (25- or 43-mutation panel) is done for newborns with IRT1 above the cut-off used (96^{th} or 99.5^{th}). If at least one mutation is found, newborn is referred for sweat test.
IRT_DNA_IRT	DNA CFTR mutation analysis (25- or 43-mutation panel) is done for newborns with IRT1 above the cut-off used (96^{th} or 99.5^{th}). If at least one mutation is found or if no mutations are found but IRT1>99.9^{th} percentile, newborn is referred for sweat test.
IRT_PAP	PAP test is done for newborns with IRT1 above the cut-off used (96^{th} or 99.5^{th}). The result is positive if PAP test is > 1.8 ng/ml if the first IRT is > 96^{th} percentile or 1 ng/ml if the first IRT is > 99.5^{th} percentile. Newborn is then referred for sweat test.
IRT_PAP_DNA	PAP test is done for newborns with IRT1 above the cut-off used (96^{th} or 99.5^{th}). The result is positive if PAP test is > 1.8 ng/ml if the first IRT is > 96^{th} percentile or 1 ng/ml if the first IRT is > 99.5^{th} percentile. Thereafter, DNA CFTR mutation analysis (25- or 43-mutation panel). If at least one mutation is found, newborn is referred for sweat test.

Table 2.Model input parameters and costs

Parameter		Baseline	Sensitivity analysis	Reference
Number of newborns per year	2011	87 221		[21]
	2012	86 755		
	2013	86 106		
	2014	85 872		
	2015	86 080		
Probability of being clinically diagnosed according to age,%	0-1 year	70.4		[24]
	1-2 year	11.7		
	2-3 year	9.4		
	3-4 year	4.0		
	4-5 year	2.2		
	> 5 year	2.3		
Annual CF incidence		0.0004	0.0006-0.00025	[4]
CF newborns with *meconium ileus*, %		15	10-20	[4]
IRT1 sensitivity (cutoff 96$^{th)}$, %		96.2	92-98	[2, 16-17, 32-33]
IRT1 sensitivity (cutoff 99.5th), %		80	78-85	[16, 33-38]
Sensitivity IRT2,%		92	80-95	[15, 17]
Specificity IRT2,%		94	90-95	
Sensitivity DNA 25-mutation panel,%		97	95-100	[17, 38]
Sensitivity DNA43–mutation panel,%		99	95-100	[38]
Specificity DNA,%		99.99	95-100	[36, 38-39]
Sensitivity PAP,%		85,7	75-95	[40-42]
Specificity PAP		99.991	95-100	
Parents consenting to NBS, %		99	95-100	[22]
Consenting for genetic counseling, %		90	50-100	[15]
Parental consent for DNA testing (conditional to acceptation of genetic		50	50-100	[15]

counseling),%					
Adherence to second IRT testing (conditional to positive first IRT), %			90	90-100	[16]
NBS	Visits		6	4-8	[24]
	Hospitalization	Probability	0,2	0.1-0.25	
		Number	1.1	1-2.2	
		Length of stay	8	6-10	
Absence of NBS (before diagnosis)	Visits		5	3-7	
	Hospitalization	Probability	0.72	0.51-0.90	
		Number	1.6	1-3.1	
		Length of stay	9.14	5-13	
Absence of NBS (after diagnosis)	Visits		5	3-5	
	Hospitalization	Probability	0.58	0.40-0.70	
		Number	1.3	1-2.6	
		Length of stay	9.35	6-12	
Cost IRT1, CAD$			2.65	1-5	[43]
Cost IRT2, CAD$			20.65	19-23	[43]
Cost DNA multi-mutation analysis, CAD$			315.5	100-500	[43]
Sweat test, CAD$			218.4	150-300	[43]
PAP, CAD$			10	5-15	[44]
Genetic counseling cost, CAD$			124.4	100-200	[20]
CF hospitalization cost, CAD$			1912/day	1200-2700	[45]
Clinic visits cost (including physician fees), CAD$			128.73/visit	100-150	[20, 24]
Lab tests (chest X-ray, pulmonary function test, microbiology, blood/urine tests), CAD$			410.223/visit	350-500	[24, 46]

Outpatient medications (oral and inhaled antibiotics, inhaled and oral corticosteroids, pancreatic enzymes, bronchodilatators, vitamins) + pharmacist fees, CAD$	13740.02/year	10000-20000	[24, 30, 46]
Home IV treatment , CAD$	72.14/day	50-110	[24, 46]
Oxygen therapy, CAD$	74.33/day	50-110	[24, 46]

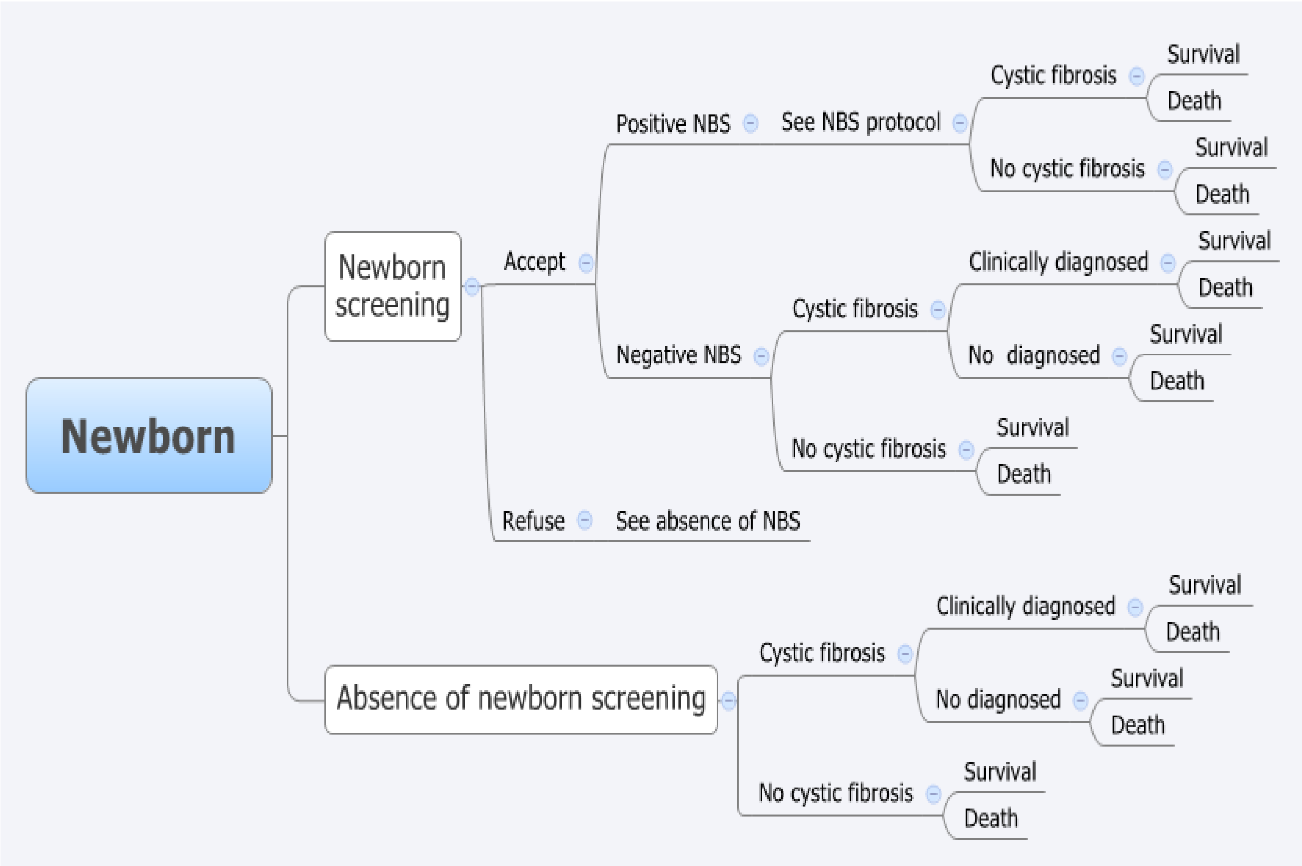
Table 3. Base case scenario results

Option	Total costs	Total cases detected over 5 years[1]	cost/CF case detected	Cost per additional CF case detected
IRT^{96}_PAP	4 606 040	162	28 432	
IRT^{96}_IRT	4 705 345	164	28 691	49 653
IRT^{96}_PAP_DNA_43mut	4 757 684	162	29 368	Dominated[2]
IRT^{96}_PAP_DNA_25mut	4 760 827	161	29 570	Dominated
$IRT^{99.5}$_IRT	4 846 455	157	30 869	Dominated
IRT^{96}_IRT_DNA_43mut	4 864 426	164	29 661	Dominated
IRT^{96}_IRT_DNA_25mut	4 916 765	164	29 980	Dominated
$IRT^{99.5}$_DNA_43mut	4 949 418	162	30 551	Dominated
$IRT^{99.5}$_IRT_DNA_43mut	4 967 856	157	31 642	Dominated
$IRT^{99.5}$_DNA_43mut_IRT	4 979 282	162	30 736	Dominated
$IRT^{99.5}$_DNA_25mut_IRT	4 986 294	162	30 779	Dominated
$IRT^{99.5}$_DNA_25mut	5 001 776	162	30 875	Dominated
$IRT^{99.5}$_PAP	5 017 831	155	32 373	Dominated
$IRT^{99.5}$_IRT_DNA_25mut	5 019 528	156	32 176	Dominated
$IRT^{99.5}$_PAP_DNA_43mut	5 083 014	154	33 006	Dominated
$IRT^{99.5}$_PAP_DNA_25mut	5 134 686	154	33 342	Dominated
IRT^{96}_DNA_43mut	7 549 282	169	44 670	406 278
IRT^{96}_DNA_25mut	7 611 016	168	45 303	Dominated
IRT^{96}_DNA_43mut_IRT	7 851 878	169	46 460	Dominated
IRT^{96}_DNA_25mut_IRT	7 858 894	169	46 502	Dominated
Absence of NBS	8 646 422	152	56 884	Dominated

IRT^{96} = IRT above 96th percentile; $IRT^{99.5}$ = IRT above 99.5th percentile

[1] Based on an estimate of 174 children born with CF over the five-year period, excluding those diagnosed clinically with a *meconium ileus*
[2] Dominated strategies are those that were found to be less efficacious and more expensive than another strategy (strict dominance) or to have an incremental cost effectiveness ratio that is greater than that of the next, more effective, and more expensive alternative (extended dominance)

Figure1


Newborn
Newborn screening
Accept
Positive NBS
See NBS protocol
Cystic fibrosis
Survival
Death
No cystic fibrosis
Survival
Death
Negative NBS
Cystic fibrosis
Clinically diagnosed
Survival
Death
No diagnosed
Survival
Death
No cystic fibrosis
Survival
Death
Refuse
See absence of NBS
Absence of newborn screening
Cystic fibrosis
Clinically diagnosed
Survival
Death
No diagnosed
Survival
Death
No cystic fibrosis
Survival
Death