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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.

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Keywords: Cystic fibrosis; Newborn screening; Cost effectiveness; Immune-reactive trypsinogen (IRT); Pancreatic-associated protein (PAP); CFTR; Simulation

1. 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

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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. [14] 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 Gynecologists [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 among 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.

2. Methods

2.1. 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.

2.2. Modeling

The simplified model structure is presented in Fig. 1. The model, divided into cycles of 1 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].

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