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Review

Strategies for newborn screening for cystic fibrosis: A systematic review of health economic evaluations

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Abstract

Background: Early detection of cystic fibrosis through newborn screening has significant clinical benefits. Cost-effectiveness plays an important role in selecting the optimal screening strategy from the many available options.
Objectives: The objectives of this study are (1) to summarize study estimates of cost-effectiveness of cystic fibrosis newborn screening (CFNBS) strategies as compared to other strategies, (2) to assess the quality of the studies identified, and (3) to identify determinants of cost-effectiveness.
Methods: Electronic databases were searched from 2007 to June 2017. Health economic evaluations describing the cost-effectiveness of two or more CFNBS strategies were included.
Results: Six health economic evaluations were found. Where included in the comparison, IRT/PAP consistently was the most cost-effective strategy in terms of cost per case detected or life years gained. However, some heterogeneity with respect to cut-off values used and the number of DNA mutations included in the screening strategies was observed, and the methodological quality differed considerably between studies.
Conclusions: The evidence suggested that (i) all screening strategies are cost-effective as compared to the no-screening option and (ii) IRT-PAP seems to be the most cost-effective screening strategy towards CFNBS. Methodological and contextual differences of the individual studies make it difficult to derive strong conclusions from this evidence. Nevertheless, from a health-economic perspective, IRT-PAP should be included as an alternative when deciding on the screening strategy in the implementation of CFNBS.

Keywords: Cystic fibrosis; Newborn screening; Health economic evaluation; Systematic review

Contents

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CRD, Centre of Research and Dissemination; DNA, deoxyribonucleic acid; HAS, Haute Autorité de Santé; HTA, health technology assessment; ICER, incremental cost effectiveness ratio; INAHTA, International Network of Agencies for Health Technology Assessment; IRT, immunoreactive trypsinogen; NBS, Newborn screening; CFNBS, cystic fibrosis newborn screening; PAP, pancreatitis associated protein; PWCF, People with CF; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Protocols

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1. Introduction

Cystic fibrosis (CF) is a life-shortening, autosomal recessive inherited disease. The disease is caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that leads to the accumulation of thick, viscous mucus in the pancreas, lungs, and other organs, severely impairing their function [1]. In 2014, 70,000 people were affected by CF worldwide. However, due to underreporting, the true number of people with CF (PWCF) may be even higher [2]. Currently, CF cannot be cured, and the mean age at death for PWCF in Europe in 2014 was just below twenty-nine years [3]. Fortunately, early diagnosis, comprehensive multidisciplinary CF care, nutritional support, new inhaled therapies, new anti-infective treatment, and lung transplantation have all lead to improved survival of PWCF. Furthermore, it is anticipated that new therapeutic strategies, including CFTR modulators, gene therapy and mRNA repair, will increase life expectancy even more [2].

Early diagnosis through newborn screening (NBS) has important clinical benefits for children born with CF in terms of improved nutritional status and lung function [4,5], with some evidence that cystic fibrosis newborn screening (CFNBS) may result in improved child survival [6]. These benefits of CFNBS, when combined with appropriate early treatment and intervention, outweigh the risks of unintentional detection of carrier status and diagnostic uncertainty inherent to the screening practice, as described in different consensus papers [7].

CFNBS can be performed in many forms, but all screening strategies start with the measurement of immunoreactive trypsinogen (IRT_1) levels in the blood sample taken during the first days of life (3–5 days) (i.e. the neonatal heel prick or Guthrie test). The IRT-test may be followed by a second IRT test (IRT_2), measurement of pancreatitis-associated protein (PAP), and/or DNA mutation analysis of the CFTR gene, with or without extended gene sequencing. A sweat test is used to confirm a diagnosis of CF in all positive screened babies, regardless of the adopted screening strategy. Apart from the different algorithms, CFNBS strategies may differ in the timing of IRT_1-sampling, IRT cut-off values (floating or fixed) and reference values for PAP, and the number of mutations included in the DNA mutation panel [8]. Often, strategies include a 'failsafe' or 'ultra-high IRT' strategy in which infants with a high IRT_1 but no mutations recognized in the DNA analysis are referred to further testing. In some cases this results in an immediate referral to a sweat test; in other cases, an additional dried blood sample for IRT is taken on day 21 (IRT_2), where the infant will only be referred to a sweat test if IRT_2 is raised too. In France, the failsafe strategy is also used in case of an absent parental written consent for DNA testing [8]. Fig. 1 shows the general structure of a IRT-DNA, IRT_1-IRT_2, and IRT-DNA-failsafe (IRT_2) strategy for CFNBS.

NBS priorities generally vary from region to region, and the choice of strategy depends on a range of factors, as population-based factors influencing the prevalence of certain CFTR-mutations and costs [7]. Health economic evaluations can help local and regional decision-makers in this selection process by providing a comparison of different screening strategies in terms of both their costs and consequences [9]. English language publications on the cost-effectiveness of NBS for phenylketonuria and cystic fibrosis have been reviewed and eloquently discussed in 2015 by Scott D. Grosse [10]. Grosse's review was primarily meant to illustrate challenges in quantifying the effectiveness and cost-effectiveness in NBS in general, and did not apply a systematic approach in the identification of the literature and/or the quality assessment of individual studies. Therefore, the aim of the current study is to strengthen the existing knowledge by:

1. summarizing study estimates of cost-effectiveness of CFNBS strategies as compared to other strategies (evidence synthesis);
2. systematically assessing the methodological quality of the studies identified; and
3. identifying the factors influencing cost-effectiveness of different CFNBS strategies.

2. Methods

A research protocol was developed prior to the start of the systematic review, following the PRISMA-P 2015 checklist [11], which is available upon request from the corresponding author.

A literature search was performed in MEDLINE (via PubMed), Embase (via Embase.com), Web of Science (via Web of Knowledge), the Cochrane Library, EconLit, and the Centre for Reviews and Dissemination (CRD)'s NHS Economic Evaluation (NHS EED) and Health Technology Assessments (HTA) Databases. In addition, the member websites of the International Network of Agencies for Health Technology Assessments were searched for relevant reports and publications on economic aspects of CFNBS. For each database, a search strategy was developed consisting of synonyms related to the disease (e.g. 'cystic fibrosis'), intervention (e.g. 'neonatal screening'), and health economics. For the keywords related to the disease and intervention, a clinical expert was consulted to ensure all relevant keywords and synonyms were included. The keywords related to health economics were based on validated search strategies found in the literature [12,13]. The electronic searches were all performed on June 22nd, 2017, with the exception of Embase, where the search

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