Newborn screening for cystic fibrosis is associated with the lowest healthcare costs : a 10-year observational follow-up study in France

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Abbreviations:

ANT: Antenatal period

BIC: Bayesian information criterion

chCF: children with CF

CF: Cystic Fibrosis

CFTR: Cystic fibrosis transmembrane conductance regulator

CFTRm: CFTR modulators

ETI: elexacaftor-tezacaftor-ivacaftor

FCFR: French CF Registry

FEV1: Forced expiratory volume in one second

HC: Healthcare

HEMT: Highly effective modulator therapy

LS: Later based on the symptoms

MI: Meconium ileus

NBS: Newborn screening

NICU: Neonatal intensive care units

SD: Standard deviation

SNDS: Système National des Données de Santé - national system of health data

Abstract

**Objectives**: This study aims to study the healthcare (HC) costs associated with cystic fibrosis (CF) in children diagnosed prenatally (ANT), through newborn screening (NBS), after birth due to meconium ileus (MI), or later based on symptoms (LS). Additionally, it seeks to clinically characterize children with CF (chCF) with different trajectories of HC costs.

**Study design:** A retrospective observational study was conducted on data from the French CF Registry (FCFR) and the French National Claims Database (SNDS) linked from 2006 to 2021. HC costs related to CF diagnosis circumstances were estimated per year of life among chCF up to age 10. Group-based trajectory modeling was performed to identify subgroups with similar cost trajectories.

**Results:** Between 2006 and 2011, data from 1,065 chCF were recorded in the FCFR. 973 (91.4%) were matched with SNDS, and 779 (73.1%) had at least 10 years of follow-up. NBS resulted in the lowest costs. During the first year, HC costs of chCF diagnosed with MI and ANT were higher than for those diagnosed with NBS or LS. Expenses declined in the second year of life and then gradually increased to approximately €20,000 by the tenth year. Three groups with different cost trajectories were identified. Groups with the highest costs had a lower lung function at 6 and 10 years and the lowest weight and height z-scores at 2 and 10 years (all p<0.05).

**Conclusion:** HC costs were lower in chCF diagnosed by NBS, and high HC costs could occur at the earliest stages of CF.

# Introduction

Healthcare (HC) costs and treatment evolution associated with early cystic fibrosis (CF) management since the introduction of newborn screening (NBS) are poorly known. Although some data are available, they do not always specify diagnosis circumstances for children with CF (chCF), diagnosed after NBS, or due to symptoms such as meconium ileus (MI). In the USA, the average HC cost for chCF increased from US$58,512 (€54,000) in 2010 to US$116,171 (€107,100) in 2016 (1). The sharpest increase in HC costs occurred between 2013 and 2015 with the introduction of ivacaftor, and ivacaftor/lumacaftor treatments, respectively. A study showed that HC costs could significantly rise from the neonatal period onwards, particularly when children are initially hospitalized for MI (2). Our previous work demonstrated that the average annual cost in the 7-11 age group was around €15,000, rising to €24,000 in adolescence and adulthood (3). Recently, Irish authors have shown that clinically diagnosed CF cases witnessed a nearly 3-fold increase in direct HC costs per year during the first two years of life in comparison to newborn screened infants (4).

The advent of cystic fibrosis transmembrane conductance regulator modulators (CFTRm), and the triple combination therapy has changed CF presentation, even in young children (5-7). Early introduction of CFTRm will increase HC costs substantially, without any doubt. However, studying HC costs can also be seen as a surrogate of the treatment burden and, by extent, disease severity. This will be particularly important in tracking this cohort of minimally symptomatic children. Recent data collected from the CF Swedish population of pwCF indicate that in the year following the introduction of the double combination therapy Lumacaftor-Ivacaftor, a decrease in some direct (oral antibiotic days of use) and indirect (caregivers days of work lost) costs were captured (8).

Therefore, our primary objective was to describe the evolution of HC costs over the first 10 years of the life of chCF, since the introduction of NBS in France and before the introduction of CFTRm, while distinguishing diagnosis circumstances. Our secondary objective was to characterize *a priori* population of chCF with different trajectories of costs, given the possible heterogeneity of the CF population, even at the youngest ages. Our hypothesis was that NBS was associated with lower HC costs.

# Materials and Methods

## Study design, data sources, and linkage

This retrospective observational study used two datasets: the French Cystic Fibrosis Registry (FCFR) and the Système National des Données de Santé (SNDS). The FCFR is based on an annual review of chCF followed in one of the 37 CF centers in France, and gathers information on medical history, treatments, as well as clinical and microbiological data. The SNDS is the French health claims database, which contains anonymous individual data for the entire French population, including sociodemographic information, accurate healthcare expenditures, and medical diagnoses for patients with specific chronic conditions such as CF (9). Clinical data (anthropometrics, lung function, and microbiology) were sourced from the FCFR, while the healthcare resource utilization and directly related costs were retrieved from the SNDS.

The linkage between the FCFR and the SNDS has already been used and described in previous studies (3, 10). Briefly, individuals’ anonymous data from 2006-2021 gathered from both the FCFR and the SNDS were linked using a scoring system and decision algorithm. The process included five rounds of matching based on points assigned to common variables (i.e., gender, birth date, date of spirometry tests, area of residence, date of sweat tests, CF care centers, use of CFTRm, presence of comorbidities or transplantations, and death status). Notably, cross-verification ensured consistency for death and transplant data.

## Data analysis

This study involved chCF recorded in the FCFR that were born between 2006 and 2011, for whom linkage with the SNDS could be achieved successfully. ChCF were followed up during the period between the index date (i.e. the last day of the month and the year of birth, a proxy of birth date) and the end of follow-up. The latter was defined by the occurrence of one of the following events, whichever occurred first: death, loss to follow-up, first dispensing of CFTRm, or the end of the study period (December 31, 2021). ChCF with at least ten years of follow-up (i.e., at least 10 years of life) were included in the analyses.

Subgroup analysis was defined according to CF diagnosis circumstances: prenatal diagnosis (ANT), after meconium ileus (MI), after NBS (NBS) or later based on symptoms (LS). In the case of several concomitant circumstances of CF diagnosis, chCF was classified first in the ANT group, then in the MI group, followed by the NBS group, and finally by exclusion in the LS group. In the ANT group, 13 children presented with MI at birth, and the remaining (n = 26) had no symptoms of MI at birth. For analysis purposes, data from both infants who had MI and those who did not were merged as there was no satisfying categorization process for these two subgroups due to small sample sizes.

For the SNDS variable “hospitalization”, a distinction was made between one-day hospitalization (which is current practice in France for chCF follow-up in CF centers as it best covers the costs of multiple healthcare professional interventions) and conventional hospitalization, which is mostly related to acute care events.

## Statistical methods

Study outcomes of interest were described either by sample size (N), mean and standard deviation (SD), or median, interquartile range (Q1–Q3) for quantitative variables, and by sample size (N) and frequency for qualitative variables.

Sex and age at diagnosis were described overall and by analysis subgroup. Mean HC costs were recorded over 10 years from the index date (i.e. proxy of the birth date), segmented into 12-month periods, and categorized by category of expense, and circumstances of diagnosis.

Based on total HC costs per year and per child, group-based trajectory modeling was performed to identify subgroups with similar cost trajectories. The best model was selected using the Bayesian information criterion (BIC), the average probability of assignment to a group, and an acceptable distribution of patients in the groups. The average cost per patient and year was described for each trajectory group. The association between demographic and clinical characteristics and trajectory groups was assessed independently with Chi-square tests (or with Fisher’s exact test wherever applicable) for categorical variables and ANOVA for continuous variables.

## Ethics

This study was conducted using anonymized data after seeking approval from the French Institute for Health Data (approval n◦ 6708222, on 12/15/2021) and the French Data Protection Authority (approval n◦ DR-2022-119, on 05/05/2022). According to national regulations, written informed consent was not necessary for participation in this study; however, individuals from the FCFR were informed by letter that they could object to data collection and publication.

# Results

## Study population

The study entailed 1,065 data of chCF included in the FCFR that were born between 2006 and 2011. Among them, 973 chCF (91.4%) had their records successfully linked to the SNDS. Finally, 779 chCF (73.1%) were followed up for at least 10 years and were included in the study (Figure S1). During the study period, chCF were mostly diagnosed by NBS (N=601, 77.2%), after MI (N=101, 13.0%), after ANT (N=39, 5.0%), or LS (N=38, 4.9%).

In the NBS group, CF was confirmed at an average of 1.2 (±3.1) months, at 0.5 (±0.8) months for the MI group, and 28.3 (±31.9) months for the LS group (Table 1).

## HC costs during the first ten years of life.

Overall, the evolution of HC costs followed a similar trajectory in the four diagnosis groups. Costs were higher in the first year of life, decreased during the second year of life, and then increased steadily throughout the first 10 years of life. However, differences in cost patterns were found in line with diagnosis circumstances (Figure 1).

During the first year of follow-up, the highest mean annual costs per patient were found in the MI and ANT groups (€20,752 ± €23,453 and €19,659 ± €17,225, respectively). The lowest mean costs were found in the NBS and LS groups (€12,056 ± €10,073 and €13,861 ± €17,492, respectively). The majority of these costs were driven by hospitalizations, which accounted for 78.7% of costs in the LS group, 65.8% in the ANT group, 65.4% in the MI group, and 51.6% in the NBS group (Supplementary Material, Figure S2). When looking at data on hospitalizations during the first year in detail, we found that chCF diagnosed after NBS had more one-day hospitalizations than those in the ANT and MI groups (3.7 ± 3.9 days, vs 2.9 ± 3.2 days and 3.1 ± 3.4 days respectively). However, infants with MI had more conventional hospitalization and longer duration of stays in comparison to those diagnosed by NBS (31 days vs 17.1 days respectively) (Supplementary Material, Table S1).

Mean HC costs decreased during the second year of life in all groups but then increased steadily over time. During the 10th year, mean annual costs were €22,954 ± €13,975 for the MI group, €21,885 ± €17,841 for the ANT group, €20,711 ± €18,915 for the LS group, and €19,083 ± €15,783 for the NBS group. From the second year to the tenth year, the proportion of hospital admissions and medical visits decreased in the NBS group (from 30.8% to 25.5% for hospital stays), while the proportion of medication costs increased (from 26.7% to 47.2%). In the MI and ANT groups, the proportion of hospital stays remained relatively stable (23% to 31% and 31% to 25% respectively), while the proportion of medical visits decreased (36% to 21% and 33% to 19% respectively). However, the proportion of medication costs increased (from 32% to 40.2% and 29% to 49% respectively) (Supplementary Material, Figure S2).

## HC costs trajectories over the 10 first years of life.

The *a priori* analysis of the total HC costs per year and per patient identified three distinct groups with different cost trajectories (Figure 2, and Supplementary Material, Figure S3). The first group of 553 patients (71.0%), exhibited “low” and steady HC costs. The second group of 200 patients (25.7%), had “high” initial HC costs followed by a smooth gradual increase. The third and final group of 26 patients (3.3%), had the “highest” initial HC costs followed by a steeper increase over time.

In the "low" group, the mean cost was around €11,015 ± €9,253 in the first year of follow-up and rose slightly to €12,948 ± €7,444 in the tenth year. The "high" and "highest" groups had a mean cost of around €20k in the first year, which rose to €32,987 ± €13,001 and €64,233 ± €27,957 in the tenth year, respectively. In the first year, most of these costs were driven by hospitalization-related costs, which accounted for 60.4% for the high group, 58.5% for the highest group, and 54.1% for the low group. From the second to the tenth year, the proportion of hospitalization costs decreased as the proportion of medical visits increased.

## ChCF characteristics of each trajectory

Clinical characteristics from chCF from each trajectory were compared (Table 2). No significant difference between groups was observed regarding gender, circumstances of diagnosis, and nature of *CFTR* mutations. A similar proportion of NBS patients ended up in the 3 groups: 79% in "low," 72% in "high," and 76.9% in "highest. For MI, the proportion was lower in the low group (11.9%) than in the high group (16.9%), yet the difference was not statistically significant. However, differences were observed for FEV1 at 6 y (p=0.002) and 10 y (p<0.0001); groups "high" and "highest" had the lowest FEV1 at both 6 and 10 y depicting a more severe CF lung disease. Similarly, groups “high” and “highest” had a lower weight z-score at 2 y (p=0.014), and height z-score at 10 y (p=0.022) than chCF in the group “low”. Pancreatic insufficiency was also more frequent in the “high” and “highest” groups. According to their most severe CF phenotype, chCF from groups “high” and “highest” suffered more respiratory comorbidities such as allergic bronchopulmonary aspergillosis (11.5% in the group “high” versus 4.5% in the group “low”). Additionally, chCF of groups “high” and “highest” were infected by *Pseudomonas aeruginosa* at an earlier age and had a higher percentage of chronic colonization by *Pseudomonas aeruginosa* at 6 and 10 y. They received more IV antibiotics for longer periods.

# Discussion

Our study adds new knowledge on direct HC costs involved in young chCF and shows that diagnosis of CF by NBS confers the lowest healthcare expenses. Conversely, prenatal and MI diagnoses result in the highest costs, despite the narrowed gaps between the groups by the time chCF acquires the age of 10 years. Direct HC costs were high during the first year of life for all diagnosis circumstances, mainly driven by one-day hospitalizations related to chCF routine visits. Nonetheless, costs decreased during the second year of life and increased thereafter. Two high HC cost trajectories (representing one-third of our study population) were identified, highlighting a high burden of care and disease severity that pleads in favor of the early CFTRm introduction in the pediatric population.

## NBS for CF: infant health benefits at the lowest cost.

NBS for CF was generalized in France at the end of 2002. Both French (11) and European (12) guidelines for the management of infants with CF insist on the prevention of malnutrition and CF-related lung disease. Several countries have reported multiple short- and medium-term benefits of NBS for CF well before CFTRm was available. NBS for CF has repeatedly been shown to be associated with clinical benefits, including respiratory and nutritional benefits in short and medium terms (13-17). The benefits conferred by NBS were equally evident over the long term, with significant advantages in both respiratory and nutritional terms (18-21). Finally, survival advantage from pediatric age onwards has been demonstrated, along with the reduction in mortality (22, 23). In our study, we found that diagnosis of CF after NBS was associated with the lowest HC costs during the first 10 years of life, even if differences between diagnosis groups lessened over time. The first year of expenses was 12,056 € in the NBS group, while it was €13 661, €19 659, and €20752 in the symptoms-based, antenatal, and meconium ileus groups respectively. In a paper published in 2007, Sims et al. forecasted potential savings in treatment costs attributable to NBS. They showed that the cost of therapy for patients diagnosed with NBS was significantly lower than equivalent therapies for clinically diagnosed patients (24). Our real-world data thus align with their forecast and studies that have explored the cost-effectiveness of NBS for CF (25). At 10 y, HC costs were still the lowest in the NBS group although differences with other groups had diminished. It is still unknown if these differences remain or not after 10 years of age, by reaching adolescence where HC costs have been described to increase substantially (2, 3). Recently, the ICOS (Irish Comparative Outcome Study), put in place in 2013 to assess the impact of NBS on CF in Ireland, has shown that symptom-based chCF (n = 72; excluding chCF with MI), incurred 2.62 times higher direct costs during the two first years of life in comparison to those diagnosed after NBS (n = 69). As shown in this study, inpatient admissions were the main driver of the differences between direct costs for NBS (€5070) and symptom-based patients (€10 940) (4). We found a very similar result, as in our case, for chCF in the NBS group, the first and second-year direct costs for hospitalization were €6222 and €3204 respectively; while it was €10 906 and €5625 for chCF diagnosed on symptoms. Our results extend these findings by showing that, in a larger study population with a longer follow-up, the cost differences narrow over time.

## Early and high HC cost trajectories are possible even at the youngest ages.

Our study shows that chCF may experience significant HCRU even in the early stages of their lives. We identified three different HC cost trajectories. The first group of chCF was small in number (26 out of 779; 3.3%) but experienced high and increasing HC costs over time, reaching around €60 000 at the end of follow-up. The second group of 200 chCF (25.7%) witnessed high but stable HC costs (around €30 000 at the end of follow-up) while the remaining chCF (N=553; 71%) had low and consistent HC (around €10 000 at year 10). Clinical characteristics indicated that the chCF in the highest HC group had a more severe phenotype of CF, as evidenced by poorer nutritional and respiratory health status at 6 and 10 years. It is noteworthy that chCF with the “highest” and “high” trajectory had HC costs that doubled those of the “low” group as soon as the first year of their lives. This was related to a higher number of hospital admissions (mainly conventional hospitalization) and medical visits which we unfortunately could not detail further. In those incidences of chCF, early introduction of CFTRm might limit early clinical deterioration and reduce non-CFTRm-related HC costs.

## Hospitalization costs were high during the first year of life, even in chCF diagnosed after NBS.

Direct costs related to hospital stays emerged as the most important HC costs during the first year of life for all diagnosis groups. It ranged from around €20,000 for infants diagnosed in the prenatal period and for those with MI to €13,000 for those diagnosed clinically or after NBS.

Hospitalization accounted for 50% of the total HC costs for newborn screened babies during the first year of life which we considered to be high. As explained earlier, one-day hospitalization is standard practice in CF centers in France and may partially explain this finding. For every chCF diagnosed after NBS, 9 routine one-day hospitalizations are scheduled during the first year of follow-up; this comes with a higher cost than a simple "medical visit". However, the first year's high costs related to hospital stays can also have other explanations. Previous work conducted on US CF registry data shows that during the first nine years of 6,354 chCF diagnosed after NBS, one-third were hospitalized during the first year of their life. The rate of hospitalization then decreases while chCF gets older. In the vast majority of cases, hospitalizations were CF-related and because of pulmonary exacerbation, likely of viral origin in this age group as has been shown previously (20, 26). Whether costs related to first-year hospitalization of infants with CF diagnosed after NBS will be reduced by early use of CFTRm or not remains to be determined. However, recently, Linbald et al showed that the dual combination Lumacaftor-Ivacaftor reduced direct costs such as oral antibiotic use expenses, but had no effect on the number and duration of hospitalizations (8).

## Meconium ileus was associated with a higher early burden of care and HC costs.

MI was associated with the highest HC costs during the 1st year of life as well as throughout the first 10 years. As in the other groups, expenses were distributed across hospitalizations, outpatient visits, and CF-related treatments. We were not totally surprised by this result, as MI usually requires prolonged hospitalization in the neonatal intensive care unit (NICU) and surgical interventions in complicated cases (27). A similar picture was seen for infants whose diagnosis of CF was done prenatally on ultrasonographic signs of MI. Thirteen out of 39 (33%) presented MI at birth, but given the high risk of complicated MI, it’s likely that they were all hospitalized in the NICU for initial surveillance and management.

MI is associated with a high burden of care; and has a major psychological impact on both infants and parents. As mentioned above, it also comes with high HC and associated costs. Some authors have reported the beneficial use of CFTRm for mothers of fetuses presenting ultrasonographic signs of MI (28, 29). Given the potential of this approach in directly treating MI and in indirectly avoiding future nonmedical consequences while being potentially cost-saving, fetal therapy using CFTRm should probably be considered an important therapeutic option in the future.

Finally, we found that chCF diagnosed with MI were those incurring the highest HC costs during the 10 years onwards. Differences between groups in terms of cost repartition indicated that patients with a history of MI used more CF medications. While multiple studies have indicated that chCF with MI yields similar respiratory outcomes as those without (30, 31), MI is still recognized as a factor for gastrointestinal symptoms and distal intestinal obstruction syndrome, which are conditions related to higher HC (32, 33).

## Strengths and limitations of our study

Our study is the first to describe the first ten years of healthcare utilization resources evolution of chCF after the introduction of NBS for CF in France. It shows how diagnosis circumstances impact HC and enriches the discussion on the early use of CFTRm. However, our study had limitations. To ensure a minimum follow-up of 10 years, we limited our study to chCF born before 2011, excluding around half of the chCF population. Furthermore, we could not have access to data from the French claims database between 2002 and 2006, further restricting the sample size included in our analysis. Lastly, due to these “time windows” limitations, we were unable to analyze data during adolescence, which is a critical period where HC has been shown to increase (3).

# Conclusion

This retrospective study examined the pediatric healthcare costs in France after the implementation of NBS. By linking patient registry data and health claims, we found that HC costs varied depending on the diagnosis circumstances, with NBS being associated with the lowest HC costs and MI with the highest. Expenses were notably high for those diagnosed before birth, probably driven by the one-third of cases who experienced MI. Additionally, the study described three HC cost groups over the first 10 years of life, with the two highest HC cost groups representing around one-third of the total cohort. The results emphasize the potential benefits of evaluating the impact of early use of CFTRm by conducting a before-after study, employing the same methodological approach. Given the specificity of the French healthcare system, caution needs to be exercised while extrapolating the generalizability of these results to other countries around the world**.**

Author contribution:

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# References

1. Grosse SD, Do TQN, Vu M, Feng LB, Berry JG, Sawicki GS. Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016. Pediatr Pulmonol. 2018;53(12):1611-8.

2. Thorat T, McGarry LJ, Bonafede MM, Limone BL, Rubin JL, Jariwala-Parikh K, et al. Healthcare resource utilization and costs among children with cystic fibrosis in the United States. Pediatr Pulmonol. 2021;56(9):2833-44.

3. Durieu I, Dalon F, Reynaud Q, Lemonnier L, Dehillotte C, Berard M, et al. Temporal trends in healthcare resource use and associated costs of patients with cystic fibrosis. J Cyst Fibros. 2022;21(1):88-95.

4. Somerville R, Fitzgerald C, Segurado R, Kapur K, George S, Bhardwaj N, et al. Direct healthcare costs in the first 2 years of life: A comparison of screened and clinically diagnosed children with cystic fibrosis - The Irish comparative outcomes study of CF (ICOS). J Cyst Fibros. 2024;23(5):896-902.

5. Mall MA, Brugha R, Gartner S, Legg J, Moeller A, Mondejar-Lopez P, et al. Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3b, Randomized, Placebo-controlled Study. Am J Respir Crit Care Med. 2022;206(11):1361-9.

6. McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. Lancet Respir Med. 2019;7(4):325-35.

7. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med. 2021;203(12):1522-32.

8. Lindblad A, Monestrol I, Gilljam M, Krantz C, McGarry LJ, Banefelt J, et al. Clinical, economic, and societal burden of cystic fibrosis and the impact of the CFTR modulator, lumacaftor/ivacaftor: an assessment using linked registry data in Sweden. Journal of medical economics. 2024;27(1):897-906.

9. Tuppin P, Rudant J, Constantinou P, Gastaldi-Menager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the systeme national d'information interregimes de l'Assurance Maladie (SNIIRAM) to the systeme national des donnees de sante (SNDS) in France. Rev Epidemiol Sante Publique. 2017;65 Suppl 4:S149-S67.

10. Guyot E, Reynaud Q, Belhassen M, Berard M, Dehillotte C, Lemonnier L, et al. Health care resource utilization preceding death or lung transplantation in people with cystic fibrosis: HCRU before transplant or death in cystic fibrosis. J Cyst Fibros. 2024.

11. Sermet-Gaudelus I, Mayell SJ, Southern KW, European Cystic Fibrosis Society NSWG. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. J Cyst Fibros. 2010;9(5):323-9.

12. Sermet-Gaudelus I, Couderc L, Vrielynck S, Brouard J, Weiss L, Wizla N, et al. [National French guidelines for management of infants with cystic fibrosis]. Arch Pediatr. 2014;21(6):654-62.

13. Southern KW, Merelle MM, Dankert-Roelse JE, Nagelkerke AD. Newborn screening for cystic fibrosis. The Cochrane database of systematic reviews. 2009;2009(1):CD001402.

14. Schluter DK, Southern KW, Dryden C, Diggle P, Taylor-Robinson D. Impact of newborn screening on outcomes and social inequalities in cystic fibrosis: a UK CF registry-based study. Thorax. 2020;75(2):123-31.

15. Farrell PM, Kosorok MR, Rock MJ, Laxova A, Zeng L, Lai HC, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics. 2001;107(1):1-13.

16. Collins MS, Abbott MA, Wakefield DB, Lapin CD, Drapeau G, Hopfer SM, et al. Improved pulmonary and growth outcomes in cystic fibrosis by newborn screening. Pediatr Pulmonol. 2008;43(7):648-55.

17. Festini F, Taccetti G, Galici V, Campana S, Mergni G, Repetto T. Long-term health outcomes of neonatal screening for cystic fibrosis. Archives of disease in childhood. 2008;93(4):357-8.

18. Siret D, Bretaudeau G, Branger B, Dabadie A, Dagorne M, David V, et al. Comparing the clinical evolution of cystic fibrosis screened neonatally to that of cystic fibrosis diagnosed from clinical symptoms: a 10-year retrospective study in a French region (Brittany). Pediatr Pulmonol. 2003;35(5):342-9.

19. Reid DW, Blizzard CL, Shugg DM, Flowers C, Cash C, Greville HM. Changes in cystic fibrosis mortality in Australia, 1979-2005. The Medical Journal of Australia. 2011;195(7):392-5.

20. Martiniano SL, Elbert AA, Farrell PM, Ren CL, Sontag MK, Wu R, et al. Outcomes of infants born during the first 9 years of CF newborn screening in the United States: A retrospective Cystic Fibrosis Foundation Patient Registry cohort study. Pediatr Pulmonol. 2021;56(12):3758-67.

21. McKay KO, Waters DL, Gaskin KJ. The influence of newborn screening for cystic fibrosis on pulmonary outcomes in New South Wales. The Journal of Pediatrics. 2005;147(3 Suppl):S47-50.

22. Tridello G, Castellani C, Meneghelli I, Tamanini A, Assael BM. Early diagnosis from newborn screening maximises survival in severe cystic fibrosis. ERJ Open Res. 2018;4(2).

23. Grosse SD, Rosenfeld M, Devine OJ, Lai HJ, Farrell PM. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. The Journal of Pediatrics. 2006;149(3):362-6.

24. Sims EJ, Mugford M, Clark A, Aitken D, McCormick J, Mehta G, et al. Economic implications of newborn screening for cystic fibrosis: a cost of illness retrospective cohort study. Lancet. 2007;369(9568):1187-95.

25. van der Ploeg CP, van den Akker-van Marle ME, Vernooij-van Langen AM, Elvers LH, Gille JJ, Verkerk PH, et al. Cost-effectiveness of newborn screening for cystic fibrosis determined with real-life data. J Cyst Fibros. 2015;14(2):194-202.

26. Eymery M, Morfin F, Doleans-Jordheim A, Perceval M, Ohlmann C, Mainguy C, et al. Viral respiratory tract infections in young children with cystic fibrosis: a prospective full-year seasonal study. Virol J. 2019;16(1):111.

27. Long AM, Jones IH, Knight M, McNally J, Baps C. Early management of meconium ileus in infants with cystic fibrosis: A prospective population cohort study. J Pediatr Surg. 2021;56(8):1287-92.

28. Gomez-Montes E, Salcedo Lobato E, Galindo Izquierdo A, Garcia Alcazar D, Villalain Gonzalez C, Moral-Pumarega MT, et al. Prenatal Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy: A Promising Way to Change the Impact of Cystic Fibrosis. Fetal Diagn Ther. 2023;50(2):136-42.

29. Szentpetery S, Foil K, Hendrix S, Gray S, Mingora C, Head B, et al. A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus. J Cyst Fibros. 2022;21(4):721-4.

30. Munck A, Gerardin M, Alberti C, Ajzenman C, Lebourgeois M, Aigrain Y, et al. Clinical outcome of cystic fibrosis presenting with or without meconium ileus: a matched cohort study. J Pediatr Surg. 2006;41(9):1556-60.

31. Kappler M, Feilcke M, Schroter C, Kraxner A, Griese M. Long-term pulmonary outcome after meconium ileus in cystic fibrosis. Pediatr Pulmonol. 2009;44(12):1201-6.

32. Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros. 2011;10 Suppl 2:S24-8.

33. Aksit MA, Ling H, Pace RG, Raraigh KS, Onchiri F, Faino AV, et al. Pleiotropic modifiers of age-related diabetes and neonatal intestinal obstruction in cystic fibrosis. Am J Hum Genet. 2022;109(10):1894-908.

**Figures legends**

Figure 1. Evolution of the mean healthcare costs in euros per patient, type of expense, and year of life during the first ten years of life depending on diagnosis circumstances

Figure 2. Annual evolution of healthcare costs over the first 10 years of life of children with CF.