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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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Keywords: CFTR modulator | cost trajectories | french cystic fibrosis registry | health claims data | newborn screening

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 1065 chCF were recorded in the FCFR. Nine hundred seventy-three (91.4%) were matched with SNDS, and 779 (73.1%) had at least 10 years of follow-up. During the first year, HC costs of chCF diagnosed with NBS were lower than for those diagnosed with MI and ANT (all $p < 0.05$). However, by the tenth year HC were no longer different between groups. 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: NBS is associated with the lowest HC costs during the first year of life.

Abbreviations: ANT, antenatal period; BIC, Bayesian information criterion; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, CFTR modulators; chCF, children with CF; ETI, elexacaftor-tezacaftor-ivacaftor; FCFR, French CF Registry; FEV_1, forced expiratory volume in 1 s; 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.

1 | 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 threefold increase in direct HC costs per year during the first 2 years of life in comparison to newborn screened infants [4].

NBS for CF was generalized in France at the end of 2002. Both French [5] and European [6] 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 [7–11]. The benefits conferred by NBS were equally evident over the long term, with significant advantages in both respiratory and nutritional terms [12–15]. Finally, the survival advantage from pediatric age onwards has been demonstrated, along with the reduction in mortality [16, 17]. While knowing the clinical advantages of NBS for CF, there is no data on the HC costs generated by this approach, and how it compares with other diagnosis circumstances.

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 in the late 2002, 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.

2 | Materials and Methods

2.1 | Study Design, Data Sources, and Linkage

This retrospective observational study used two datasets: the French CF 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 National Health Insurance database which covers 98.8% of the population living in France [18]. This real-world data set contains comprehensive, anonymous, and individual information on sociodemographic characteristics (gender, year of birth, month and year of death, Couverture Maladie Universelle complémentaire (CMU-c) affiliation (for socio-economically disadvantaged people—as a proxy of social deprivation), and department of residence; out-of-hospital reimbursed public and private HC expenditures (including treatments, outpatient visits, medical procedures, medical devices and laboratory tests); and hospital discharge summaries with International Classification of Diseases (ICD)–10 codes. The SNDS does not contain clinical, functional or biological results. Clinical data (anthropometrics, lung function, and microbiology) were sourced from the FCFR, while the Health care resource utilization (HCRU) 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, 19]. Briefly, individuals' anonymous data from 2006 to 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.

2.2 | 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 10 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 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. Among the children detected prenatally (ANT group), 13 had MI at birth, while the remaining 26 showed 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.

Type of HC categories include those previously described [3, 19], namely: transports, emergency room visits, hospital stays, medical devices, medical and biological procedures, medical visits, CF-related medications.

For the SNDS variable "hospitalization," a distinction was made between 1-day hospitalization (which is current practice in France for chCF follow-up in CF centers as it best covers the costs of multiple HC professional interventions) and conventional hospitalization, which is mostly related to acute care events.

2.3 | 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. HCRU and costs were compared using Chi-square tests or ANOVA to assess overall differences among groups across the 10 years of follow-up. For pairwise comparisons, Bonferroni-Holm or Tukey post-hoc tests were performed.

Based on total HC costs per year and per child, group-based trajectory modeling was performed to identify subgroups with similar cost trajectories without any *priori*. The cost trajectory model was conducted in two phases: first, models with 2 to 5 groups were tested to determine the optimal number of groups. Secondly, the shape of the trajectory curves (linear, quadratic, cubic) was selected. 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.

2.4 | 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.

3 | Results

3.1 | Study Population

The study entailed 1065 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 (Supporting Information S1: Figure 1). 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).

3.2 | HC Costs During the First 10 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, mean annual costs per patient were lower €12,056 ± €10,073 in the NBS group than in

TABLE 1 | Study population sex ratio, age at diagnosis and duration of follow-up.

	Overall ($N = 779$)	ANT-group ($N = 39$)	MI-group ($N = 101$)	NBS-group ($N = 601$)	LS-group ($N = 38$)
Sex, *n* (%)					
Male	385 (49.4%)	13 (33.3%)	52 (51.5%)	295 (49.1%)	25 (65.8%)
Female	394 (50.6%)	26 (66.7%)	49 (48.5%)	306 (50.9%)	13 (34.2%)
Age at diagnosis (in months)					
N (%)	736 (94.5%)	—	101 (100.0%)	600 (99.8%)	35 (92.1%)
Mean (SD)	2.4 (9.4)	—	0.5 (0.8)	1.2 (3.1)	28.3 (31.9)
Median (Q1−Q3)	0.7 (0.3–1.2)	—	0.1 (0.0−0.8)	0.7 (0.3−1.2)	12.7 (5.0−44.1)
Min−Max	0.0−124.3	—	0.0−4.5	0.0−40.1*	0.0−124.3

Note: Data on gender comes from SNDS, data on age at diagnosis comes from the FCFR. *The maximum value corresponds to a patient with genetically proven CF in the CF kit used for NBS in France whose sweat test was done 40.1 months after diagnosis confirmation. The date sweat test was used as a confirmation marker of CF and not CFTR variants found after NBS.
Abbreviations: ANT, antenatal diagnosis; LS, later based on symptoms; MI, meconium ileus; NBS, newborn screening.

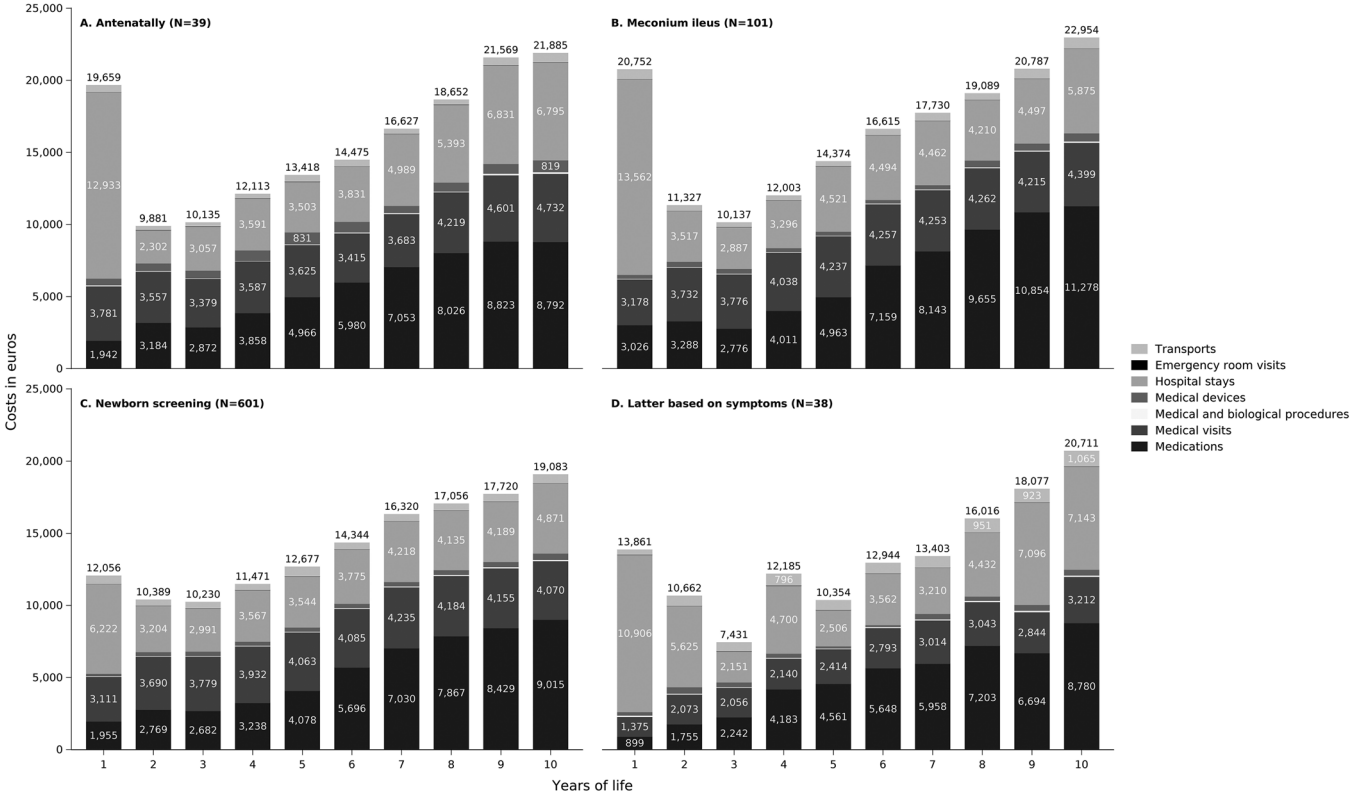

FIGURE 1 | Evolution of the mean healthcare costs in euros per patient, type of expense, and year of life during the first 10 years of life depending on diagnosis circumstances.

the other groups (€20,752 ± €23,453 in the MI; €19,659 ± €17,225 in the ANT and €13,861 ± €17,493 in the LS group [all $p < 0.05$]). Most 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 (Supporting Information Material, Supporting Information S1: Figure 2). When looking at data on hospitalizations during the first year in detail, we found that chCF diagnosed after NBS and MI had more 1-day hospitalizations than those in the LS groups (3.7 ± 3.9 and 3.1 ± 3.4 days vs. 1.2 ± 2.2 days respectively, all $p < 0.05$). However, infants with MI had more conventional hospitalization and longer duration of stays in comparison to those diagnosed by NBS (3.6 ± 16.6 vs. 1.1 ± 1.7 hospitalizations and 31.1 ± 56.1 vs. 17.1 ± 22.8 days, respectively, all $p < 0.05$) (Supporting Information Material, Supporting Information S1: Table 1).

Mean HC costs decreased between the first and second year of life in all groups and then increased steadily between the second and tenth year of life (all $p < 0.05$). During the 10th year, mean annual costs were similar between the groups: €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, $p < 0.0001$), while the proportion of medication costs increased (from 26.7% to 47.2%, $p < 0.0001$). In the ANT and MI groups, the proportion of hospital stays costs evolved from 23.3% to 31.0% and from 31.0% to 25.6% respectively (all $p < 0.0001$) and the proportion of medical visits costs decreased (36.0% to 21.6% and 33.0% to 19.2% respectively, all $p < 0.0001$). However, the proportion of medication costs increased (from 32.2% to 40.2% and 29.0% to 49.1% respectively, all $p < 0.0001$) (Supporting Information Material, Supporting Information S1: Figure 2).

3.3 | HC Costs Trajectories Over the 10 First Years of Life

The analysis of the total HC costs per year and per patient identified three distinct groups with different cost trajectories (Figure 2, and Supporting Information Material, Supporting Information S1: Figure 3). 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 ± €9253 in the first year of follow-up and rose slightly to €12,948 ± €7444 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.

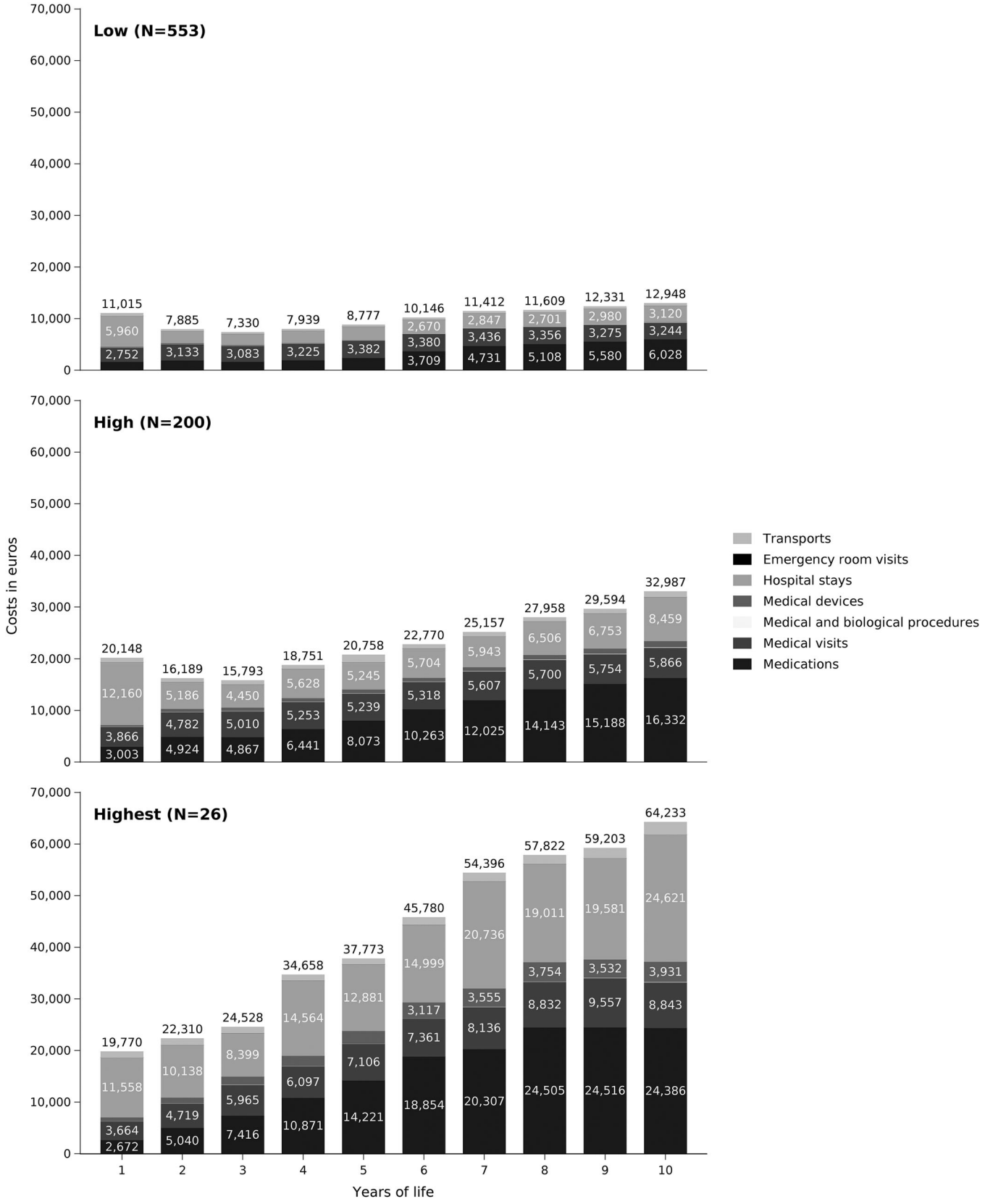

FIGURE 2 | Annual evolution of healthcare costs over the first 10 years of life of children with CF.

3.4 | 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: 79.0% in "low," 72.0% in "high," and 76.9% in "highest." For MI, the proportion was lower in the low

TABLE 2 | Comparison of clinical characteristics of children with CF between trajectory groups.

Characteristics	Overall ($N = 779$)	Group "low" ($N = 553$)	Group "high" ($N = 200$)	Group "highest" ($N = 26$)	p value
Gender					
Male	385 (49.4%)	280 (50.6%)	94 (47.0%)	11 (42.3%)	0.517
Female	394 (50.6%)	273 (49.4%)	106 (53.0%)	15 (57.7%)	
CMU-c (proxy for social deprivation)	192 (24.7%)	117 (21.2%)	66 (33.0%)	< 11	0.002
Circumstances of CF diagnosis					
Newborn screening	601 (77.2%)	437 (79.0%)	144 (72.0%)	20 (76.9%)	0.300[a]
Meconium ileus	101 (13.0%)	66 (11.9%)	33 (16.5%)	< 11	
Symptoms-based	38 (4.9%)	26 (4.7%)	< 11	< 11	
Antenatal	39 (5.0%)	24 (4.3%)	13 (6.5%)	< 11	
CFTR mutations					
F508del/F508del	308 (39.5%)	215 (38.9%)	80 (40.0%)	13 (50.0%)	0.391[a]
F508del/Other	332 (42.6%)	243 (43.9%)	79 (39.5%)	< 11	
F508del/Gating	< 11	< 11	0 (0%)	0 (0%)	
Others	132 (16, 9%)	88 (15, 9%)	41 (20, 5%)	< 11	
Anthropometrics[c]					
Weight z-score, at 2 year	−0.6 (1.1)	−0.5 (1.0)	−0.7 (1.2)	−1.2 (1.6)	0.014
Weight z-score, at 6 year	−0.4 (1.0)	−0.4 (1.0)	−0.5 (1.0)	−0.6 (0.7)	0.163
Weight z-score, at 10 year	−0.5 (1.0)	−0.5 (1.0)	−0.6 (1.0)	−1.0 (0.7)	0.05
Height z-score at 2 year	−0.3 (1.0)	−0.3 (1.0)	−0.3 (1.2)	−0.8 (1.2)	0.134
Height z-score at 6 year	−0.2 (1.0)	−0.2 (1.0)	−0.2 (1.0)	−0.6 (0.9)	0.182
Height z-score at 10 year	−0.4 (1.0)	−0.3 (0.9)	−0.4 (1.0)	−0.9 (0.9)	0.022
Pulmonary function tests[c]					
%pred FEV_1 at 6 year	102.0 (17.8)	103.3 (17.1)	100.4 (19.3)	89.7 (16.9)	0.002
%pred FEV_1 at 10 year	98.5 (16.8)	100.5 (14.8)	95.4 (19.0)	73.1 (20.1)	< 0.0001
Comorbidities over 10 years[b]					
Pancreatic insufficiency	693 (89.0%)	473 (85.5%)	195 (97.5%)	25 (96.2%)	< 0.0001
Distal intestinal obstruction syndrome occurrence	96 (12.3%)	69 (12.5%)	26 (13.0%)	< 11	0.401
CF-related liver disease	107 (13.7%)	70 (12.7%)	34 (17.0%)	< 11	0.294
CF-related diabetes (treated or not with insulin)	36 (4.6%)	13 (2.4%)	18 (9.0%)	< 11	< 0.0001
Microbiology over 10 years[b]					
Age at first PA colonization[c]	3.4 (2.9)	3.9 (3.1)	2.7 (2.4)	2.2 (1.7)	< 0.0001
Chronic PA infection	103 (13.2%)	33 (6.0%)	57 (28.5%)	13 (50.0%)	< 0.0001
Allergic bronchopulmonary aspergillosis[d]	52 (6.7%)	25 (4.5%)	23 (11.5%)	< 11	< 0.001
Haemophilus influenzae colonization	692 (88.8%)	490 (88.6%)	178 (89.0%)	24 (92.3%)	0.839
Staphylococcus aureus colonization	767 (98.5%)	541 (97.8%)	200 (100.0%)	26 (100.0%)	0.108[a]
Nebulized treatment prescribed over 10 years[b]					

(Continues)

TABLE 2 | (Continued)

Characteristics	Overall ($N = 779$)	Group "low" ($N = 553$)	Group "high" ($N = 200$)	Group "highest" ($N = 26$)	p value
Colistin[d]	139 (17.8%)	50 (9.0%)	75 (37.5%)	14 (53.9%)	< 0.0001
Tobramycin[d]	181 (23.2%)	92 (16.6%)	79 (39.5%)	< 11	< 0.0001
RhDNase[e]	481 (61.8%)	320 (57.9%)	145 (72.5%)	16 (61.5%)	0.001
Intravenous (IV) antibiotic therapy use					
During the sixth year of life					
Occurrence of at least one IV therapy	76 (9.8%)	17 (3.1%)	40 (20.0%)	19 (73.1%)	< 0.0001
Mean IV therapies administered yearly	1.6 (0.9)	1.1 (0.3)	1.5 (0.7)	2.3 (1.3)	< 0.001
During the tenth year of life					
Occurrence of at least one IV therapy	128 (16.4%)	48 (8.7%)	64 (32.0%)	16 (61.5%)	< 0.0001
Mean IV therapies administered yearly	1.8 (1.3)	1.3 (0.6)	1.8 (1.1)	3.6 (2.1)	< 0.0001

Note: Data comes from the FCFR and are presented as mean (SD) or *N* (%). The "< 11" designation is employed for statistical confidentiality, as figures below 11 typically should not be disclosed. Nevertheless, this restriction does not hinder the execution of comparison tests. *p* value is for non-parametric chi-square test (or Fisher's exact test if a theoretical number less than 6) or ANOVA. Comparison tests do not include missing data.
Abbreviations: PA: Pseudomonas aeruginosa.
[a]Fisher's exact test.
[b]At least one instance within the 10-year follow-up timeframe.
[c]Data available for 70%−80% of patients.
[d]Variable available since 2017.
[e]Variable not available between 2013 and 2016 inclusive.

group (11.9%) than in the high group (16.5%), yet the difference was not statistically significant. However, differences were observed for FEV_1 at 6 year ($p = 0.002$) and 10 year ($p < 0.0001$); groups "high" and "highest" had the lowest FEV_1 at both 6 and 10 year, depicting a more severe CF lung disease. Similarly, groups "high" and "highest" had a lower weight *z*-score at 2 year ($p = 0.014$), and height *z*-score at 10 year ($p = 0.022$) 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" vs. 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 *P. aeruginosa* at 6 and 10 year. They received more IV antibiotics for longer periods.

4 | Discussion

Our study adds new knowledge of direct HC costs involved in young chCF and shows that diagnosis of CF by NBS confers the lowest HC expenses during the early years of life. Conversely, prenatal and MI diagnoses result in the highest costs. However, the gaps between the groups by the time chCF acquires the age of 10 years narrowed resulting in similar costs over a 10-year follow-up. Direct HC costs were high during the first year of life for all diagnosis circumstances, mainly driven by hospitalizations related to chCF. Nonetheless, costs decreased during the second year of life and increased thereafter. Two high HC cost trajectories (representing one-third of the 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.

4.1 | NBS for CF: Infant Health Benefits at the Lowest Cost

In our study, we found that diagnosis of CF after NBS was associated with the lowest HC costs compared to MI and ANT in the first year of life but differences between diagnosis' circumstances narrowed over time resulting in similar costs after 10-year of follow-up. 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 [20]. Our real-world data for early life thus align with their forecast and studies that have explored the cost-effectiveness of NBS for CF [21]. Over time, the increase in HC costs was mainly driven by costly medications introduction that was gradual and relatively similar among the four diagnosis groups. This is in total accordance with what was reported in a cohort-based study conducted in Ireland. Indeed, 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 ($n = 69$). Our results extend these findings by showing that, in a larger study population with a longer follow-up, the cost differences tend to narrow over time. There are several reasons why NBS confers the lowest costs in comparison to the other diagnosis groups, particularly during the first years of life. Firstly, babies and their families are rapidly taken in charge in an efficient model of care with a structured CF team specifically dedicated to CF management. This was proven to be highly efficient well before the arrival of CFTRm [22]. Preventive respiratory and nutritional strategies put in place will come with a costs (i.e., chest physiotherapist, which is in France done by a physiotherapist at home or in a private facility from 3 to 5 days a week), but they will avoid some hospitalizations (for pulmonary exacerbations), which are the main driver of HC costs during the first year of CF babies's lives. This is likely related to the better health status of NBS children and lower treatment burden, as reported by other groups at short and midterms [7–11]. However, our study also showed a great overlap of costs between groups, meaning that individually, a newborn screened baby can sometimes mobilize larger costs than a baby born with MI. This point was also found in the cost trajectory analysis were NBS babies were equally represented in the "low," "high," and "highest" groups. This means that being NBS diagnosed does not prevent from developing a severe form of the disease despite standard of cares.

The advent of CF transmembrane conductance regulator modulators (CFTRm), and the triple combination therapy has changed CF presentation, even in young children [23–25]. Early introduction of CFTRm in the immediate following of NBS diagnosis will increase HC costs substantially but will also improve patients' conditions by either avoiding irreversible lung damage to occur or by stabilizing established complications. 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 [26].

4.2 | Early and High HC Cost Trajectories Are Possible Even at the Youngest Ages

Our study shows that chCF may experience significant HC utilization resources trajectories even in the early stages of their lives. Indeed, we identified three different HC cost trajectories that were modelized a priori based on evolution of HC costs over the first 10 years of follow-up. 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). The "low" group corresponds to children who remained extremely stable under treatment and have no need for further hospitalization or costly medication to be introduced. The "high" and "highest" groups can be identified early and strategies to avoid these trajectories are possible such as early nutritional support for instance. The results also emphasized the need for an early and aggressive eradication of *P. aeruginosa* in these young children, as failure to eradicate and chronic colonization are known risk factors of worth clinical evolution [27]. These strategies remain highly clinically pertinent. 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 further detail. In those incidences of chCF, early introduction of CFTRm might limit early clinical deterioration and reduce non-CFTRm-related HC costs.

4.3 | 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. These costs 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. As explained earlier, 1-day hospitalization is standard practice in CF centers in France and may partially explain this finding. For every chCF diagnosed after NBS, nine routine 1-day hospitalizations are scheduled during the first year of follow-up; this comes with a higher cost than a simple outpatient "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 9 years of 6354 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 [14, 28]. 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 [26].

4.4 | MI was Associated With a Higher Early Burden of Care and HC Costs

MI was associated with higher HC costs during the 1st year of life compared to NBS and LS groups. 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 [29]. A similar picture was seen for infants whose diagnosis of CF was made prenatally on ultrasonographic signs of MI. Thirteen out of 39 (33%) presented MI at birth, but given the high risk of complicated MI, they were probably 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 [30, 31]. 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 incurred HC costs during the 10 years onwards. This finding is coherent with multiple studies indicating that chCF with MI yields similar respiratory outcomes as those without [32, 33]. On the other hand, MI is still recognized as a factor for gastrointestinal symptoms and distal intestinal obstruction syndrome, which are conditions related to higher HC [34, 35].

4.5 | Strengths and Limitations of Our Study

Our study is the first to describe the first 10 years of HC 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. Unfortunately, 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]. We would also have liked to study the impact of CFTRm introduction on HC costs in the pediatric population, but at the time the study was conceived, the percentage of children declared to receive a CFTRm in the FCFR was too low (respectively 1.5% in the 10–14 age group and 4.3% in the 15–19 age group) to allow a robust statistical analysis.

Lastly, our study does not include important additional factors in our analysis such as ethnicity and race that can impact diagnostic group and age at diagnosis. Indeed, there are emerging data on HC disparities based on CFTR analysis included in NBS [36], including later age at first event noted in PwCF from non-European backgrounds [37] and impact on clinical outcomes [38].

5 | Conclusion

This retrospective study examined the pediatric HC 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 at the beginning of life. However, after 10 years of follow-up, differences between diagnosis's circumstances group did not persist.

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. These results emphasize the need to conduct similar study on the impact of early use of CFTRm by conducting a before-after study, employing the same methodological approach. Given the specificity of the French HC system, caution needs to be exercised while extrapolating the generalizability of these results to other countries around the world.

Author Contributions

Erika Guyot: software, data curation, investigation, formal analysis, writing – original draft, writing – review and editing. **Floriane Deygas:** software, data curation, investigation, formal analysis, writing – review and editing, project administration. **Manon Belhassen:** conceptualization, methodology, supervision, funding acquisition, writing – review and editing, project administration. **Marjorie Berard:** software, data curation, investigation, validation, formal analysis, writing – review and editing. **Eric Van Ganse:** writing – review and editing, supervision. **Isabelle Sermet-Gaudelus:** supervision, writing – review and editing. **Sabrine Tiaiba:** conceptualization, writing – review and editing. **Jean-Christophe Dubus:** supervision, writing–review and editing. **Isabelle Durieu:** supervision, writing – review and editing. **Philippe Reix:** conceptualization, methodology, supervision, funding acquisition, project administration, writing – original draft, writing–review and editing.

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Conflicts of Interest

E. Guyot, F. Deygas, M. Belhassen, and M. Berard are full-time employees of PELyon. E. Van Ganse was the scientific advisor and shareholder of PELyon at the time of the present study. He declares personal consulting fees from PELyon in and outside the scope of this study and support for attending meetings and/or travel from AstraZeneca. P. Reix declares funding from the Association Vaincre La Mucoviscidose to her institution for the present manuscript and grants from Vertex Pharmaceuticals. I. Sermet-Gaudelus declares funding from the Association Vaincre La Mucoviscidose to her institution for other research studies unrelated to this study and grants from Vertex Pharmaceuticals. I. Durieu declares funding from the Association Vaincre La Mucoviscidose to her institution for other research studies unrelated to this study and support for attending meetings and/or travel from Mylan. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this study, the author(s) used "TrueEditors. Proofreading services" to edit English. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.