PHARMACOECONOMICS

Cost of Care for Individuals with Cystic Fibrosis: A Regression Approach to Determining the Impact of Recombinant Human DNase

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We estimated direct medical costs of care and important determinants of the costs in patients with cystic fibrosis (CF), including therapy with recombinant human DNase (rhDNase). Costs were estimated with resource use data from the Epidemiologic Study of Cystic Fibrosis. Ordinary least squares regression was used to determine the effect of clinical and demographic variables on individual cost of care. The estimated cost of caring for 303 patients in Alberta was $2,279,801 in 1996. The mean cost of care was $7524 (range $386–92,376)/patient. Regression results indicated that age and forced expiratory volume predicted had a negative association with costs. Being female, receiving rhDNase, and having *Pseudomonas aeruginosa* or *Burkholderia cepacia* were all associated with high costs. Our estimates indicated large interindividual variation in cost of care for patients with CF.
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Cystic fibrosis (CF) is an inherited, multisystem disorder affecting approximately 1 in every 2500–3500 live births in North America.[1] It is one of the most common lethal inherited disorders among Caucasians, with 3.3% being carriers of the defective gene. It is a chronic disease that is quite variable with respect to both the systems involved and severity of symptoms.[2] The basic defect is abnormal chloride ion transport, which results in increased viscosity of mucus secretions.

The morbidity and mortality in patients with CF are primarily due to pulmonary disease.[1] Increased viscosity and decreased mucociliary clearance of sputum leads to chronic endobronchial bacterial colonization, usually with *Staphylococcus aureus* or *Pseudomonas aeruginosa*. The range of the disease's features includes an asymptomatic level with no outward appearance of ill health, to symptoms of chronic obstructive pulmonary disease with production of large amounts of sputum, wheezing, dyspnea, and limited exercise tolerance. Complications of CF, apart from pulmonary symptoms, include pancreatic insufficiency in 85% of patients, leading to malabsorption of fat and malnutrition, diabetes mellitus, biliary cirrhosis, subacute bowel obstructions, arthritis, and infertility.

Although the prevalence of CF is relatively low, the treatment burden per patient may be quite

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Table 1. Unit Costs of Medical Resource Use by Patients with CF

Unit	Cost Estimate ($Canadian)	Source
Clinic visit (including physician fee)	228.50/visit	Alberta Health Care Billing Office, reference 10
Hospital admission	476.13/day	Alberta Health Care Billing Office, reference 10
rhDNase	35.00/day	Capital Health Authority (CHA) drug list
Dispensing fee, rhDNase	19.70/30 days	Provincial dispensing fee
Oral antibiotics	5.02/day	Alberta Health Drug Benefit List (1997)
Inhaled antibiotics	6.88/day	Alberta Health Drug Benefit List (1997)
Home i.v. including supplies and nursing time	150.96/day	Alberta Health Drug Benefit List (1997), CHA pharmacy, CHA Home Care Program
Dispensing fee, antibiotics	9.70/prescription	Provincial dispensing fee
Chest radiograph	21.64/test	Alberta Health Care Insurance Plan – Schedule of Medical Benefits
Pulmonary function test	123.51/test	Garneau Lung Laboratory, Edmonton
Microbiology (sputum, throat, etc.)	52.43/test	U of A Hospital – Microbiology and Public Health Department
Blood and urine tests, adults	159.02/test	Alberta Health Care Insurance Plan – Schedule of Medical Benefits
Blood and urine tests, children	104.57/test	Alberta Health Care Insurance Plan – Schedule of Medical Benefits

high. The economic impact of CF is therefore of interest. Given clear identification of independent prognostic factors and large interindividual variation in disease severity,[2] it is appropriate to estimate costs of care at the individual level. A literature review on cost of care in CF identified three papers that presented annual costs based on individual resource use under conventional treatment conditions, and were not randomized, controlled trials (RCTs).[3–5]

As pulmonary disease is the leading cause of sickness and death in these patients, therapies aimed at ameliorating pulmonary infections and improving lung function are of primary importance.[1] One such therapy, recombinant human DNase (rhDNase), has received considerable attention. The agent acts to reduce the viscosity of pulmonary secretions by breaking down high-molecular-weight DNA that is present in high concentrations in the sputum of patients with CF. In a major phase III clinical trial, rhDNase administered once or twice/day over 24 weeks resulted in significant reductions in the number of exacerbations of respiratory symptoms requiring parenteral antibiotics and significant improvements in pulmonary function measures compared with placebo.[6]

Three economic evaluations of rhDNase were conducted, all based on results of the phase III clinical trial.[7–9] In all evaluations, the annual cost of rhDNase therapy was offset only partly (~ 15–35%) by reductions in pulmonary exacerbations and hospitalizations. The cost of rhDNase is a significant amount for a relatively small number of patients, and therefore it is important to determine what impact the drug has on the outcomes of these patients. However, because these economic evaluations were based on RCTs in which clinicians were following trial protocol, they may not reflect costs of conventional care in real-world clinical settings.

The objectives of this study were to estimate costs of treatment for Alberta patients with CF under conventional (nonrandomized) conditions using individual-level data; to determine which demographic and clinical variables had an effect on individual cost of care using multivariate linear regression analyses; and to determine the impact of rhDNase therapy on cost of care. The study was reviewed and approved by the institution's health research ethic board.

Methods

Patients and Resource Use

Patient and resource use data were drawn from the Epidemiologic Study of Cystic Fibrosis (ESCF) data base, which contains variables on clinical status, demographics, diagnostic information, and resource use. This information was collected at all participating CF centers across North America and compiled in one

central data base by ClinTrials, Inc., a contract research organization, on behalf of Roche Canada, Inc. and Genentech in the United States. Complete ESCF data (up to December 1997) for all participating patients from the four CF centers (two pediatric, two adult) in Alberta, Canada, were used. The Alberta centers began participating in the ESCF program in 1994, and all had patients enrolled by 1995 (patient participation rate ~ 90%). For purposes of this study, only patients enrolled and participating in the ESCF program for the calendar year 1996 were included.

Resource Unit Costs

Data were collected for several direct medical costs (Table 1): clinic visits (including physician fees), hospital admissions, outpatient drug costs and dispensing fees, and outpatient laboratory tests (chest radiograph, pulmonary function test, microbiology, blood and urine tests). Outpatient drug costs included antibiotics (oral and inhaled) and rhDNase. Home intravenous therapy costs (drugs, supplies, nursing time) also were estimated. Standard unit costs were used and multiplied by individual resource use data to determine resource use costs. All cost values are in Canadian dollars.

Daily antibiotic costs were based on an estimated average daily dose for the most common therapies. For example, tobramycin was recorded as the inhaled antibiotic in pediatric patients for over 90% of entries in the ESCF files. Typical regimens for inhaled tobramycin were 80–160 mg twice/day. For purposes of this analysis, a conservative estimate of 80 mg twice/day was used as the cost of inhaled antibiotics. Costs of oral and home intravenous antibiotic therapies were estimated by a similar approach. Costs of drugs were obtained from the Alberta Health Drug Benefit List.

The per diem hospital cost estimate was taken from a published study.[10] It was calculated based on standard costs for inpatient services, estimated by case-mix group for CF-related hospital admissions in Alberta. Case-mix group costs bundle together all inpatient costs and services, including drugs, laboratory tests, nursing time, and hospital costs for patients with similar diagnoses and characteristics; physician costs were not included. Clinic costs were calculated as the cost of a visit to a specialty ambulatory clinic, based on statistical cross-sectional analysis.[10]

Costs were assessed from the perspective of the provincial Ministry of Health. In Canadian provincial health care systems, costs are actual amounts paid by the Ministry, as opposed to patient charges in the United States. Only direct medical costs were included in our analysis, although our cost estimate was not exhaustive. Most morbidity and mortality in CF are due to impairments in lung function and pulmonary infections and exacerbations; we therefore focused on rhDNase and antibiotic costs.

Other drug costs were not included primarily because of limited information on them in the ESCF file. For example, more than 91% of patients were reported to have taken pancreatic enzymes. Including those costs would have resulted in simply adding a constant value to each individual's cost since the reporting of enzyme use in the data set was in the form of a dichotomous (yes or no) question and did not vary by age, gender, or other variable. Based on our study objectives, we did not believe it was necessary to add this constant to each individual's costs. The same consideration was given to bronchodilators, since more than 90% of patients in the ESCF data file used them. Other resources that were excluded were dietary supplements, physiotherapy, and oxygen therapy.

Direct nonmedical costs, such as out-of-pocket expenses for dietary recommendations and travel to receive care at urban CF clinics by rural patients, were not included. Indirect or productivity costs for lost work or wages for patients or their parents also were not included.

Data Analysis

Ordinary least squares regression analyses were performed to determine the effect of the various independent variables on cost of care. Cost of care was estimated as the individual's aggregate of different resource components. The dependent variable for the initial regression (model 1) was "Costs," but because its distribution was positively skewed, the natural log was used as a transformation of the variable Costs.[11] Therefore, Ln Costs became the dependent variable for the second regression (model 2). Descriptive statistics and analysis of the residuals were performed to determine the adequacy of the regression models.

The independent variables were abstracted from ESCF data files, as they are recognized as important prognostic[12, 13] or confounding[2] data in

Table 2. Descriptive Statistics for Independent Variables

Variable	Number	%
Age distribution		
Children (< 18 yrs)	171	56.4
Adults	132	43.6
Females	144	47.5
Males	159	52.5
Impairment of lung function (n=244)		
Mild (%$FEV_1 \geq 70$)	159	65.2
Moderate ($40 \leq$ %$FEV_1 < 70$)	52	21.3
Severe (%$FEV_1 < 40$)	33	13.5
P. aeruginosa		
Present	170	56.1
Not present	133	43.9
B. cepacia		
Present	9	3.0
Not present	294	97.0
Other microorganisms		
Present	158	52.1
Not present	145	47.9
rhDNase therapy in 1996		
Taken	100	33.0
Not taken	203	67.0

evaluating outcomes in patients with CF. The variables consisted of age, gender, forced expiratory volume in 1 second (FEV_1, average percentage predicted in 1996), microbiology status (*Pseudomonas aeruginosa*, *Burkholderia cepacia*, other microorganisms), rhDNase use, and body mass index (BMI). Lung function was included in the model as the average FEV_1 % predicted (%FEV_1) or as a categoric severity index. Average %FEV_1 was the average of all spirometry results during 1996. An interaction term, representing the severity of disease for patients taking rhDNase (rhDNase multiplied by %FEV_1), also was tested. We hypothesized that as illness progressed, patients would require and receive rhDNase therapy, therefore having a more significant impact on overall cost of care.

Results

Patient Characteristics

Of the 340 individuals included in the ESCF file from 1994–1997, 9 died before 1996, 14 were not enrolled or diagnosed until after 1996, and 14 were lost to follow-up. These 37 people were not included in our analyses. Thus, data on 303 patients were available for analysis. The mean age for all patients was 17.6 yrs (SD 11.1 yrs). Fifty-six percent of the sample were children, and their mean age was 9.5 yrs (SD 4.3 yrs). The mean age for adults was 28.1 yrs (SD 7.9 yrs; Table 2).

The mean BMI, which was available for 300 people, was 18.7 (SD 3.6). The mean %FEV_1 in 1996 was 74.6% (SD 26.6%), although it was available for only 244 people. For those who received rhDNase in 1996, the %FEV_1 was statistically significantly lower (63.6 ± 26.1%) than for the whole group (p=0.001).

The mean age of the 59 people for whom %FEV_1 was missing was 4.78 years, ranging from 0–9 years. They probably had not had a spirometry test because they were too young,[2, 12] or their symptoms were not severe enough to warrant testing. The %FEV_1 was considered an important explanatory variable and required in the analysis. These children thus were excluded in the initial multivariate regression models.

Cost of Care

The estimated cost of care for the 303 patients in 1996 was $2,279,801 (Figure 1), with rhDNase accounting for 44% of that amount. Hospital visits were the second highest component at 33%. Clinic visits (12%), laboratory tests (8%), and antibiotics (3%) accounted for the remainder.

The mean cost of care was $7524/patient (median $1917, range $386–92,376). It appeared that a few people had relatively high costs, skewing the distribution to the right. Median costs for hospitalizations, antibiotics, and rhDNase were zero, yet mean costs were relatively high, especially for hospitalization and

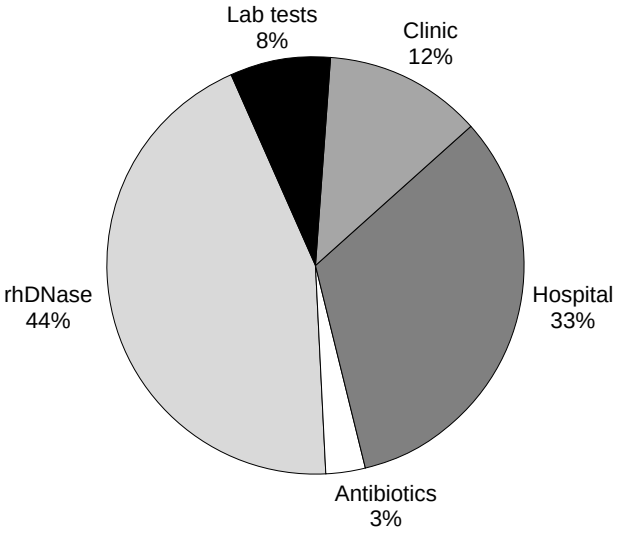

Figure 1. Components of annual cost of care for 303 patients.

Table 3. Annual Costs for Patients Who Incurred Costs ($Canadian)

Resource	Number	Mean	SE	Median	Range	25th Percentile	75th Percentile
Clinic	301	898.82	30.10	914.00	228.50–3427.50	685.50	1142.50
Hospital	71	10,488.27	1530.95	6189.69	476.13–83,798.88	3809.04	13,331.64
Antibiotics	135	483.87	66.77	170.78	9.70–4078.42	106.02	361.02
rhDNase	100	10,109.67	438.25	13,011.40	264.70–13,011.40	8187.90	13,011.40
Laboratory tests	301	625.58	23.40	544.68	126.21–2625.17	334.96	777.54
Totals	303	7524.10	605.99	1916.57	385.50–92,376.10	1141.95	13,907.36

rhDNase. However, whereas those two mean costs tended to be high when they were incurred (Table 3), most patients did not incur them. Only 71 patients were hospitalized and 100 took rhDNase at some time in 1996.

Figure 2 shows the average annual cost of care for patients with CF per year of age. The average cost per age group is represented by dots, and the line represents the 5-year moving average (costs for 5 consecutive years averaged together). The costs were averaged for all people in each age group. The nine patients over age 40 years ranged from 41–59 years. They are not included in this graph because they were, for the most part, the only patients in the age group and therefore an average is meaningless. Their individual costs ranged from $792–92,376 (mean $19,510). It should be kept in mind that, although values on the graph are averages, certain age groups had small numbers of patients, and the data should be interpreted carefully.

Regression Analyses

In model 2, with Ln Costs as the dependent variable, independent variables explained 82% of variance in costs (Table 4). The interaction term between $\%FEV_1$ and rhDNase was not statistically significant, thus having only a minimal effect on costs. It therefore was excluded from subsequent analyses.

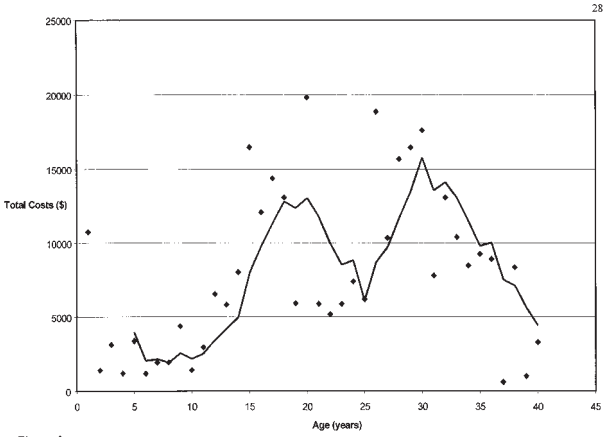

Figure 2. Average cost of care for patients with CF per age up to 40 years.

Table 4. Ordinary Least Squares Regression Results

	Model 2 - Dependent Variable Ln (Cost)	
Independent Variable	β (SE)	T
Constant	7.601 (0.331)	22.947[a]
Age	-0.003 (0.008)	-4.385[a]
Gender	0.268 (0.090)	2.971[a]
BMI	0.006 (0.018)	3.424[a]
$\%FEV_1$[b]	-0.001 (0.002)	-6.048[a]
rhDNase[c]	1.781 (0.100)	17.770[a]
P. aeruginosa[c]	0.581 (0.100)	5.834[a]
B. cepacia[c]	0.606 (0.256)	2.370[d]
Other organisms[c]	0.101 (0.098)	1.054
R^2	0.82	

[a]$p \leq 0.01$.
[b]Average % FEV_1.
[c]Variable coded 1 = present, 0 = not present.
[d]$p < 0.05$.

The results of model 2 indicated that age and $\%FEV_1$ were statistically significant and negative, implying that they were negatively associated with Ln Costs (i.e., as age increased, costs decreased). Gender, BMI, rhDNase, *P. aeruginosa*, and *B. cepacia* were statistically significant and positive, implying positive effects on Ln Costs (i.e., as BMI increased, costs increased). The other microorganisms variable was not significantly different from zero, thus having no association with Ln Costs.

Discussion

To our knowledge, this is the first attempt to estimate cost of care of patients with CF at the individual level in North America, and the first analysis of rhDNase under conditions of conventional care (as opposed to RCT). The cost of care in Alberta for this group of 303 patients in 1996 was over $2 million. The mean annual cost of care was $7524/patient. However, like clinical status in CF, cost showed considerable

interindividual variation.

Results of regression analyses generally confirmed what might have been expected based on epidemiologic evidence in the literature.[12, 13] That is, known predictors of morbidity and mortality in CF also tend to determine use and costs of care. Lung function had a significant negative association with overall costs. This result was not surprising since $\%FEV_1$ scores represent severity (lower scores = more severe disease), and it would be assumed that patients with more severe CF would require more medical care.[12] Furthermore, the presence of *P. aeruginosa* and *B. cepacia* led to higher costs, whereas the presence of other microorganisms did not have a significant effect. Others found that *P. aeruginosa* reflected the effect of declining FEV_1 in survival analysis and that *B. cepacia* significantly increased the risk of mortality at all levels of FEV_1.[13]

We had hypothesized that sicker patients were more likely to receive rhDNase, and therefore included an interaction term of these variables in the multiple regression model. On univariate analysis, our hypothesis appeared to hold true, as patients taking rhDNase had significantly lower average $\%FEV_1$. However, the interaction term was not significant when included in the regression model. This suggests that severity of disease is an important cost determinant, independent of rhDNase therapy. However, lack of an interaction may be a function of the limitation of average $\%FEV_1$ as a measure of lung function.

Older patients had lower overall costs, a result that was not immediately explained. One might expect that as patients with CF age, the disease would become more severe and they would require more health services. However, patients with less severe disease are likely to have longer survival, such that those who are older are less likely to be sick, thus producing lower costs of CF care. The coefficient for age was negative and highly significant in a model predicting mortality, confirming that for given values of these measurements, younger patients were at higher risk of death than were older patients.[12]

Gender was statistically significant and positive, implying that being female was associated with higher costs, which is consistent with the literature. Female gender was a significant predictor of a higher mortality rate in one model,[12] and survival rates were better for males than females.[13]

Body mass index was also significant and positive, implying that having a higher BMI is associated with higher costs. This result was not expected based on clinical experience and requires further evaluation. One would assume that increased body mass, in a group that tends to have below average BMIs, would indicate a healthier state, thus requiring fewer health care resources.

Having received rhDNase significantly contributed to higher costs. This was consistent with what we would expect, as this therapy is expensive. It also makes sense in general, because people with most severe CF were expected to be taking the drug, and also would tend to require other resources (antibiotics, hospitalization, etc.). The results affirm the importance of severity of disease in patients taking rhDNase in determining costs.

The annual cost of care for CF was estimated in several previous studies but usually from aggregate perspectives. Aggregate studies typically take the total cost incurred by the group with CF and divide by the number of patients. Often no information is provided on which costs are included and excluded or how they are calculated. It is difficult to compare these results with our figures with any degree of accuracy. Only two published studies estimated individual annual medical costs of care for CF under conventional (nonrandom) conditions.

One group calculated an average annual cost of care of £8679/patient in The Netherlands in 1991,[3] which would convert to $13,927 (1996 Canadian $). (Purchasing power parties [PPP] were used as a crude measure to convert currencies for comparison purposes. Cost estimates were also inflated using annual inflation rates to be comparable in the same year of analysis.) This was almost double the average cost per patient in Alberta. The other provided detailed costs of resources used by 119 patients attending a CF clinic in the United Kingdom in 1989–1990.[4] Total annual cost of treatment was £908,646, with an average cost of £8,241/patient ($14,636 1996 Canadian $). Large variations were observed among four categories of treatment intensity. Although both articles provided an indication of univariate predictors of total cost (increasing costs with increasing age or with higher treatment intensity), our analysis used a multivariate approach, simultaneously controlling for numerous confounding variables in determining predictors of costs of care.

We found lower costs for adults in Alberta than both previous studies. However, the results of

our analyses must be considered in light of limitations imposed by the research design. Of particular concern is the scope of costs included in our estimates and to what degree this underestimated the total cost of care. Data on resource use were taken from the ESCF clinical data base, which was developed specifically for epidemiologic studies such as this, rather than administrative data bases collected for billing purposes. Thus, the quality of ESCF data for research purposes would be expected to be higher than administrative data. However, it was not possible to include total health care resource use, as full detail on additional resources was not available in the ESCF files.

For example, adjuvant therapies such as pancreatic enzymes, bronchodilators, and corticosteroids were recorded as a dichotomous variable of use, not on actual level of use. Furthermore, we estimated outpatient antibiotic costs based on typical regimens for the most frequently prescribed antibiotics, according to ESCF data. Given that our estimates of antibiotic costs represented only a small proportion of costs (< 3%), we thought this approach would be reasonable for our analyses. Finally, use of other important therapies (flutter devices, nutrition supplements) was not recorded in the ESCF data base and were excluded from our estimates.

Another limitation of these analyses is missing data. When certain data elements were missing, individuals had to be excluded from the analyses, as was the case with information on lung function. Because of the relatively large number of pediatric patients without spirometry readings in the ESCF data files, these individuals were excluded from regression analyses. To determine the impact of these exclusions, regression analyses were conducted to include the 59 children who did not have $\%FEV_1$ scores. This was accomplished by arbitrarily assigning a mild severity index score ($\%FEV_1 \geq 70$), to these children. In our sample, 88% of children had mild, 10% moderate, and only 2% severe CF. It was then possible to run regressions with this group using dummy variables for severity scores, instead of actual $\%FEV_1$ scores. The models were reestimated including the 59 children (n=300). The models remained essentially the same, with patients with moderate and severe disease contributing to significantly higher costs than those with mild CF.

The results of this study suggest that the cost of rhDNase represents almost half of the cost incurred by these patients in 1996, when, in fact, most of them did not take the drug. However, interpretation of these results is not that straightforward. First, exclusion of costs for other treatments would inflate this percentage. Second, most new health technologies result in increased expenditures. An important question is what benefits are gained by that increased expenditure. Benefits are not always gained in the health care budget but rather in improvements in clinical status and patient functioning. Our results generally agree with those of published economic evaluations of rhDNase therapy[7–9] in which the total cost of the drug is only partly offset by reductions in antibiotic therapy and hospitalizations to treat acute exacerbations. Unlike the protocol-driven nature of a phase III clinical trial, however, our cost analysis was based on real-world epidemiologic data. Although both types of data have strengths and weaknesses, it is important to be able to assess real-world treatments and their associated costs.[14]

Our analyses, however, did not take into account potential benefits of the drug on patient-reported health status and health-related quality of life (HRQOL). Additional research is required to incorporate the positive impact of rhDNase.[15, 16] This may be possible by applying a similar regression-based approach to annual changes in HRQOL and comparing coefficients for the variable of the treatment of interest.[17] Data on HRQOL in a portion of these patients were obtained and are the subject of additional analyses.[18]

Summary

Given ever-increasing costs of care for chronic conditions such as CF and the introduction of new and expensive therapies, methods for determining the overall economic impact of the disease are important. For example, introduction of a new drug such as rhDNase will increase expenses for drug therapy; however, it is also important to determine the net impact on resource use and costs outside the drug budget, such as hospitalizations and physician visits. Additional research is required that links the economic impact to HRQOL outcomes of the drug to determine the value of that expenditure. The regression approach we applied indicates which factors determine large interindividual variations in costs of care and provides a method to determine overall economic impact of new interventions in CF.

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