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Understanding the Costs of Care for Cystic Fibrosis: An Analysis by Age and Health State

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ABSTRACT

Objectives: Cystic fibrosis (CF) is an inherited disease that requires more intensive treatments as the disease progresses. Recent medical advancements have improved survival but have also increased costs. Our lack of understanding on the relationship between disease severity and lifetime health care costs is a major impediment to the timely economic assessment of new treatments. **Methods:** Using data from three waves of the Australian Cystic Fibrosis Australia Data Registry, we estimate the annual costs of CF care by age and health state. We define health states on the basis of annual lung-function scores and patient's organ transplant status. We exploit the longitudinal nature of the data to model disease progression, and we use this to estimate lifetime health care costs. **Results:** The mean annual health care cost for treating CF is US $15,571. Costs for patients with mild, moderate, and severe disease are US $10,151, US $25,647, and US $33,691, respectively. Lifetime health care costs are approximately US $306,332 (3.5% discount rate). The majority of costs are accounted for by hospital inpatients (58%), followed by pharmaceuticals (29%), medical services (10%), complications (2%), and diagnostic tests (1%). **Conclusions:** Our study is the first of its kind using the Australian Cystic Fibrosis Data Registry, and demonstrates the utility of longitudinal registry data for the purpose of economic analysis. Our results can be used as an input to future economic evaluations by providing analysts with a better understanding of the long-term cost impact when new treatments are developed.

Keywords: Australia, cost of illness, cystic fibrosis, registry data.

Introduction

Cystic fibrosis (CF) is the most common life-shortening genetic disease, with an incidence of 1 in 2500 and carrier frequency of 1 in 25, among Caucasians [1]. With recent advances in treatment, most children with CF now can expect to survive into adulthood and life expectancy has improved considerably. CF is a progressive disease that affects many organ systems. As the disease progresses, patients require more intensive health care that includes home-based care, medications, more frequent and prolonged hospital admissions, and, in around half of all cases, lung transplantation [2,3]. With the advent of new and improved treatment options, the patterns of care have changed and this has had an impact on both health care costs and patient outcomes. For example, two of the key medications developed in the last 15 years, dornase alfa (Pulmozyme) and tobramycin (Tobi), cost around US $10,000 per annum and more sophisticated technology, such as gene-based treatments, may be even more expensive. Ever increasing pressures on health care budgets mean that health care decision makers are expected to require evidence on the cost-effectiveness of new treatments before funding is approved.

Cost-effectiveness analysis requires a sound understanding of the long-term costs of care for CF. In particular, information on how treatment costs are altered when disease progression is slowed would be a valuable input to future economic analysis. The aim of this study was to provide researchers with estimates of the long-term costs and consequences of CF progression. Such estimates will be of particular value to policymakers and evaluators who wish to examine the potential cost impact of new technologies. The results reported in this study will allow short-term clinical trial results to be extrapolated over the longer term.

Previous Literature

There have been a small number of studies that examined the cost of care associated with CF. A systematic review identified eight cost-of-illness studies, but only five of these were based on individual patient care data, with the other three based on cost estimates provided by clinical experts [4]. We have identified four further studies that were published after the Krauth et al. [4] review. Table 1 summarizes each of the studies that were based on patient data. The average annual health care cost ranged from US $8,148 to US $50,723 (in constant 2009 dollars). Some studies found considerable cost variation among patients with CF depending on the patient's lung function, whereas others found no significant effect. For example, the study by Lieu et al. [10] found that the average annual health care cost for a patient with

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Table 1 – Summary of previous studies—health care cost of treating cystic fibrosis.

Source	Study year	Study country	Patients (n)	Mean age (y)	Age range (y)	Mean annual cost* (US $)
Robson et al. [5]	1990	UK	119	21	16–44	21,533
Wildhagen et al. [6]	1991	The Netherlands	81	14	0–37	22,737
Ireys et al. [7]	1993	USA	204		0–18	20,147
Baumann et al. [8]	1996	Germany	138		0–18	33,039
Johnson et al. [9]	1996	Canada	303	18		8,148
Lieu et al. [10]	1996	USA	136	17	0–56	17,546
Heimeshoff et al. [11]	2004	Germany	212	20	0– adult	50,723
Horvais et al. [12]	2001	France	65			21,830
Eidt-Koch et al. [13]	2006	Germany	301			27,999
DeWitt et al. [14]	2008	USA	352	14.6	5– adult	40,037

* All originally reported national currencies converted to US $ at 2009 price levels applying OECD PPP conversion rates and using the CCEMG – EPPI-Centre Cost Converter (see http://eppi.ioe.ac.uk/costconversion/default.aspx); blank values, not stated.

poor lung function was seven times greater than for a person with relative good lung function status. A more recent study by DeWitt et al. [14] found that baseline lung function score was not a significant predictor of health care costs.

These studies have been limited by their data. The small sample size of all studies (ranging from 65 to 352) limits their ability to examine differences in the cost among different population groups. For example, the study by Baumann et al. [8] relied on children's resource use data to estimate costs of adult patients. Other studies were limited by the scope of the data collection. For example, Horvais et al. [12] included out-of-hospital costs but did not have data on inpatient treatments and Heimeshoff et al. [11] focused on patients treated in one center. Consequently, these studies are limited in their ability to provide an overall assessment of the lifetime health care costs for the entire CF population.

Our study is based on the Australian Cystic Fibrosis Data Registry (ACFDR). The longitudinal nature of this data allows us to estimate the rate of CF progression, and its large sample size allows us to calculate the rate of disease progression for various age groups and health states as well as the health care costs associated with treating CF. The results from the transition and cost analysis are then combined to arrive at the estimated lifetime costs of CF.

Methods

Data

Three years of data from the ACFDR were used (2003, 2004, and 2005), with de-identified data from participants that can be linked across these years. The ACFDR includes information on clinical measures, mortality, demographics, complications, and health care resource use. For more information on the ACFDR, including descriptive analysis and data items, see the reports published by Cystic Fibrosis Australia [15,16].

Estimating Transitional Probabilities to Model Disease Progression

The ACFDR contains data on the forced expiratory volume in 1 second as a percentage of predicted volume (FEV_1%)—a standard measure of lung function. Severity of lung disease is the key to the quality and length of life [17] of patients with CF. The best recorded FEV_1% measure in each year was used to classify health states. We chose the FEV_1% cutoff scores for severity states 1, 2, and 3 on the basis that these were consistent with a previous US study that examined the cost of CF care [10]. We generated a separate category for patients who had received a lung transplant because these patients require medications and health care services that are in addition to standard CF care [18]. For this reason, transplant patients were assumed to remain in health state 4 unless a death was recorded. Death is the fifth and absorbing health state. Patients can therefore progress through five health states, defined as follows:

- Health state 1—mild disease where $FEV_1\% \geq 70$
- Health state 2—moderate disease where $40 \leq FEV_1\% < 70$
- Health state 3—severe disease where $FEV_1\% < 40$
- Health state 4—where a patient has received a heart and/or lung transplant
- Health state 5—where a patient has died.

Patients in the CF registry with FEV_1% observations in at least two separate years were included in estimating the transition probabilities. Those with fewer than two health state

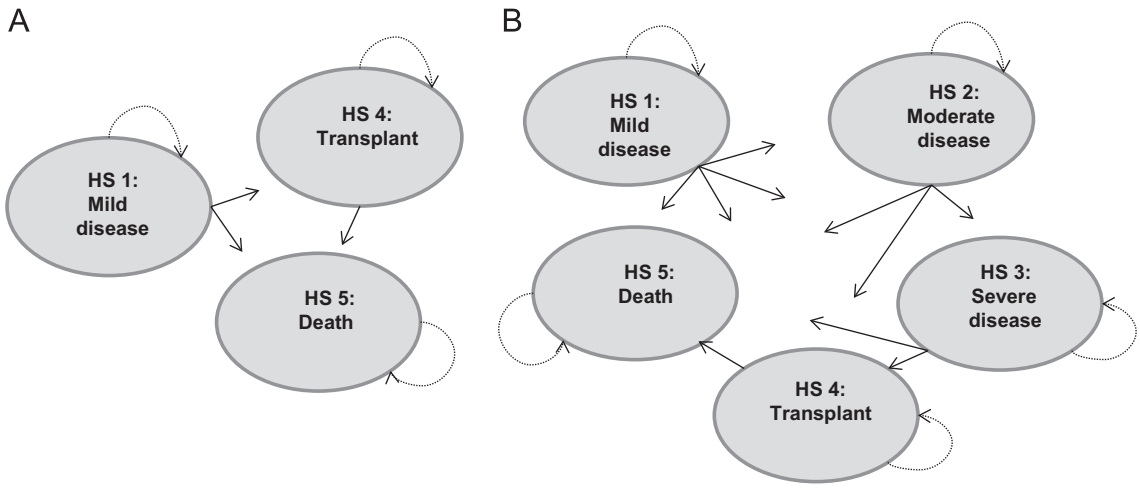

Fig. 1 – Disease progression model. (A) Age 0 to 7 years. (B) Age 8 years and older. HS, health state.

observations were excluded in calculating transition probabilities (n = 877). Generally, lung function tests cannot be performed by children younger than 8 years. We therefore combined health states 1, 2, and 3 for this age group.

By using data from the ACFDR, we employed a Markov approach to estimate the annual probability of disease progression for patients with CF. Figure 1 illustrates the disease progression model. Figure 1A shows the model for children younger than 8 years, and Figure 1B shows the model for everyone else. A discrete time transition matrix was calculated for each age group, allowing transition probabilities to vary as the cohort moves from one age group to the next. The probabilities were estimated on the basis of the number of patients in a given health state in the second observation, conditional on their health state in the first observation. We used a constant annual cycle length to model disease progression and used the life table solution to compensate for the underestimation of state membership that occurs in a discrete Markov process [19].

Each patient observation was assigned to 1 of 14 age groups. Each age group represents 3 years, with the exception of the last age group, which represents all those aged 38 years and older, and the third age group, representing children aged 6 and 7 years. We chose the maximum number of age groups while ensuring that each group contained at least 30 patients and that each age group

Table 2 – Australian unit prices and annual costs for CF-related medicines (converted to US $ 2009) – rounded to nearest dollar.

CF registry data item	Name	Units per year	Unit price ($)	Unit cost per annum ($)
Oral/inhaled antibiotics (as required)	Amoxycillin with clavulanic acid[a]	8	13	105
Oral/inhaled antibiotics (continuous)	Amoxycillin with clavulanic acid[a]	52	13	668
Pulmozyme	Dornase alfa (Pulmozyme)[a]	12	814	9770
Pancreatic enzyme (age ≤10 y)	Creon 5000[a]	11	84	918
Pancreatic enzyme (age >10 y)	Creon Forte[a]	27	97	2660
Vitamins (age ≤12 y)	VitABDECK[b]	6	16	96
Vitamins (age > 12 y)	VitABDECK[b]	12	16	191
Oral corticosteroid (age ≤10 y)	Panafcortelone solone (5 mg)[a]	6	6	32
Oral corticosteroid (age >10 y)	Panafcortelone solone (25 mg)[a]	12	7	83
Inhaled corticosteroid	Budesonide (powder)[a]	12	23	276
Macrolides (age ≤ 10 y)	Zithromax 500 mg[a]	39	18	707
Macrolides (age >10 y)	Zithromax 500 mg	78	18	1415
Bronchodilators	Salbutamol sulfate (Ventolin)[a]	12	9	106
	Terbutaline sulfate (Bricanyl)[a]	12	16	188
	Average		0	147
Salt (age ≤ 12 y)	Toppin salt tablets[c]	4	8	30
Salt (age > 12 y)	Toppin salt tablets[c]	8	8	61
Antihypercalcemics	Bisphosphonates—Risedronate sodium 35 mg[a]	13	37	481
Gastric acid reduction	Omeprazol (Acimax)[a]	12	29	348
Nutritional supplement	Energy drink[d]	365	1	493

Sources. a = DOHA [20]; b = Cystic Fibrosis NSW [24]; c = online pharmacy; d = Government of Western Australia [25].
CF, cystic fibrosis.

Table 3 – Australian unit prices for CF-related medical services, procedures, and hospitalizations (converted to 2009 US $).

CF registry data item	Description	Unit cost ($)
Clinical visit (first annual visit)[a]	A clinical visit comprises an initial specialist consultation and three allied health services (i.e., dietetics, occupational therapy, and physiotherapy). The unit cost is based on relevant MBS Fees items (MBS items 132, 10954, 10958, and 10960)	286
Clinical visit (subsequent visit)[a]	A clinical visit comprises a subsequent specialist consultation and three allied health services (i.e., dietetics, occupational therapy, and physiotherapy). Assumes that subsequent visits take less specialists' time. The unit cost is based on relevant MBS Fees items (MBS items 133, 10954, 10958, and 10960)	204
Lung function test[a]	Respiratory Function Tests (MBS item 11503)	86
Sweat chloride test[a]	Performance of sweat collection by iontophoresis for chloride analysis	35
Genotyping[b]	CFTR mutation detection for 12 mutations	152
General pathology tests and pancreatic insufficiency tests[a]	The average unit cost per pathology test is composed of a microbiology sputum culture, full blood cell count and liver function tests, vitamin (A, D, and E) level measurement, oral glucose tolerance test, fecel fat (MBS items 69318, 66674, 66677, 65070, and 66500)	43
Endoscopy[a]	This service is composed of a specialist and anesthetist consultation, bronchoscopy for children or an endoscopy for adults (MBS items 104, 17610, 20520 and 41889 or 30473)	277
Home IV[c]	Based on the average treatment cost for home IV therapy based on a randomized controlled study in Queensland (n = 82)	6,794
Oxygen therapy[d]	Continuous therapy or nocturnal therapy	2,372
Oxygen therapy (temporary)[d]	Temporary—based on 6-mo usage per year	1,185
CF-related hospital stay[e]	Average inpatient cost per day (based on AR-DRG E60A and E60B)	932
Transplant surgery[e]	Cost of lung/heart transplant surgery. The cost has been annualized by dividing surgery cost by the expected number of life years remaining	69,756

Sources. a = [23]; b = Genetic Health Services Victoria—personal communication; c = [25]; d = [24]; e= [21].
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; IV, intravenous; MBS, Medicare Benefits Schedule.

represented a similar number of years. The annual transition probabilities vary between age groups but not within an age group.

For the purpose of modeling CF transitions, the disease was assumed to be progressive, meaning that patients could not improve their health state. The data showed that out of 2255 patients, 83 patients contradicted this assumption and improved their FEV_1% score and thereby also improved their health state. After we allowed a margin of error of 10% in the cutoff scores for health states 1, 2, and 3, only nine patients still improved their health state. For the purposes of ensuring a progressive disease model, we deleted these nine records from the transition probability calculations.

Resource Use and Unit Costs Data

The ACFDR contains resource use data on the number of CF-related hospitalizations in a year, the prescription medications administered, types of dietary supplements used, number of clinical visits, use of oxygen therapy, and some pathology tests. In addition, data exist on whether a patient has undergone a lung transplant and on death status. Resource use for medicines and pathology tests is reported as a binary value in the ACFDR, indicating whether a particular patient is consuming a type of medication or has undertaken a test that year. The clinical authors (J.M. and M.D.) supplemented the ACFDR data by providing the drug names typically used in the management of CF as well as information on the typical number of scripts required per year. In some instances, the type of drug and the number of scripts depend on the age of the patients. These variations have been incorporated into the analysis.

Unit cost information was obtained from standard Australian sources that are routinely used in economic evaluations: the National Hospital Cost Data Collection, the Pharmaceutical Benefits Schedule for all prescription drug costs, and the Medicare Benefits Schedule for medical consultations and diagnostic test costs [20–23]. Where necessary, these were supplemented by cost information from the literature [24–27].

Table 2 lists the unit prices for each CF-related medicine identified in the ACFDR. In most instances, CF-related medicines are listed on the Pharmaceutical Benefits Schedule, which entitles patients to a government subsidy, although they may still face co-payments. Unit prices include the cost to government and patient. Some CF-related medicines such as vitamins are not listed on the Pharmaceutical Benefits Schedule, and patients have to pay the full amount out of their own pocket.

Table 3 lists the unit prices for each of the CF-related medical services, procedures, and hospitalizations that are identified in the ACFDR. In most instances, CF-related services are subsidized by Australia's universal Medicare program. Based on clinical advice, a clinical visit comprises consultations with a specialist medical practitioner and three allied health care workers, which may include nutritionists, physiotherapists, and social workers and nurses.

Cost Analysis

For each patient, a total annual health care cost was estimated on the basis of the individual patient's resource use for that year. For each age group, health care costs were aggregated for four out of five health states. No costs could be incurred after death. The immediate costs associated with transplants were based on the Australian National Hospital Cost Data Collection [21]. To obtain an annualized cost, the cost of transplant surgery was divided by the difference between the patient's age at surgery and the maximum age in the data set (47 years). Thus, the average annual surgery cost increases as the age of the patient at the time of the transplant increases. Ongoing health care costs for transplant patients, incurred postsurgery, were estimated by using data from the ACFDR.

The lifetime costs were estimated on the basis of the sum of the expected costs for each year of life, as set out in Equation 1:

$$\text{Lifetime\_costs} = \sum_{a=0}^{47} \sum_{s=1}^{4} P_{as} C_{as} \quad (1)$$

where P is the probability of a patient with CF at age a, and in health state s, and C is the discounted annual health care costs of managing a patient with CF. The main lifetime cost results are based on a life expectancy of 47 years. We chose this cutoff point because this was the age of the oldest patient in the data set. As a test of sensitivity, however, we also report the lifetime cost up to age 65 years. Future health care costs were discounted at 0%, 3.5%, and 5%.

Because of the skewness of cost data, we report both mean and median costs for each health state and age group. In addition, we estimated a 95% confidence interval of mean costs by using a bootstrap method. The confidence intervals were estimated on the basis of 2000 replications for each age group and health state. The lower and upper bounds of the interval were used in the sensitivity analysis for the lifetime cost analyses.

The perspective taken in this analysis is that of the health care system. While this approach ignores important patient and family costs associated with the disease (such as lost productivity by parents and patients as well as travel costs associated with receiving care), it is consistent with most economic evaluations in health care and is certainly advocated by Australian guidelines on health economic evaluation and elsewhere [28]. Wherever possible, we have attempted to use the overall health system costs including contributions made by third-party payers (usually government) as well as out-of-pocket costs incurred by patients for prescription drugs. All costs reported use 2009 price levels and, where necessary, prices have been adjusted by using the Australian Bureau of Statistics' Consumer Price Index [29]. All currencies have been converted to US dollars by applying OECD GDP purchasing power parities (PPP) conversion rates and using the Campbell and Cochrane Economics Methods Group (CCEMG) – Evidence for Policy and Practice Information and Co-ordination (EPPI)-Centre Cost Converter (see http://eppi.ioe.ac.uk/costconversion/default.aspx for more details). The PPP conversion rate used in this study was US $1 is equal to AU $1.45.

Table 4 – Baseline characteristics for transition probabilities sample.

Variable	Sample	SD
Patients	2255	
Proportion male	0.52	0.50
Mean FEV_1% PP (aged 8 y and older only)	78.58	23.69
Mean age (y)	15.43	11.52
Age profile, proportion (y):		
Aged 0–8	0.32	0.47
Aged 9–16	0.28	0.45
Aged 17–25	0.20	0.40
Aged 26–37	0.14	0.35
Aged older than 37	0.06	0.23
HS, proportion		
HS 1: mild disease	0.75	0.43
HS 2: moderate disease	0.16	0.36
HS 3: severe disease	0.05	0.22
HS 4: transplant patient	0.04	0.19

HS, health state.

Results

Transitional Probabilities

The three waves of ACFDR data provided 4032 transition records from 2255 individual patients. Patients with FEV_1% data in all three waves (n = 1623 patients) provided two transition records (i.e., the probabilities of transition from first-year data to the second-year data and from the second to the third year). For patients with an FEV_1% observation in the first and third years (2003 and 2005), we linearly extrapolated the FEV_1% lung-function score for the second year and then allocated a health state accordingly (n = 154). These patients also provided two transition records. A further 478 patients provided FEV_1% observation in two subsequent ACFDR years. These observations were used to calculate one transition record. Those patients who died during the observation period but had no prior FEV_1% values recorded were assumed to have suffered from severe disease prior to death (health state 3). Table 4 shows the baseline patient characteristics for the 2255 patients in the sample used to calculate transitions. The mean age was 15 years, and slightly more than half the sample was male. The average FEV_1% score for those aged 8 years and older was 78.6, indicating that the mean health state is mild disease. Around one third of the sample was aged 8 years or younger, and only 6% of the patients were older than 37 years.

The transitional probabilities for disease progression for each of our five health states are reported in Table 5, with each row representing a different age group. The numbers in the table represent the annual likelihood of remaining in the same health state or moving to another state, conditional on last year's health state. For example, between the ages of 8 and 10 years, there

Table 5 – Annual CF disease progression transition probability matrix by age group (standard error).

Age group (y)	From HS 1 to HS 1 to 5					From HS 2 to HS 2 to 5				From HS 3 to HS 3 to 5			From HS 4 to HS 4 or 5		Absorbing state
	1|1	2|1	3|1	4|1	5|1	2|2	3|2	4|2	5|2	3|3	4|3	5|3	4|4	5|4	5|5
0–2	1			0	0								1	0	1
	–			–	–								–	–	–
3–5	1			0	0								1	0	1
	–			–	–								–	–	–
6–7	0.997			0.000	0.003								1	0	1
	(0.001)	–	–	–	(0.001)	–	–	–	–	–	–	–	–	–	–
8–10	0.973	0.027	0.000	0.000	0.000	1	0	0	0	1	0	0	1	0	1
	(0.004)	(0.004)	–	–	–	–	–	–	–	–	–	–	–	–	–
11–13	0.966	0.031	0.000	0.003	0.000	0.935	0.065	0	0	0.5	0	0.5	1	0	1
	(0.004)	(0.004)	–	(0.001)	–	(0.016)	(0.016)	–	–	(0.224)	–	(0.224)	–	–	–
14–16	0.952	0.045	0.000	0.003	0.000	0.9	0.075	0	0.025	0.5	0.167	0.333	0.833	0.167	1
	(0.005)	(0.005)	–	(0.001)	–	(0.021)	(0.019)	–	(0.011)	(0.100)	(0.075)	(0.094)	(0.075)	(0.075)	–
17–19	0.885	0.109	0.000	0.000	0.005	0.947	0.053	0	0	0.8	0.2	0	1	0	1
	(0.011)	(0.010)	–	–	(0.002)	(0.013)	(0.013)	–	–	(0.060)	(0.060)	–	–	–	–
20–22	0.879	0.121	0.000	0.000	0.000	0.92	0.08	0	0	0.806	0.032	0.161	1	0	1
	(0.011)	(0.011)	–	–	–	(0.013)	(0.013)	–	–	(0.032)	(0.014)	(0.030)	–	–	–
23–25	0.904	0.096	0.000	0.000	0.000	0.897	0.09	0	0.013	0.769	0	0.231	0.909	0.091	1
	(0.013)	(0.013)	–	–	–	(0.015)	(0.015)	–	(0.006)	(0.054)	–	(0.054)	(0.028)	(0.028)	–
26–28	0.917	0.083	0.000	0.000	0.000	0.902	0.082	0.016	0	0.765	0	0.235	0.95	0.05	1
	(0.015)	(0.015)	–	–	–	(0.017)	(0.016)	(0.007)	–	(0.047)	–	(0.047)	(0.022)	(0.022)	–
29–31	0.857	0.143	0.000	0.000	0.000	0.986	0	0	0.014	0.75	0.05	0.2	1	0	1
	(0.023)	(0.023)	–	–	–	(0.006)	–	–	(0.006)	(0.044)	(0.022)	(0.041)	–	–	–
32–34	0.839	0.161	0.000	0.000	0.000	0.911	0.054	0.018	0.018	0.667	0.167	0.167	0.933	0.067	1
	(0.030)	(0.030)	–	–	–	(0.017)	(0.014)	(0.008)	(0.008)	(0.064)	(0.050)	(0.050)	(0.030)	(0.030)	–
35–37	0.788	0.212	0.000	0.000	0.000	0.9	0.1	0	0	0.783	0	0.217	0.944	0.056	1
	(0.032)	(0.032)	–	–	–	(0.021)	(0.021)	–	–	(0.039)	–	(0.039)	(0.025)	(0.025)	–
>37	0.884	0.116	0.000	0.000	0.000	0.914	0.057	0.014	0.014	0.844	0.044	0.111	0.94	0.06	1
	(0.022)	(0.022)	–	–	–	(0.015)	(0.012)	(0.006)	(0.006)	(0.024)	(0.014)	(0.021)	(0.015)	(0.015)	–

Note. Lung function cannot be identified in the data for children aged younger than 8 y and therefore health states 1, 2, and 3 were aggregated for this group of patients. Absolute patient numbers are available on request to the corresponding author. CF, cystic fibrosis.

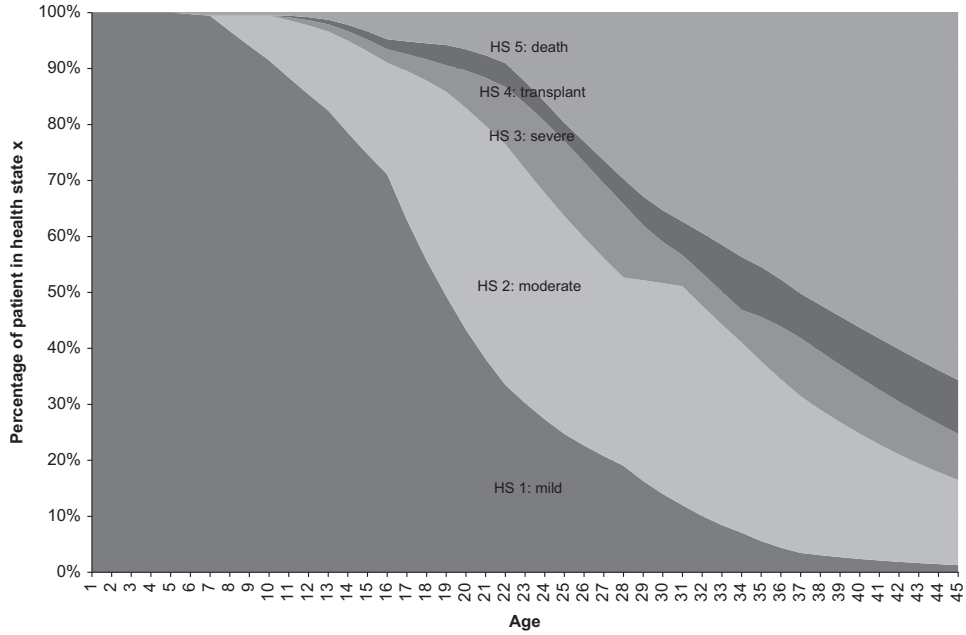

Fig. 2 – Proportion of patients in each health state (HS) by age.

is an annual 2.7% chance that a patient will move from health state 1 to 2.

Figure 2 illustrates how, over time, the cohort progress from one health state to another. At age 45 years, the model predicts that approximately two-thirds of the cohort have died, approximately 10% have received a transplant, and 1%, 15%, and 8% are in health states 1, 2, and 3, respectively.

Resource Use

To estimate cost and resource use, we include all observations in the registry with an identifiable health state. The sample for this part of the analysis consisted of 3149 patients providing 5938 observation records. This is larger than the transition probabilities sample size because patients had to provide only one health

Table 6 – Proportion of patients using medicines and medical services.

	Health state			
	1	2	3	4
Gastric acid reduction	0.046	0.100	0.176	0.204
Oral antibiotics (as required)	0.496	0.488	0.545	0.333
Oral antibiotics (continuous)	0.247	0.306	0.325	0.401
Inhaled antibiotics (as required)	0.264	0.387	0.388	0.185
Inhaled antibiotics (continuous)	0.103	0.269	0.339	0.148
Macrolides	0.062	0.254	0.380	0.247
Nutritional supplements	0.121	0.270	0.449	0.173
Salt tablets	0.209	0.218	0.218	0.105
Antihypercalcemics	0.002	0.010	0.028	0.037
Vitamin supplementation	0.562	0.662	0.699	0.537
Oxygen therapy (continuous)	0.000	0.002	0.050	0.056
Oxygen therapy (nocturnal)	0.001	0.011	0.079	0.043
Oxygen therapy (as required)	0.000	0.003	0.006	0.043
Endoscopy	0.022	0.037	0.061	0.105
Home IV therapy	0.088	0.256	0.337	0.266
Dornase alfa (Pulmozyme)	0.157	0.418	0.485	0.241
Pancreatic enzymes	0.678	0.747	0.766	0.642
Bronchodilators	0.372	0.601	0.672	0.327
Corticosteroids (inhaled)	0.236	0.398	0.391	0.296
Corticosteroids (oral)	0.070	0.107	0.083	0.457
Therapeutic bronchial artery embolization	0.001	0.013	0.017	0.012
Sweat chloride test	0.015	0.001	0.000	0.000
CFTR mutation analysis	0.021	0.006	0.008	0.000

CFTR, cystic fibrosis transmembrane conductance regulator; IV, intravenous.

Table 7 – Number of services used per annum by patients with CF.

	Health state			
	1	2	3	4
Pathology tests	2.7	4.7	6.0	4.6
Lung function test	1.7	3.7	3.1	1.8
Clinical visits	4.6	5.9	6.1	5.0
Hospital days	6.1	17.4	24.5	17.5
Hospital separations	0.9	1.7	2.2	1.7

CF, cystic fibrosis.

state record (instead of at least two) to be included in the cost analysis.

Table 6 provides a summary of the proportion of patients who are consuming medicines identified in the CF registry data as well as tests and medical services. The use of some medicines such as antibiotics appears to be stable across health states, but the use of most treatments rises as the disease progresses. Tests such as cystic fibrosis transmembrane conductance regulator analysis and sweat chloride tests are undertaken more often when patients are in the early severity stages of CF. This is an indication that such tests are used for the initial CF diagnosis.

Table 7 summarizes the annual number of medical services used by patients with CF according to their severity. On average, patients in health state 1 were admitted to hospital for 6.1 days for CF-related purposes. This number rises to 24.9 days for those in health state 3 and falls to 17.5 days for those who have undergone transplant surgery, although it should be noted that this does not include the days spent in the hospital for the actual transplant surgery.

Annual Costs

Table 8 shows the annual health care costs associated with the management of CF and associated complications for each age group and health state. The mean, bootstrapped standard error, and median are presented. Overall, the mean annual cost associated with CF management is US $15,571, with a 95% confidence interval range of US $15,032 to US $16,110. For health states combined, annual health care costs decline somewhat after age 2 years, then generally rise until patients reach their early thirties, then plateau at around US $20,000 to US $25,000 per year. Based on the standard errors reported in Table 8, the decrease in health care after age 2 years is statistically significant, as are the increases in the teenage years. The overall median health care cost is US $6,233 per year and ranges from US $2,269 for children aged 6 to 7 years to US $16,704 for 26- to 28-year-old patients. The difference between the mean and median statistics indicates that health care costs are highly skewed. This is not unusual in health care cost data where a small number of patients are very high users of health care resources and thereby greatly influence mean costs.

Both mean and median costs rise significantly as the disease progresses from health state 1 to 3. For all ages combined, when patients progress from health state 1 to 2, both mean and median health care costs increase by around US $15,000. While the average annual cost for health state 4 (patients who have received a transplant) is higher than that for health state 3, the difference is not statistically significant. The median cost for health state 4 is slightly lower than that for health state 3.

Cost by Health Care Sector

Figure 3 illustrates the distribution of total costs by main health care sector for each health state. The figure demonstrates that

Table 8 – Annual health care costs (converted to 2009 US $) stratified by age and health state.

Age (y)	Health state 1			Health state 2			Health state 3			Health state 4			Overall		
	Mean	SE*	Median	Mean	SE*	Median	Mean	SE*	Median	Mean	SE*	Median	Mean	SE*	Median
0–2	8,536	821	3,532										8,536	821	3,532
3–5	6,390	445	2,657										6,390	445	2,657
6–7	5,566	449	2,269										5,566	449	2,269
8–10	7,722	446	3,123	22,929	6,189	12,409							9,157	716	3,242
11–13	11,110	582	5,027	23,944	2,534	17,964	39,334	11,648	40,028	26,425	4,742	26,425	13,255	645	3,532
14–16	13,883	830	5,668	26,437	2,623	19,499	47,311	13,157	18,704	97,286	7,732	93,856	17,235	898	2,657
17–19	13,253	786	5,811	32,282	2,510	24,849	46,158	9,869	29,248	45,383	8,384	34,297	20,150	1,039	2,269
20–22	12,318	894	5,845	25,449	1,664	20,295	40,443	4,222	35,118	39,990	12,299	16,869	20,796	1,029	3,242
23–25	14,369	1,056	7,656	26,407	1,807	22,882	40,914	4,906	36,409	29,398	5,652	18,780	22,772	1,143	5,383
26–28	16,388	1,337	10,791	28,216	2,580	19,160	36,676	5,899	30,298	29,034	10,077	16,853	23,479	1,428	10,665
29–31	11,352	1,564	5,887	21,393	1,982	15,448	24,831	2,626	24,856	38,285	11,992	19,418	19,532	1,343	13,173
32–34	12,046	1,700	6,612	27,528	2,963	17,904	32,929	4,544	27,667	40,734	6,747	19,454	25,638	1,945	14,501
35–37	11,966	2,258	7,887	28,729	3,610	17,423	27,070	3,859	23,301	20,392	1,203	21,915	23,464	2,079	16,610
≥38	13,384	1,879	6,627	16,611	1,461	14,335	27,323	3,551	19,435	36,741	4,590	27,073	21,711	1,397	16,704
Total	10,151	222	4,331	25,647	771	18,230	33,691	1,649	27,108	38,344	2,827	22,915	15,571	275	6,233

* Bootstrapped standard errors.

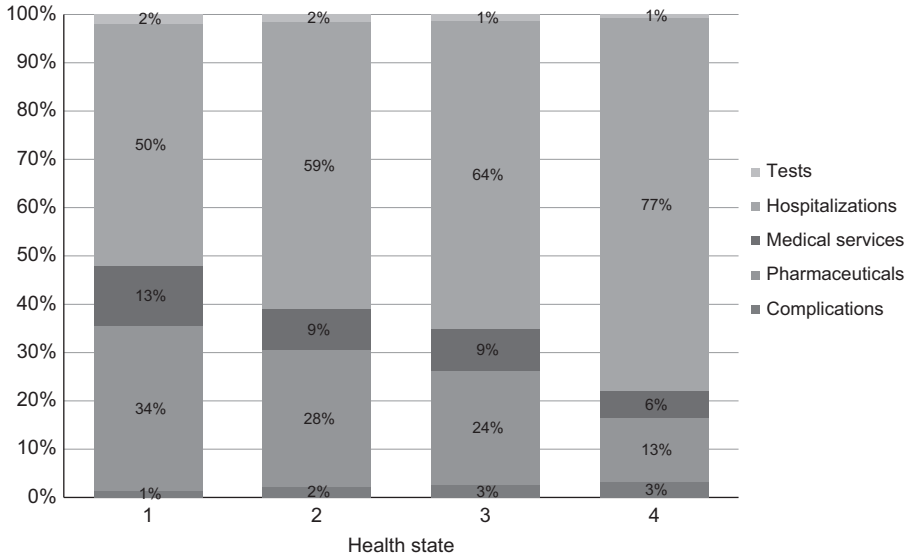

Fig. 3 – Distribution of CF health care costs by health state. CF, cystic fibrosis.

the greatest proportion of costs in the management of CF is incurred in the hospital sector, ranging from 50% for patients with mild disease (health state 1) to 77% for patients who have undergone a transplant operation (health state 4). The next biggest sector is pharmaceuticals, ranging from 13% in patients with severe disease (health state 3) to 33% for patients with mild disease (health state 1). This provides some indication that, in relative terms, care shifts from pharmaceutical management to hospital management as CF progresses.

Lifetime Costs and Total Health System Cost

Table 9 presents the results on lifetime health care costs up to age 47 years. Two estimates based on mean and median annual costs are produced. As a large proportion of health care costs is incurred in future years, it is appropriate that a discount rate is applied. Table 9 presents results where future health care costs are discounted at 0%, 3.5%, and 5% per year after the first year. Using a 3.5% discount rate, mean and median lifetime health care costs are estimated to be around US $306k and US $190k, respectively. If we were to run the model up to age 65 years, the mean (median) lifetime health care costs are estimated to be $320k ($200k) applying a 3.5% discount rate. On the basis that there are around 3000 patients with CF in Australia, the annual health system costs is in the vicinity of US $47 million.

Conclusions

We have successfully developed a model of CF disease progression to estimate the cost of medical care for people with CF. The mean annual cost for managing patients with CF is US $15,571, with a lifetime cost of US $306k. The health care costs rise as a patient's disease progresses. Average costs for patients with severe disease were three times higher than those for patients with mild disease. This indicates that potential new therapies that can delay disease progression may have important cost-offsets that need to be incorporated in economic evaluations.

There are several limitations in this study. First, the scope of ACFDR is not complete. Patients with CF who do not attend one of the participating treatment centers will not be captured by the data. Although a recent report by Cystic Fibrosis Australia estimates that its registry now captures around 90% of all patients [30], the percentage was lower in the data available for this study. Second, coverage of the CF registry in terms of resource use is also not complete. As a result, some health care costs such as general practitioner attendances are not included in the analysis. Similarly, CF registry data may not be comprehensive in capturing resource use associated with CF-related complications such as diabetes and liver disease. We have tried to overcome such gaps by using cost evidence from other studies, but these tend to be estimated on a population basis. It may well be the case that this is an underestimate of the true costs. This is because the cost of treating complications among patients with CF may be higher than the cost of treating similar complications in those who do not have CF and are otherwise healthy. These issues could be addressed by linking ACFDR with administrative data sets that provide detailed information on health care use and costs. The ACFDR would be further enhanced by seeking quality-of-life information from patients and carers. The addition of quality-of-life data and improved resource use data would make the ACFDR a powerful tool for future analysis, and a truly unique

Table 9 – Total lifetime costs—mean, median, and 95% confidence interval (converted US $)—by discount rate.

Discount rate (%)	Mean	95% confidence interval		Median
		Low	High	
0	637,943	520,142	781,487	419,734
3.5	306,332	256,098	375,304	189,825
5	235,666	198,942	288,800	141,955

asset in Australia. This data set can be used to undertake important economic and outcomes research. Third, the analysis uses only 3 years of registry data, limiting our ability to examine disease progression over a longer period of time. Cystic Fibrosis Australia is currently undertaking work to enable more linkage across waves. When this work is complete, it will allow researchers to utilize the panel structure of the data more fully.

Finally, there was a large number of missing FEV_1% values in the ACFDR. These are most likely due to issues of data collection, rather than patient selection. Despite these high numbers, our sample captures around 80% of the CF population. As children cannot generally perform the required lung function test, FEV_1% values are also missing for those younger than 8 years. As a result, we made an assumption about these children's health states. An important area for future research will be to model disease progression among the very young by using alternative markers of severity [31].

Notwithstanding these limitations, our results appear to be consistent with earlier research. Our assumption that CF is a strictly progressive disease (i.e., lung function does not improve) after taking into account patients who had undergone transplant surgery also appears to be validated by the data. Our estimate, in terms of mean annual costs, is less than those found in some studies but greater than the mean costs found in the 1996 Canadian study by Johnson et al. [6,12,13,32]. Care should be taken in comparing these results because there are differences in methodologies and patient groups. For example, Eidt-Koch et al. [13] focused only on outpatient medication costs and the patient group studied in Heimeshoff et al. [11] was older and suffered more severe disease compared with the group in the present study. The results of the current study are similar to those reported by Robson et al. [5], Ireys et al. [7], and Lieu et al. [10]. In the case of Lieu et al. [10], the median costs are also similar to those in the present study.

This study makes a number of important contributions to the existing literature. It is the first analysis to develop a model of disease progression and thereby estimate lifetime costs, by using longitudinal registry data. Second, this study has used a much larger sample size than previous studies, enabling us to estimate costs on the basis of age and severity. Third, we have incorporated transplantation costs into the analysis and examined the impact of such surgery separately to other categories of severity. Fourth, reporting resource use and standard costs facilitates more transparent translating of study results to other jurisdictions.

The value of our approach in estimating health care costs alongside disease progression is that it will enable future researchers to estimate the long-term impact of new treatments and health services. The model can extrapolate the short-term results of new treatments on outcomes and cost over the longer term. This will enable more timely evaluation of new treatments, with consistent and reliable evidence that reduces the degree of uncertainty in funding decisions. This will become even more important with the promise of new therapies in the R&D pipeline [33,34].

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