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Understanding the costs of care for cystic fibrosis: an analysis by age and severity

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Project team

Kees Van Gool (MEc)[a]
Richard Norman (MSc)[a]
Martin B Delatycki (PhD)[b]
Jane Hall (PhD) [a]
John Massie (PhD)[c]

[a] Centre for Health Economics Research and Evaluation (CHERE)
University of Technology Sydney, Broadway 2007 New South Wales.

[b] The Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, 10th Floor, Royal Children's Hospital, Flemington Rd, Parkville, Vic, 3052, Australia.

[c.] The Royal Children's Hospital, Melbourne, Flemington Road, Parkville, Vic, 3052, Australia.

Corresponding author:
Kees van Gool, e-mail: kees.vangool@chere.uts.edu.au; Phone: +61 (0)2 9514 4729.

Contact details

Mr Kees Van Gool
Centre for Health Economics Research and Evaluation (CHERE)
University of Technology, Sydney
City Campus
PO Box 123 Broadway
NSW 2007

Tel: + 61 2 9514 4729
Fax: + 61 2 9514 4730
Email: kees.vangool@chere.uts.edu.au

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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, amongst Caucasians (Welsh, Ramsey et al. 2001). 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 which affects many organ systems and as the disease progresses patients require more intensive health care that includes home based care and medications, along with more frequent and prolonged hospital admissions, and in around half of all cases lung transplantation.(Jason, Leah et al. 2009; Paul, Leah et al. 2009). As new and improving treatment options become available, the pattern of care will change, which will impact on the costs of treatment and on patient outcomes. For example, two of the key medications developed in the last 15 years, Pulmozyme and TOBI (not licensed for use in Australia) cost A$14,000 pa; and more sophisticated technology, such as gene-based treatments will be equally, or more expensive. Thus health care policy makers and funders will expect rigorous assessments of the cost-effectiveness of new treatments.

Previous literature

Cost-effectiveness analysis requires a sound understanding of the costs of care for CF, and how these will change with changes in disease progression. There have been a small number of studies that examined the cost of care associated with CF. A review by Krauth et al identified eight cost-of-illness studies but only five of these were based on individual patient care data (sample sizes 81-303), with the other three based on cost estimates provided by clinical experts (2003). A subsequent study reported on outpatient medication costs only with a small sample size (n= 301); while another reported patients treated in only two medical centres, again with a small sample size (n= 65) (Horvais, Touzet et al. 2006; Eidt-Koch, Wagner et al. 2010). We identified two further studies published subsequently to the review by Krauth et al . One further study by Sims et al (2007) examined the cost of care of children aged nine or less, but the focus of this study was on identifying cost differences (rather than total costs) between those diagnosed clinically versus those diagnosed via new-born screening.

Table 1 provides details of each of the seven studies based on patient data. For the purposes of comparison, we update the main results of these studies to 2009 price levels and convert all currencies to Australian dollars, using OECD published exchange rates. The average annual cost ranged from $10,000 to $40,000 (in 2009 AU$). Some studies found considerable cost variation among CF patients. For example, the study by Lieu et al (1999) found that the average annual healthcare cost for a patient with mild disease was around $10,000, moderate disease was $19,000 and severe disease was $71,000. Furthermore, Wildhagen et al (1996) found that the annual cost of healthcare for adults was almost double compared to children.

A study by Eidt-Koch et al (2010) reported on the outpatient medication costs on a sample of 301 German CF patients. This study concluded that age, the presence of co-morbidities and clinical indicators such as lung function and bacterial colonization were significant predictors of

medication costs. A French study of 65 patients treated in two medical centres estimated that the annual treatment costs were around AU$32,504 (Horvais, Touzet et al. 2006).

Table 1: Mean annual cost comparisons with previous studies

Source	Study year	Study country	Patient observ	Mean age	Age range	Mean cost	Converted (AU$ 2009)
Robson et al (1992)	1990	UK	119	21	16 - 44	UK£8,241	27,567
Wildhagen et al (1996)	1991	Neth	81	14	0 -37	UK£9,264	30,002
Ireys et al (1997)	1993	USA	204		0 - 18	US$14,377	25,499
Johnson et al (1996)	1996	Can	303	18		CAN$7,524	10,736
Lieu et al (1999)	1996	USA	136	17	0 - 56	US$13,300	21,725
Horvais et al (2006)	2001	France	65			Eur16,189	32,504
Eidt-Koch et al (2010)	2006	Germany	301			Eur21,603	39,688

These studies provide some evidence that severity and age are important in explaining healthcare costs. However, because of their small sample size and scope in terms of the population (e.g. children only) or data collection (e.g. medications only) these studies are limited in their ability to provide an estimate of healthcare costs that captures the heterogeneity in health needs within the CF population. Such evidence would facilitate future economic evaluations to assess the cost-effectiveness of new CF treatments. In turn, economic evidence will aid policy makers and insurers in their decision to adopt new treatments.

Methods

Data

Three years of data from the CF Australia data registry (ACFDR) were used (2003, 2004, 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 healthcare resource use. For more information on the ACFDR, including descriptive analysis and data items, see the reports published by Cystic Fibrosis Australia (Cystic Fibrosis Australia 2005; 2009). Available data included the Forced Expiratory Volume in 1 second as a percentage of predicted volume (FEV1%). Resource use data contains information on the number of CF-related hospitalisations 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, there is data on whether or not a patient has undergone a lung transplant and on death status.

Unit cost information was obtained from standard Australian sources; the National Hospital Cost Data Collection, the Pharmaceutical Benefits Schedule for all prescription drug costs, and the Medicare Benefit Schedule for medical consultations and diagnostic test costs (DOHA 2002; 2009; 2009; 2009). Where necessary, these were supplemented by cost information from the literature (e.g. cost data on oxygen therapy was obtained from Serginson et al (2009)).

Transitional probabilities

Five health states of disease severity were generated. These were defined as follows:

- Severity 1 – mild disease where FEV1% ≥70
- Severity 2 – moderate disease where 30 ≤ FEV1% < 70
- Severity 3 – severe disease where FEV1% < 30
- Severity 4 – where a patient has received a heart and/or lung transplant
- Severity 5 – where a patient has died.

The best recorded FEV1% measure in each year was used to classify severity. Severity of lung disease is the key to the quality of and length of life (NIH Consensus Development Panel on Genetic Testing for Cystic Fibrosis 1999). We chose the FEV1% cut-off 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 (Lieu, Ray et al. 1999).

As a lung function test cannot generally be performed by children under 8 years of age, we classified this group as severity class 1. We generated a separate category for patients who had received a lung transplant because there are high and quite different costs associated with those patients (Anyanwu, McGuire et al. 2002). Post-transplant, they were assumed to remain in severity category 4 unless a death was recorded.

Patients in the CF registry with at least two years of severity data were included in estimating the transition probabilities. The transitional probabilities for patients who provided severity state data in each of the three waves of data were estimated twice (i.e. the probabilities of transition from first year data to the second year data and from the second to the third year were estimated). For patients with a severity record in the first and third year (2003 and 2005), we extrapolated the severity status for the second year (2004). This meant we had two transition records for these patients. Only one transition record was recorded for patients with severity status data in years 2003 and 2004 or in years 2004 and 2005. Those with one or no severity state records were not used in this part of the analysis.

All deaths that occurred during the first year of the data (2003) were assumed to have taken place at the start of the second year – so that patients could not start the model in severity group 5. Patients who died in any of the three years and had no prior FEV1% values recorded were assumed to have suffered from severe disease prior to death. For the purpose of

modelling CF transitions, the disease was assumed to be progressive, meaning that patients could not improve their severity status.

Cost analysis

For each patient a total annual healthcare cost was estimated based on the individual patient's resource use for that year. For each age group, healthcare costs were aggregated for four out of five severity categories, leaving out the death severity category. The immediate costs associated with transplants were based on the Australian National Hospital Cost Data Collection (NHCDC).(DOHA 2009) To obtain an annualised cost, the cost of transplant surgery was divided by the number of years of life-expectancy remaining at the time of the patient's surgery. Thus the average annual surgery cost associated with surgery increases as the age of the patient at the time of the transplant increases. Ongoing health care costs for transplant patients, incurred post surgery, were estimated using data from the Australian Cystic Fibrosis Data Registry (ACFDR).

The lifetime costs were estimated on the basis of the sum of the expected costs for each year of life. The oldest patient in the dataset was 47 and therefore we restrict the lifetime cost analysis to this age. Future healthcare costs were discounted at 0%, 5% and 10%.

The perspective taken in this analysis is that of the healthcare system. Whilst 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. (PBAC 2008) Wherever possible, we have attempted to use the overall health system costs associated with managing CF including contributions made by third party payers (usually government) and patients through co-payments. All costs reported use 2009 price levels and, where necessary, prices have been adjusted using the Australian Bureau of Statistics' Consumer Price Index.(ABS 2010) All costs reported in this paper are in Australian dollars which, at the time of writing this paper, is close to parity with the US dollar.

Results

Transitional probabilities

To estimate disease progression, we excluded (1) patients aged 8 and under (these patients were assumed to have mild disease) and (2) patients who provided less than two FEV1% results and did not receive a transplant or were deceased. This left 2,264 patients in the final sample. In all, there were 47 recorded deaths and 164 transplants in the dataset. We tested whether our assumption on disease progression held in the data (i.e. no person improved in severity category over time). Eighty-three patients did improve severity category – however after we allowed a margin of error of 10% for each severity cut off score– only 7 patients still improved severity category. For the purposes of ensuring a progressive disease model we deleted these records from the transition probability calculations, leaving us with 4,032 transition records.

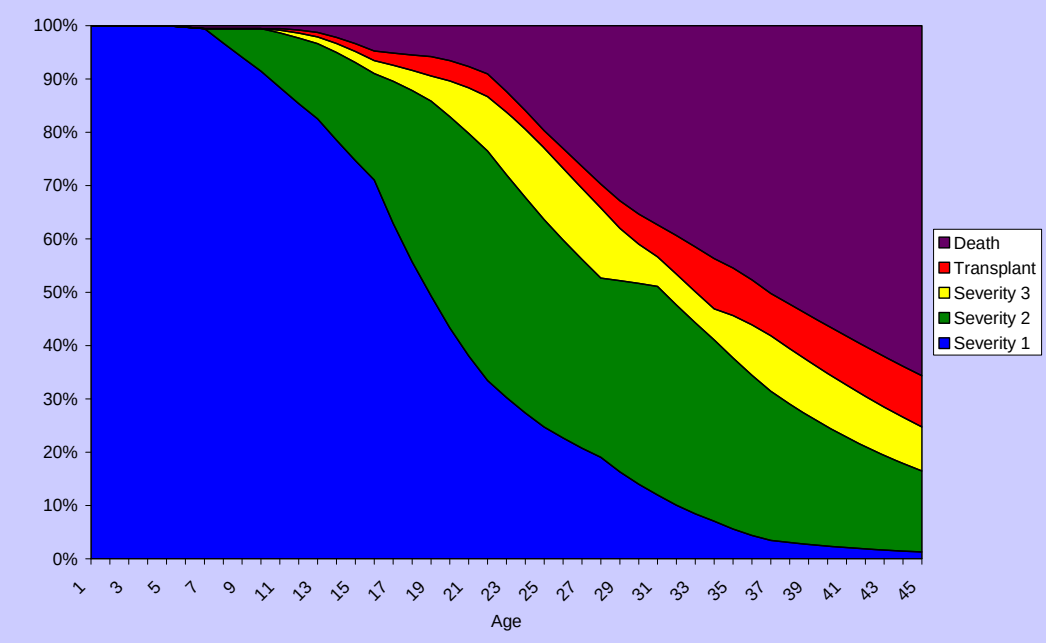
Transitional probabilities are reported in Table 1. The proportions in each row in this table add up to one and provide the probability of a cohort being in a given severity state at any age group. By assumption, the proportion of patients in the least severe category is equal to one for all those aged less than eight years (age groups 1, 2 and 3). Note that the proportions are the annual transition probabilities whereas each age group represent, generally, three years.

Table 1: Probability of disease state by age group

AGEGROUP	AGE	SEVERITY					
		1	2	3	4	5	All
1	0 to 2	1.000	0.000	0.000	0.000	0.000	1.00
2	3 to 5	1.000	0.000	0.000	0.000	0.000	1.00
3	6 to 7	0.997	0.000	0.000	0.000	0.003	1.00
4	8 to 10	0.970	0.027	0.000	0.000	0.003	1.00
5	11 to 13	0.937	0.055	0.002	0.003	0.003	1.00
6	14 to 16	0.892	0.092	0.005	0.006	0.005	1.00
7	17 to 19	0.789	0.185	0.009	0.007	0.010	1.00
8	20 to 22	0.694	0.266	0.022	0.007	0.012	1.00
9	23 to 25	0.627	0.305	0.041	0.006	0.021	1.00
10	26 to 28	0.575	0.328	0.056	0.011	0.031	1.00
11	29 to 31	0.493	0.405	0.042	0.014	0.047	1.00
12	32 to 34	0.413	0.448	0.050	0.027	0.062	1.00
13	35 to 37	0.326	0.491	0.084	0.026	0.074	1.00
14	≥ 38	0.288	0.487	0.099	0.035	0.092	1.00

Figure 1 illustrates how, over time, the cohort progress from one severity category to another. At age 45 the model predicts that approximately two-thirds of the cohort has died. Of the cohort that is alive, approximately 10% have received a transplant and 1%, 15%, and 8% are in severity categories 1, 2, and 3, respectively. On the basis of these results, life-expectancy at birth for this cohort is 38 years.

Figure 1: Proportion of patients in each severity category by age



Complications and resource use

To estimate cost and resource use we included all patients in the registry. The sample for this part of the analysis consisted of 3,149 patients providing 5,938 observation records. Table 2 provides a synopsis of the complications suffered by CF patients stratified by severity category. The figures in Table 2 indicate that a large proportion of CF patients also suffer from chronic diseases such as diabetes and osteoporosis. Generally, complications arise as patients get older and their disease progresses.

Table 2: Proportion of patients with additional complications - by CF severity category

	SEVERITY CATEGORY			
	1	2	3	4
Pneumothorax	0.001	0.006	0.016	0.025
CF-related diabetes	0.047	0.170	0.250	0.414
Haemoptysis (major or massive)	0.007	0.053	0.065	0.043
Osteoporosis	0.042	0.212	0.411	0.395

Table 3 summarises the annual number of medical services used by CF patients according to their severity. On average, patients in severity category 1 were admitted to hospital for 6.1 days for CF-related purposes. This number rises to 24·9 days for those in severity category 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 hospital for the actual transplant surgery.

Table 3: Number of services used per annum by CF patients

	SEVERITY CATEGORY			
	1	2	3	4
Pathology tests	2.7	4.7	5.9	4.6
Lung function test	1.8	3.6	3.3	1.8
Clinical visits	4.6	5.8	6.2	5.0
Hospital days	6.1	17.4	24.9	17.5
Hospital separations	0.9	1.7	2.1	1.7

More detailed information on resource use is available from the authors.

Annual costs

Table 4 shows the annual healthcare costs associated with the management of CF and associated complications for each age group. Mean, median and the cost of the bottom and top quartile of observations are presented. Overall, the mean annual cost associated with CF management is $22,366 whereas the median cost is $8,738. Overall, 25% of patient observations incur a cost of less than $3206 per year and 25% incur a cost higher than $30,092. These statistics indicate that healthcare costs are highly skewed. This is not unusual in healthcare cost data where a small number of patients are very high users of healthcare resources and thereby greatly influence mean costs. Annual healthcare costs decline somewhat after age 2 but then rise until patients reach their early thirties.

Table 4: Annual healthcare costs - mean, median and range stratified by age

AGE GROUP	AGE	MEAN	MEDIAN	QUARTILE (25%)	QUARTILE (75%)	OBS
		$	$	$	$	
1	0 to 2	12,210	4,783	505	14,705	296
2	3 to 5	9,102	3,670	415	7,963	656
3	6 to 7	7,940	3,159	415	6,151	495
4	8 to 10	13,121	4,497	2,537	19,483	525
5	11 to 13	19,062	7,664	4,953	24,744	609
6	14 to 16	24,799	14,951	5,042	34,228	636
7	17 to 19	29,009	19,007	5,657	37,931	625
8	20 to 22	29,867	20,872	6,269	40,662	474
9	23 to 25	32,702	23,689	7,185	45,154	396
10	26 to 28	33,731	24,063	7,288	45,623	280
11	29 to 31	28,059	21,017	6,218	38,993	238
12	32 to 34	36,833	23,884	9,340	45,651	202
13	35 to 37	33,779	23,181	6,832	44,773	166
14	≥ 38	31,224	23,689	6,151	41,825	340
Total		**22,366**	**8,738**	**3,206**	**30,092**	**5,938**

Table 5 summarises annual healthcare stratified by severity. As before, the table shows mean, median, and the bottom and top quartiles. Both mean and median costs rise as the disease progresses, although the median costs for severity category 4 (patients who have received a transplant) is slightly lower compared to patients in severity category 3. Annual healthcare costs rise substantially when patients progress from severity category 1 to 2. Both mean and median healthcare costs increase by around $20,000 for these patients.

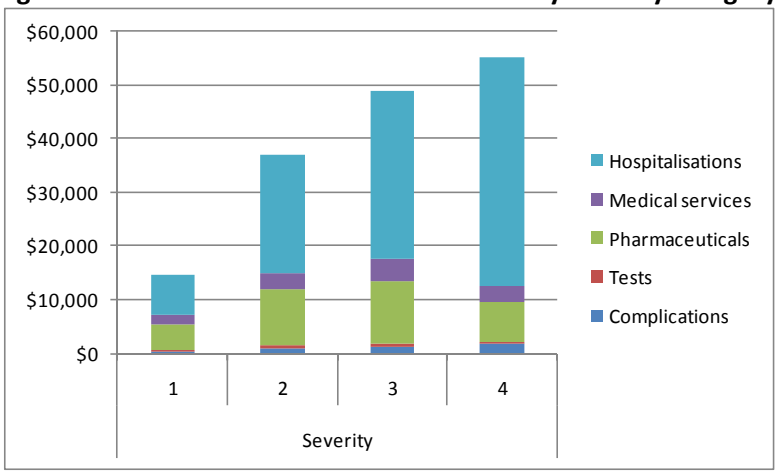
Table 5: Total annual healthcare costs - stratified by severity

Severity	Mean	Median	Quartile (25%)	Quartile (75%)	Freq
	$	$	$	$	
1	14,542	6,107	2,397	21,221	4,194
2	37,023	26,271	8,208	51,147	1,216
3	48,745	36,936	19,946	62,602	366
4	55,293	33,172	21,769	76,058	162
Total	22,366	8,738	3,206	30,092	5,938

Cost by health care sector

Figure 2 illustrates the distribution of total costs by main health care sector for each severity category. The figure demonstrates that the greatest proportion of costs in the management of CF is incurred in the hospital sector, ranging from 50% for patients with mild disease to 77% for patients who have undergone a transplant operation. The next biggest sector is pharmaceuticals ranging from 13% in patients with severe disease to 33% for patients with mild disease. This provides some indication that, in relative terms, care shifts from pharmaceutical management to hospital management as CF progresses.

Figure 2: Distribution of CF healthcare costs by severity category



Lifetime costs

Table 6 presents the results on lifetime healthcare costs. Two estimates based on mean and median annual costs are produced. As a large proportion of healthcare costs are incurred in future years it is appropriate that a discount rate is applied. Table 6 presents results where future health care costs are discounted at 0, 5%, and 10% per year after the first year. Using a 5% discount rate, mean and median lifetime health care costs are estimated to be around $335k and $200k, respectively.

Table 6: Total lifetime costs – mean and median

	DISCOUNT RATE		
	0%	5%	10%
Mean	897,063	334,820	168,246
Median	585,532	199,552	90,525

Discussion

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 $22,366. Costs increase according to disease severity and age of the patients. Mean annual costs for patients with mild, moderate, and severe disease, defined on the basis of lung function, is $14,542, $37,023, and $48,745, respectively. The lifetime health system cost of managing CF, using a 5% discount rate, is around $336k. On the basis that there are around 3,000 patients with CF in Australia, the annual health system costs is in the vicinity of $67 million. The majority of these costs are incurred in the inpatient hospital sector (58%), followed by pharmaceuticals (29%), medical services (10%), complications (2%), and diagnostic tests (1%). There is a greater reliance on inpatient care as the disease progresses.

There are several limitations in this study. First, the scope of ACFDR is not complete. CF patients who do not attend one of the participating treatment centres will not be captured by

the data. Although a recent report by CF Australia estimates that its registry now captures around 90% of all patients (Stewart 2009) the percentage was lower in the data available for this study. Secondly, coverage of the CF registry in terms of resource use is also not complete. As a result, some health care costs such as GP 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 because treating complications amongst patient with CF may be higher compared to the cost of treating similar complications in those who don't have CF and are otherwise healthy. Finally, the analysis only uses three years of registry data, limiting our ability to examine disease progression over a longer period of time.

Notwithstanding these limitations, our results appear to be consistent with earlier research. Our estimate, in terms of mean annual costs, is slightly less than those found by Eidt-Koch et al, Horvais et al, and Wildhagen et al but greater than the mean costs found in the 1996 Canadian study by Johnson et al (Johnson, Connolly et al. 1996; Wildhagen, Verheij et al. 1996; Horvais, Touzet et al. 2006; Eidt-Koch, Wagner et al. 2010). The results of the current study are similar to those reported by Ireys et al (1997), Robson et al (1992) and Lieu et al (1999). In the case of Lieu et al the median costs are also similar to the present study.

Our disease progression model predicts life-expectancy of around 38 years of age, which is comparable to the median survival age of 37 reported by the US Cystic Fibrosis Foundation in 2008 (Cystic Fibrosis Foundation 2011). Furthermore, 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 appears to be valid.

This study makes an important contribution 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 and standard costs facilitates more transparent translating of study results to other jurisdictions. Finally, with the advent of new and likely expensive therapies, the costs of these can be estimated using our model.

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Conflict of interest

We declare that we have no conflicts of interest.

Ethics committee approval

The use of the Australian Cystic Fibrosis Data Registry was approved by the Sydney South West Area Health Service Ethics Review Committee.

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