Economic implications of newborn screening for cystic fibrosis: a cost of illness retrospective cohort study

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Summary

Background **Newborn screening for cystic fibrosis might not be introduced if implementation and running costs are perceived as prohibitive. Compared with clinical diagnosis, newborn screening is associated with clinical benefit and reduced treatment needs. We estimate the potential savings in treatment costs attributable to newborn screening.**

Methods **Using the UK Cystic Fibrosis Database, we used a prevalence strategy to undertake a cost of illness retrospective snapshot cohort study. We estimated yearly costs of long-term therapies and intravenous antibiotics for 184 patients who were diagnosed as a result of screening as newborn babies, and 950 patients who were clinically diagnosed aged 1–9 years in 2002. Costs of adding cystic fibrosis screening to an established newborn screening service in Scotland were adjusted to 2002 prices and applied to the UK as a whole. Costs were recalculated in US$.**

Findings **Cost of therapy for patients diagnosed by newborn screening was significantly lower than equivalent therapies for clinically diagnosed patients: mean ($7228 *vs* $12 008, 95% CI of difference −6736 to −2028, p<0·0001) and median ($352 *vs* $2442, −1916 to −180, p<0·0001). When we limited the clinically diagnosed group to only those diagnosable with a 31 cystic fibrosis transmembrane regulator mutation assay and assumed similar disease progression in the clinically diagnosed group as in the newborn screening group, we showed that mean ($3 397 344) or median ($947 032) drug cost savings could have offset the estimated cost of adding cystic fibrosis to a UK national newborn screening service ($2 971 551).**

Interpretation **Including indirect costs savings, newborn screening for cystic fibrosis might have even greater financial benefits to society than our estimate shows. Clinical, social, and now economic evidence suggests that universal newborn screening programmes for cystic fibrosis should be adopted internationally.**

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Introduction

Many governments are debating the relative benefits of newborn screening compared with clinical diagnosis for several inherited disorders. If a national newborn screening programme is implemented, the set-up costs should balance with the potential health or other benefits to the patient and economic benefits to the state. Cystic fibrosis is an example of such a disease for which early diagnosis is associated with improvements in some but not all clinical outcomes. Indeed, governments in the UK, France, Australia, Italy, and 23 US states have agreed to implement newborn screening for this common life-limiting autosomal recessive disease.

Newborn screening for cystic fibrosis aids diagnosis within 2 months of age for about 90% of patients. Without such screening, the age at clinical presentation (or clinical diagnosis) is variable, with some patients presenting with symptoms within hours or days of birth (eg, meconium ileus), weeks of birth (eg, failure to thrive), or in mild cases, in adult life (eg, recurrent respiratory infection). Cost-effectiveness studies have mainly examined the potential costs of implementing newborn screening programmes for cystic fibrosis compared with sweat testing—the only other viable screening method to establish a diagnosis of cystic fibrosis,[1–3] but have not included the potential cost savings.[4] Lee and colleagues[2] estimated that compared with sweat testing, a newborn screening programme using an immunoreactive trypsinogen or serum trypsinogen test or a DNA strategy for all newborn babies has the potential for cost savings. Additionally, evidence is growing that early presymptomatic diagnosis of cystic fibrosis via a newborn screening programme is associated with improved clinical and health benefit.[5–12] Furthermore, for a similar number of clinic attendances per year, we reported that this clinical benefit in those screened as newborn babies is associated with a lower treatment burden when compared with clinically diagnosed groups.[13] However, whether these potential cost savings attributed to reduced therapeutic requirements could materially offset the cost of a newborn screening programme is not known. Using the UK Cystic Fibrosis Database, a validated disease register,[10,13,14] we assessed the cost of therapies given to those screened as newborn babies and as clinically diagnosed patients, and tested whether any cost savings could offset the known costs of a national newborn screening programme (as used in Scotland), when scaled to the UK as a whole. However, since newborn screening can only benefit patients who would otherwise have presented after 2 months of age, we also completed a sensitivity analysis to determine the effect of restricting our cost estimate to patients diagnosed after the age of 2 months, and to those diagnosable with a 31 cystic fibrosis transmembrane regulator (CFTR) mutation assay (as used in the Scottish Newborn Screening Laboratory[15]).

For more information about the **UK Cystic Fibrosis Database** see http://www.cystic-fibrosis.org.uk

	UK CF Database category	Intensity of giving and monitoring therapy
Inhaled corticosteroids	Inhaled therapies	Low
Inhaled or nebulised β2 agonist	Inhaled therapies	Low
Inhaled or nebulised antimuscarinic	Inhaled therapies	Low
Oral antibiotic (ie, flucloxacillin)	Anti-staphylococcal therapy	Low
Colomycin	Nebulised antibiotic	Medium
Gentamicin	Nebulised antibiotic	Medium
Tobramycin	Nebulised antibiotic	Medium
Other	Nebulised antibiotic	Medium
Oral steroid	Oral corticosteroid	Medium
rhDNase	Nebulised mucolytic	Medium

Therapies represent, according to the UK Cystic Fibrosis Database and with the exception of pancreatic enzyme replacement therapy (PERT), the most commonly prescribed long-term cystic fibrosis therapies. PERT was excluded because similar proportions of patients were given PERT in both study groups, substantial variability in doses, and known discrepancy between dose prescribed and dose taken.

Table 1: **Long-term therapies (given for 3 months or more)**

Methods

Participants

Data from the UK Cystic Fibrosis Database taken from 41 cystic fibrosis centres and 12 smaller cystic fibrosis clinics in years 2000–02, were collected, verified, and error checked as previously described.[10,16] All procedures were compliant with multicentre research ethics protocols and UK legislation on patient confidentiality. Patients aged 1–9 years were divided into two groups (newborn screening and clinically diagnosed). Patients in the newborn screening group were those who were identified by newborn screening within 2 months of birth, and clinically diagnosed patients were those who presented at any time by clinical diagnosis. Patients presenting with meconium ileus or with a family history of cystic fibrosis of any relative were excluded, since these patients would have been diagnosed early irrespective of a newborn screening programme. The newborn screening and clinically diagnosed groups were the same people as used in other studies.[10,13] Patients were further subgrouped by age (1–3 years, 4–6 years, and 7–9 years). Because cystic fibrosis genotype varies and is partly associated with phenotype,[17] this was deemed to be a potential confounding factor. We therefore undertook a sub-analysis using homozygous ΔF508 newborn screening and clinically diagnosed subgroups.

Procedures

For the purposes of this study, we calculated 1-year treatment costs for the 12 months preceding the 2002 yearly review. Discounting—ie, annual adjustment for interest—was not undertaken. In the UK Cystic Fibrosis Database, long-term treatment[16] (defined as a therapy prescribed for at least 3 months [table 1] and home and hospital intravenous therapy) needs are recorded yearly. We estimated the yearly cost of long-term treatment, nebulised therapies, and intravenous antibiotics using the British National Formulary.[18] Doses of inhaled therapies and nebulised antibiotics were based on British National Formulary[18] and Cystic Fibrosis Trust guidelines,[19] respectively. The number of days and location (home or hospital) of intravenous treatment are also recorded yearly. Owing to limitations in data collection, we could not determine which type of antibiotics had been prescribed in all cases. However, we identified that of the 438 (of 1435, 31%) eligible patients given intravenous antibiotics, 227 (52%) received a recognised standard combination of tobramycin with ceftazidime at least once during the 12 months before the 2002 yearly review. We therefore estimated the daily cost of intravenous tobramycin and ceftazidime when given at home or in hospital and applied this cost to all patients. Since most patients receive intravenous antibiotics for *Pseudomonas aeruginosa* infection, this assumption is not unreasonable. We calculated doses of tobramycin and ceftazidime per kg bodyweight using Cystic Fibrosis Trust guidelines[19] where indicated. Cost of home intravenous antibiotics was estimated with a current quotation provided by Clinovia (Glasgow, UK) adjusted to 2002 prices using the Consumer Price Index for Medical Services and Paramedical Services.[20] Hospital intravenous administration was based on the cost per day in 2002 of a medical paediatric bed in a university hospital with a cystic fibrosis Specialist Paediatric Centre (GB£569 per day; Ninewells Hospital, Dundee, UK), respectively. All prices were converted to US$ (£1=US$1·639).[21] With the data available from the UK Cystic Fibrosis Database, assessment of the effect of newborn screening on indirect costs (ie, economic effects on carers, productivity of patients with cystic fibrosis, and other non-health-sector costs) was not possible.

To test whether cost of treatment was related to disease severity we used *P aeruginosa* infection status as a surrogate marker of severity. The UK Cystic Fibrosis Database defines *P aeruginosa* infection as either intermittent (one or two positive cultures in 12 months) or chronic (three or more positive cultures in 12 months). We stratified newborn screening and clinically diagnosed groups according to *P aeruginosa* infection status and compared estimated therapy costs.

Incremental cost estimates for staff, overheads, and consumables used in adding newborn screening for cystic fibrosis to an established newborn screening programme (for phenylketonuria and congenital hypothyroidism) in Scotland from January to December, 2004, were provided by D Aitken (table 2). Since the Scottish Newborn Screening Laboratory uses an immunoreactive trypsinogen/DNA/immunoreactive trypsinogen screening protocol, costs are divided into those attributable to the immunoreactive trypsinogen or serum trypsinogen test assays and those attributable to DNA assays (Biosystems oligonucleotide ligation assay, California, USA; cystic fibrosis mutation kit, which screens for 31 mutations in genomic DNA). The costs

detailed are based on actual yearly salary costs adjusted for the proportion of time each member of staff devoted to cystic fibrosis screening, the audited costs of overheads including equipment maintenance and capital charges, and the suppliers discounted costs of reagents and consumables, which are based on laboratory workload. The costs of midwife or health visitor counselling, collection of blood spots, and health promotion are not included. Cost estimates were first adjusted to 2002 prices using the Consumer Price Index for Health,[22] and then to the number of livebirths in Scotland in 2002.[23] Cost estimates were then converted to US$ (£1=US$1·639).[21] Assuming that the cost of newborn screening for cystic fibrosis did not differ across the UK, and using the combined number of recorded livebirths for 2002 for England and Wales,[24] Northern Ireland[25] and Scotland,[23] we estimated the cost (in US$) of providing a universal newborn screening service for the UK.

Statistical analysis

We did statistical analyses using Microsoft Access 2000 and Excel 2000, MINITAB version 13.1 and R.1.9.2. Because the cost data were not normally distributed, we present median and mean results. Mann-Whitney two-sample rank test and student's t test (unpaired) were used to determine differences between population medians and means, respectively. To account for subdivision of populations, p=0·01 was deemed significant for 3-year age-group comparisons, for comparison of total populations α error was set at 0·05. To validate our results, we used linear regression analysis (including *P aeruginosa* infection status and age-group as cofactors) to determine differences in estimated costs between newborn screening and clinically diagnosed patients. Because the data were not normally distributed, we used the bootstrap method (with 9999 replications) to estimate the 95% CI and p values.[26]

Role of the funding source

The funding sources had no role in study design, data extraction, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had responsibility for the decision to submit for publication.

Results

1909 patients aged 1–9 years were identified. Clinical data for 2002 was available for 1516 patients, of whom 1134 (75%) met the study requirements. 382 patients were excluded, 301 owing to presentation by meconium ileus, which occurs before newborn screening can report, and 81 owing to unknown date of diagnosis, unknown mode of presentation, or a family history of cystic fibrosis that contributed at least in part to the diagnosis. 184 newborn screened and 950 clinically diagnosed patients were identified, of which 98 (53% in the newborn screened group) and 531 (56% in the clinically diagnosed group) patients were homozygous for the ΔF508 genotype. Biographical characteristics of these cohorts have been presented previously.[10]

Patients diagnosed by newborn screening aged between 1 and 9 years cost significantly less to treat than those who were diagnosed clinically (table 3). For the mixed genotype patients, the median cost for the clinically diagnosed group was 400% of that for the newborn screened group. The results were much the same for the 1–3 year-olds, with the clinically diagnosed group given more than 500% of the estimated treatment given to the newborn screened group. For 4–6 and 7–9 year-olds in the newborn screened group, median (but not mean) estimated treatment costs were significantly lower than

	2004 Scottish population (n)	2004 Scottish costs (£)	2002 Scottish population* (n)	2002 Scottish costs*† (£)	2002 Scottish costs‡ (US$)	2002 UK population§ (n)	2002 UK costs§ (US$)
Refused screening	42	-	39	-	-	514	-
IRT screening	54 600		51 231			668 263	
Staff costs (including employers' costs)		63 066		55 447	90 877		1 185 410
Overheads and capital charges		17 148		15 076	24 710		322 320
Consumables (IRT test)		62 940		55 336	90 695		1 183 042
Total IRT screening costs		143 154		125 859	206 282		2 690 772
DNA mutation screen	372	14 940	349	13 133	21 525	4557	280 780
Total cost		157 744		138 992	227 808		2 971 551
Estimated number of patients diagnosed with cystic fibrosis	28		26			343	
Cost per patient diagnosed with cystic fibrosis		5634		5346	8769		8663

IRT=immunoreactive trypsinogen or serum trypsinogen test. Estimated costs provided for 2004. 2004 prices adjusted *to 2002 prices with consumer price index and †to number of livebirths in Scotland in 2002.[20] ‡Costs converted to US$ (£1=$1·639). §Derived costs then applied to recorded UK livebirths.[20-22] Refusal rate of 0·08% in 2004 Scottish Population applied throughout cost analysis.

Table 2: **Cost of adding screening for cystic fibrosis to an established newborn screening service in Scotland**

	1–3 years			4–6 years			7–9 years			Combined (1–9 years)		
	Newborn screening *vs* clinical diagnosis	Difference between groups (95% CI)	p	Newborn screening *vs* clinical diagnosis	Difference between groups (95% CI)	p	Newborn screening *vs* clinical diagnosis	Difference between groups (95% CI)	p	Newborn screening *vs* clinical diagnosis	Difference between groups (95% CI)	p
Mixed												
Median	252 (n=72) *vs* 2286 (n=235)	−1355 (−1916 to −129)	<0·0001	2195 (n=60) *vs* 2442 (n=332)	−180 (−1915 to −0·0)	0·0099	2245 (n=52) *vs* 4020 (n=383)	−1627 (−2492 to −92)	0·0036	352 (n=184) *vs* 2442 (n=950)	−1589 (−1916 to −180)	<0·0001
Mean	4498 *vs* 9944	−4992 (−8138 to −1847)	0·002	8993 *vs* 11 425	−2230 (−6649 to 2189)		8971 *vs* 13 780	−4408 (−9714 to 897)		7228 *vs* 12 008	−4382 (−6736 to −2028)	<0·0001
ΔF508												
Median	252 (n=39) *vs* 2342 (n=129)	−1773 (−2852 to −143)	0·0003	197 (n=28) *vs* 2442 (n=183)	−1773 (−2238 to −92)	0·0038	2342 (n=29) *vs* 4076 (n=219)	−1627 (−6623 to 0·2)	0·007	2090 (n=96) *vs* 2516 (n=531)	−1864 (−2096 to −221)	0·0001
Mean	3297 *vs* 11 637	−7644 (−12 240 to −3048)	0·001	9184 *vs* 11 525	−2146 (−9665 to 5373)		7560 *vs* 14 989	−6810 (−11 701 to −1918)		6302 *vs* 12 981	−6122 (−9123 to −3121)	

Table 3: **Mean and median estimated yearly treatment costs per patient (US$) in 2002, by genotype and age-group**

the age-matched clinically diagnosed group. The trends were similar for the ΔF508 subgroups.

We used a cumulative frequency plot to compare the costs associated with the two groups (figure 1). The disparity in differences between mean and median estimated costs could be attributed to the distribution of the treatment costs for the 3-year age-groups. For example, 70% of 1–3 year-olds diagnosed by newborn screening received treatment costing less than an estimated $1000 a year, but only 30% of age-matched

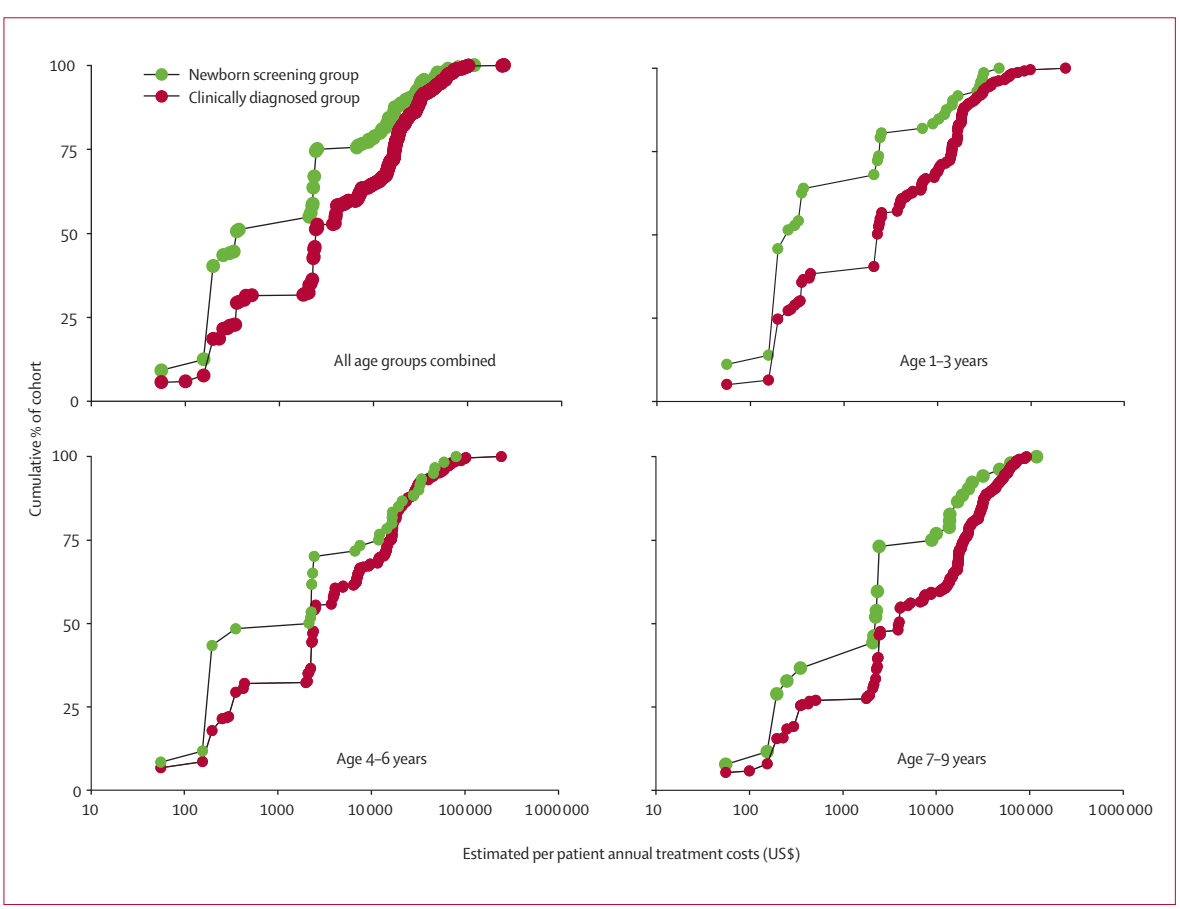

Figure 1: **Cumulative frequency plots of newborn screening and clinically diagnosed groups, by estimated yearly treatment costs per patient (US$)**
Mean and median costs shown in table 2.

clinically diagnosed patients received such low-cost treatment. The trends were reversed for patients given treatment costing more than $10 000 a year, with significantly fewer newborn screened patients than age-matched clinically diagnosed patients.

Treatment costs increased significantly with increasing *P aeruginosa* infection status (a surrogate marker of severity) for both groups, irrespective of age (figure 2). For patients free of *P aeruginosa* infection, mean and median treatment costs for newborn screened patients were significantly lower than age-matched clinically diagnosed controls. By contrast, cost differences were minimal between the two groups in chronically or intermittently infected patients. Findings were much the same for the 3-year age-groups (data not shown).

After adjustment for *P aeruginosa* infection status and age-group, with linear regression analysis, clinically diagnosed patients received an estimated $3126 (95% CI 138–5778, p=0·02, r^2=0·17) greater treatment per patient than newborn screening patients for the mixed genotype cohort (table 4). For genetically matched homozygous ΔF508 patients, this difference rose to $4739 (95% CI 500–8372, p=0·009, r^2=0·17).

In Scotland, 54 600 babies were screened for cystic fibrosis in 2004 (table 2). After adjustment of this screened population to livebirths recorded in 2002 and estimated 2004 costs to 2002 prices, the estimated yearly cost of the screening programme in Scotland was $227 808 (table 2). In 2002, 668 777 livebirths were recorded for the UK.[23–25] On the assumption that the incidence of cystic fibrosis in the UK is similar to that in Scotland in 2004, then in 2002, a UK national newborn screening programme would have cost an estimated $2 971 551. A UK national cystic fibrosis newborn screening programme will begin in 2007.

To estimate the potential savings in treatment costs as a result of implementation of a newborn screening programme, we assumed that all clinically diagnosed patients in our study would have been diagnosed by newborn screening, and that the progression of disease in the clinically diagnosed group would have been similar in outcome to that of the existing UK newborn screened group, resulting in similar lower use of therapies. With differences in cost estimates shown in table 3 for the 3-year age-group matched newborn screened and clinically diagnosed groups, mean and median estimates of cost savings for the mixed genotype group were $3 601 744 and $1 001 326, respectively. On the assumption that the estimated cost saving was between the mean and median, these estimated treatment cost savings could offset between 34% and 121% of the incremental cost of implementing an add-on cystic fibrosis newborn screening programme. For the homozygous ΔF508 group alone, estimated mean and median cost savings were $2 870 184 and $909 489, respectively. Furthermore, assuming that the cost differences estimated with linear regression analysis are indicative of potential cost savings, estimated cost savings in 2002 would have been $2 969 700 ($2 516 409 for ΔF508 patients only) or 100% (85% for ΔF508 patients) of the estimated cost of implementing a newborn screening programme.

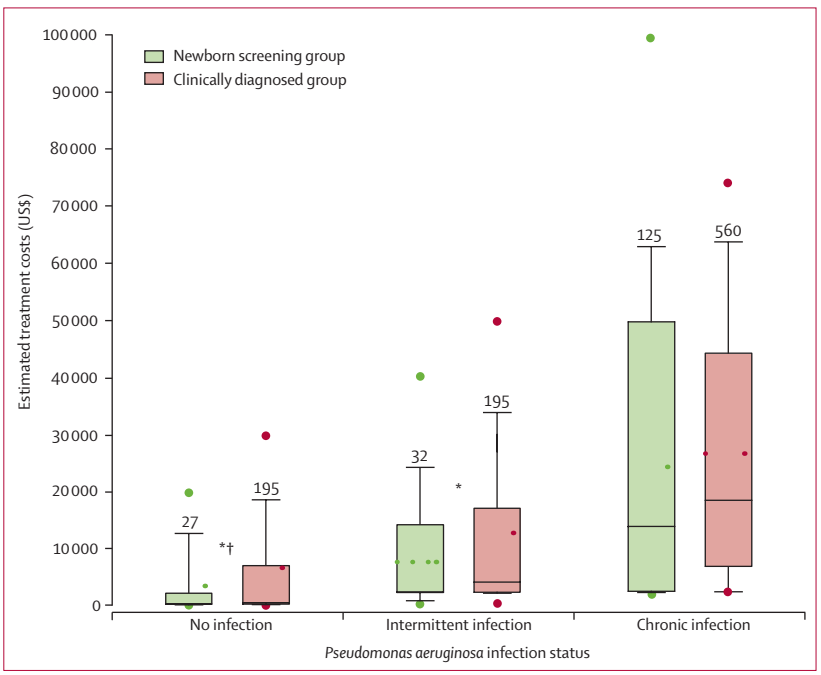

Figure 2: **Effect of *Pseudomonas aeruginosa* infection on estimated yearly treatment costs for newborn screening and clinically diagnosed groups**
Results shown for combined age-group (1–9 years). Solid line=median. Circles=5th–95th percentiles. Dotted line=mean. p value for difference between *medians p<0·0001 and †means p=0·01. For intermittant infection p=0·002. Results were similar for the 3-year age-groups (data not shown). Numbers above each bar are number of patients.

	Estimate	95% CI	p
Reference group (clinically diagnosed patients)	22 295 (22 287)	18 719 to 26 222 (17 372 to 27 903)	0·0002 (0·0002)
Age-group			
1–3 years	0		
4–6 years	1182 (–536)	–1514 to 3850 (–4273 to 3044)	0·3834 (0·7788)
7–9 years	2230 (595)	–416 to 4886 (–3059 to 4182)	0·1010 (0·7404)
P aeruginosa status			
Free	0		
Intermittent	–14 168 (–14 001)	–17 572 to –10 914 (–18 446 to –9424)	0·0002 (0·0002)
Chronic	–20 047 (–19 637)	–22 914 to –17 419 (–23 456 to –16 165)	0·0002 (0·0002)
Mode of diagnosis			
Screening	0		
Clinical	3126 (4739)	138 to 5778 (500 to 8372)	0·0176 (0·0086)

Results show mean difference in cost of therapy given to a patient diagnosed after newborn screening compared with a clinically diagnosed patient, corrected for age-group and *Pseudomonas aeruginosa* infection status, and separately the effect of increasing age and increasing *P aeruginosa* infection status on estimated cost of therapy per patient. Values in parentheses indicate results for homozygous ΔF508 subgroups. Regression diagnostics for mixed genotype and homozygous ΔF508 analyses were, respectively: r^2=0·1675, p=0·0002; and r^2=0·1715, p=0·0002.

Table 4: **Linear regression analysis results for mixed genotype and homozygous ΔF508 patients**

	1–3 year age-group	4–6 year age-group	7–9 year age-group	All age-groups combined	Estimated treatment-cost savings if newborn screening had been used (US$)		
					Mean	Median	Mean*
Clinically diagnosed patients (n=950)[14]							
Patients with two mutations identified	187 (80%)	258 (78%)	300 (78%)	745 (78%)	2 831 244 (94·3%)	787 925 (26·5%)	2 328 870 (78·3%)
Patients with one or two mutations identified	218 (93%)	312 (94%)	366 (96%)	896 (94%)	3 397 344 (114·3%)	947 032 (31·9%)	2 800 896 (93·8%)
Patients clinically diagnosed after 2 months of age (n=733)							
Patients with two mutations identified	131 (77%)	200 (77%)	242 (80%)	573 (78%)	2 166 688 (72·9%)	607 239 (20·4%)	1 791 198 (60·2%)
Patients with one or two mutations identified	155 (91%)	245 (94%)	290 (96%)	690 (94%)	2 598 430 (87·5%)	725 955 (24·4%)	2 156 940 (72·6%)

Data are number (%) unless otherwise indicated. *Potential cost savings on basis of linear regression analysis with boot strapping (table 3) with cost estimates for mixed genotype population.

Table 5: **Effects of screening using a 31 CFTR mutation assay and age at diagnosis on estimated cost savings to the estimated cost of a newborn screening programme for cystic fibrosis**

However, what if only a proportion of the clinically diagnosed population was diagnosed by newborn screening? Indeed, unusual genotypes would not be identified with a 31 mutation CFTR DNA mutation assay (as was used in the Scottish Newborn Screening Laboratory[15]). Furthermore, even after exclusion of patients presenting with meconium ileus, not all clinically diagnosed patients would benefit from a newborn screening programme, since some would present with symptoms (eg, failure to thrive or respiratory infection) before 2 months of age. Table 5 shows the effects of limiting our analysis to first, only patients with one or both mutations that could be identified with a 31 CFTR mutation assay, and second, patients who presented with symptoms after the age of 2 months. As shown, 60–73% of the cost of running a national newborn screening programme would be offset even if we limit our cost estimates to patients with one or both mutations identifiable with a 31 CFTR mutation assay who had not presented with symptoms within the first 2 months of life.

Discussion

We have shown that patients with cystic fibrosis (at least up to 9 years of age) diagnosed on the basis of clinical presentation alone received therapy costing an estimated 60–400% more than that received by patients diagnosed by newborn screening. Had this estimated cost saving been available in 2002, a significant part of the estimated cost of running a UK-wide newborn screening programme for cystic fibrosis could have been offset. Furthermore, because both groups received treatment appropriate to the severity of disease, our results are unlikely to be subject to selection bias. Our findings are relevant for governments that are assessing the financial viability of a newborn screening programme for cystic fibrosis. In agreement with our previous results,[10,13] our data support the hypothesis that implementation of a newborn screening programme has benefits for patients with cystic fibrosis in terms of improved clinical outcome and reduced morbidity.[10] Such screening would also provide social and schooling benefits to the family via reduced need for time consuming nebulised and intravenous therapy,[13] and economic benefits to the state from reduced treatment in the early years. Even if cost savings do not offset the total costs of a screening programme, improvements in health resulting from the programme justify implementation, if the ratio of costs and benefits are within an acceptable margin.

Our study has several limitations. First, our cost estimates for the newborn screened and clinically diagnosed groups were based on the proportion of patients for whom clinical data were available. In view of the similar age, age at diagnosis, and proportion of patients with the homozygous ΔF508 genotype in the registered and study populations, similar disease severity and treatment needs can be reasonably assumed. On application of this assumption, because clinical data are available for about 75% of our registered patients with cystic fibrosis,[16] our cost savings are likely to be underestimates. This shortfall is similar to an updated analysis of the UK cystic fibrosis population, suggesting under-reporting of patients aged 1–9 years to the UK Cystic Fibrosis Database by 25% (1909 registered patients compared with 2539 estimated patients [Exeter D, Boyle P, University of St Andrew's, personal communication]), thus resulting in further underestimation of the potential cost savings available. In terms of the UK cystic fibrosis population that could benefit from a newborn screening programme, 25% of patients are anticipated to present with symptoms within 2 months of birth,[15] of which about 17% present with meconium ileus and 8% with other symptoms (eg, failure to thrive or respiratory infection; Sims EJ, unpublished data). Indeed, our initial analysis excluded only patients presenting with meconium ileus. However, excluding all patients presenting with symptoms within 2 months of birth from our cost analysis and further restricting our study to patients with two mutations that could be identified with a 31 CFTR mutation assay, more than 70% of the estimated cost of the newborn screening programme could be offset by savings in the treatment budget. Since the clinically diagnosed group was larger than the screened group, and in view of the heterogeneity of cystic fibrosis disease, the diversity of disease progression could differ from that of the newborn screened group had the clinically diagnosed cohort been diagnosed by newborn screening. However, such a difference is difficult to quantify in a cross-sectional

analysis and would require a longitudinal study with a larger newborn screened group.

Second, our analysis might result in overestimation of the cost savings available. Our estimation of treatment costs did not include costs of short-term therapies, because these are not reliably reported to the UK Cystic Fibrosis Database, or other long-term therapies, such as pancreatic-enzyme replacement therapy. But since about 90% of patients with cystic fibrosis, irrespective of mode of diagnosis, have pancreatic insufficiency and therefore receive pancreatic-enzyme replacement therapy,[27] cost differences from that source are unlikely. Similarly, we did not include costs associated with supplemental feeding by gastrostomy or nasogastric tube, since the proportion of patients receiving supplemental feeding by either route was similar in the two groups (data not shown). Additionally, our analysis might be subject to confounding by physician preferences towards use of prophylactic therapy or early precautionary therapies, or both. However, our results both here and previously, indicate that therapy is prescribed according to severity (eg, *P aeruginosa* infection status) irrespective of mode of diagnosis[13,28] and predominant mode of presentation of the clinic population.[13] Also, we did not include the costs associated with midwife or health-visitor counselling, collection of blood spots, and health promotion, which suggests that our results might underestimate the cost of implementation and running of a newborn screening programme and therefore overestimate the potential cost savings. However, these costs occur irrespective of the cystic fibrosis newborn screening programme, because they accrue from other screened diseases.

Third, we have also assumed that the demography of the UK as a whole is similar to that of Scotland. However, the percentage of the population who are not white is higher in England and Wales (6%) than in Scotland (<1·5%), which might further confound this analysis, because the severity of disease is greater in patients from ethnic minority backgrounds than in white people.[29] Indeed, many of the genotypes in this proportion of the general population are not included the 31 CFTR mutation assay used in Scottish Newborn Screening Laboratory.[15] However, the incidence of cystic fibrosis in UK Asian and African populations is significantly lower (1 in 31 000[15] and 1 in 15 000,[30] respectively) than in the UK white (1 in 2500) population. Therefore, these differences between Scottish and UK populations are unlikely to have a significant effect on our analysis, particularly since only one in 60 patients with cystic fibrosis in the UK are of Asian origin.[15] Conversely, no Asian patients with cystic fibrosis older than 40 years are alive in the UK (McCormick J, unpublished) and newborn screening might disproportionately benefit this minority.

The cost for the newborn screening programme per screened baby in Scotland, which uses a 31-DNA mutation screen, was $4·44. This cost was almost double that reported by Lee and colleagues,[2] for the State of Wisconsin's cystic fibrosis neonatal screening programme ($2·66) which used a single DNA mutation (ΔF508) screen. Additionally, Rosenberg and Farrell,[31] reported that the cost of a screening programme with a multi-DNA-mutation screen ($4·16) was almost double that of a single-DNA-mutation screen ($2·77). Although this suggests that the newborn screening programme in Scotland is similar in terms of cost to that estimated by Rosenberg and Farrell, the estimated cost per patient of immunoreactive-trypsinogen screening alone in Scotland is $4·03, suggesting that the cost of immunoreactive-trypsinogen analysis is higher in Scotland than in Wisconsin, but vice versa for DNA-mutation screening. Assuming that the cost of screening per patient could be reduced to a similar level as reported for Wisconsin (eg, $2·66 per screened baby), the estimated laboratory costs of a newborn screening programme in the UK for 2002 would have been $1777 580; more than 120% of which could have been offset by our most conservative estimate of the savings to the treatment budget ($2 166 688). In the planned UK national newborn screening programme, the plan for immunoreactive-trypsinogen-screen positive babies is to initially screen for four common alleles. If only one mutation is identified, a secondary 31 mutation screen will be done.

For more information on the **planned UK National Newborn Screening Programme** see http://www.newbornscreening-bloodspot.org.uk

Simpson and colleagues[32] used a hypothetical decision model to conclude that diagnosis of cystic fibrosis by newborn screening is "relatively expensive", and that a delay in the presentation of symptoms by 11 months would make a newborn screening programme cost effective. However, compared with the cost per newly diagnosed child with conventional sweat testing alone ($4·79 per screened baby), Lee and colleagues[2] reported that the cost per newly diagnosed child by newborn screening is almost halved to $2·79 per screened baby, suggesting that compared with conventional diagnostic procedures, diagnosis of cystic fibrosis by newborn screening is cost effective. Additionally, our clinical and treatment data seem to support the rationale that early diagnosis by newborn screening reduces the rate of disease progression (presumably owing to aggressive nutritional management and early intervention at the first signs of respiratory infection), with patients remaining on low-intensity therapy alone for longer than do clinically diagnosed controls.[10,13] This reduction in the rate of disease progression would obviously have a greater influence on cost-effectiveness strategies than a delay on the presentation of symptoms by 11 months.

Indirect costs (ie, those owing to lost employment attributable to ill health or morbidity) are an important element of any economic assessment. However, data obtained for the UK Cystic Fibrosis Database provides no specific information about time invested in therapy by patients or carers and only minimum information for work or school time lost. However, for 1996, the US government estimated that patients and relatives spent almost 40 days in cystic fibrosis therapy.[33] Furthermore,

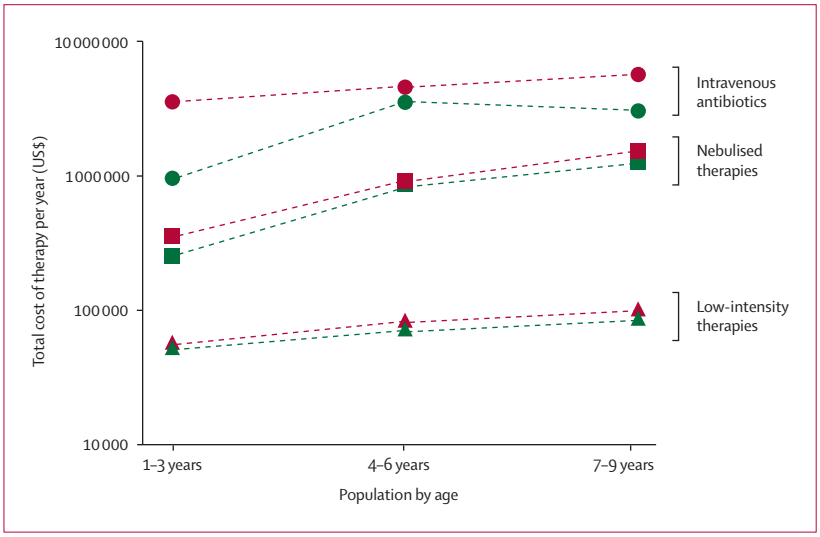

***Figure 3*: Estimated cost of low-intensity therapy, nebulised therapy, and intravenous antibiotic therapy for newborn screening (green) and clinically diagnosed (red) groups**
Data adjusted for cohort size.

for 1996, they estimated that these indirect costs were equivalent to 94% of the direct treatment costs.

Figure 3 shows that the higher treatment costs in the clinically diagnosed group are mainly driven by the greater use of intravenous therapies in these patients. Indeed this trend is especially true for the 1–3 year-olds, for whom the cost of intravenous therapy in the clinically diagnosed group is about 400% of that for the newborn screening group, presumably owing to the higher proportion of patients with intermittent *P aeruginosa* infection in the clinically diagnosed group than in the newborn screening group.[10] However, therapeutic and care management protocols for the treatment of cystic fibrosis are constantly changing. Since 2002, when the data for this study were obtained, three-times daily intravenous tobramycin protocols have been changed in favour of once daily regimens, which would reduce our yearly treatment-cost estimates.[34] Similarly, because a home course of intravenous therapy costs about half that of giving the treatment in a hospital, a trend towards community-based care and increased provision of home intravenous-therapy services could further reduce yearly treatment-cost estimates. Conversely, treatment with recombinant human DNA 1 (rhDNase), which costs $11 473 a year per patient, is now used mainly in those with moderate to severe cystic fibrosis lung disease. However, in view of evidence that patients with mild disease might have a greater benefit than others,[35,36] universal prescription of rhDNase would be likely to add substantial costs to the yearly drug budget. However, universal prescription of rhDNase is likely to occur irrespective of a newborn screening programme.

Diagnosis of cystic fibrosis by newborn screening means that patients often attend cystic fibrosis clinics from a much younger age than had they been diagnosed clinically. This difference has been reported to be associated with an earlier acquisition of *P aeruginosa* infection.[11] However, more recent data from the Wisconsin group show that when patients are stratified into clinics according to a *P aeruginosa*-driven segregation policy, age of acquisition of *P aeruginosa* in newborn screening patients is similar to that of clinically diagnosed patients.[12] This finding would suggest that newborn screening must be accompanied by prompt and appropriate specialist care and treatment (including infection segregation policies).

A common misconception of newborn screening for cystic fibrosis is that it will aid diagnosis of all patients with cystic fibrosis mutations. However because of the heterogeneity of the disease, newborn screening will identify only about 90% of patients. All newborn screening protocols for cystic fibrosis are based on identification of patients with very high immunoreactive trypsinogen concentrations (≥99·5th centile), which is indicative of a blocked or damaged pancreas (often called pancreatic insufficiency). These patients are the most at risk of malnutrition, early *P aeruginosa* infection, lung disease, morbidity, and reduced survival. Provision of aggressive nutritional support to these patients as soon after birth as possible will slow the cycle of decline by which worse nutrition leads to an increased rate of decline in lung function.[10] By comparison, patients with sufficient pancreatic function (about 10% of the cystic fibrosis population) will mostly have an immunoreactive trypsinogen concentration of less than the 99·5th centile and will therefore be missed by newborn screening. But since these patients will not present with symptoms until later in life, have a much slower rate of decline in lung disease (assuming they present with lung disease at all), and have a much better survival than those with pancreatic insufficiency, an early diagnosis will have little effect on their management (other than increasing their insurance premiums).

We conclude that newborn screening is associated with lower estimated treatment costs and reduced hospital admissions for invasive therapy than for clinically diagnosed patients, which suggests that indirect costs and disruption to family life will also be less. Furthermore, the potential cost savings to the yearly treatment budget could offset some, if not all, of the costs of a national newborn screening service. Inclusion of indirect costs could increase the cost savings further. Therefore, the argument that to wait until patients present with symptoms is potentially more cost effective than to diagnose early and presymptomatically, thereby saving the money that would otherwise have been spent on prophylactic and preventative treatment, does not hold true. Should universal newborn screening programmes for cystic fibrosis be adopted internationally? We believe that the weight of clinical, social, and economic evidence suggests that the answer to this question should be, unreservedly, yes.

Contributors

E J Sims, M Mugford, D Aitken, and A Mehta planned and undertook the statistical analysis and reporting for this study, A Clark undertook the statistical analysis and reporting, J McCormick planned and reported the study, and G Mehta undertook project management, database design, and reporting.

Conflict of interest statement

E J Sims was funded by the Cystic Fibrosis Trust when this work was undertaken. A Mehta is director of the UK Cystic Fibrosis Database and has received funding from the Cystic Fibrosis Trust and the National Services Division of NHS (Scotland). G Mehta was manager of the UK Cystic Fibrosis Database and funded by the Cystic Fibrosis Trust when this study was undertaken. D Aitken is director of the Scottish Newborn Screening Laboratory and provided the incremental cost data for the addition of cystic fibrosis screening to the Scottish Newborn Screening Programme. J McCormick has received travel sponsorship from the Cystic Fibrosis Trust to attend international meetings. M Mugford and A Clark declare that they have no conflict of interest.

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References

1 McCabe ERB, McCabe LL. State-of-the-art for DNA technology in newborn screening. *Acta Paediatr Supp* 1999; **432:** 58–60.

2 Lee DS, Rosenberg MA, Peterson A, et al. Analysis of the costs of diagnosing cystic fibrosis with a newborn screening program. *J Pediatr* 2003; **142:** 617–23.

3 Newborn screening for cystic fibrosis: a paradigm for public health genetics policy development: proceedings of a 1997 workshop. *MMWR Recomm Rep* 1997; **46:** 1–24.

4 Pollitt RJ, Green A, McCabe CJ, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. *Health Technol Assess* 1997; **1:** i–202.

5 Farrell PM, Kosorok MR, Laxova A, et al for the Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Nutritional benefits of neonatal screening for cystic fibrosis. *N Engl J Med* 1997; **337:** 963–69.

6 Waters DL, Wilcken B, Irwing L, et al. Clinical outcomes of newborn screening for cystic fibrosis. *Arch Dis Child* 1999; **80:** F1–7.

7 Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *Pediatrics* 2001; **107:** 1–13.

8 Mastella G, Zanolla L, Castellani C, et al. Neonatal screening for cystic fibrosis: long-term clinical balance. *Pancreatology* 2001; **1:** 531–37.

9 Siret D, Bretaudeau G, Branger B, et al. Comparing the clinical evolution of cystic fibrosis screened neonatally to that of cystic fibrosis diagnosed from clinical symptoms: a 10-year retrospective study in a French region (Brittany). *Pediatr Pulmonol* 2003; **35:** 342–49.

10 Sims EJ, McCormick J, Mehta G, Mehta A. Neonatal screening for cystic fibrosis is beneficial even in the context of modern treatment. *J Pediatr* 2005; **147:** S42–46.

11 Farrell PM, Shen G, Splaingard M, et al. Acquisition of *Pseudomonas aeruginosa* in children with cystic fibrosis. *Pediatrics* 1997; **100:** E2.

12 Farrell PM, Li Z, Kosorok MR, et al. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. *Am J Respir Crit Care Med* 2003; **168:** 1100–08.

13 Sims EJ, McCormick J, Mehta G, Mehta A. Newborn screening for cystic fibrosis associates with reduced treatment intensity. *J Pediatr* 2005; **147:** 306–11.

14 Sims EJ, Green MW, Mehta A. Decreased lung function in female but not male subjects with established cystic fibrosis-related diabetes. *Diabetes Care* 2005; **28:** 1581–87.

15 McCormick J, Green MW, Mehta G, Culross F, Mehta A. Demographics of the UK cystic fibrosis population: implications for neonatal screening. *Eur J Hum Genet* 2002; **10:** 583–90.

16 Mehta G, Sims EJ, Culross F, McCormick J, Mehta A. Potential benefits of the UK Cystic Fibrosis Database. *J R Soc Med* 2004; **97** (suppl 44)**:** 60–71.

17 Zielenski J. Genotype and phenotype in cystic fibrosis. *Respiration* 2000; **67:** 117–33.

18 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary, 44th edn. London: British Medical Association, Royal Pharmaceutical Society of Great Britain, 2002.

19 Littlewood JM, Bevan A, Connett G, et al. Antibiotic treatment for cystic fibrosis: report of the UK Cystic Fibrosis Trust Antibiotic Group, 2nd edn. Bromley: Cystic Fibrosis Trust, 2002.

20 UK National Statistics. Consumer price indices Index 06.2.1: Medical services and paramedical services: Dec 2005. http://www.statistics.gov.uk/statbase/tsdtables1.asp?vlnk=mm23, (accessed March 9, 2005).

21 Organisation for Economic Co-operation and Development. Purchasing power parities for OECD countries 1980–2004. http://www.oecd.org/dataoecd/61/56/1876133.xls (accessed May 9, 2005).

22 Organisation for economic co-operation and development. Consumer price indices index: health, estimated pre-1997. http://www.statistics.gov.uk/statbase/tsdtables1.asp?vlnk=mm23 (accessed June 29, 2005).

23 Randall J. Scotland's population 2002: the registrar general's annual review of demographic trends. http://www.gro-scotland.gov.uk/files/02annual-report.pdf (accessed July 14, 2005).

24 Office for National Statistics. Birth statistics 2002. http://www.statistics.gov.uk/downloads/theme_population/Fm1_31/FM1_31.pdf (accessed July 14, 2005).

25 Northern Ireland Statistics and Research Agency. Eighty-first annual report of the registrar general, 2002. http://www.nisra.gov.uk/statistics/financeandpersonnel/DMB/2002RG_Report/Chapter03.pdf (accessed July 14, 2005).

26 Hall P, Wilson S. Two guidelines for bootstrap hypothesis testing. *Biometrics* 1991; **47:** 757–62.

27 Mehta A. Further comments on fibrosing colonopathy study. *Lancet* 2001; **358:** 1546–47.

28 Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A, on behalf of the UK CF Database Steering Committee. Cystic fibrosis diagnosed after two months of age leads to worse outcomes and requires more therapy. *Pediatrics* 2007; **119:** 19–28.

29 McCormick J, Ogston SA, Sims EJ, Mehta A. Asians with cystic fibrosis in the UK have worse disease outcomes than clinic matched white homozygous delta F508 controls. *J Cyst Fibros* 2005; **4:** 53–58.

30 Hamosh A, FitzSimmons SC, Macek M Jr, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *J Pediatr* 1998; **132:** 255–59.

31 Rosenberg MA, Farrell PM. Assessing the cost of cystic fibrosis diagnosis and treatment. *J Pediatr* 2005; **147:** S101–05.

32 Simpson N, Anderson R, Sassi F, et al. The cost-effectiveness of neonatal screening for cystic fibrosis: an analysis of alternative scenarios using a decision model. *Cost Eff Resour Alloc* 2005; **3:** 8.

33 US Congress Office of Technology Assessment. Cystis fibrosis and DNA tests: implications of carrier screening. Washington: US Government Printing Office, 1992.

34 Smyth A, Tan KHV, Hyman-Taylor P, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial. *Lancet* 2005; **365:** 573–78.

35 Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001; **139:** 813–20.

36 Paul K, Rietschel E, Ballmann M, et al. Effect of treatment with dornase alpha on airway inflammation in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2004; **169:** 719–25.