obliterative process in the smallest of the conducting airways and the inflammatory/fibrotic process that thickens and narrows the larger airways that are visible on CT.

In summary, the results of Martinez *et al*[1] raise important questions about the relationship between structural changes in the lung, abnormalities of lung function and respiratory related symptoms, physical activity and psychosocial impacts. It is somewhat paradoxical that the authors chose to compare more precise morphological features of COPD with composite measures of function and symptoms since the COPD community is striving to separate subphenotypes of COPD based on pathogenetic mechanisms and structural changes. However, by identifying the relationships between these CT features and the components of the composite scores, the authors have allowed us to more precisely determine their relationship to CT features and in so doing have raised important issues.

Contributors PDP and PGC contributed equally to this editorial.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

Thorax 2012;**67**:380–382.
doi:10.1136/thoraxjnl-2012-201769

REFERENCES

1. **Martinez C,** Chen Y-H, Westgate PM, *et al*. Relationship between quantitative CT metrics andhealth status and BODE in chronic obstructive pulmonary disease. *Thorax* 2012:**67**;399–406.
2. **Celli BR,** Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:1005–12.
3. **Jones PW,** Quirk FH, Baveystock CM. The St. George's respiratory questionnaire. *Respir Med* 1991;**85**(Suppl B):25–31.
4. **Burrows B,** Bloom JW, Traver GA, *et al*. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med* 1987;**317**:1309–14.
5. **Nakano Y,** Muro S, Sakai H, *et al*. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;**162**:1102–8.
6. **Patel BD,** Coxson HO, Pillai SG, *et al*; International COPD Genetics Network. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;**178**:500–5.
7. **Yuan R,** Hogg JC, Paré PD, *et al*. Prediction of the rate of decline in FEV(1) in smokers using quantitative Computed Tomography. *Thorax* 2009;**64**:944–9.
8. **Bergin C,** Müller N, Nichols DM, *et al*. The diagnosis of emphysema. A computed tomographic-pathologic correlation. *Am Rev Respir Dis* 1986;**133**:541–6.
9. **Bankier AA,** De Maertelaer V, Keyzer C, *et al*. Pulmonary emphysema: subjective visual grading versus objective quantification with macroscopic morphometry and thin-section CT densitometry. *Radiology* 1999;**211**:851–8.
10. **Gevenois PA,** de Maertelaer V, De Vuyst P, *et al*. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;**152**:653–7.
11. **Kuwano K,** Matsuba K, Ikeda T, *et al*. The diagnosis of mild emphysema. Correlation of computed tomography and pathology scores. *Am Rev Respir Dis* 1990;**141**:169–78.
12. **Nakano Y,** Wong JC, de Jong PA, *et al*. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med* 2005;**171**:142–6.
13. **Mets OM,** Murphy K, Zanen P, *et al*. The relationship between lung function impairment and quantitative computed tomography in chronic obstructive pulmonary disease. *Eur Radiol* 2012;**22**:120–8.
14. **Grydeland TB,** Thorsen E, Dirksen A, *et al*. Quantitative CT measures of emphysema and airway wall thickness are related to D(L)CO. *Respir Med* 2011;**105**:343–51.
15. **Grydeland TB,** Dirksen A, Coxson HO, *et al*. Quantitative computed tomography measures of emphysema and airway wall thickness are related to respiratory symptoms. *Am J Respir Crit Care Med* 2010;**181**:353–9.
16. **Han MK,** Bartholmai B, Liu LX, *et al*. Clinical significance of radiologic characterizations in COPD. *COPD* 2009;**6**:459–67.
17. **Gietema HA,** Müller NL, Fauerbach PV, *et al*; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators. Quantifying the extent of emphysema: factors associated with radiologists' estimations and quantitative indices of emphysema severity using the ECLIPSE cohort. *Acad Radiol* 2011;**18**:661–71.
18. **Diaz AA,** Bartholmai B, San José Estépar R. Relationship of emphysema and airway disease assessed by CT to exercise capacity in COPD. *Respir Med* 2010;**104**:1145–51.
19. **Lee YK,** Oh YM, Lee JH, *et al*; KOLD Study Group. Quantitative assessment of emphysema, air trapping and airway thickening on computed tomography. *Lung* 2008;**186**:157–65.
20. **Ogawa E,** Nakano Y, Ohara T, *et al*. Body mass index in male patients with COPD: correlation with low attenuation areas on CT. *Thorax* 2009;**64**:20–5.
21. **Camp PG,** Coxson HO, Levy RD, *et al*. Sex differences in emphysema and airway disease in smokers. *Chest* 2009;**136**:1480–8.
22. **McDonough JE,** Yuan R, Suzuki M, *et al*. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011;**365**:1567–75.

Hot off the breath: 'I've a cost for'—the 64 million dollar question

Andrew Bush,[1] Nicholas J Simmonds[2]

On 12 January 2012, the US Food and Drug Administration (FDA) licensed Ivacaftor for use in patients with cystic fibrosis (CF) aged 6 years and over, who carry at least one copy of the class 111 mutation G551D. The cost per patient year in the USA will be a staggering US $294 000. Given that patients with G551D account for around 5% of the total CF population, and assuming that the price will be similar in the UK, if these patients are to receive this medication, there will be a hole in someone's budget to the extent of £60 million, because the one absolute certainty is that the government will not be making any more money available to cover the costs of this medication. To give context—the total national budget for CF care is of the order of £110 million. This is certainly a 'wow-factor' price; is it a wow-factor medication? What are the ethics of having a 50% hike in the CF drug budget driven by 5% of the population? And where do we go from here?

The history of CF treatment has been by any standards a major success story. Median survival has risen from less than a year in 1938 to a predicted value for current newborns of around 50 years.[1] This has arisen from advances in the multidisciplinary treatment of the condition, and latterly with earlier diagnosis through newborn screening. Although standard treatment is increasingly successful, it leads to considerable burdens on the patients and their families, and largely comprises fire-fighting, namely treating the downstream consequences of the CF transmembrane regulator (CFTR) gene dysfunction, such as airway infection. However, Ivacaftor represents a stupendous paradigm shift, the

[1]Department of Paediatric Respiratory Medicine, Imperial College and Royal Brompton Harefield NHS Foundation Trust, Sydney Street, London, UK; [2]Department of Cystic Fibrosis, Imperial College and Royal Brompton Harefield NHS Foundation Trust, Sydney Street, London, UK

Correspondence to Professor Andrew Bush, Department of Paediatric Respiratory Medicine, Imperial College and Royal Brompton Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK; a.bush@imperial.ac.uk

first licensed CF medication actually addressing the primary consequences of CFTR dysfunction and therefore potentially truly disease modifying. Table 1 summarises the different classes of mutations, their consequences and the potential gene class specific therapies. Clearly these sorts of approaches, correcting the basic defect before any downstream consequences appear, must be the future goals of CF treatment.

There are a number of class 111 mutations, of which the commonest is G551D. The mutated CFTR reaches its normal billet on the apical cell membrane, but the ion channel has a reduced open time. Ivacaftor acts directly to increase channel opening, thus correcting at least one of the abnormal functions of G551D CFTR. It was first developed as the result of a highly expensive programme, screening millions of compounds for in vitro efficacy, without bothering too much about the nuances of the exact molecular mechanisms, which to this day are undetermined. A recent phase III study[2] (in <200 patients) showed that over 48 weeks, the active compound led to an increase in forced expiratory volume in 1 s (FEV_1) of 10.6%; a 55% reduction in CF lung attacks; improvement in quality of life; a weight gain of 2.7 kg more than placebo; and staggeringly, a halving of sweat chloride values, a reduction of a magnitude never approached by any other medication. There were no increased adverse effects compared with placebo. Clearly, if Ivacaftor was cheap and of proven safety, everyone with CF and at least one copy of G551D would want a therapeutic trial. At US$294 000 a year, and given neither presupposition is known to be correct, should this happen, and if so, how? Patients with severe disease and limited therapeutic options are understandably already requesting a trial. They may benefit the least due to irreversible downstream damage but is it fair to deny them the opportunity? However, patients identified with G551D at newborn screening may benefit the most over their lifetime, including, theoretically, a reduction in the need for other long-term treatments, but is taking the drug over decades safe and is it financially viable?

In these days of monstrously inflated bonuses for bankers and civil servants, it is worth considering whether the fiscal cost is justified. Ivacaftor was developed as a result of an enormously expensive process, and the bulk of the risk was born by Vertex Pharmaceuticals (Cambridge, Massachusetts, USA), the company making the medication. Their share prices rose by 50% in the aftermath of the FDA licensing the product. It is right that they should recoup their costs, and right that a profit-making company should be allowed to make a profit, otherwise they will abandon the field to academia and governments, neither of which would have been likely to produce the present result. Furthermore, in the USA the company is endeavouring to ensure that poverty is not a barrier to receiving the medication, which is commendable. However, what is unclear to us is exactly what business model has been used to calculate costs, and how big the profits will actually be. Is this legitimate profit or a huge gravy train powered by the hopes and fears of people with a life-shortening illness? People are justly suspicious when colossal sums of money change hands without proper clarity and justification, and more openness from Vertex Pharmaceuticals is needed.

So, is this a 'wow-factor' medication? The two wow factors are that it is active at the level of the basic mutation, rather than downstream, and it has halved sweat chloride, an effect never seen before with any other intervention. However, does this translate at the present time to a real clinical benefit? The changes in spirometry, CF lung attacks and weight are similar in magnitude to the effects obtained with rhDNase,[3] hypertonic saline[4] and azithromycin,[5 6] at a fraction of the cost. Furthermore, CFTR is a multifunctional protein, and there is at least some evidence that CF lung disease relates to loss of regulation of the sodium transporter ENaC by CFTR, rather than being due to chloride transport abnormalities.[7 8] The change in FEV_1 is certainly encouraging, but there are many unknowns; does Ivacaftor affect the airway microbiome and airway inflammation, and in what way? How safe is it? A serious adverse event with a frequency as high as 1% would have been missed by the present study.[2] The key question that all patients want to know is, will this increase my life expectancy? We simply do not know, and unlike cancer drugs, we are not able to balance out months of extension of life versus cost, nor are we ever likely to be able to do so.

Is buying Ivacaftor at this colossal price worthwhile? It has been argued elsewhere that rationing is inevitable under any healthcare system,[9] given the ever-increasing cost and complexity of medications and therapeutic interventions. For the price of a year of Ivacaftor, we could employ perhaps four specialist physiotherapists, nurses and dieticians. The asthma literature is very clear that increasing interactions between patients and professionals, attention to detail and getting the basics right leads to big improvements in outcomes.[10 11] Would a patient with G551D do better with a full-time personal CF nurse than with Ivacaftor? Perhaps commencing Ivacaftor early enough may offset some of this cost by reducing the overall burden of treatment, but it is difficult to see beyond a huge financial burden even if no other CF treatment was needed (highly unlikely to be the case).

Overall, despite the negative comments above, the data suggest that we should explore the use of Ivacaftor if we possibly can. If ever there was a time when this should be done in a protocolised manner, it is now. Merely adding Ivacaftor on the end of the prescription list, without making a detailed efficacy and safety assessment, is unwarranted. We suggest that there should be a pre-trial run-in period of at least 3 months, with every effort made to optimise therapy, perhaps using aspects of the protocol that we have advocated for 'challenging CF'.[12] There should be mandatory, protocolised follow-up visits at least monthly initially, with measurements of spirometry at least, bacteriology, and relevant biomarkers. Surely this should be the case even for those given access to Ivacaftor

Table 1 Classes of CFTR mutations, their effects and potential treatments

Class number	Consequence	Exemplar genotype	Potential therapies
Class I	No CFTR synthesis (premature stop codon)	G542X	PTC_{124}
Class II	CFTR processed incorrectly and does not reach apical cell membrane	DF_{508}	VX-809
Class III	CFTR reaches apical membrane, but channel regulation is abnormal	G551D	VX-770
Class IV	CFTR reaches apical membrane, but channel open time is reduced	R334W	
Class V	Reduced CFTR synthesis	R117H	
Class VI	CFTR reaches apical cell membrane, but has a shortened half life due to more rapid turnover	1811+1.6kbA>G	

CFTR, cystic fibrosis transmembrane regulator.

on compassionate grounds. Subgroups could be tested in a more sophisticated manner, for example, using transepithelial potential differences. An obvious and important question is whether twice daily treatment is needed. This question could easily be addressed in a crossover or parallel group study built into the introduction of Ivacaftor. Is it unreasonable to make participating in randomised controlled trials of treatment, when there is genuine uncertainty, a pre-condition of receiving this medication? This sort of strategy would allow the collection of important data, including safety, and allow us to refine the use of the medication.

The issue of expensive medications for chronic conditions will not go away, and indeed will get worse. If, as seems likely, Ivacaftor is efficacious in other CFTR mutations, or in other diseases characterised by CFTR dysfunction (which may even include chronic obstructive pulmonary disease[13]!), how will this be funded? Trials are underway investigating compounds for other mutation classes, including the most common allele, ΔF508.[14] As 50% of patients with CF in the UK are homozygous for this mutation, the cost implications are potentially staggering. Will the price come down at all? The immediate future looks likely to be characterised by fights between desperate patients with CF with very high hopes, and equally desperate regulators already coping with potential NHS financial meltdown (aka 'efficiency savings', those popular Coalition weasel words). The regulators will probably say (rightly) that the 10% increase in FEV_1 is at a price many fold greater than that of standard therapies[3–6] which have the same effects (correct), and that no-one has shown that a fall in sweat chloride has translated into a survival benefit (also correct). It seems likely that very few patients, and only the sickest, will have a chance to trial Ivacaftor. But a wake-up call for Vertex Pharmaceuticals is that, if Ivacaftor is beyond the nation's pocket for well infants with CF, it could be argued that the planned further testing of the medication in this group in the UK is unethical, and contrary to the Helsinki convention, because they will never benefit from it. And the same will be said about other genotype-specific therapies in the pipeline unless guarantees about affordability can be given. (Did the very honourable clinicians investigating Ivacaftor realise that the price would be as high as quoted? And would they have been just as keen to organise trials if they had known?) All concerned must be heartily congratulated on the production of a designer medication, targeting a basic gene dysfunction, with very promising results. However, for those who have to balance the books, this is a loud and strident wake-up call.

Contributors AB conceived the article and wrote the first draft, NS reviewed and edited it, and both take full responsibility for the final version.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

Published Online First 10 March 2012

Thorax 2012;**67**:382–384.
doi:10.1136/thoraxjnl-2012-201798

REFERENCES

1. **Dodge JA,** Lewis PA, Stanton M, *et al*. Cystic fibrosis mortality and survival in the UK: 1947–2003. *Eur Respir J* 2007;**29**:522–6.
2. **Accurso FJ,** Rowe SM, Clancy JP, *et al*. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010;**363**:1991–2003.
3. **Fuchs HJ,** Borowitz DS, Christiansen DH, *et al*. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994;**331**:637–42.
4. **Elkins MR,** Robinson M, Rose BR, *et al*; National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;**354**:229–40.
5. **Equi A,** Balfour-Lynn IM, Bush A, *et al*. Long term azithromycin in children with cystic fibrosis: a randomized, placebo-controlled crossover trial. *Lancet* 2002;**360**:978–84.
6. **Saiman L,** Anstead M, Mayer-Hamblett N, *et al*; AZ0004 Azithromycin Study Group. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2010;**303**:1707–15.
7. **Knowles M,** Gatzy J, Boucher R. Increased bioelectric potential difference across respiratory epithelia in cystic fibrosis. *N Engl J Med* 1981;**305**:1489–95.
8. **Mall M,** Grubb BR, Harkema JR, *et al*. Increased airway epithelial Na+ absorption produces cystic fibrosis-like lung disease in mice. *Nat Med* 2004;**10**:487–93.
9. **Bush A,** Lenney W, Spencer D, *et al*. Not NICE: a better way forward? *Arch Dis Child* 2011;**96**:907–8.
10. **Szefler SJ,** Mitchell H, Sorkness CA, *et al*. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;**372**:1065–72.
11. **Bush A,** Saglani S. Management of severe asthma in children. *Lancet* 2010;**376**:814–25.
12. **Bush A.** Up the cystic fibrosis pulmonary creek in a barbed wire canoe. *Pediatr Pulmonol* 2011;(Supp 34):118–19.
13. **Cantin AM,** Hanrahan JW, Bilodeau G, *et al*. Cystic fibrosis transmembrane conductance regulator function is suppressed in cigarette smokers. *Am J Respir Crit Care Med* 2006;**173**:1139–44.
14. **Clancy JP,** Rowe SM, Accurso FJ, *et al*. Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation. *Thorax* 2012;**67**:12–18.