group may be an issue, demonstrating that smokers are less likely to participate in lung cancer screening programmes than ex-smokers.[18] Patel et al[3] reported on the acceptance of annual CT scans, sputum cytology and bronchoscopy surveillance in smokers and ex-smokers with mild to moderate chronic obstructive pulmonary disease (COPD) who had already consented to take part in the Lung-SEARCH trial. Although the majority of participants found the interventions acceptable, there was evidence of doubt about the value of early detection, particularly in older patients. They also found evidence to support the hypothesis that worry is a factor that deters people from participating in screening. Such considerations clearly need to be built in to cost-effectiveness analyses of any national screening programme.

While it is vital we continue to push for effective screening programmes, those that use current technology are likely to be of limited benefit, costly and not likely to be implemented in the near future, at least in the UK. Strenuous efforts are also needed to find better screening methods that can eventually supersede CT scanning. We simply cannot wait and have to trial—and carefully evaluate—a variety of approaches to promote earlier diagnosis in patients who already have symptoms of lung cancer.

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Airway disease and emphysema on CT: not just phenotypes of lung pathology

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In this issue of the journal, Martinez et al[1] examined the relationships between quantitative CT (QCT) parameters of emphysema, airway wall remodelling and airway narrowing and composite clinical and physiological indices of chronic obstructive pulmonary disease (COPD), the BODE index[2] and the St George's Respiratory Questionnaire (SGRQ).[3] BODE stands for Body mass index (BMI), airflow Obstruction, Dyspnoea and Exercise capacity.

Not surprisingly, these QCT estimates of pathological changes were related to measures of clinical impact. More interestingly, the authors found that there were differences in the strength of the associations between measures of emphysema and airway disease and the composite indices. Measures of emphysema were more closely related with the BODE index while the airway wall abnormalities were better predictors of the SGRQ.

While it has long been recognised that there is a spectrum of changes in the airways and parenchyma in COPD,[4] the separation of the airway predominant phenotype from the parenchymal predominant phenotype was largely limited to the autopsy room until the advent of CT. CT has confirmed that some patients have airflow obstruction with little emphysema while others have predominant emphysema with little airway disease. Such individuals form the extremes while the majority of patients have various combinations of airway disease and emphysema.[5] In addition, there is evidence that the predominant pattern is to some extent familial[6] and is associated with different rates of decline of lung function.[7] The presence of airway disease and emphysema on CT can be assessed qualitatively or quantitatively. The power

of the quantitative indices, as used in the present study, is that they are completely reproducible provided that similar scanners, imaging parameters and software are used. The hope is that the separate mechanisms that lead to these pathological changes in COPD can be individually targeted by specific therapy and followed non-invasively with repeat imaging.

Since CT allows a measure of anatomic derangement, its validation has largely been by comparison with pathological estimates of emphysema and airway disease. Many studies have shown that CT provides an accurate estimate of the extent and severity of emphysema,[8–11] although only a few have compared CT measures of airway lumen narrowing and wall remodelling with pathological changes.[12]

More recently, there have been a number of studies in which quantitative estimates of CT phenotypes have been compared with clinical phenotypes, measures of lung function and symptoms.[13–19] The reasoning is that, in the absence of a structural gold standard, lung function and symptoms can act as surrogates for test validity. If CT can accurately assess anatomic derangement of lung structure and if structural damage correlates with lung function and symptoms, then there should be good relationships between the CT measures and these clinical features. In general, the results of these studies have been reasonably robust, supporting the idea that CT can be used to grade the clinical as well as the pathological severity of COPD. Martinez et al[1] have added a new dimension to the puzzle. By comparing the CT measures of emphysema and airway disease with the SGRQ and the BODE index they have found that specific 'pathological' features are more closely related to certain combinations of clinical features.

To understand their results more fully we need to examine what goes into determining the SGRQ and BODE scores. The SGRQ (http://www.healthstatus.sgul.ac.uk/sgrq-downloads/sgrq-c-downloads) is a 50-item questionnaire that assesses respiratory symptoms, physical activity and psychosocial well-being. In addition to providing a total score, scores for the three domains can be determined independently. The SGRQ correlates significantly with other measures of disease activity such as cough, dyspnoea, 6-minute walk distance (6MWD) and forced expiratory volume in one second (FEV1) as well as measures of general health status such as the SF36. The BODE index is more complex and was developed to predict risk of death in COPD. It is

derived from the combination of a measure of nutritional status (BMI), the degree of airflow obstruction (FEV1 % predicted), the severity of dyspnoea (Modified Medical Research Council (MMRC) dyspnoea scale), and the 6MWD.

Fortunately Martinez et al,[1] in their supplementary data, also report the relationship between QCT measures and the components of the SGRQ and BODE index so that we can appreciate which were the primary drivers for the relationships. Interestingly, all the measures which contribute to the BODE index were significantly related (by univariate Spearman correlation) to both emphysema score and Pi10 as a marker of airway remodelling. However, the relationship between emphysema and FEV1 % predicted was the strongest of the four components of the BODE (r=−0.54, p<0.001). Nakano et al[5] compared QCT measures of emphysema and airway wall remodelling with FEV1 % predicted and also found that there was a substantially better correlation with emphysema than with airway wall parameters. CT emphysema was also significantly related to BMI with lower BMI in subjects who had worse emphysema (r=−0.27, p<0.001). It is well known that for equal degrees of airflow obstruction, individuals who have worse emphysema have lower BMI (or persons with low BMI have worse emphysema—the direction of this relationship is unclear).[20] Thus the stronger relationship of BODE with QCT emphysema could be driven by these two factors. However, the emphysema score was also related to the other two components of the BODE, the 6MWD and the MMRC dyspnoea index. Diaz et al[18] have examined the relationship between 6MWD and QCT-defined measures of emphysema and airway disease and found that emphysema was better correlated with the 6MWD than airway remodelling parameters. In the present study, the strength of the association, as assessed by r values was slightly stronger for Pi10 (r=−0.33, p<0.001) than for emphysema (r=−0.24, p<0.001). Interestingly, the factor that may contribute to the weaker relationship between the BODE index and airway scores is the completely opposite, but significant, relationship between BMI and airway remodelling (Pi10). Individuals who have thicker airways have significantly greater BMI (r=0.17, p<0.001). This positive relationship between measures of airway wall remodelling and BMI (or body weight) has been previously reported by Lee et al[19] and Camp et al,[21] but its cause and significance is unknown.

More surprising to us was the closer relationship of airway wall parameters to respiratory health status as measured by the SGRQ. Why would respiratory health status measures be more closely related to airway pathology than emphysema? Previous studies have reported an association of measures of altered airway dimensions with *symptoms* such as cough, sputum, wheeze and dyspnoea. For example, Lee et al[19] reported that CT-measured wall area and wall area per cent correlated with dyspnoea as measured with the MMRC, whereas the CT measure of emphysema did not. In supplementary table 2 Martinez et al[1] used multivariate analysis to determine the independent contribution of the three SGRQ domains to the relationships with airway remodelling and emphysema. All three domains—symptoms, impacts and activity—were significantly associated with airway wall remodelling (Pi10). On the other hand, quantitative emphysema was only associated with the activity score and unrelated to symptoms and impacts. It is understandable that the symptoms of cough, sputum and wheeze are more closely related to airway morphology than to emphysema. The relationship of emphysema to activity is also logical since dynamic hyperinflation during exercise is an expected consequence of the loss of lung recoil that is characteristic of emphysema. What is unclear is why the impacts domain, which measures psychosocial impacts of COPD (including questions on panic during symptoms, or feeling one is a burden to friends or family), relates to airway disease measures but not to emphysema. We are unaware of any study that has probed the relationships between phenotypes of COPD and psychosocial functioning, but if the relationship between the airway measurements and the SGRQ impacts component can be confirmed, this could lead to an intriguing area of investigation.

It is especially impressive that airway measurements correlated so well with the SGRQ since the airways that are assessed using high resolution CT are relatively large airways which are not the site of major airway resistance in COPD. The fact that large airway dimensions are related to respiratory health status as measured by the SGRQ supports the suggestion that airway wall remodelling in large airways is a reflection of generalised airway narrowing and/or obliteration as has been suggested by Nakano et al.[12] McDonough et al[22] have recently shown that an early lesion in COPD is the loss of terminal bronchioles. Perhaps there is a relationship between this

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.

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

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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