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Prevalence and radiological outcomes of lung nodules in alpha 1-antitrypsin deficiency

Deepak R. Subramanian [a], Ross Edgar [b], Helen Ward [b], David G. Parr [a], Robert A. Stockley [b,*]

[a] *Department of Respiratory Medicine, University Hospitals Coventry and Warwickshire, Clifford Bridge Road, Coventry, CV2 2DX, UK*
[b] *Lung Function and Sleep Department, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham B15 2WB, UK*

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Summary
Pulmonary nodules are a frequent incidental finding on computed tomography (CT) imaging. This study sought to investigate the prevalence and radiological outcomes of lung nodules in patients with alpha 1-antitrypsin deficiency (AATD), and determine any association with systemic inflammation and disease progression.

A retrospective study was conducted using thoracic CT imaging from 494 patients on the AATD UK registry. Patients were categorised according to radiological and clinical outcome, and comparisons made with respect to baseline demographics, lung function and high-sensitivity CRP (hs-CRP).

Sixty-four patients (13%) had a nodule present on baseline imaging, and in total 132 patients (27%) had a nodule on at least one scan, of which 2 were malignant. The presence of a lung nodule was associated with significantly lower baseline percent predicted forced expiratory volume in 1 s (FEV_1 % predicted) ($p = 0.037$) and percent predicted transfer coefficient of the lung for carbon monoxide (Kco % predicted, $p = 0.001$). Patients with self-resolving nodules had higher baseline hs-CRP concentrations ($p < 0.01$) and more rapid decline in Kco ($p = 0.03$) compared to patients in whom no nodules were observed.

The prevalence of 'incidental' pulmonary nodules on CT imaging in patients with AATD was 13%. Self-resolving pulmonary nodules were associated with increased systemic inflammation and progression of emphysema and may therefore reflect an important component of emphysema pathogenesis or a marker of emphysema.

* Corresponding author. Tel.: +44 121 371 3885; fax: +44 121 371 3887.
E-mail address: r.a.stockley@bham.ac.uk (R.A. Stockley).

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Introduction

Solitary pulmonary nodules identified on thoracic CT imaging are defined as rounded opacities, smaller than 3 cm in diameter and surrounded by lung parenchyma.[1] Population-based CT studies screening for lung cancer demonstrate a prevalence ranging from 5 to 60%[2] and they are also a frequent finding in routine clinical imaging.[3] Despite a low risk of malignancy[4] they require further investigation, and interval CT scanning is advised by the Fleischner Society[5] for up to 2 years depending on features such as the size of the lesion and clinical risk factors.

Alpha 1-antitrypsin deficiency (AATD) is a hereditary COPD phenotype, associated with a predisposition to developing early onset emphysema that is traditionally believed to arise from the relatively unopposed action of neutrophil elastase and increased neutrophilic inflammation.[6] AATD-associated emphysema is predominantly panacinar and distributed in the basal region of the lung, in comparison to usual COPD where emphysema is classically centrilobular and distributed in the apical region.[7,8] The frequency and clinical significance of pulmonary nodules in patients with AATD is unknown, and consequently, we undertook a retrospective study of CT imaging in patients with AATD on the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) UK registry.

The aim of the study was to determine both the prevalence and radiological outcomes of pulmonary nodules identified on CT scanning in patients with AATD, to enable comparison with published CT screening studies. In addition, we sought to assess whether the presence of non-malignant nodules were associated with increased systemic inflammation and disease progression.

Materials and methods

Study subjects

Subjects with the PiZ phenotype and who had at least one thoracic CT scan at our centre between November 1996 and September 2009 were selected for this retrospective study. All patients had given written informed consent and the programme was approved by the South Birmingham Research and Ethics Committee. Alpha 1-antitrypsin level and phenotype were verified by immunoassay and isoelectric focussing, respectively, using a dried finger prick blood spot (Heredilab; Salt Lake City, UT).

Study design

Clinical records, including radiology reports and, where applicable, histopathology results, were reviewed for all subjects. Initially patients were classified into a 'nodule present' group, if a nodule was recorded in any scan, and 'nodule absent' group if no nodules were detected from all CT imaging. Patients were subsequently classified into the following four groups according to radiological and clinical outcome: A resolved/resolving nodule, B-unchanged nodule, C-malignant nodule and D-no nodule on at least 3 CT scans.

Comparisons between the groups were performed with respect to baseline demographics, baseline lung function, decline in forced expiratory volume in 1 s (FEV_1) and transfer coefficient of the lung for carbon monoxide (Kco), and plasma high-sensitivity CRP (hs-CRP). Mean hs-CRP comparisons were made before and after the exclusion of those patients with known coexisting inflammatory disease (e.g. rheumatoid arthritis) and those experiencing an exacerbation within 6 weeks of blood sampling.

The proportion of subjects with a history of a resolved/resolving nodule (group A) was compared in patients with 'no FEV_1 decline' over the study period ($\leq$0 ml/year) and a 'fast FEV_1 decline' group (decline $\geq$ 100 ml/year). Similarly, a comparison was performed between a 'no Kco decline' group ($\leq$0 mmol/min/L/year) and 'fast Kco decline' group (decline $\geq$ 0.06 mmol/min/L/year).

Methods

Patients were scanned at full inspiration without the use of intravascular contrast, as previously described.[7,9] Further imaging was performed in those patients with a lung nodule at the discretion of the clinican or multi-disciplinary team according to clinical need. ^{18}Fluorodeoxyglucose Positron Emission Tomograpy—Computed Tomograpy (^{18}FDG PET-CT) was performed with a General Electric Discovery STE PET-CT scanner (incorporating a Lightspeed 8-slice CT scanner) in one patient as part of another study but in whom an unsuspected nodule was also seen during the investigation and, in a further two patients, where diagnostic uncertainty existed. All imaging was assessed by a single thoracic radiologist and the presence of non-calcified pulmonary nodules, rounded pulmonary opacification or nodular infiltrates were recorded. Additional data on nodule size and smoking history were obtained from radiology reports and clinical records.

Post-bronchodilator spirometry (CareFusion; San Diego, CA) and carbon monoxide gas transfer (either on Benchmark; P.K. Morgan; Kent, UK or Jaeger Master Screen PFT; CareFusion; San Diego, CA) were measured according to the Association of Respiratory Technicians and Physiologists/British Thoracic Society) guidelines.[10] A minimum of 3 measurements over at least 3 years were used to determine decline in FEV_1 and Kco by linear regression. Normal values for FEV_1 and Kco were derived from the European Community for Coal and Steel normal regression equations[11] and Cotes equation respectively.[12]

Plasma sampling for high-sensitivity C-reactive protein (hs-CRP) measurements were available in a subset of patients, and concentrations were determined using a commercial enzyme-linked immunosorbent assay (Quantikine; R&D Systems Inc; Minneapolis, MN).

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc.; Chicago, IL), with statistical significance defined as a p value $\leq$ 0.05. The Chi-square test was used to compare proportions between groups, the Student's t test for continuous normally distributed variables and the

Mann–Whitney *U* test for nonparametric analysis. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive value for hs-CRP to recognise nodules which subsequently resolved. Pearson correlations were undertaken to compare continuous variables.

Results

CT imaging was performed on 494 patients and, out of a total of 1280 scans, a nodule was identified in 269 (21%). Sixty-four patients (13%) had a nodule present on the baseline imaging, and in total 132 patients (27%) were noted to have a nodule on at least one CT scan. Patient characteristics at baseline according to the presence or absence of a nodule are shown in Table 1. Pulmonary nodules were more frequently observed in smokers and ex-smoker compared to never-smokers ($p = 0.014$). The presence of a nodule was associated lower baseline percent predicted FEV_1 ($p = 0.037$) and percent predicted Kco ($p = 0.001$).

Sixty-one percent of patients with a nodule ($n = 80$) were assigned to group A (resolved or resolving nodules, see Fig. 1), and a further 27% ($n = 36$) to group B (stable radiological appearance). In the 2 patients in group C, the nodules were shown to be malignant on histopathology of tissue biopsies (1-bronchial adenocarcinoma, 1-non-hodgkin's lymphoma). Nodule size was greater than 5 mm in 54 patients, including the 2 patients with malignant disease. The 14 patients who were found to have a nodule and subsequently withdrew from the programme, were advised to undergo follow up imaging at a local centre In group D, no nodules were detected at any time in 95 patients who had undergone at least 3 scans.

Comparison between groups A and D (see Table 2) showed that there were no statistically significant differences with respect to age ($p = 0.135$), smoking history ($p = 0.108$), baseline FEV_1 ($p = 0.180$), FEV_1 decline ($p = 0.851$) or Kco decline ($p = 0.355$). However, group A had significantly lower baseline Kco ($p = 0.012$) and higher hs-CRP concentration ($p = 0.004$; see Fig. 2) than group D.

No significant differences were observed between the proportion of patients with a history of a resolved/resolving nodule (i.e. from group A) in the 'fast FEV_1 decline' group ($n = 52$) and the 'slow FEV_1 decline' group ($n = 51$; 19.6% versus 15.4% respectively; $p = 0.573$). There was a greater proportion of patients from group A in the 'fast Kco decline' group ($n = 54$) when compared with the group with 'slow Kco decline' ($n = 57$; 35.2% versus 17.5% respectively; $p = 0.034$). A significant correlation between hs-CRP concentration and Kco decline was observed ($n = 191$, $r = -0.147$, $p = 0.04$).

Positron Emission Tomography-CT (PET-CT) imaging was performed in 3 patients, and in each case the nodules were shown to be metabolically active, although resolution occurred without therapeutic intervention.

Fig. 3 depicts the ROC curve for hs-CRP in predicting which nodules subsequently resolved. Hs-CRP data was available in 230 patients and included 50 cases of a resolved or resolving nodule. The area under the curve was 0.619 (95% confidence intervals, 0.533–0.705; $p = 0.01$).

Discussion

This retrospective study has shown that pulmonary nodules are commonly observed in patients with AATD, and that the majority of these are non-malignant. In many patients the nodules remained static with time but patients with a resolving nodule on serial CT imaging were those with more severe lung disease, higher plasma hs-CRP concentration and an accelerated physiological progression, when assessed by decline in gas transfer.

CT-based screening studies for lung cancer have provided data on the prevalence of pulmonary nodules and malignant lesions in asymptomatic subjects[4,13] but there have been no previous studies which have reported the prevalence of pulmonary nodules in patients with usual COPD or, as in the current cohort, in subjects with AATD. The Early Lung Cancer Action Project[14] included 1000 asymptomatic smokers or ex-smokers, above the age of 60 and with at least a 10 pack year smoking history. Twenty three percent of subjects were found to have a non-calcified nodule after baseline screening, which was comparable to the results from a recent Canadian Study.[15] A lower nodule frequency of 5% has been reported in a further study, in which 54% of subjects were never-smokers.[16] Collectively, these data suggest an association between the presence of lung nodules and smoking, a finding which was

Table 1 Comparison of patient characteristics and lung physiology at baseline in the 'nodule absent' and 'nodule present' groups ($n = 494$).

	Nodule present	Nodule absent	*p* Value
Number (% of total)	132 (27)	362 (73)	
Number of Males (%)	90 (68)	211 (58)	0.046*
Age, years	52.0 (9.8)	50.0 (10.4)	0.066
Smoker or Ex-smoker, %	84.0	72.7	0.014*
Pack year history[a]	19.8 (12.5–27.9)	19.8 (10.0–27.0)	0.373
Baseline FEV_1, L[a]	1.37 (0.98–1.81)	1.48 (1.00–2.27)	0.131
Baseline FEV_1, % predicted[a]	42.4 (32.7–57.2)	49.1 (33.0–70.7)	0.037*
Baseline Kco, mmol/min/kPa/L	0.96 (0.33)	1.10 (0.39)	0.007*
Baseline Kco, % predicted	61.2 (19.93)	67.5 (2.39)	0.001*

Data are presented as mean (SD) unless highlighted. The asterisk indicates significant difference between groups.
[a] Expressed as median (interquartile range).

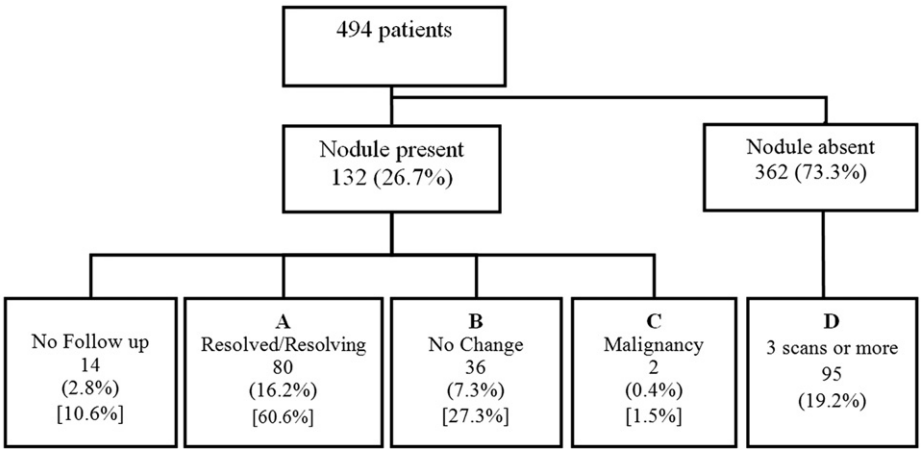

Figure 1 Flow diagram showing the outcomes of nodules in AATD patients undergoing thoracic CT scanning. Data are presented as *n* (% of scanned patients); [% of patients with a nodule present].

also observed in the study reported here. In comparison to the screening studies mentioned, our population had a lower mean age and included 22% of never-smokers and, consequently, represented a group with a lower risk of malignancy. Neverthless, the incidence of non-calicified nodules at baseline imaging was 13% and, overall, 27% of subjects had a nodule on at least 1 scan, which represented a significant proportion of patients who conventionally required additional investigations.

In our cohort, a nodule subsequently proven to be malignant was found in only 2 patients and, in both cases, a high clinical suspicion was evident from the initial scan, based on a spiculated appearance that was not evident on non-malignant nodules. In one further patient, an increase in nodule size occurred over 4 months raising the suspicion of malignancy, although subsequent investigations (that included thoracotomy) found no evidence of malignancy. Thus in keeping with previous studies[14,17] we observed a low malignacy rate. Recommendations of the Fleischner Society advise confirmation of nodule stability on serial imaging over at least a 2 year period before categorising the nodule as benign, with some investigators advocating an even longer period of follow up.[18] The increased cost to health care services, patient anxiety, and the additional radiation exposure (which may itself lead to an increased risk of cancer[19]) are factors which have led some authors to express concerns regarding the benefits of repeatedly imaging indeterminate small nodules, whilst the reported risk of malignancy is low.[20,21] Alternatively, others favour the early use of videothoracoscopic surgery in patients with good respiratory function[22,23] to achieve a definitive diagnosis, and thereby avoiding serial imaging.

The current study did not identify any further malignancies through the use of serial CT imaging and clinical follow up. This suggests not only that such lesions are common but that the application of Fleischner Society recommendations for serial scans or surgical removal of smooth nodules is likely to be unnecessary in the current patient group, especially in subjects of a young age or never-smokers. Detailed radiological characterisation was not performed in this study, however, features reported to favour a benign lesion include calcification within the nodule, a smooth edge contour (as in all but 2 of our observed nodules) and a lack of enhancement following the

Table 2 Comparison of patient characteristics and lung physiology in groups A (resolved/resolving nodule) and D (no nodule in at least 3 scans).

	Group A	Group D	*p* Value
Number	80	95	
Males (%)	59 (74)	60 (63)	0.135
Age, years	51.7 (9.3)	49.9 (8.5)	0.216
Smokers or Ex-smoker (%)	84.0	73.7	0.108
Pack year history[a]	20.4 (11.6—29.0)	23.0 (13.5—29.5)	0.475
Baseline FEV_1, L[a]	1.36 (0.97—1.81)	1.54 (1.06—2.18)	0.180
Baseline FEV_1, % predicted [a]	41.2 (31.6—55.9)	46.6 (32.5—69.7)	0.118
Baseline Kco, mmol/min/kPa/L	0.95 (0.31)	1.09 (0.38)	0.012*
Baseline Kco, % predicted	60.6 (19.1)	67.8 (21.8)	0.032*
FEV_1 decline, ml/year	48.8 (53.4)	50.5 (57.5)	0.851
Kco decline, mmol/min/kPa/L/year	0.036 (0.042)	0.030 (0.034)	0.355

Data are presented as mean (SD) unless highlighted. The asterisk indicates significant difference between groups.
[a] Expressed as median (interquartile range).

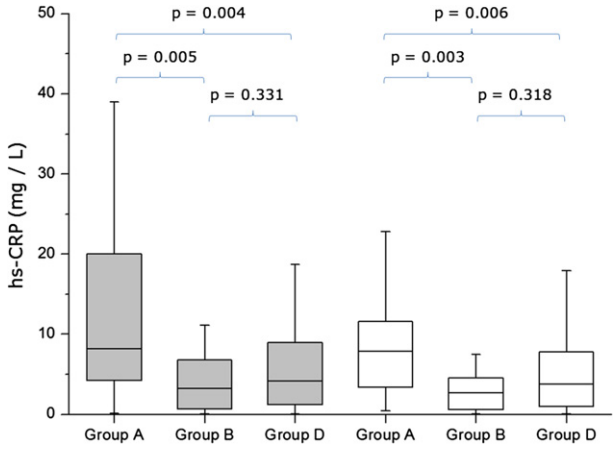

Figure 2 Box plot of hs-CRP levels between patients in groups A, B and D. Before (shaded) and after (unshaded) exclusion of patients with a recent exacerbation or coexisting inflammatory disease. The outer edges of the box plot are 25% and 75% points, the solid line is the median and bars indicate the 1.5-fold of the whole box length, *p* values shown for the comparison between groups (Mann—Whitney *U* test).

administration of intravenous contrast.[24] Spiculated[25] or lobulated[26] contours are more suggestive of a malignancy, as seen in the 2 patients in our study. However, in patients with emphysema, it can be more difficult to distinguish between benign and malignant lesions based solely on CT appearance.[27] Predictive models using multiple radiological and clinical features have been shown to improve the diagnostic accuracy even of experienced radiologists[25,28] and may represent a potential tool for routine clinical practice. The specificity for predicting malignancy in

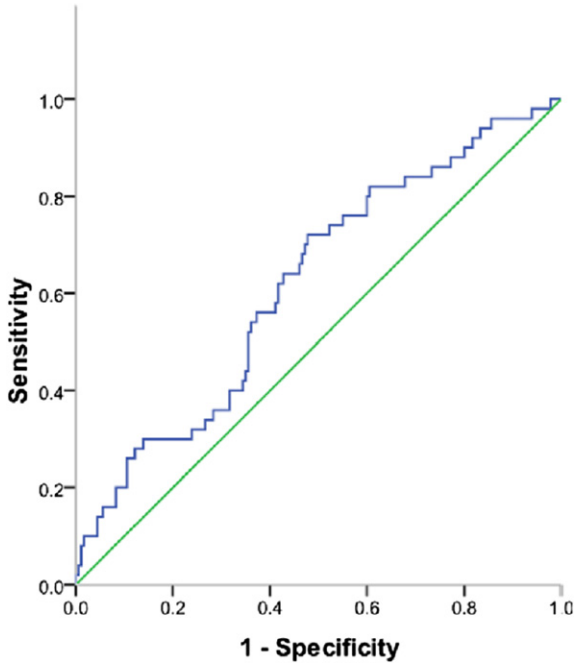

Figure 3 Diagnostic testing of the predictive value of hs-CRP for a resolving nodule by ROC curve.

lesions greater than 7 mm on CT can be increased from 41% to 89%[29] through the supplemental use of PET-CT which therefore has a role some management algorithms.[30] However, even this approach can be misleading as demonstrated in the current study where ^{18}FDG uptake was assessed and shown to be increased in three subjects with a pulmonary nodule, suggestive of malignancy, even though the nodule subsequently resolved in each case.

Whilst the current and previous data indicate that the vast majority of incidental nodules are non-malignant, the cellular composition and clinical significance of these nodules is largely unknown. In studies that have explored nodule causation in unselected populations, it has been shown that 80% are infectious granulomas,[31,32] 10% hamartomas and the remaining 10% are caused by a variety of rarer disorders including non-infectious granulomas and other benign tumours.[33,34] However, it has been proposed that the nodular changes seen on imaging in smokers could be the precursor of emphysema. Remy-Jardin et al.[35] conducted a longitudinal study of 111 volunteers, including 57 persistent smokers. Micronodular abnormalities were present in 19 persistent smokers at baseline imaging, and in 14 cases they increased or were unchanged during the course of the study. In five cases nodules had been replaced by emphysema and, consequently, it was hypothesised that this sequential change may reflect a causal link between localised inflammation and the development of emphysema. In our cohort, resolving lung nodules were more prevalent in patients with evidence of accelerated disease progression, based on contemporaneous Kco decline; however, although Kco and CT densitometry correlate cross-sectionally[36] it was not possible to assess objectively whether there was an association between nodule formation and the subsequent parenchymal destruction as the subsequent scans were performed in a limited and diagnostic manner over a short period and hence were not suitable for quantitative assessment.

Nevertheless, the current study found that all three of the non-malignant-pulmonary nodules which were assessed using PET-CT, showed increased ^{18}FDG uptake, which is suggestive of pulmonary neutrophilic inflammation[37] underlying the pathophysiology of these lesions. Consequently, it is possible that nodule formation may be driven by neutrophilic inflammation and the natural history of nodule resolution is the development of emphysema as proposed in the study of Remy-Jardin et al.[35]

In the current study, the observation that hs-CRP concentration was higher in patients with transient lung nodules supports an inflammatory process and indicates that these patients have greater levels of systemic inflammation and an association between systemic inflammation and the formation of these resolving but 'benign' nodules. However, cross-sectional COPD studies have shown that CRP concentrations are inversely related to lung function,[38] and our finding of an elevated hs-CRP concentration in group A may, therefore, be a reflection of the greater physiological impairment seen in this group. Despite the aforementioned association, the measurement of hs-CRP concentrations in the AATD population was not shown to be a specific clinical marker for the prediction of a resolving nodule and, there is no data to support its' role in monitoring nodule activity

other than in general. However, the observation that hs-CRP concentration correlates with Kco decline indicates a possible link between systemic inflammation and alveolar destruction. It would be therefore be of interest to determine whether this association is replicated in patients with usual COPD particularly with an emphysematous phenotype.

One of the limitations of the current study was that the research scanning protocol used for densitometry from the start of the ADAPT programme in 1996, when quantitative CT was in its' infancy, was not the method of choice for the imaging of nodules for clinical monitoring, It was therefore not possible using this scanning protocol to determine emphysema progression using CT lung densitometry, which is now recognised to be a more sensitive and specific method for the assessment of emphysema progression than physiology.[39–41] The consistent use of a volumetric protocol, which was subsequently adopted in preference to the original high-resolution protocol, would also have allowed additional factors such as nodule volume and regional changes in lung density to be determined more clearly, and would be a useful adjunct for future prospective studies. However the gas transfer corrected for alveolar volume (Kco), which is still a good marker of emphysema and its' progression albeit less sensitive than densitometry,[42] does show a correlation with nodule characteristics suggesting the 2 are related perhaps with a common inflammatory background. The incidence of lung cancer was low in the current study and the true incidence may only be confirmed or determined by pooling data from multiple AATD databases. Furthermore, as this was a retrospective study there was incomplete data for measurements such as hs-CRP concentration which was only performed in 230 of the 494 patients. Thus although a relationship to the nature of the nodule was observed this should be confirmed with a further prospective study.

In conclusion, the prevalence of nodules detected on CT scanning in patients with AATD in our study was 13%. In the few cases where malignancy was confirmed, the initial nodule had a spiculated appearance not seen in the others. Serial CT imaging of patients with incidental lung nodules did not identify the development of malignant change and therefore extended monitoring in nodules with a smooth outline is likely to be unnecessary. Nodules that underwent spontaneous resolution appeared to be associated with a systemic inflammatory response and accelerated decline in gas transfer, suggesting a link between inflammation, nodule formation and the progression of emphysema.

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Conflict of interest

Deepak Subramanian

DS declares that there is no conflict of financial or personal interest related to this manuscript.

Ross Edgar

RE declares that there is no conflict of financial or personal interest related to this manuscript.

Helen Ward

HW declares that there is no conflict of financial or personal interest related to this manuscript.

David Parr

DGP has acted as an independent consultant to Talecris Biopharmaceuticals and Hoffman-La Roche, receiving consultancy fees and support to attend conferences, with travel and accommodation, amounting to approximately $20,000. DGP has received financial support for conference attendance and fees for consulting on issues on COPD and alpha 1-antitrypsin deficiency from the following pharmaceutical companies: Talecris Biotherapeutics, Boehringer Ingelheim, Hoffman-La Roche and Chiesi. DGP's wife is an employee of Talecris Biotherapeutics.

Robert Stockley

RAS has acted as an advisor to Roche Pharmaceutical in the design and delivery of the REPAIR study as well as being one of the PI's involved in the study delivery. RAS has acted as an advisor to Baxter, Kamada and Talecris, all of whom have treatements used in the management of Alpha 1-antitrypsin deficiency and he has lectured for Talecris, Glaxo SmithKline, Nycomed, Boehringer Ingelheim and received non-commercial grant funding from Talecris.

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