almost all be similarly categorised using the LLN or other criteria. The differences that we would find relate to the mild category. In the BOLD study, GOLD stage 1 was not included in the overall estimates, although others have shown that people in this category have increased morbidity and mortality. While mild disease may be more “treatable” it may also be part of the spectrum of “normal”. It may also be true that early evidence of disease may be more important as an indicator of non-respiratory disease, such as cardiovascular disease. Furthermore, in mild to moderate disease the recommended interventions are based on treating symptoms, whereas in severe to very severe disease they are based on both treating symptoms and preventing exacerbations.

To answer the question posed in the title, I do not believe that the use of statistics and mathematical “norms” is the best way to diagnose and classify disease. If everybody fails, nobody passes (but the tests and the teaching need to be critically evaluated). I continue to believe that a disease classification scheme that is easy to remember (such as the fixed FEV1/FVC ratio) and to teach others remains useful. I also strongly believe that interventions need to be based on factors other than lung function, particularly in mild to moderate disease. I also support continuing to evaluate this problem by focusing on outcomes and not simply mathematical distributions of data in populations.

**Competing interests:** DMM has received research grants from GlaxoSmithKline, Pfizer and Novartis, and serves as a consultant to GlaxoSmithKline, Pfizer, Boehringer-Ingelheim, Astra-Zeneca, Dey, Sepracor and Novartis.


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and (4) sufficient information so that changes in the concentration of the biomarkers can be clinically relevant.10

There are significant limitations to CC-16 as a marker of the disease components of COPD. In the cohorts studied, there was no correlation between the presence or severity of emphysema and the serum CC-16 level. Also, there was no correlation between the serum CC-16 level and the symptoms of chronic bronchitis. The use of inhaled corticosteroids or long-acting β2 agonists in the ECLIPSE cohort was not reflected in significant differences in serum CC-16 levels. We must be aware that, at present, it is not known if the serum CC-16 level is specific for COPD alone or only to exposure to tobacco smoke or ozone. Testing is required of CC-16 serum levels in other diseases of the lung. Also, studies are required in COPD to determine whether CC-16 can indicate disease progression or regression.

This report of CC-16 from the ECLIPSE study does provide baseline data on several patient cohorts in this large-scale study. Additional data are needed to establish whether CC-16 can reflect short-term or long-term progression or regression of COPD parameters of pulmonary function, clinical state or radiological indices of bronchial structure or, possibly, responses to treatment.

We need to establish where CC-16 might be considered in the spectrum of possible biomarkers of COPD. COPD is a systemic disease beyond the lung with inflammation as a significant contributor,11 and markers of the inflammatory state such as C-reactive protein (CRP)12,13 and interleukin of the inflammatory state such as C-necrosis factor α (TNF-α)14 have been found to be raised in COPD; significant increases in tumour necrosis factor α (TNFα) in COPD have also been reported.15 However, these reflect augmentation of the systemic inflammatory state in COPD which can be influenced by co-morbid conditions in the cardiovascular system or metabolic co-morbidities. Thus, biomarkers of the pathological state of patients with COPD may be indicators of extrapulmonary processes as well as pulmonary pathology per se. CC-16 has the advantage of being an indicator anchored to the Clara cells of the bronchial epithelium, which gives it a potential relevance to effects on the diseased lung.

Competing interests: None.


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Acute lung injury (ALI), and its more severe counterpart the acute respiratory distress syndrome (ARDS), are syndromes of acute respiratory failure associated with pulmonary oedema caused by increased permeability of the alveolar–capillary membrane. Many clinical scenarios are recognised as being associated with a high incidence of ALI, including the archetypal direct pulmonary and blood borne insults of pneumonia and severe sepsis, respectively. The internationally accepted diagnostic criteria are non-specific to the point of including patients with relatively mild hypoxia and patients with lung pathology that may be different from the classical diffuse alveolar damage. ALI is not uncommon but it is challenging to study, partly because the patients are heterogeneous in the causes and severity of their illness. Furthermore, RAGE: a biomarker for acute lung injury

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