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Title: Identifying a 'frequent exacerbator' phenotype in a cohort of COPD patients (EXACO study)

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Body: Background: Exacerbations are a major cause of morbidity and mortality in patients with COPD. Objectives: To determine whether it is possible to identify a sub-group of 'frequent exacerbators', i.e. COPD patients who experience a high number of exacerbations every year, and to compare their characteristics to that of non-frequent exacerbators. Methods: In this french prospective observational study, respiratory physicians (n=132) included 835 COPD patients followed over 4 years. Sociodemographic data, clinical history, symptoms, lung function data and treatments were initially recorded. COPD clinical features, pulmonary function tests, treatments and the onset of exacerbations were recorded by the investigators at follow-up visits. Patients also completed exacerbation diaries. The KmL method was used to identify frequent and non-frequent exacerbators. This analysis was conducted in 464 patients with complete exacerbation-related data. Results: 2 groups with homogeneous numbers of exacerbations were identified. The 1st group consisted of 114 (24.6%) patients who were frequent exacerbators (mean, 3.5 exacerbations/patient/year, SD: 1.3).The 2nd group consisted of 350 patients (75.4%) who experienced fewer exacerbations (mean, 0.9 exacerbations/patient/year, SD: 0.7). Frequent exacerbators were found to have a higher dyspnea score, a lower FEV1 (43.8% of predicted vs 50.3% P<0.0001) and reported more impaired daily activities (38% vs 18%, p < 0.0001), more frequent chronic cough (p < 0,01) and sputum production (p < 0.001) more frequently. Their slope of FEV1 decline was steeper. Conclusion: Frequent

exacerbators appear to belong to a distinct, clinically relevant, COPD phenotype.