Update in COPD 2016

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Introduction

Chronic Obstructive Pulmonary Disease describes a predominantly smoking-induced small airways and/or emphysematous disease associated with airflow limitation. Considered progressive, irreversible and responsible for substantial morbidity and mortality worldwide, COPD remains the subject of vigorous study and advances made during 2016 are already reflected in the GOLD 2017 guidelines (1). Researchers continue to explore strategies, pharmacological or otherwise, to improve the lives of those who have developed this condition and hopefully by improving phenotyping of this heterogenous disease we might ultimately deliver personalised medicine. Debate remains over how to identify undiagnosed COPD in individuals who would benefit from intervention, whilst avoiding over-diagnosis and these controversies perhaps highlight shortcomings in accepted disease definitions. Not unrelatedly, renewed interest has emerged in explaining why some individuals develop COPD and identifying the formative stages of COPD development.

Therapy

A series of studies have been published during 2016 exploring how we might improve treatment of those who have developed COPD.

Therapy for frequent exacerbators

Although the GOLD guidelines advocate escalation and de-escalation of therapy (1), few studies are available demonstrating the impact of this approach. The effect of stepping up from twice daily LABA-ICS (formoterol fumarate and beclometasone dipropionate) to LABA-LAMA-ICS single combination inhaler (formoterol fumarate, glycopyrronium bromide and beclometasone dipropionate) was tested within the TRILOGY trial (2). This double-blind randomised control trial
studied 1368 patients with severe to very severe COPD, a moderate-severe exacerbation within the preceding 12 months and chronic respiratory symptoms. Stepping up to triple therapy for 1 year improved spirometric readings and a 23% lower exacerbation rate without a significance increase in adverse events. Unfortunately, this study was not enriched for exacerbations and the low exacerbation rate within this study makes interpretation more difficult.

An alternative approach to those at high-risk of COPD exacerbation was tested by the FLAME study which compared combined twice daily LABA-ICS (salmeterol-fluticasone) with once daily LABA-LAMA (indacaterol-glycoperonium) (3). FLAME studied individuals with COPD and FEV1<60% predicted who had received treatment for an exacerbation in the preceding year and demonstrated LABA-LAMA to be superior to LABA-ICS in reducing exacerbation rate. Within the LABA-LAMA group, overall exacerbation rate was 11% lower, with a 17% reduction in moderate/severe exacerbations, defined as exacerbations requiring the use of health care services. LABA-LAMA therapy was also associated with both greater improvements in both FEV1 and health status (greater decreases in St George’s Respiratory Questionnaire Score) but lower rates of pneumonia, without any difference in mortality. These findings suggest dual bronchodilator therapy among high-risk COPD patients is safe and effective at reducing exacerbation rate and improving both lung function and health status.

Studies are now required to compare LABA-LAMA versus LABA-LAMA-ICS to determine whether triple therapy adds any incremental benefit over dual bronchodilator therapy (4). Future studies recruiting patients with a wider range of comorbidities may also prove useful in determining how treatment guidelines may be improved (5).

The applicability to everyday practice of clinical trials, which by design usually include highly selected patient groups, is frequently questioned. The Salford Lung Study aimed to address this issue evaluating the effectiveness and safety of combination once daily LABA-ICS (vilanterol and fluticasone furoate) versus usual care within a “real-world population” across 75 family practices (6). By totally avoiding smoking or spirometric inclusion criteria, and instead basing enrolment upon a
general practitioner documented COPD exacerbation within the previous three years together with long term maintenance inhaler therapy prescription, the authors reported a pragmatic approach to studying patients to whom the findings from COPD trials are often applied (7). Indeed, 50% of the study sample was previously receiving triple therapy despite preserved lung function. The study reported an 8.4% lower moderate to severe exacerbation rate in those using combined LABA-ICS than usual care (P=0.02) without an increase in serious adverse events. Subpopulation analysis also showed that this change was driven by patients previous treated with ICS, LABA-ICS and LAMA-ICS therapy. Although the open label nature of the study may have led to bias, perhaps responsible for the high number of treatment switches, the innovative design arguably delivers a more “real world” study providing safety data complimentary to those from more traditionally designed clinical trials.

Conversely, the RE\textsuperscript{2}SPOND (Roflumilast Effect on Exacerbations in Patients on Dual (LABA/ICS) Therapy) trial illustrates how recruiting very specific patient sub-groups may reveal treatments particularly beneficial to those individuals. This study investigated the effect on exacerbation rate of adding Roflumilast to standard COPD care (8) enrolling patients with at least severe grade COPD, chronic bronchitis and two or more exacerbations within the preceding year. Roflumilast is a phosphodiesterase-4 inhibitor, known to reduce both neutrophilic and eosinophilic inflammation, which is already licensed for use in COPD patients with chronic bronchitis and FEV\textsubscript{1}<50% predicted.

Overall, this study found Roflumilast had no significant impact upon exacerbation rate and the trial therefore failed to meet its predetermined primary end-point. However, post hoc analysis did show a 39% reduction in exacerbation frequency with Roflumilast use, relative to placebo, among those who had experienced three or more exacerbation within the previous year (P=0.03) (Figure 1), supporting the results of the earlier published Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy (REACT) study (8). Those with very frequent exacerbations, who perhaps should be considered “super-exacerbators”(9), may therefore obtain particular benefit, perhaps because they have enhanced airway inflammation which responds to Roflumilast (9). Better
understanding the pathophysiological mechanisms underlying “super-exacerbators” together with studies of therapy among these “super-exacerbators”, coupled with rigorous exacerbation recording, may not only reveal therapeutic benefits for this subgroup but ways to substantially lessen the overall burden COPD exacerbations on healthcare services. Further studies of triple therapy are expected to be reported in the near future.

**Figure 1:** Data from the RE2SPOND (Roflumilast Effect on Exacerbations in Patients on Dual (LABA/ICS) Therapy) trial. Rate of moderate or severe exacerbations per patient per year at Week 52 by exacerbation history (intention-to-treat population). Fifteen participants (nine roflumilast and six placebo) had fewer than two exacerbations in the 12 months before randomization and were excluded from this analysis. Reproduced from Martinez F.J. et al (8).
Drug adherence and healthcare delivery

Adherence to prescribed inhaler therapy was examined in a prospective observational study by Sulaiman et al (10) using an electronic audio recording device to quantify frequency and technique of inhaler use. Worryingly, this small study of 244 patients recently discharged from hospital found a mean actual adherence of only 22.6% with only six percent using maintenance inhaler therapy regularly and with correct technique >80% of the time. These data highlight a major obstacle to delivering treatment benefits to patients.

Simplifying treatment regimens, such as using once daily maintenance inhaler therapies as investigated within the FLAME(3) and Salford studies(7), may improve adherence. However, the challenges described by Sulaiman et al (10) are unlikely to be solved purely through novel inhaler formulations, perhaps instead requiring tailored healthcare provision to encourage long-term behavioural change.

The effect of comprehensive health coaching on readmissions was examined by Benzo et al within a randomised 1 year-long trial. Coaching was found to both improve health status and reduce hospital admission for up to six months (11), perhaps explainable through improved motivation, behaviour change and enhanced medication adherence. Instead of being seen as a treatment itself, coaching and similar programs might be considered as process or the manner in which long-term healthcare is provided (12) and as another component of personalised medicine. Pulmonary rehabilitation has features in common with health coaching and within a multicentre randomised control trial of 143 patients with moderate to severe COPD, Guel et al have shown that participating in a 3-year maintenance program after an initial course of rehabilitation results in better maintenance of functional improvement and patient reported outcomes relative to a control group (13). Modifying behaviour or lifestyle is notoriously difficult, but these studies suggest personalised strategies assist in this challenge and should be better incorporated into everyday patient care.
Long term oxygen therapy

Long-term oxygen therapy (LTOT) improves survival amongst those with chronic respiratory failure and severe resting hypoxaemia, but a landmark study in 2016 showed that LTOT amongst those with more moderate hypoxaemia does not alter mortality, time to hospitalisation or other patient centred outcomes (14). This large study randomised 738 patients with COPD and mild to moderate hypoxaemia at rest or during a six-minute walk test to receive either LTOT or no LTOT. The lack of clinical effectiveness supports guideline advice that LTOT should not be routinely provided to those with stable COPD and moderate hypoxaemia. (1, 15).

Emphysema and endobronchial valves

Endobronchial valves are already a therapeutic option for those with heterogenous emphysema but their use may also be beneficial to those with homogenous emphysema. The IMPACT (Improving Patient Outcomes by Selective Implantation of the Zephyr EBV) study randomised 93 patients with homogenous emphysema, without collateral ventilation, to receive standard care versus unilateral lobar occlusion targeting the worse affected lobe (16). Although the 17% difference in FEV$_1$ achieved between groups is smaller relative to interventions in heterogenous emphysema, this was accompanied by improvements in exercise tolerance and quality of life scores (Figure 2). Endobronchial valve insertion is not without risk, procedure related pneumothoraces occurred in 26% of the study sample, and careful patient selection with multidisciplinary input will remain essential to extending this therapy to this wider population (17).
**Figure 2**: Data from the IMPACT (Improving Patient Outcomes by Selective Implantation of the Zephyr EBV) study. Changes from baseline to 3 months for (A) 6MWD, (B) SGRQ, and (C) RV for the ITT population. Each open symbol represents individual subject data from EBV subjects (open circles) and SoC subjects (open squares). Mean values (solid circles, solid squares) and the 95% confidence intervals are presented. P values are by two-sample t test analysis. 6MWD = 6-minute-walk distance; EBV = endobronchial valve; ITT = intention to treat; RV = residual volume; SGRQ = St. George’s Respiratory Questionnaire; SoC = standard of care. Reproduced from Valipour A. et al (16)
Phenotyping and biomarkers

Several of the therapies already discussed target specific clinical COPD phenotypes, such as the frequent exacerbator, those with chronic bronchitis and those with significant emphysema. Efforts continue to enhance phenotypic characterisation and the quantification of underlying variability through biomarkers, aiming to predict therapy response and thereby facilitate precision medicine (18).

Asthma-COPD Overlap

Given the high prevalence of asthma-life features, such as bronchodilator reversibility, atopy and eosinophilia among those with COPD, and the historical failure to include such individuals in either asthma or COPD trials, an asthma-like COPD phenotype remains a key area of active research. However, defining the asthma-COPD overlap syndrome (ACOS) remains controversial, especially without a unifying targetable molecular pathway or understanding how such overlap impacts upon the clinical disease course (19, 20).

The influence of ACOS defining criteria on prognosis was highlighted by Suzuki et al who investigated how asthma-like features influenced the clinical course of patients with COPD after excluding those with physician diagnosed asthma (21). Within this 10-year Japanese multicentre observational study, neither bronchodilator reversibility, blood eosinophilia or atopy were associated with worse clinical outcome. Instead, and perhaps surprisingly, blood eosinophilia was associated with slower annual FEV$_1$ decline than those without eosinophilia and those with two or more asthma-life features had significantly lower 10-year all-cause mortality than those with one or no asthma-life features. Similarly, a prospective Spanish study found that the 15% of 831 COPD patients who met ACOS criteria had lower one year mortality than those without ACOS (22). Better responsiveness to
already implemented therapies might explain these findings (19) although proving this using observational studies of COPD patients, often already established on therapy, will be challenging.

**Eosinophils as a biomarker**

Eosinophilic inflammation is central to asthma phenotyping, yet the role or peripheral blood eosinophils as a biomarker in COPD or ACOS is less clear. Using the population based Copenhagen General Population Study, Vedel-Krogh et al showed that an increased baseline blood eosinophil levels among those with COPD was associated with greater risk of exacerbations (23) (Figure 3). ROC curves determined the optimal cut-off point as $0.34 \times 10^9$ cells per litre, above which eosinophilia was associated with a 1.76-fold increased risk of severe exacerbations (23), suggesting that absolute rather than relative blood eosinophil count may be a more robust predictor of exacerbation frequency (24). It remains to be seen, however, whether this relationship indicates a susceptibility to exacerbations, perhaps driven by eosinophilia, or if eosinophilia represents a residual marker of preceding exacerbations or viral infections.
Figure 3: Data from the Copenhagen General Population Study. Risk of severe and moderate exacerbations in individuals with chronic obstructive pulmonary disease (COPD) and individuals with clinical COPD using the cut points for blood eosinophils of $0.34 \times 10^6$ cells per litre and 3.3%. N is the number of individuals and events is the total number of events. Incidence rate ratios (IRRs) are given with 95% confidence intervals (CIs). Models were multivariable adjusted for age, sex, FEV1 as a percentage of predicted value, smoking status, cumulative smoking, education and body mass index.

Reproduced from Vedel-Krogh S. et al (23).
Pavord et al investigated how peripheral eosinophilia might predict how the initiation of combined LABA-ICS (fluticasone propionate/Salmeterol) influences COPD exacerbation rate (25). This retrospective analysis of data from three randomised trials: combined therapy versus tiotropium (INSPIRE); combined therapy versus mono-constituents versus placebo (TRISTAN); combined therapy versus fluticasone propionate versus placebo (SCO3002), found blood eosinophilia of 2% or greater to be associated with a subsequent reduction in exacerbation frequency within two of the three studies.

Additionally, a pooled meta-analysis including 10,861 patients, enrolled within ten randomised controlled trials involving an inhaled corticosteroid arm, suggests those with blood eosinophil counts of less than 2% more commonly developed pneumonia, perhaps indicating an impaired resilience to infection (26). Likewise, amongst those using inhaled corticosteroids, the authors found a plausible, yet non-significant, trend towards pneumonia developing more commonly if eosinophils count was less than 2% rather than greater than 2%, reinforcing a potential role for blood eosinophils in guiding long term therapy. However, although these data suggest eosinophils levels predict a better response to corticosteroid, it does not necessarily follow this is the optimal therapy. The prospectively designed FLAME study found that in both those with eosinophils of less than 2% and those with eosinophils of 2% or greater, exacerbations were lower in the LAMA-LABA arm than the LABA-ICS (3). Data from the WISDOM study also suggests that dual bronchodilator therapy may disrupt the usefulness of a 2% peripheral eosinophil cut-off in predicting how ICS may reduce exacerbation rate (27). WISDOM included patients with severe of very severe COPD, commenced LAMA-LABA-ICS and then compared exacerbation rates after stepping down therapy from LAMA-LABA-ICS to LAMA-LABA versus continuing triple therapy (27). Although the main findings from this study were published in 2014 (28), a recent post-hoc analysis tested the hypothesis that patients with higher baseline eosinophils would be more likely to “relapse” and experience more frequent exacerbations following ICS withdrawal. However, this analysis found that a treatment-by-subgroup interaction only became apparent when baseline peripheral eosinophilia reached 4% (27).
Peripheral eosinophilia bears hallmarks of a promising biomarker to guide ICS use. However, exacerbation rate can also be reduced through dual bronchodilator therapy and determining the eosinophil cut-off at which patients using dual bronchodilators will benefit from additional ICS requires prospective studies comparing triple therapy versus dual bronchodilator therapy.

Other biomarkers

For biomarkers to be useful within the COPD population, they must not only be predictive but their associations should be reproducible across different COPD studies. Keene et al studied the associations of 90 candidate blood biomarkers across two large, high quality, well characterised COPD cohorts SPRIOMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) and COPDgene cohorts (Genetic Factors in COPD) which prospectively record exacerbations (29). After biomarker association with exacerbation risk was adjusted for age, sex, FEV\textsubscript{1}, smoking, health status and reported gastroesophageal reflux, no biomarker, including eosinophils or fibrinogen, was reproducibly associated with future exacerbation frequency. In contrast, clinical variables, such as prior exacerbation history, dyspnoea, spirometry and gastroesophageal reflux) predicted future exacerbation across both cohorts, and the biomarkers studied added little to such predictions. One explanation for these findings, as the authors highlight, is that exacerbations are aetiologically heterogenous in nature and that seeking a single, or even combination blood marker, to predicts such events may be an unrealistic goal.

Although disappointing, this high-quality study reinforces the importance of clinical indicators, and with better phenotyping of patients and exacerbations, reproducible biomarker associations may become apparent (24, 29, 30).
Cardiovascular/multimorbidity

Vascular diseases and COPD

A well-documented link exists between lung function impairment and both cardiovascular and cerebrovascular diseases (31, 32), although the mechanisms underlying this relationship remain unclear. Within a large population-based prospective study spanning ten years, Portegies et al. found both ischaemic and haemorrhagic strokes more commonly occurred amongst those with COPD (33). Adjustment for smoking diminished this relationship (33) suggesting part of the reason these respiratory and cardiovascular conditions coexist is because of their shared smoking aetiology, although some also argue that pulmonary impairment represents a marker of early life adversity which predisposes to cardiovascular disease development (34). Importantly, Portegies et al. also found a six-fold higher stroke risk within seven weeks post-COPD exacerbation onset (33). Therefore, exacerbation-related systemic inflammation, hypoxia and ensuing endothelial dysfunction may contribute to vascular reactivity, rupture of atherosclerotic plaques and stroke development (31).

Evidence has also emerged suggesting a possible link between peripheral artery disease and emphysema (35) (Figure 4). The multicentre COSYCONET (COPD and Systemic Consequences–Comorbidities Network) cohort study found not only is peripheral vascular disease more common amongst those with COPD, substantially adding to functional impairment, but that its presence was associated with impaired diffusion capacity even after adjustment for multiple confounders (36). Crucially, within the COSYCONET study peripheral artery disease appeared unrecognised in two thirds of COPD patient affected (36). Conversely, the Airflow Limitation in Cardiac Diseases in Europe (ALICE) study found that 30.5% of those with ischaemic heart disease (IHD) also had airflow limitation but that less than a third of these individuals had received a relevant diagnosis, despite a heavy symptom burden and poorer patient related outcomes (37).
The overlapping symptom profiles of these conditions may contribute to the substantial underdiagnoses of COPD among those already diagnosed with vascular disease and vice versa, but this may also reflect super-specialisation and an underappreciation of how closely these conditions are related (32). Although we are not yet in a position to therapeutically target an overarching pulmonary-cardiovascular syndrome, when encountering patients with COPD, these data should prompt us to pay attention not only to smoking cessation but other cardiovascular risk factors, such as hypertension and hypercholesterolaemia (31), and consider if cardiovascular disease might already be present.

**Figure 4:** Association of chronic obstructive pulmonary disease (COPD) and peripheral artery disease.

Reproduced from Brusselle G. et al (35)
Impact of COPD treatments on the cardiovascular system

The exclusion of individuals with both COPD and cardiovascular disease from randomised controlled drug trials has left uncertainty regarding the cardiac effects of drugs targeting COPD, especially given the differing pharmacological receptors profile present across the cardiopulmonary system.

To partly address this knowledge gap, the three year multi-centre double-blind placebo-controlled Study to Understand Mortality and Morbidity (SUMMIT) enrolled 16,590 patients with symptomatic moderate COPD who reported a history of, or were at increased risk of having developed, cardiovascular disease (38).

The study investigated the mortality effects of once daily treatment with inhaled fluticasone furoate (100 microgram), vilaterol (25 microgram) versus combination fluticasone furoate (100 microgram) and vilaterol (25 microgram) (38). The main finding was that neither LABA-ICS nor its constituents improved survival, even among a sample enriched for cardiovascular comorbidities. Despite this negative primary end-point, it is perhaps reassuring that neither did these widely used therapies appear to worsen cardiovascular outcomes.

Although no improvement in cardiovascular mortality or events was found by SUMMIT, Stone et al reported the use of combination fluticasone furoate/vilaterol may favourably alter cardiac function (39). Using magnetic resonance imaging this double-blinded placebo controlled crossover study showed that decreases in residual volume following short term treatment with combination fluticasone furoate/vilaterol combination was accompanied by improved cardiac function and increased artery pulsatility (39). Although small, this is the first well-designed study providing evidence that pharmacologically treating hyperinflation can improve cardiac function, presumably by targeting cardiac underfilling (40). It remains unclear how long these cardiac effects may last and if dual bronchodilator therapy could provide even greater benefit (40). Determining how these
reported improvements translate clinically, and which patients might benefit most, may reconcile these findings with those from SUMMIT.

**Case finding and accurate Diagnosis**

COPD frequently remains undiagnosed suggesting the actual disease burden is considerably greater than recorded. However, it remains unclear how beneficial diagnosing these “missed” individuals would be (41-43). An uncomfortable tension exists between ensuring those with clinically relevant COPD are correctly identified and appropriately treated versus overmedicalizing individuals with mildly abnormal spirometric results.

The population-based CanCOLD study found that those with spirometric evidence of COPD but without a physician diagnosis had milder disease, and perhaps relatedly, reported fewer symptoms, better patient reported outcomes and fewer exacerbations than individuals who had received a physician diagnosis of COPD (43). However, when those with undiagnosed COPD developed an exacerbation, there was a significant impact on healthcare services, events which might be avoided if affected individuals were identified and appropriately treated earlier (41, 43). Simple questionnaires combined with selective peak flow screening may offer one option for sensitive and specific case finding methodology within primary care (42), but wider validation and data regarding both the clinical benefit and the implications of diagnosing these individuals are required.

Expanding knowledge of what constitutes normal versus abnormal spirometric values across different ages and ethnicities is also providing scope to refine the spirometric COPD diagnosis and severity classification criteria (44). The GOLD guidelines currently promote use of fixed $\text{FEV}_1/FVC<0.7$ and $\text{FEV}_1$ percent predicted criteria, which although useful in many respects, with advancing age may overestimate both airflow limitation presence and predicted $\text{FEV}_1$ (44, 45). The Global Lung Initiative (GLI) equations calculate spirometric $z$ scores defining lower limit of normal values as the fifth
percentile of distribution and appear to reduce over-diagnosis of airflow limitation among the elderly (45). Given the ageing population, accurate diagnosis among the elderly is essential to avoid rising iatrogenic harm and unnecessary expenditure.

Using COPDGene data, Vaz Fragoso et al has now shown that GLI-equation based severity grading of COPD as mild, moderate or severe correlates in a graded manner with respiratory-related phenotypes, such as breathlessness, quality of life, exercise performance, emphysema and gas trapping (46). Such studies may lead to a scientifically-based diagnostic and grading, which not only reduces misdiagnosis but is more meaningful in terms of disease burden, offering hope in the quest to identify those in need of our attention.

**Shifting focus towards Disease Development and Early COPD**

The controversies regarding those with borderline diagnosable disease perhaps highlight shortcomings regarding a concept of COPD, constrained by the historical practice of studying older individuals with already well-established disease rather than studying how this disease develops. Identifying how COPD develops, and ultimately early COPD, is an increasing attractive topic, as early disease identification may permit early intervention to prevent progression to more severe disease stages.

**Symptomatic smokers without airflow limitation**

The inclusion of smokers/ex-smokers both with and without airflow limitation within the large COPDGene and SPRIOMICS studies cohorts has allowed investigators to provide new insights into the presence of pathology and morbidity amongst those with COPD-like features but without airflow limitation.
Bhatt and co-workers analysed data from the 1,508 individuals enrolled within the COPDgene study using parametric response mapping (PRM) (Figure 5) to analyse the associations between small airway disease, emphysema and FEV₁ decline over 5 years of follow-up (47). PRM, matches inspiratory and expiratory CT scans, together with density thresholds allowing functional small airways disease to be distinguished from emphysema. Bhatt et al found that among those with GOLD grade 1-4 COPD, both emphysema and small airways disease was associated with accelerated future FEV₁ decline. However, these investigators also reported that although both emphysema and small airways disease increase with disease grade, amongst the GOLD 0 group the presence of small airways disease, but not emphysema, indicated accelerated FEV₁ decline. This may suggest that small airways disease precedes emphysema (48).

Parametric response mapping was also employed by Martinez et al (49) within a cross-sectional analysis SPIROMICS cohort data. Using this indirect measure of small airway function, the authors found a roughly 2% increase in functional small airway abnormality per decade after age 50. This was a study of individuals of different ages rather than a study if ageing within the same individuals and therefore these data cannot definitively show disease development with ageing. However, this study does illustrate the potential difficulties in distinguishing the development of diseases, such as COPD, from airway abnormalities which accompany advancing age and thereby highlights the need to further refine our COPD diagnostic thresholds.
Figure 5: Data from COPDGene (Genetic Epidemiology of COPD). Graphic representation of the parametric response mapping (PRM) methodology. Chronic obstructive pulmonary disease of GOLD (Global Initiative for Chronic Obstructive Lung Disease) grades 1-4 are shown in rows. Inspiratory and expiratory computed tomography (CT) images respectively, are shown on the left. PRM emphysema (PRM_{Emph}) voxels in red and PRM functional small airways (PRM_{fSAD}) voxels in yellow are shown on the right. Although every voxel receives an individual categorical assignment, in this example PRM_{Emph} and PRM_{fSAD} are distributed throughout the lung. Greater intensity of colour indicates more voxel classified in each category. Reproduced from Bhatt S.P et al (47)
A second paper from the SPIROMICS group this year examined GOLD 0 current or ex-smokers (50) and showed chronic symptoms among smokers without airflow limitation identified a group who experienced exacerbations, had increased airway thickening, diminished FEV₁ and FVC readings and exhibiting lower exercise tolerance (50). This publication further highlights how current spirometric COPD definitions fail to reflect the spectrum of smoking associated lung disease (51). However, this mild grade disease, identified in a sample mostly older than 50, does not necessarily equate early phase COPD, and follow-up studies examining progression to established COPD will be keenly awaited.

The development of disease across life

Two studies published within the AJRCCM during 2016 offer a longer perspective on COPD development. Tagiyeva et al reported data collected from the 239 individuals followed within the Aberdeen WHEASE cohort recruited at age 10-15 years and followed until age 60-65 years (52). Within adjusted multivariate analysis, both wheezy bronchitis and childhood asthma were associated with impaired adult lung function the development of COPD. Although this study contained low number of smokers, it adds to the growing literature indicating the importance of early life events on the development of adult disease such as COPD (53) and how physiological “snapshots” during later life insufficiently explain adult disease patterns.

The nationally representative MRC National Survey of Health and Development reported data from almost two thousand individuals followed since enrolment at birth in March 1946 (54). This study showed how the relationship between chronic mucus hypersecretion CMH, also known as chronic bronchitis, and smoking evolves between age 20 and 64 years and that the longer CMH is present, the greater the FEV₁ lost. CMH presence among smokers escalated between age 36 and 43 years (Figure 6), and identified smokers at higher risk of having COPD in their seventh decade. Therefore,
CMH presence during midlife may indicate early stage COPD development. Unlike many studies, the NSHD highlighted the dynamic course of CMH across life. Although most (60%) of those who developed COPD had experienced a phase of CMH across the study, only half of these individuals still reported CMH at age 65 years (55). Such life spanning studies can offer precious insights into how disease develops over decades and by challenging existing assumptions they may reveal new diagnostic, mechanistic and therapeutic approaches to the condition currently labelled as COPD.
**Figure 6:** Data from the NSHD (National Survey of Health and Development) 1946 birth cohort. The prevalence of chronic mucus hypersecretion (CMH) (with 95% confidence intervals) and median smoking cigarette consumption during five time-periods over adult life within the National Survey of Health and Development according to concurrent cigarette smoking behaviour. **P<0.01; ***P<0.001, change in symptom prevalence during each period analysed using McNemar’s test according to smoking behaviour group (coloured accordingly). †Mann-Whitney U tests; ‡Wilcoxon signed rank tests. IQR=interquartile range. Reproduced from Allinson J.P. et al (54)
Genetic predisposition

Although it is widely believed that COPD develops partly due to genetic susceptibility, the overall heritability of COPD has been difficult to conclusively prove, aside from those risks associated with alpha-1 antitrypsin deficiency (56).

Qiao et al explored if rare genetic variants might partly explain the presence of severe COPD within the Boston Early-Onset COPD (EOCOPD) study by conducting whole-exome sequencing among 347 members. The authors explored if candidate variants identified were associated with COPD within the COPDGene cohort (57). Although novel because it targeted COPD using whole-exome sequencing, this study found only trends of association which were non-significant. This might indicate the need for larger studies better powered to detect rare variants, but which might also be capable of investigating interactions between genes and smoking (56). It is also possible, as the authors point out that susceptibility to COPD is determined by multiple rather than just a few gene (57).

A cross-sectional genetic study, published by Kusko et al, was even smaller in size, but this study is also one of the first to use unsupervised network approaches to try to identify common transcriptomic pathways across different lung disease, in this case COPD and idiopathic pulmonary fibrosis (58). Using RNA sequencing these authors showed that the p53/hypoxia pathway was activated within lung tissue taken from both patients with COPD and patients with idiopathic pulmonary fibrosis relative to samples taken from healthy lungs, perhaps suggesting these diseases share a common tissue remodelling pathway. This study reveals the potential for next-generation sequencing to help identify common disease pathways across traditional disease boundaries (59). However, given the findings from the longitudinal population studies discussed earlier, it would be surprising if such cross-sectional genetic studies prove able to fully explain COPD heterogeneity. Instead, future studies need to be powered to study interactions between genes and environment. Furthermore, these relationships need to be explored over extended periods to delineate how
genetics, environmental exposures and the ageing process together influence chronic disease development.

**Conclusion**

This update covers an important, yet small portion of the COPD research published during 2016. Advances have been made regarding how we should use existing therapies, by both identifying recipients who might benefit most and determining how the benefits acquired from therapies might be optimised. The studies discussed also highlight opportunities to tailor COPD therapy to an individual patient by considering their clinical phenotype, the nature of their airway inflammation and their comorbidities. Additionally, the approach by which therapy is delivered can also be personalised to help the individual optimally manage their long-term condition. Whilst smoking cessation and avoidance remain central to COPD prevention and progression, the lack of therapies capable of modifying established disease remains frustrating. Perhaps by better understanding the mechanisms by which COPD develops and how disease heterogeneity evolves across life we might discover those game-changing therapeutic approaches which have thus far remained elusive.


