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Introduction

A key output of the Global Obstructive Lung Disease (GOLD) initiative is the annual report, developed by the GOLD Science Committee. The report is based on the best scientific information available, is released around World Chronic Obstructive Pulmonary Disease (COPD) Day, and is presented first at the GOLD International COPD Conference. Over the last 9 years, in the context of presenting the yearly update of the GOLD report, this conference is organized to address the most important advances in the field of COPD. The meeting gathers some of the top national and international leaders to address topics that the organizing committee recognizes as novel, timely and important for health care professionals caring for patients with COPD. This document summarizes the content of those presentations, as a useful resource to anyone interested in the most recent advances in the changing field of COPD.

The opinions expressed in the contents of this document are those of the faculty and do not necessarily represent the views of any organization associated with this activity.

The information presented in this document is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this document should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Session 1: New treatments for patients with COPD

Ensifentrine – where does it fit in the current paradigm?

Frank Sciurba, University of Pittsburgh, Pittsburgh, PA, USA

Ensifentrine is an inhaled, selective inhibitor of phosphodiesterase (PDE) 3 and 4, with an affinity for PDE3 more than 3000 times that for PDE4. It has three key mechanisms of action: relaxation of airway smooth muscle; decreased activation and recruitment of inflammatory cells (neutrophils, eosinophils, epithelial cells, lymphocytes, macrophages and fibroblasts); and increased ciliary function on epithelial cells.[1–8]

This presentation focused on individual study data and pooled analyses of the two studies in ensifentrine's pivotal Phase 3 program – ENHANCE-1 and ENHANCE-2.[9] More than 1500 patients were enrolled, with recruitment not enhanced for exacerbations. Further, patients could have been receiving no COPD medication, or a single long-acting bronchodilator with or without an inhaled corticosteroid [ICS]), although patients had to be symptomatic (modified Medical Research Council dyspnea score ≥2). The primary endpoint of both studies was lung function (forced expiratory volume in 1 sec [FEV1] area under the curve [AUC] over 12 hours at Week 12), with key secondary endpoints that included the Evaluating-Respiratory Symptoms score (E-RS), St. George's Respiratory Questionnaire (SGRQ) and Transition Dyspnea Index (TDI). COPD exacerbations were evaluated as an additional endpoint.

The primary endpoint was met in both studies, with significant 87 and 94 mL improvements vs. placebo in average change from baseline in FEV1 AUC0–12h. Using pooled data, there was a significant early (i.e., following first dose) improvement vs. placebo in peak FEV1 that was sustained to Week 24, with improvements vs. placebo in trough FEV1. In addition, there were clinically relevant improvements in TDI at all assessment timepoints, reaching statistical significance vs. placebo for both E-RS and SGRQ in ENHANCE-1 (although not in ENHANCE-2). An unexpected finding (given recruitment was not enhanced for exacerbations) was a reduction in the rate of exacerbations for ensifentrine vs. placebo in both studies, independent of baseline blood eosinophil count. Importantly, the adverse event profile of ensifentrine was similar to that of placebo.

Ensifentrine was approved by the US Food and Drug Administration (FDA) in June 2024. The Institute for Clinical and Economic Review (ICER) stated that ensifentrine, when added to maintenance therapy, results in at least a small net health benefit, although warned that the amount of added healthcare costs may be difficult for the health system to absorb over the short term.[10] UpToDate recommends use of ensifentrine as add-on to one or more long-acting bronchodilator (with or without an ICS), and in the updated 2025 report, GOLD suggests considering adding ensifentrine to long-acting β2-agonist plus long-acting muscarinic antagonist (LABA+LAMA) therapy in patients with dyspnea.[11] Of the patients who have been prescribed ensifentrine since approval, 50% are receiving triple LAMA/LABA/ICS. Given this is not a group of patients recruited into ENHANCE-1 or 2, further studies are needed to clarify the positioning of this medication in the treatment algorithm of patients with COPD.

Updates on interventional trials for chronic bronchitis: Bronchial rheoplasty for chronic bronchitis

Carla Lamb, Lahey Hospital and Medical Center, Burlington, MA, USA

Chronic bronchitis, which is defined as productive cough that lasts at least three months over the course of two years, is both underreported and underdiagnosed, with a prevalence of 3–22% in the general population and at least 74% in patients with COPD. The presence of chronic bronchitis is important as it is associated with a more rapid decline in FEV1, increased mortality, and poor quality-of-life (QoL). Exposure to cigarette smoke or other pollutants leads to production of mucus to expel irritants, with chronic inflammation causing the production of more mucus resulting in airway obstruction.

Bronchial rheoplasty utilizes non-thermal pulsed electric fields to reduce airway goblet cell hyperplasia and improve the symptoms of chronic bronchitis. The technique targets epithelium, smooth muscle, and submucosal glands, removing dysfunctional cells and debris while leaving the extracellular matrix intact (Figure 1). It is administered under general anesthesia as two procedures 30 days apart, the first on the right lung and the second on the left lung, with patients usually discharged on the day of each procedure.

The technique is being evaluated in a series of studies.[12–14] Overall, the safety profile of the procedure has been good, with no significant adverse events (mucosal scarring was reported in one patient, but this was due to biopsies conducted during the study, not the bronchial rheoplasty). In all studies, bronchial rheoplasty resulted in significant, clinically relevant, and sustained improvements from baseline in mean COPD Assessment Test (CAT) and SGRQ total scores, with 38% and 31% reductions in COPD exacerbation rates in one study at Months 12 and 24, respectively.[12,14] In addition, in one of the studies that included airway biopsies there was a statistically significant 39% reduction from baseline in goblet cell counts. These preliminary studies indicate that bronchial rheoplasty appears to be feasible and to have a good overall safety profile in this phenotype of patients. The pivotal multicenter prospective randomized sham controlled trial in patients with chronic bronchitis (NCT04677465) has completed enrollment but its results are not yet reported. The results of the pivotal study will provide evidence whether rheoplasty has significant additional benefit in the treatment of patients with chronic bronchitis.

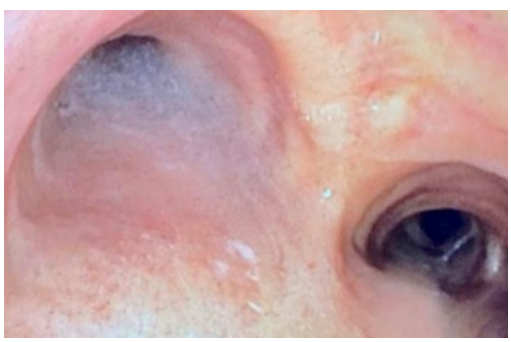


Figure 1. Photo taken at initial airway inspection, one month after treatment of right lung, prior to any suctioning. The left lung is untreated; the right lung was previously treated. Reproduced with permission from Galvanize, Inc.

Results of AIRFLOW-3: Targeted lung denervation for patients with exacerbation of COPD

Pallav L Shah, Royal Brompton Hospital Imperial College, London, UK

Acetylcholine (ACh) released from parasympathetic nerves is a key mediator of bronchial tone and mucus production, and may be involved in infection, such that dysfunction or dysregulation likely contributes to the pathogenesis of COPD.[15] Pharmacologic disruption of parasympathetic lung innervation by inhaled LAMA therapy is the mainstay of COPD treatment. However, permanent disruption or attenuation of parasympathetic nerves may have a more prolonged effect. Targeted lung denervation (TLD) is a novel bronchoscopic treatment to disrupt parasympathetic innervation of the lungs. This is achieved with the use of a cooling balloon inserted via bronchoscopy, to deliver radiofrequency energy.[16]

The procedure has been evaluated in three studies. The majority of recruited patients had ≥3 exacerbations prior to the procedure, and more than 90% were on triple therapy. In AIRFLOW-1, the magnitudes of improvement in FEV1 and the COPD-specific version of the SGRQ (SGRQ-C) were similar following TLD to bronchodilator alone.[16] In AIRFLOW-2, compared with a sham procedure, TLD was associated with a reduction in COPD exacerbations (over 3–6.5 months of follow-up), especially of severe exacerbations.[17] Further, TLD provided non-significant improvements in SGRQ-C and FEV1 over that delivered by bronchodilators. There was one early death related to the device and procedure (an esophageal fistula); other deaths during the 2-year follow-up were unrelated to device or procedure, and the most common serious adverse event was COPD exacerbations. Overall, the preliminary data from AIRFLOW-1 and AIRFLOW-2 suggest TLD delivers durable efficacy, with exacerbation reductions and health-related QoL improvements consistent with those provided by drug therapy.

In AIRFLOW-1, no consideration was taken of the position of the esophagus when TLD was applied, and consequently approximately 20% of patients had gastrointestinal adverse effects. In AIRFLOW-2, an esophageal balloon was inserted, with energy only delivered if the distance from the electrode to the balloon was at least 12–15 mm. The improvements in the technique significantly improved the safety profile.

The pivotal study AIRFLOW-3 (NCT 03639051) has completed enrollment, with 388 patients randomized, with results pending. Recruitment into the study was enhanced for exacerbation history (the recruited patients were to have ≥2 moderate or ≥1 severe COPD exacerbations over the prior 12 months, ≥1 of which was to occur while on optimal medical therapy). In addition, the technique was further developed, with the esophageal balloon cooled, the impact of which on gastrointestinal adverse effects is pending. The results of this study will determine whether TLD can prevent exacerbations and improve COPD-related symptoms in the COPD patient population at risk for moderate and severe exacerbations.

Session 2: Updates in current pharmacological treatments of COPD

ACO – Where have we gone? And does it matter?

Nicola Hanania, Baylor College of Medicine, Houston, TX, USA

The 'Dutch hypothesis' stipulates that asthma and COPD are on a continuum of one disease and have common pathogenetic mechanisms. However, the 'British hypothesis' refutes that hypothesis and states that asthma and COPD are two distinct diseases, with different risks and mechanisms – asthma being primarily triggered by allergies whereas COPD is mainly related to exposure to irritants or smoking. Regardless of which hypothesis is correct, a proportion of patients have characteristics of both diseases, termed 'asthma–COPD overlap' (ACO). These patients typically have increased symptom burden, are more likely to exacerbate, and have lower lung function (FEV1) than patients with either asthma or COPD. However, there is no consistent consensus on the definition of ACO,[18,19] and GOLD and the Global Initiative for Asthma (GINA) no longer refer to ACO, with GOLD stating "asthma and COPD are different disorders."[11] The lack of a consistent definition means that the published prevalence of ACO varies widely, although a meta-analysis estimated that it is 26.5% in patients with asthma and 29.6% in those with COPD.[20]

Although ACO is characterized by features of both asthma and COPD, it is possible that ACO is a unique disease. A number of genetic loci may predispose to ACO (rather than asthma or COPD alone),[21] and several single nucleotide polymorphisms have been identified in patients with ACO.[22] In addition, studies have suggested an important role of cytokines and inflammatory cells in ACO,[23] with sputum cluster analysis identifying specific biomarkers of ACO.[24]

Further, in metabolomic profiling of healthy individuals and patients with asthma, COPD, or ACO, a number of metabolites were significantly altered in ACO compared to the other groups.[25] However, ACO appears to be a complex entity with multiple phenotypes. One phenotype includes patients with asthma who smoke and have fixed airflow obstruction; a second includes patients with asthma and neutrophilic inflammation; others include patients with COPD and bronchodilator reversibility or those with eosinophilic inflammation. This variability in ACO phenotypes makes it very difficult to include a homogenous population of ACO in clinical trials.

Current treatment of ACO is based on expert opinion, given the lack of supporting randomized clinical trials. This includes the early initiation of ICS, and in more severe disease evidence suggests that ICS+LABA+LAMA therapy is more effective than ICS+LABA therapy.[26] Available data on the efficacy of monoclonal antibody therapy are limited to a single post-hoc analysis of an observational study in patients with asthma, in which omalizumab was similarly effective in patients with and without ACO.[27]

Given the lack of studies in this population, there is an urgent need to fill the gaps in understanding of ACO pathophysiology and its phenotypes, to reach a consensus on its definition, and conduct studies specifically designed to optimize treatment of these patients.

What is a biologic and when is it needed?

Stephanie Christenson, University of California, San Francisco, CA, USA

Biologic therapies enable a shift from phenotype-targeted therapies to precision medicine in populations defined by their biology (i.e., endotype-targeted). Biologics (including monoclonal antibodies, which are designed to bind specific targets in the body) are molecules made from living organisms or that contain components of living organisms. Unlike traditional small-molecule, chemically synthesized drugs, biologics are typically large, complex molecules that tend to be heat sensitive and susceptible to microbial contamination.

Airway-targeted biologics have focused on T2 inflammation, initially in asthma but more recently in COPD. The easiest biomarker of T2 inflammation is the blood eosinophil level, with a number of post-hoc analyses of ICS/LABA and ICS/LABA/LAMA studies in COPD showing that blood eosinophil levels can predict treatment response to inhaled corticostroids.[28–34] These data suggested that a subset of patients being treated for COPD have T2 inflammation.

Currently available biologics that target T2 inflammation work on the inflammatory cascade via interleukins (IL) 4, 5 and 13 (Table 1).[35–41] In the METREX study, mepolizumab reduced the COPD exacerbation rate by a statistically significant 18% vs. placebo, although this was not replicated in METREO and there was no difference in symptoms scores in either study.[35] Further, benralizumab had no effect on COPD exacerbations in either GALATHEA or TERRANOVA, although there was an improvement in lung function.[36] However, post-hoc analyses suggest that the efficacy of both molecules was greater in patients with higher baseline eosinophil values, and the subsequent mepolizumab MATINEE study recruited patients with COPD who had blood eosinophil values ≥300 cells//µL at screening AND >150 cells/µL in the prior year – initial results communicated in a press release were that mepolizumab was associated with a statistically significant and clinically meaningful reduction in the annualized rate of moderate/severe exacerbations vs. placebo.

Table 1. Biologics in development in COPD.*

Biologic	Target	Trial
Mepolizumab	IL-5	METREX & METREO (Pavord et al NEJM 2017)[35] MATINEE (Completed, not peer reviewed)
Benralizumab	IL-5R	GALATHEA & TERRANOVA (Criner et al NEJM 2019)[36] RESOLUTE (Ongoing, estimated completion: 6/25)
Dupilumab	IL4R (IL-4 & IL-13)	BOREAS (Bhatt et al NEJM 2023)[37] NOTUS (Bhatt et al NEJM 2024)[38]
Tezepelumab	TSLP	COURSE (Phase 2a, Completed: 1/24)
Itepekimab	IL-33	NCT03546907 (Phase 2, Rabe et al Lancet Respir Med 2021)[39] AERIFY-1 & 2 (Ongoing, estimated completion: 11/25)
Tozorakimab	IL-33	FRONTIER-4 (Phase 2a, Singh et al presented at BTS 2024)[40] OBERON & PROSPERO (Ongoing, estimated completion: 8/25)
Astegolimab	ST2	COPD-ST2OP (Phase 2a, Yousef et al Lancet Resp Med 2022)[41] ALIENTO & ARNASA (Ongoing, estimated completion: 6/25)

*Only dupilumab is FDA approved for use in COPD. IL, interleukin; TSLP, thymic stromal lymphopoietin; ST2, interleukin 1 receptor-like 1; BTS, British Thoracic Society winter meeting.

The dupilumab COPD studies also recruited patients with blood eosinophil values ≥300 cells/μL, but who also had chronic bronchitis at baseline, with efficacy demonstrated in both BOREAS and NOTUS in terms of exacerbations, lung function, and symptoms (although not SGRQ).[37,38] Dupilumab was subsequently approved by the FDA for 'uncontrolled' COPD, although with no guidance on the definition of 'uncontrolled'.

In contrast to therapies that target T2 inflammation, the alarmins IL-33 and thymic stromal lymphopoietin (TSLP) are released from the epithelium to direct the overall inflammatory cascade. There is some evidence that they are pleiotropic, such that the same drug may work on different types of inflammation depending on the patient type. In a Phase 2a study, the TSLP blocker tezepelumab was effective on moderate/severe COPD exacerbations in patients with blood eosinophils ≥150 cells/μL but not <150 cells/μL.[42] Further, in subgroup analyses of two IL-33 inhibitors, itepekimab was effective in former smokers although not in current smokers,[39] whereas tozorakimab was effective in both current and former smokers.[40] To add further confusion, the efficacy of the interleukin 1 receptor-like 1 (ST2) inhibitor astegolimab in terms of exacerbation reduction was greater in patients with low eosinophil levels, whereas the improvements in FEV1 and SGRQ were greater in patients with high eosinophil levels.[41]

As Phase 3 data become available for the products in Table 1, clinicians will need to think carefully about the selection of patients to be treated with specific biologics.

Non-CF bronchiectasis and cough. New insights and therapies

Anne E. O'Donnell, Georgetown University, Washington DC, USA

There are no currently approved therapies for bronchiectasis, despite a recent estimate that US prevalence is 340,000–522,000 patients.[43] Bronchiectasis is more common in women (67%), persons ≥65 years (76%), and in Asian Americans. The prevalence increased by 8.7% between 2000 and 2007,[43,44] partly due to the availability of imaging. For example, in a lung cancer screening program, 23% of participants had previously undiagnosed bronchiectasis.[45] Further, although a range of causes have been identified, 20–30% have idiopathic disease.[46]

The pathogenesis of bronchiectasis is a vicious cycle, in which an initial insult (either infection or injury) results in neutrophilic inflammation followed by airway destruction and distortion, with abnormal mucus clearance and mucostasis facilitating bacterial colonization, further increasing neutrophilic inflammation.[47] Importantly, the interactions between these components are complex, with each step interacting with all others, and therefore a 'vortex' is perhaps a better model than a simple cycle.[48]

The clinical diagnosis of bronchiectasis includes clinical features (permanent dilatation of the airways, pulmonary function testing, respiratory cultures, differential blood count, and assessment for underlying diseases) plus confirmation by imaging (high resolution computed tomography [CT]). Comorbidities are common: In a US database of patients with non-cystic-fibrosis (CF) bronchiectasis, 20% had COPD and 29% had asthma.[49]

No currently available treatments have been shown to reverse bronchiectasis. The current focus of treatment is to prevent exacerbations, control symptoms, improve QoL, preserve lung function, and reduce mortality. First-line therapy includes airway clearance using mechanical and exercise maneuvers (see https://bronchiectasis.com.au/ for education videos), in addition to pharmacologic agents and nebulized hypertonic saline.[50]

Many patients are chronically infected with a range of pathogens, with up to 30% chronically infected by *Pseudomonas aeruginosa*,[46] increasing the risk and severity of exacerbations. Exacerbation treatment should be targeted to the infective organism, with maintenance antibiotics recommended for patients with frequent exacerbations. A range of studies have evaluated long-term oral macrolide therapy (azithromycin or erythromycin), with some patients benefiting in terms of an exacerbation reduction,[51] and inhaled antibiotics effective in others (although such use is off-label).[52] ICSs should be used with caution (and not routinely unless the patient has asthma), especially as they may promote non-tuberculosis mycobacterium infection.[53]

Given 70–80% of patients with bronchiectasis have neutrophilic inflammation, clinical trials are underway to evaluate targeting this pathway. For example, the dipeptidyl peptidase 1 (DPP-1) inhibitor brensocatib reduced the proportion of patients who exacerbated compared with placebo.[54] In addition, real-world data suggest that targeting eosinophilic inflammation (present in 22.6% of a European cohort,[55] and associated with streptococcus and pseudomonas microbiome profiles) could be beneficial in that subset of patients.[56] Finally, phage therapies, which are in early development, have shown initial benefits that need clinical trial confirmation.[57]

In summary, earlier diagnosis of bronchiectasis, through physician education, and a multi-dimensional approach have potential to improve outcomes for patients. However, novel, personalized therapies are needed.

Session 3: Spirometry in 2024: Time for a change?

What is normal or abnormal? The Global Lung Function Initiative

Sanja Stanojevic, Dalhousie University, Halifax, NS, Canada

The hallmark of COPD is airflow obstruction. Two approaches to define airflow obstruction are the American Thoracic Society/European Respiratory Society (ATS/ERS) definition of FEV1 to forced vital capacity (FVC) ratio below the lower limit of normal (LLN), and the GOLD fixed-ratio (FEV1/FVC<0.7), with ongoing debate over which is 'more correct'. There are many similarities between the two approaches, but the limitations inherent to both can lead to a delayed diagnosis in some patients – and the definition of airflow obstruction applied may influence insurance coverage and access to treatments. The updated ERS/ATS technical standard on interpretive strategies for spirometry outlines three stages to the interpretation of pulmonary function tests (PFTs). First, whether the measured value is within the range expected in a healthy population;[58] second, to characterize the underlying physiological phenotype (e.g., obstructive vs. restrictive); and third to apply the physiological interpretation in the context of symptoms, clinical history to reach a clinical diagnosis or prognosis. The LLN describes the physiological pattern of airflow obstruction that applies more broadly beyond COPD, whereas the GOLD approach focuses on the clinical interpretation, such that in the presence of symptoms and airflow obstruction a diagnosis of COPD is likely. As new evidence emerges regarding the diverse determinants of COPD, and the heterogenous pathophysiology of the condition,[59] it becomes easier to see the limitations and challenges of both these approaches.

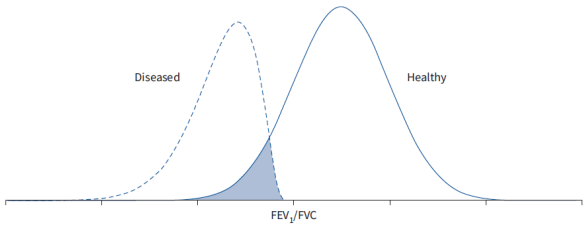
For lung function, determining whether a measured value is within the expected range of a healthy population requires a reference equation. Since taller people generally have larger lungs, males tend to have larger lungs than females for the same standing height, and aging influences the properties of the chest wall and muscle strength, it is necessary to consider these factors to define 'healthy'. The choice of reference equation is important when using the LLN to define airflow obstruction, and for defining severity of impairment (i.e., percent predicted). The Global Lung Function Initiative (GLI) was established to combine data from around the world to standardize reference equations for lung function globally.[60] Although a single equation helps to standardize interpretation, this approach is not without limitations. The LLN is sensitive to population differences (i.e., depends on who is included in the healthy population and how health is defined). For instance, if individuals with underdiagnosed lung disease are included in the healthy population, the LLN is more likely to miss classify individuals as 'healthy'. Further, lung health at the population level has been improving over time,[61] and the GLI equations do not take these changes into account. A critical evaluation of the historical use of race or ethnicity specific reference equations further challenges how we interpret PFT results. Race is a sociopolitical construct not biological, is linked with racism, is not uniformly defined across time or geography, and is not a proxy for genetics. The observed differences in lung function between people of different racial and ethnic backgrounds may represent the unmeasured effects of early life factors, air quality and other environmental variables, and so the use of race or ethnic specific equations may mask modifiable risks. As of 2023, the ATS/ERS recommend the use of race-neutral approaches to interpreting lung function.[62]

Although the fixed ratio method (i.e., FEV1/FVC<0.7) performs well at predicting subsequent COPD-related hospitalization or mortality when applied at a population level,[63] the 'one size' approach does not work equally for all individuals. It performs better for males and people with a history of smoking, whereas it is more likely to misclassify females (a higher cut-point is more predictive of exacerbation and death), never smokers, non-white populations, and younger people.

The limitations of both the LLN and fixed ratio methods highlight that there is much uncertainty when interpreting pulmonary function tests. The distribution of FEV1/FVC values in the population with healthy lungs overlaps with the distribution in those with diseased lungs (Figure 2), creating a 'zone of uncertainty'.[58] Patients with values close to either the LLN or fixed ratio cut-point may therefore need alternate tests or repeat PFTs as part of their clinical investigations.

In conclusion, regardless of whether LLN or fixed ratio is used to define airflow obstruction, the interpretation of PFT results must always consider the inherent biological variability of the test and the uncertainty of the test result.

Figure 2. Theoretical distribution of health and disease. The shaded area is the zone of uncertainty (reproduced with permission of the European Respiratory Society 2022 from Stanojevic et al. Eur Respir J 2022;60:2101499).[58]



FEV1: forced expiratory volume in 1 sec; FVC: forced vital capacity.

Implications and practicality of race-based adjustments in interpreting lung function reports

Meredith McCormack, Johns Hopkins University, Baltimore, MD, USA

Race-specific equations work by comparing data from an individual to that of a group that self-identify as the same race/ethnicity. In an analysis of National Health and Nutrition Examination Survey (NHANES) data, Black participants had lower FEV1 on average than White participants.[64] When race-specific equations were applied to these data, Black participants had 7% higher FEV1 percent predicted values than when using a multiracial approach. If the lower average lung function in Black compared with White individuals is 'normal', applying race-specific reference equations should yield a similar risk of mortality across races for a given estimated lung function, whereas a multiracial approach would overestimate mortality risk. However, this was not the case,[64] with the multiracial approach yielding similar mortality risk between groups (with similar results in other analyses for SGRQ, CAT, and exacerbation risk[65,66]). This suggests that a race-specific approach reinforces a false assumption that lower lung function is 'normal' among Black populations and does not have health implications. A race-neutral approach is now being advocated, using composite equations.

The application of race-based equations to the interpretation of PFT data can have a significant impact on a patient's resulting care. Using data from the US Department of Veterans Affairs, switching from a race-specific to a race-neutral approach would potentially result in decreased candidacy of Black individuals for lung resection, and increased candidacy of White individuals, whereas it would have the opposite effect on lung volume reduction surgery (an increase in Black and Asian candidates, and a decrease in White candidates).[67] Furthermore, the change would potentially impact disability payments, with some Asian and Black veterans experiencing increases, whereas White veterans could see a decrease. In a second database analysis, compared with a race-neutral approach, applying a race-specific approach resulted in lower lung allocation scores (used to prioritize lung transplantation) for Black patients and higher scores for White patients, potentially contributing to racially biased allocation of lung transplantation.[68] Overall, the change in approach would potentially reclassify ventilatory impairment for 12.5 million individuals across the US, medical impairment ratings for 8.16 million, occupational eligibility for 2.28 million, and COPD severity for 2 million, with military disability compensation impacted in 413,000 individuals.[69]

In conclusion, the application of race-specific approaches to the interpretation of PFTs have significant clinical and societal implications. Care should be taken over thresholds, where there is always some uncertainty, and there is an urgent need for prospective studies on the consequences of implementing race-neutral equations on important clinical outcomes.

Spirometry for healthcare workers: From theory to practice

David Mannino, COPD Foundation, Miami, FL, USA

Pre-bronchodilator testing is adequate to classify COPD into obstructive, restrictive, or preserved ratio impaired spirometry (PRISm) – and most prediction equations are based on pre-bronchodilator data, although they are used to interpret post-bronchodilator results. Bronchodilator response does not reliably distinguish between asthma and COPD, and if reversibility is to be evaluated, the bronchodilator dose administered should be clinically relevant, such as two puffs of a short-acting β2-agonist. However, using a diagnostic drug that is used to treat the disease to exclude the presence of a disease seems inherently incongruent. Further, GOLD requires the use of post-bronchodilator spirometry to not only diagnose the presence of obstruction, but also classify the disease stage. Importantly, as the level of obstruction increases, the likelihood of reversibility also increases, suggesting that significant bronchodilator responsiveness is not the same as 'reversibility' of 'obstruction'.[70]

On balance, the fixed ratio works reasonably well, and given COPD is a disease of aging, increasing prevalence with age is to be expected. In addition, other diseases with prevalence that increase with age don't adjust their diagnostic thresholds (although therapy may be adjusted). The issue of the use of race-specific or race-neutral reference values is complicated – perhaps because thoracic size is very poorly evaluated. Indeed, the relationship between lung size and height shows some inconsistency between vital capacity and sitting or standing height,[71] and analyses of NHANES data from 9569 children suggest that the sitting to standing height ratio differs between races/ethnicities.[72] Further, just because lung function is in the normal range, it does not mean that lung function is normal – even patients with FEV1 values of 80–90% predicted are at increased risk of mortality compared to those who have FEV1 110% predicted. In addition, other factors such as socioeconomic deprivation, early life exposures, occupational exposures, and infections are not captured. The 'one-size fits all' approach of the race-neutral reference values therefore seems to be moving away from precision medicine.

Overall, therefore, although post-bronchodilator data are not needed to identify patients with COPD, they do provide clinically useful information, and the fixed ratio interpretation of FEV1/FVC data is still useful. In addition, the use of race-specific or race-neutral reference values is complicated, partly as a better metric of thoracic size is needed. In the meantime, the use of NHANES or GLI-White reference values for all individuals may be more defensible than an averaged reference, which results in some individuals moving from 'abnormal' lung function to 'normal'.

Session 4: Novel drugs in COPD: Are they finally here?

Overview of potential biological targets

Stephen Rennard, University of Nebraska Medical Center, Omaha, NE, USA

Biological therapies are defined as those produced in a biological rather than a chemical system, and thus include monoclonal antibodies, proteins (including cytokines), enzymes, immunomodulators, and growth factors, with monoclonal antibodies being the center of this discussion. Whereas traditional small molecules work by interacting with receptors, biologics usually work through protein/protein or macromolecule/macromolecule interactions (although some can also interact with receptors).

The development of biologic therapies requires a knowledge of pathways to identify suitable targets. However, the pathways involved in, for example, inflammation in COPD, are diverse,[73] with potential targets in multiple cell and subcell types. To add complexity, the heterogeneity of COPD means that whereas a target may have a positive outcome in one patient, it may have a negative outcome in a second, even in the same tissue. Furthermore, the 'confusograms' used to illustrate the pathways involved in COPD development and progression, although typically detailed, are over-simplifications of the processes involved.

Multiple targets for biological therapies have been tested in patients with COPD, with some success. Importantly, however, trials to date have only made very moderate considerations of the heterogeneity of COPD (recruiting patients based on smoking history, chronic bronchitis [often with a 'soft' definition], or eosinophil counts). Unless there is a much better idea of heterogeneity, there is a risk that the results of these studies will be swamped by 'noise'.

Most studies have used exacerbations as the primary endpoint, which is sensible given the impact of exacerbations on these patients, with a few studies evaluating health status, dyspnea, FEV1 or safety as the primary endpoints. More interesting or relevant therapeutic goals would be to demonstrate restoration of a normal inflammatory response (given patients with COPD tend to have an abnormal inflammatory response), to alter disease progression, or to restore lost structure/function – or even to evaluate a treatment's systemic effects. Future developments could be repurposing treatments for other diseases, where there is a shared biology with COPD, and the use of stem cell therapy. Importantly, it may be possible to learn more about the pathobiology of COPD by studying how biological therapies work, rather than developing therapies based on knowledge of the biological systems.

The eosinophil as a Th2 marker

Mona Bafadhel, King's College London, London, UK

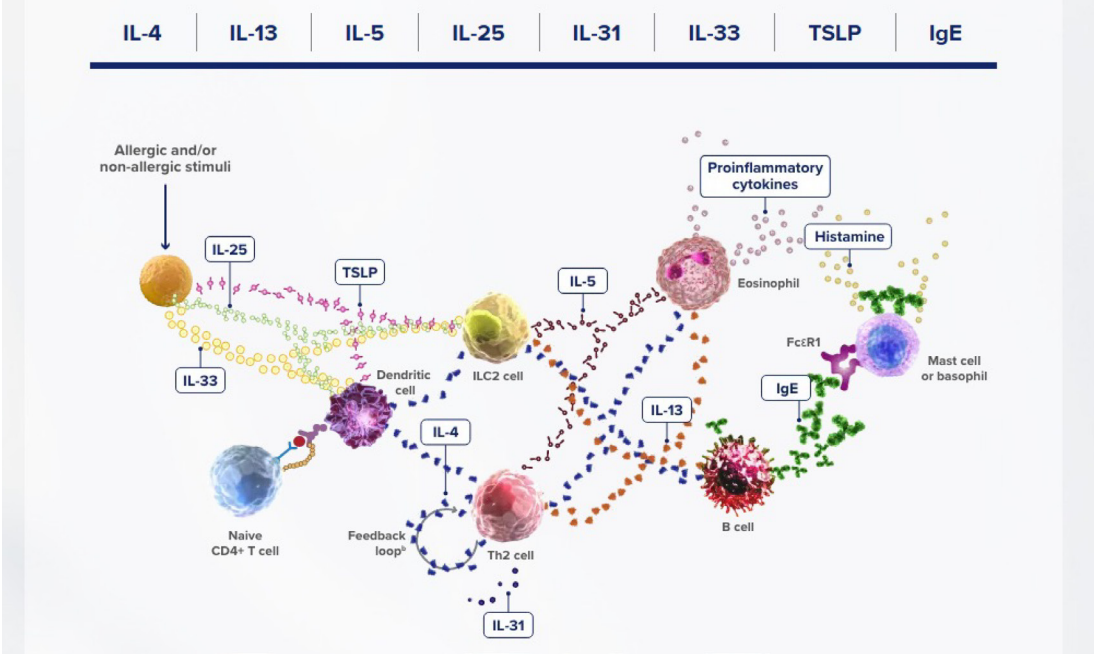
According to the FDA, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention. Eosinophils meet this definition, as levels can be measured and provide information about patients' characteristics and response to therapies. This is illustrated in the stripped-down diagram in Figure 3. Damage to the epithelium results in the release of the alarmins TSLP, IL33, and IL25, which then triggers Type 2 T helper cells (Th2), Type 2 innate lymphoid cells (ILC2) and dendritic cells to secrete IL-4, IL-13 and IL-5, which have important roles in the T2 inflammatory cascade, stimulating or promoting trafficking of eosinophils to the site of inflammation. Eosinophils in turn release IL-4, IL-13 and IL-5 (so driving further T2 inflammation), and may also have a role in a range of repair systems and may also be a regulator of the response to infections.[74]

In patients with COPD, eosinophilic inflammation is especially relevant at the time of an exacerbation – but even in the stable state up to 40% of patients with COPD have raised sputum or blood eosinophil counts.[75–77] Importantly, patients with raised blood eosinophil counts are likely to also have raised sputum eosinophil values, higher IL-5 concentrations, and increased airway tissue remodeling (although it is unclear whether this is a causative relationship).[78] Further, high blood eosinophil counts are associated with an increased rate of COPD exacerbations.[79]

Interestingly, eosinophil subtypes appear to differ between patients with asthma or COPD.[80] The implications of this are unclear, but it is possibly related to the role of eosinophils in infection response (eosinophils demonstrate antibacterial activity in murine models[81]). Further, the airway biome is differentially expressed between eosinophilic and non-eosinophilic COPD.[82]

Overall, eosinophils are important in COPD, and understanding their mechanisms of action are important, as are the standardization of the measurement of T2 inflammatory markers.

Figure 3. The type 2 inflammatory pathway (reproduced with permission from Sanofi Regeneron).



Available at: https://www.type2inflammation.com/ IL, interleukin; TSLP, thymic stromal lymphopoietin; Ig, immunoglobulin

Which biologic for which type of patient?

Dave Singh, University of Manchester, Manchester, UK

Every patient with COPD has dysregulation of their innate immune response. Although traditionally COPD was believed to involve neutrophilic inflammation (and nearly every patient does have neutrophilic inflammation in their lung tissue), some patients also have eosinophilic inflammation. A very important question is whether eosinophils are causative agents for exacerbations in patients with COPD, a biomarker of exacerbations, or both.

A key consideration when selecting a monoclonal antibody that targets cells or cytokines in patients with COPD is identifying the 'responder' population. An analysis of pooled mepolizumab data demonstrated that efficacy (in terms of the relative effect vs. placebo on exacerbation rates) increased with increasing blood eosinophil count.[35] Further, although benralizumab did not significantly reduce exacerbations compared with placebo in the two Phase 3 studies, in a pooled analysis the effect of benralizumab on exacerbations increased in patients also receiving triple therapy, increased further in those with ≥3 prior exacerbations, and was maximal in patients who also had post-bronchodilator response ≥15%.[83] In contrast, in patients with an exacerbation history and chronic bronchitis, dupilumab significantly reduced exacerbations compared with placebo, and provided an early improvement in lung function,[37] with the treatment effect higher in patients with a high forced exhaled nitric oxide (FeNO) level.[37,38]

The involvement of both eosinophilic and neutrophilic inflammation in COPD suggests that there is a potential role for biologicals targeting the alarmins IL-33 and TSLP, given these are involved in control of both T2 and non-T2 inflammation.[84] Tezepelumab is an anti-TSLP, that works well across the continuum of T2 inflammatory markers in patients with uncontrolled asthma,[85] and with COPD.[42] Further, the anti-ST2 astegolimab was similarly effective in adults with severe asthma regardless of blood eosinophil count,[86] with consistent results in an initial Phase 2a COPD study.[41] Finally, the anti-IL-33 itepekimab significantly reduced the incidence of COPD exacerbations compared to placebo in ex-smokers, but not in current smokers,[39] potentially explained by transcriptomics data that suggest IL-33 expression is lower in current smokers.[87]

In summary, in patients with COPD anti-IL-5 therapies are likely to be best suited for those with high blood eosinophil counts (≥300 cells/μL), with high FeNO potentially identifying responders to dupilumab. Tezepelumab is likely to be effective across a wider range of eosinophil counts (although not <150 cells/μL), with anti-IL-33 therapies potentially restricted to ex-smokers. However, it is important to consider other outcomes than exacerbations. Larger randomized trials, with additional biologics, will better inform the specific COPD groups likely to respond to specific biologics.

Can biologics modify COPD progression?

Klaus F. Rabe, LungenClinic Grosshansdorf, Grosshansdorf, and Christian Albrechts Universität, Kiel, Germany

Nobody knows whether biologics can modify COPD progression, and indeed none of the medications used in clinical practice has clear evidence of an impact on COPD progression.[59] Importantly, however, disease progression is not a criterion for drug approval, which is typically based on no more than 6–12 months of data. For example, lung function was sufficient from a regulatory perspective for the approval of ensifentrine (together with safety data), with the primary endpoint based on Week 12 data.[9]

There is currently no agreement on whether inflammatory biomarkers serve a role only in treatment selection in COPD, or whether levels must be normalized to halt progression – and none of the current biomarkers are used in diagnosis. Further, a range of clinical markers have been investigated in COPD and that may relate to clinical outcomes – such as body-mass index (BMI), FeNO, SGRQ, and the breathless, obstruction, dyspnea, exercise capacity (BODE) index. However, there is a paucity of information on the capacity of these various markers to measure disease progression.

Given biologics address biological processes, it is possible they will target disease progression. Biologics that target T2 inflammation may impact disease progression in the 20–40% of patients with COPD who have eosinophilic inflammation. Indeed, if exacerbations and lung function are considered markers of disease progression, BOREAS data suggest that dupilumab may stabilize progression over a 1-year period.[37] However, what about the other 60–80%? The alarmins are likely to mediate structural integrity – and to regulate inflammation *per se*,[88] especially in former smokers,[39] and so it is possible that their regulation may offer an opportunity to control disease progression. It is also possible that disease progression may be more related to genetic instability than T2 inflammatory status, with some work conducted in Germany demonstrating that a polygenic risk score combining PFT with genotyping could identify a subgroup of children at high risk for subsequent COPD.[89]

Given the high prevalence of multimorbidity in patients with COPD across the lifespan,[90] there is an argument for studying individuals at a much younger age – patients with COPD aged 20–50 years, or even pre-COPD (individuals of any age who have respiratory symptoms with or without structural and/or functional abnormalities).[91] Such studies may identify changes that characterize progression from health to disease, and therefore reveal tools that can halt disease progression.

Session 5: 2025 GOLD report and review

GOLD 2025 novel recommendations

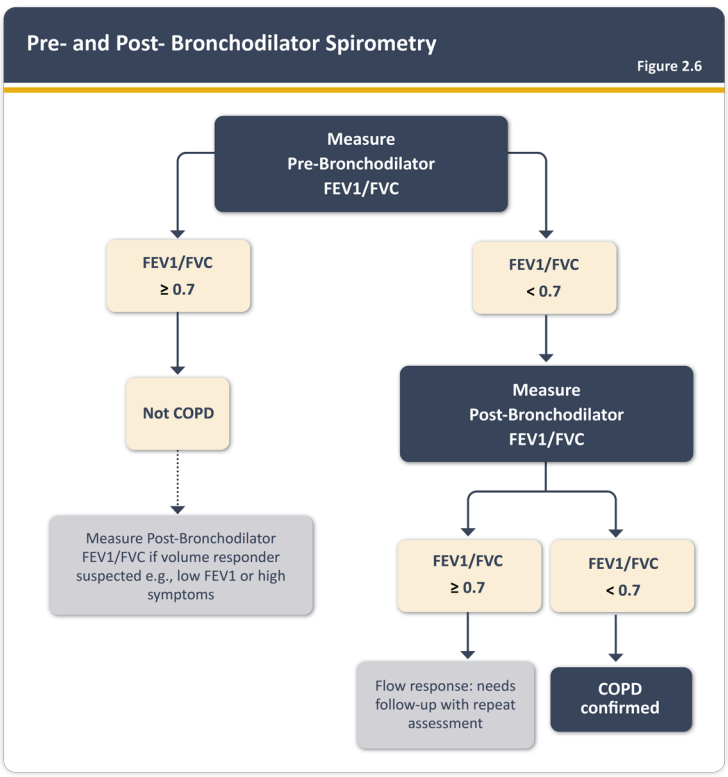
Claus F. Vogelmeier on behalf of GOLD Science Committee

To prepare the annual update of the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, the GOLD Science Committee reviews thousands of new publications released since the prior version, to ensure all recommendations are evidence-based.

In the 2025 report, the information on spirometry now includes more information on LLN values, z-scores (the number of standard deviations by which an observed value is above or below the mean), and reference values. In terms of reference values for lung function interpretation, race-neutral GLI-Global reference equations are recommended rather than race-specific equations, although the report acknowledges that there are still issues with the race-neutral approach. For example, the equations were derived from populations in a limited number of countries, and they ignore differences in body proportions.

Pre-bronchodilator spirometry can now be used as an initial test to investigate whether individuals who are symptomatic have airflow obstruction, illustrated with a new figure (Figure 4). Post-bronchodilator spirometry is still mandatory to reach the diagnosis of COPD, and the criterion remains the fixed FEV1/FVC ratio of 0.7. Use of the fixed ratio rather than the LLN has advantages – it is simple, established, and is not dependent on reference values. Further, in an analysis of NHANES data, subjects classified as normal using LLN criteria but obstructed or restricted using GOLD criteria had an increased mortality risk.[92] However, the elderly are more likely to be diagnosed as having airflow obstruction with the fixed ratio than the LLN.

Figure 4. Pre- and post-bronchodilator spirometry (© 2024, 2025, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL, USA).



FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease

Given the importance of cardiovascular disease as a comorbidity of COPD (and vice versa), a section has been added on cardiovascular risk. This covers patients both during the clinically stable state and at exacerbation (the risk of cardiovascular events or all-cause death is increased 20-fold by a severe exacerbation, and persists for up to a year[93]).

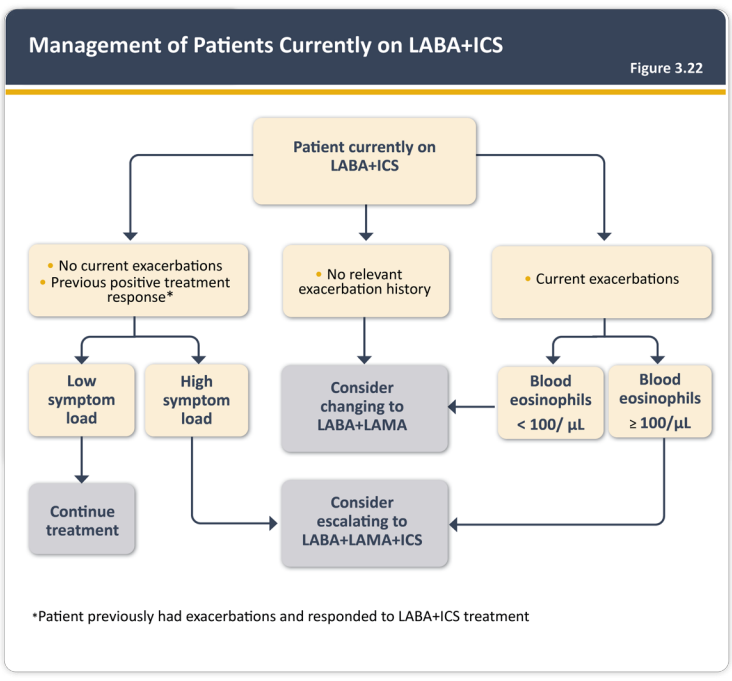
As a reflection that computerized CT imaging is becoming more and more relevant, the section on CT has been updated, and now includes information on emphysema, lung nodules, airways (including bronchiectasis), and COPD-related multimorbidity. For example, in addition to detecting lung cancer, CT imaging is often superior to clinical diagnostics in detecting comorbidities such as emphysema, bronchiectasis, coronary artery calcification, liver steatosis, and muscle weakness.[94] Given many patients already undergo CT, it is time to make more use of the images.

A section on climate change has been added to the report, recognizing the impact of both excess heat and cold on patients with COPD. Indeed, just a 1°C increase in temperatures above 23.2°C increases COPD hospitalization risk by 1.47% in both men and women.[95]

The follow-up pharmacological treatment section has been updated, to include ensifentrine as an option for patients who have dyspnea despite LABA+LAMA therapy, and dupilumab for patients who continue to exacerbate when receiving LABA+LAMA+ICS and who have blood eosinophil counts ≥300 cells/μL. In addition, given LABA+ICS is no longer recommended for patients with COPD (with LABA+LAMA+ICS superior where there is an indication for an ICS), advice is provided on how to manage these patients (Figure 5). Those who have had a previous treatment response, no current exacerbations, and a low symptom load can continue with LABA+ICS treatment; escalation to LABA+LAMA+ICS should be considered for patients who have a high symptom load, or current exacerbations and blood eosinophil counts ≥100 cells/μL. The switch to LABA+LAMA should be considered for all other patients.

Finally, a section on pulmonary hypertension (PH) has been included. The recommendation is that patients with comorbid PH and COPD should be referred to a specialist PH center for right heart catheterization and multidisciplinary assessment to guide treatment decision.

Figure 5. Management of patients currently on LABA+ICS (© 2024, 2025, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL, USA).



LABA, long-acting β2-agonist; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist.

Session 6: COPD phenotypes and their multimorbidity pattern

The diastolic dysfunction phenotype in patients with COPD

Jennifer Quint, Imperial College London, London, UK

Cardiovascular disease (and especially heart failure) is a common comorbidity of COPD (especially in younger patients) and is associated with a high burden.[96] There are many reasons for the high prevalence of cardiovascular disease in COPD, including common risk factors.[97] For example, COPD results in increased pulmonary vascular resistance, leading to cor pulmonale, and emphysema is associated with reduced cardiac output, left ventricular (LV) mass, and left and right ventricular and function.[98]

Cardiologists divide heart failure into three types – reduced, mildly reduced, or preserved ejection fraction (HFrEF, HFmrEF, or HFpEF). HFpEF involves LV diastolic dysfunction and preserved ejection fraction (>50%), but has many phenotypes, including those associated with diabetes, obesity and renal failure.[99] Between 15–20% of patients with HFpEF have COPD,[100] with HFpEF and COPD sharing symptoms, including dyspnea and exercise limitation, increasing the chance of misdiagnosing HFpEF.[101] Comorbid heart failure is more common in patients with COPD who are older, male, or have more lung function impairment.[100] Importantly, the prevalence of heart failure in patients with COPD is not increasing in the same way as in the overall population, suggesting some under-diagnosis. Indeed, in a study in patients with COPD with no known cardiac disease or cardiovascular risk factors other than smoking, 64% had significant cardiac alterations at their first hospital admission.[102] Given the prognostic and therapeutic implications of the coexistence of COPD and HFpEF (including higher mortality than COPD alone),[103–105] echocardiography should be considered in all patients with clinically significant COPD.

Heart failure therapies are generally well tolerated in patients with COPD (and β-blockers are not contraindicated), with some evidence that aggressive diagnosis and treatment of heart failure in this population may also decrease the risk of COPD exacerbations.[106] Although there are no data on the impact of ICSs on heart failure, they do not increase the incidence of cardiovascular events in patients at high cardiovascular risk. In the future, the development of rapid clinical diagnostic indicators and the early use of novel drugs such as sodium/glucose cotransporter 2 (SGLT-2) inhibitors (including dapagliflozin) and angiotensin receptor neprilysin inhibitors (ARNIs) may improve the prognosis of this population. Finally, a composite scoring system has been developed to assist in the identification of HFpEF (the H2FPEF score).[107] Unfortunately, this doesn't include any mention of COPD. Future risk scoring systems may need to take COPD into account.

In summary, HFpEF is common in patients with COPD, and the coexistence of COPD and HFpEF is associated with worse outcomes. Current heart failure guidelines are better at recognizing COPD as a risk factor for adverse events than COPD guidelines are at recognizing heart failure.

The pulmonary hypertension phenotype in patients with COPD

Gabor Kovacs, Medical University of Graz, Graz, Austria

PH is classified into five groups, one of which (Group 3) is associated with lung disease, and which contains most (although not all) patients with PH-COPD. Approximately 1% of the overall population have PH, whereas approximately 25–30% of patients with COPD have PH-COPD,[108] with higher prevalence in those with more severe COPD.[109] Further, patients with PH-COPD have a worse prognosis than those with COPD or PH alone,[110–112] and whereas the severity of airflow limitation and PH are independent risk factors for mortality, the combination is associated with a much poorer prognosis.[113]

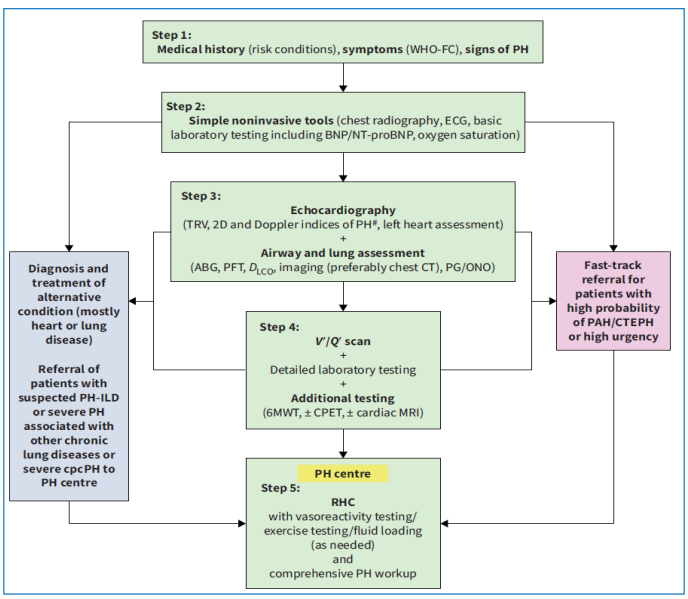
In terms of diagnosis, if COPD alone doesn't explain a patient's symptoms, it is important to look for other causes, including PH. The diagnostic approach starts with simple non-invasive tools (such as chest radiography, electrocardiogram, and laboratory testing) and continues with more specific testing (echocardiography being the most important non-invasive tool in the diagnosis of PH).

When severe PH is suspected, the patient should be referred to specialist PH centers in order to perform right heart catheterization to confirm the diagnosis and allow appropriate management (Figure 6).[114]

Treatment of PH depends on the phenotype,[115] with the guideline recommendation for PH-COPD being to optimize treatment of the underlying lung disease, and initiate oxygen therapy if indicated.[108] Phosphodiesterase-5 inhibitors have been shown to improve hemodynamics, but with inconsistent clinical benefits.[115,116]

In summary, all groups of PH may be diagnosed in patients with COPD, although Group 3 (especially with severe PH) is particularly relevant. Treatment is guided by the phenotype, although currently no specific therapy is approved for PH-COPD and well-designed randomized-controlled trials are needed. Patients with severe PH should be referred to centers with experience handling PH.

Figure 6. Suggested diagnostic approach to pulmonary hypertension (reproduced with permission of the European Respiratory Society 2024 from Kovacs et al. Eur Respir J 2024; 64:2401324).



WHO-FC, World Health Organization functional class; PH, pulmonary hypertension; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-BNP; TRV, tricuspid regurgitation velocity; 2D, two-dimensional; ABG, arterial blood gases; PFT, pulmonary function testing; DLCO, diffusion capacity of the lung for carbon monoxide; CT, computed tomography; PG, polygraphy; ONO, overnight oximetry; V'/Q' scan, ventilation/perfusion scan of the lung; 6MWT, 6-min walk test; CPET, cardiopulmonary exercise testing; MRI, magnetic resonance imaging; RHC, right heart catheterization; PH-ILD, pulmonary hypertension associated with interstitial lung disease; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; cpcPH, combined post- and pre-capillary PH.

Metabolic disorders in patients with COPD

Kristin E. Criner, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA

The multimorbidity pattern within an individual depends on the COPD phenotype. Patients with emphysema typically have increased apoptosis, necrosis, and fibrosis, and so osteoporosis and sarcopenia are typical comorbidities. In contrast, patients with chronic bronchitis typically have higher BMI and increased systemic inflammation (IL-6, tumor necrosis factor α, and C-reactive protein), with typical comorbidities being metabolic disorders, obstructive sleep apnea, and Type 2 diabetes mellitus.

Type 2 diabetes mellitus is more prevalent in patients with COPD than the overall population, not only due to increased systemic inflammation, but also adiponectin, which increases insulin sensitivity, with levels inversely associated with COPD severity.[117] Although metformin has been shown to reduce the risk of exacerbations in asthma, this is not the case for COPD. However, glucagon-like peptides (GLP-1s) have been shown to decrease airway inflammation, exacerbations and mortality risk in patients with comorbid COPD and diabetes mellitus, potentially by reducing local and systemic inflammation, airway hyperresponsiveness, and visceral adiposity.[118]

Osteoporosis is associated with deteriorating lung function, poor quality of life, pain, and increased hospitalization and mortality,[119] and is often underdiagnosed in patients with COPD. For example, in one analysis whereas 13% of patients had clinically diagnosed osteoporosis, 26% had osteoporosis detected through chest CT.[94] Therapies focus on calcium and Vitamin D supplementation, modification of risk factors, and pulmonary rehabilitation (including resistance and balance training). Bisphosphonates and anabolic therapies are useful, and if these are not tolerated selective estrogen receptor modifier therapy is recommended.

In conclusion, both Type 2 diabetes mellitus and osteoporosis are prevalent co-morbid conditions in COPD, and early detection, identification and treatment are key, alongside modification of risk factors, and avoiding unhealthy lifestyles and corticosteroid use.

Lung cancer and COPD

M. Patricia Rivera, Department of Medicine, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA

The estimated annual global incidence of lung cancer is 2.5 million cases.[120] It is the most common cause of cancer-related death, with an estimated 1.8 million deaths in 2022, forecast to increase to 2.5 million by 2040. In 2024, the incidence of lung cancer in the US was higher in women than in men for the first time.[121]

Tobacco smoking is the most common risk factor for lung cancer, implicated in approximately 80% of US cases – the other 15–20% of cases are likely due to indoor and outdoor pollution, radon exposure, occupational exposure such as asbestos, or inherited or acquired gene changes.[122–124] Individuals who have COPD have up to a 5-fold increased risk of lung cancer compared to individuals who do not smoke and have no airflow obstruction.[125,126] Interestingly, although COPD is associated with poor prognosis in patients with lung cancer, the COPD inflammatory environment may result in better response to immunotherapy.[127]

The increased prevalence of lung cancer in COPD suggests there may be common mechanisms (e.g., aging) or pathogenic factors between the conditions. In addition, a range of genes have been identified as either predisposing an individual to both COPD and lung cancer, or to the progression from airflow obstruction to lung cancer.[128,129]

In terms of risk stratification, although age and total smoking pack years are perhaps simplistic, it is a practical way to identify individuals who are eligible for lung cancer screening. The incorporation of COPD into lung cancer risk prediction models to identify those who would benefit from screening is potentially a double-edged sword, as although patients with COPD are at increased risk of lung cancer, according to an ATS research statement, "The benefit of screening those with advanced-stage COPD … is uncertain, and how best to risk stratify these patients using functional status information should be an area of research."[130] Further, patients with COPD are at increased risk of complications from screening,[131] with the relative reduction in mortality as a result of screening lower than individuals with normal lung function.[132]

In summary, COPD and lung cancer are associated with significant global morbidity and mortality. Lung cancer screening reduces lung cancer mortality.[133] However, lung cancer screening is complex, and balancing the risks and benefits in individuals with COPD and other comorbidities is critical.

Session 7: Telemedicine and digital tools: The future of COPD?

What does telemedicine look like in patients with COPD?

Jean Bourbeau, McGill University and McGill University Health Centre, Montreal, QC, Canada

The WHO defines telehealth as: "The delivery of healthcare services, where distance is a critical factor, by all health professionals using information communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interest of advancing the health of individuals and their communities."[134]

To meet this definition, interactions involve patients being physically distant from the healthcare professional and should be conducted through a suitable platform and in compliance with data protection laws (with legislation often differing between countries). Patients with COPD may face specific challenges over the use of telemedicine – in particular lack of access to devices, unreliable internet connectivity, discomfort with technology, or limited financial resources.

Literature on remote video consultations is sparse in COPD, with many studies being low or very-low quality,[135] and typically focusing on QoL, hospitalization or death in high-risk individuals.[136] The GOLD 2025 report provides guidance on telehealth in the section 'Monitoring and follow-up', with a standardized checklist included in the appendix that can be utilized whether the patient is seen in person or virtually.[11] However, data on the benefit and limitations of teleconsultation are needed, along with the short- and long-term impact of this implementation.

Telerehabilitation is the delivery of rehabilitation at a distance, can be delivered at a variety of locations including a patient's home, and may involve a range of exercise equipment, from minimal to specialized. Available data suggest telerehabilitation achieves outcomes similar to traditional center-based pulmonary rehabilitation, with no safety issues.[137] The GOLD 2025 report provides guidance in the section 'Delivery of pulmonary rehabilitation, education & self-management: in-person versus virtual'.[11] Although telerehabilitation has the potential to increase availability, access, and flexibility, with time and cost savings, such programs may not be suitable or acceptable for all patients. Importantly, checks and balances are needed to ensure that the appeal and benefits of telerehabilitation are not misused by inexperienced or unscrupulous providers.[138] Further data are needed on the optimum model, technological requirements (with standardization of delivery platforms) and training components. Importantly, most data are from studies conducted in patients with clinically stable COPD, not post-exacerbation.

The third aspect of telemedicine is tele-education (and self-management), with delivery at a distance of information having the potential to ease the working life of health practitioners, while transforming the way patients are monitored and healthcare is delivered.[139] The quality of evidence in this area is lower than telerehabilitation. In an early study, comprehensive patient education program administered through weekly visits by trained health professionals over a 2-month period with monthly telephone follow-up reduced COPD-related hospital admissions by 40%,[140] with a subsequent study showing that the self-management 'Living Well with COPD' program reduced all-cause hospitalization by 26.9% compared to standard care.[141] However, self-management includes a wide range of components,[142] and studies tend to focus on one (or a few) of these. Even then, most studies that evaluated education and information had poor methodological quality, those that examined monitoring and feedback in COPD were mostly neutral or inconsistent, and those that facilitated remote clinical review were generally neutral.[143] The only behavior to have been shown to improve with tele-education in COPD is adherence – but such studies typically don't describe the intervention or its intensity. The GOLD 2025 report states that the role of eHealth in COPD patient self-management at a distance remains to be clarified.[11]

In conclusion, telehealth for COPD is here to stay. However, higher quality studies are needed that are reported with sufficient detail to analyze the important components of the intervention and the technology used. Although telehealth could reduce healthcare disparities, it is possible that systemic shifts to telehealth could create and exacerbate these disparities.

Wearables and mobile apps –what are their role in predicting and monitoring exacerbations?

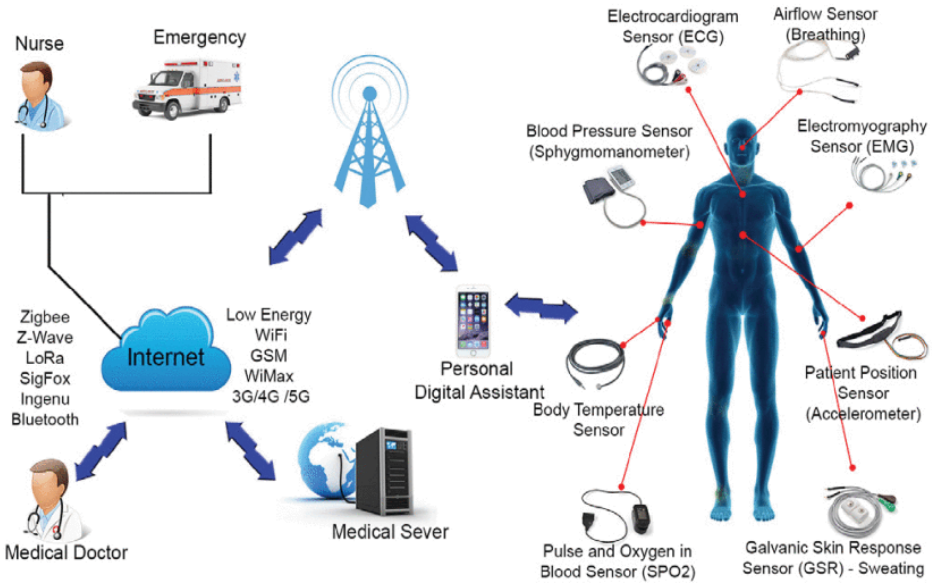
Narelle S. Cox, Monash University, Melbourne, Australia

A wide range of biometric wearable technology ('wearables') is available that utilizes wireless sensors, including smartphones, wrist bands, skin patches, objects (e.g., medication bottle caps), and equipment such as stethoscopes, and blood pressure, oxygen saturation and glucose monitors. These offer continuous or discrete (timepoint) monitoring of biological, physiological and/or behavioral data. There has been a rapid increase in publications in this field, with more than 8000 papers on the topic published in 2024, and a similar trajectory, albeit with much lower numbers, in people with COPD.

Wearables typically function by collecting data that then need to be processed (e.g., by a computer or smartphone; Figure 7). This in turn connects to a clinical server or cloud service for data processing and storage, before being transmitted to the clinician, ideally in a form that is interpretable.

The final step in the process is feedback to the patient, with information that may or may not inform clinical decision making. Wearables have been used to track a wide range of parameters in COPD, although a systematic review of more than 7000 publications included just 37 publications in the final analysis.[144] Wearable technology had little impact on quality-of-life measures – with even this impact short-lasting. Only 10 of the studies included exacerbations data, with mixed results for exacerbation avoidance and prediction.

Figure 7. Illustration of an architecture for remote healthcare monitoring system (reproduced with permission from Rodrigues et al. IEEE Access 2018;6:13129–41, © IEEE).



In terms of exacerbation prediction, there is no consensus on the best way to collect data, which data to collect, or even how often.[144] Good adherence to technology use is especially essential for exacerbation prediction. In one study, reporting compliance was 98% to daily well-being self-assessment on an app (although adherence to the other study assessments was not reported), enabling exacerbations to be identified a median of 7 days before the clinician-defined episode (sensitivity 97%, specificity 94%) with hospitalizations decreased by 98%.[145] In a second study, compliance to use of a wrist-worn device was 66–99%, with the algorithm able predict exacerbations 4.4 days before clinician validation (sensitivity 86%, specificity 84%).[146] In a third study, in which patients with COPD were provided with a smartphone and smart watch for 6 months, use of the app did not improve self-management, the primary outcome, and adherence declined over time even in those who were adherent over the first month.[147] Factors associated with adherence in this study included the complexity of monitoring/reporting, and patient factors including female sex and memory (although not age or self-reported technology familiarity). Importantly, although 88.2% had Wi-Fi at home, only 64.7% were a current or past smartphone user, and 35.3% had a smartwatch or wearable.[147] Overall, therefore, use of self-monitoring digital interventions for the management of COPD typically have little or no impact on exacerbation incidence compared to standard care, and even multicomponent interventions have an uncertain effect.[136]

Additional considerations for widespread wearable use are security and data privacy (in an analysis of more than 600 apps in 2022, the average security rating was D[148]) and cost (remote monitoring programs cost USD $275–7963 per patient per year,[149] but as they can improve access this may offer high value[150]). A final consideration is the amount of data that wearables can generate – one person's data from one timepoint had over 37,000 line-items of data, requiring cleaning and analyzing to be able to do anything clinically meaningful.

Overall, use of wearables and remote monitoring for exacerbation prediction and management appear promising, but the current evidence of effect, benefit, and usefulness remains limited. In the future, artificial intelligence (AI) and machine learning methodologies may be well suited to address the volume and complexities of wearable and remote monitoring data.

Session 8: Industry pipeline: Upcoming novel treatments for patients with COPD

Clinical endpoints, trial delivery and new therapeutic options in development for COPD patients

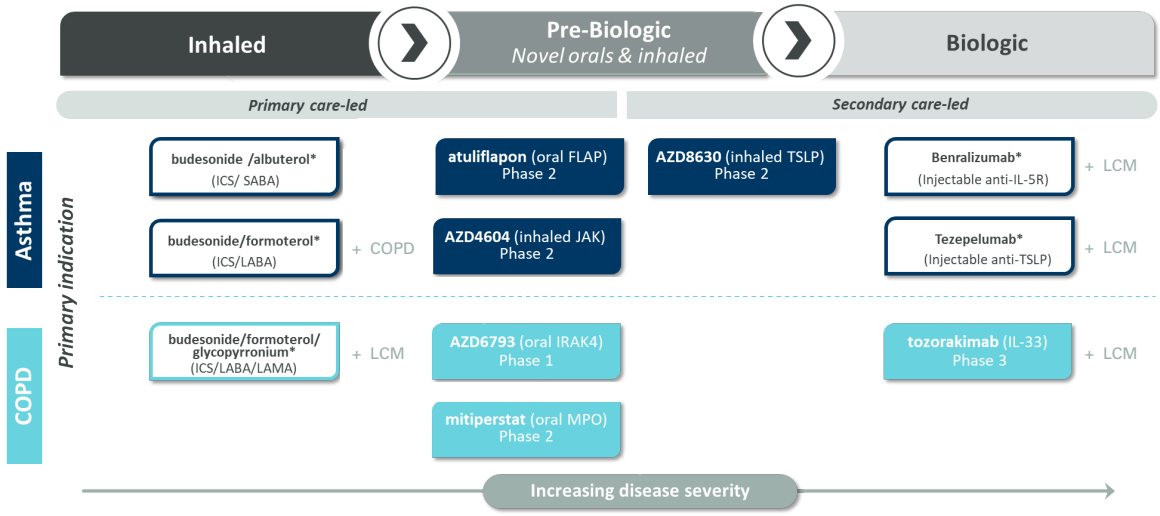
Maaria Belvisi, AstraZeneca

AstraZeneca's ambition is to utilize novel approaches to move from symptoms management to disease modification and remission, and to improve patient care. The company believes many diseases can be studied together, given common mechanisms (such as fibrosis or oxidative stress), using omics and AI approaches to extract data from clinical cohorts in a non-biased way. By employing precision medicine, the aim is to identify patients at the start who are most likely to respond – 'all comer' trials are no longer realistic. In order to move to disease-modifying therapy, new clinical trial endpoints are needed, outside of regulatory requirements, including structural imaging of the lung and longitudinal measures such as home spirometry to increase data granularity and to be more patient-centric. The current pipeline is illustrated in Figure 8.

In addition, AstraZeneca is conducting a pilot using a lung cancer screening program to identify individuals who have undiagnosed COPD for potential inclusion in clinical trials. This has so far tripled the randomization rate in participating sites over the global average for the study.

By 2030, AstraZeneca aims to have 14 new medical entities in development to address 23 respiratory and immunology indications, and to transform healthcare systems to enable more access to disease-changing therapies, so impacting the lives of more than 70 million patients.

Figure 8. The AstraZeneca asthma and COPD portfolio.



*Marketed products. ICS, inhaled corticosteroid; SABA, short-acting β2-agonist; LABA, long-acting β2-agonist; COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; FLAP, 5-lipoxygenase activating protein; JAK, Janus kinase; IRAK, interleukin-1 receptor-related kinase; MPO, myeloperoxidase; TSLP, thymic stromal lymphopoietin; IL, interleukin.

GSK respiratory clinical development pipeline

David A. Lipson, GSK

The GSK respiratory programs are summarized in Table 2. Mepolizumab completed the Phase 3 COPD METREX and METREO studies in 2017 and has just completed MATINEE. Compared with mepolizumab, the novel long-acting anti-IL-5 monoclonal antibody depemokimab has increased potency, permitting dosing every 6 months; replicate studies in the eosinophilic asthma phenotype have just been completed. Camlipixant is a highly selective P2X3 receptor antagonist in development for refractory chronic cough. GSK3923868 is a PI4K beta inhibitor currently at Phase 1b – in theory, blocking PI4K will block human rhinovirus replication, a cause of up to 25% of all COPD exacerbations.[151,152] Finally, the HFA-134a propellant in the albuterol pressurized metered-dose inhaler (pMDI) is responsible for nearly half of GSK's entire carbon footprint. A clinical program is underway to investigate transitioning this propellant to the low global warming potential propellant HFA-152a.

Table 2. GSK respiratory programs.

Compound	Type	Condition investigated	Frequency	Status
Mepolizumab[a,1–4]	Anti-IL-5 monoclonal antibody	COPD with eosinophilic inflammation	Q4W	Phase 3
Depemokimab[1,5–12]	Long-acting anti-IL-5 monoclonal antibody	SEA, EGPA, CRSwNP, HES	Every 6 months	Phase 3
Fluticasone furoate/ umeclidinium/ vilanterol[13,14]	ICS, LAMA, LABA	Asthma (Ages 12 to 17)	Once daily	Phase 3
Camlipixant[15,16]	P2X3 receptor antagonist	Refractory chronic cough	BID	Phase 3
Belimumab[17]	B lymphocyte stimulator monoclonal antibody	Systemic sclerosis associated interstitial lung disease (SSc-ILD)[18] Interstitial lung disease associated with connective tissue disease[19]	Weekly	Phase 2/3 Phase 3
GSK3923868[1,20-22]	PI4K beta inhibitor	Viral COPD exacerbations	TBD	Phase 1
GSK5462688[23]	RNA Editing oligonucleotide	Alpha-1 anti-trypsin deficiency	TBD	Phase 1/2
GSK5784283[20]	Long-acting anti-TSLP monoclonal antibody	Asthma	TBD	Phase 2
Albuterol MDI with propellant HFA-152a[20]	Beta-2 agonist	Asthma	TBD	Phase 3

[a]Previously filed with FDA with complete response letter received on September 7, 2018. BID, twice daily; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; FDA, Food and Drug Administration; HES, hypereosinophilic syndrome; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β2-agonist; LAMA; long-acting muscarinic antagonist; PI4K, phosphatidylinositol 4-kinase; Q4W, every 4 weeks; SEA, severe eosinophilic asthma; TBD, to be determined; TSLP, thymic stromal lymphopoietin. 1. GSK Annual Report 2022. Accessed October 28, 2024. 2. ClinicalTrials.gov identifier NCT02105948. Accessed October 28, 2024. 3. ClinicalTrials.gov identifier NCT02105961. Accessed October 28, 2024. 4. ClinicalTrials.gov identifier NCT04133909. Accessed October 28, 2024. 5. ClinicalTrials.gov identifier NCT04719832. Accessed October 28, 2024. 6. ClinicalTrials.gov identifier NCT04718103. Accessed October 28, 2024. 7. ClinicalTrials.gov identifier NCT04718389. Accessed October 28, 2024. 8. ClinicalTrials.gov identifier NCT05243680. Accessed October 28, 2024. 9. ClinicalTrials.gov identifier NCT05263934. Accessed October 28, 2024. 10. ClinicalTrials.gov identifier NCT05274750. Accessed October 28, 2024. 11. ClinicalTrials.gov identifier NCT05281523. Accessed October 28, 2024. 12. ClinicalTrials.gov identifier NCT05334368. Accessed October 28, 2024. 13. ClinicalTrials.gov identifier NCT05757102. Accessed October 28, 2024. 14. Data on File. Study 206867 (NCT05757102). 15. ClinicalTrials.gov identifier NCT05599191. Accessed October 28, 2024. 16. ClinicalTrials.gov identifier NCT05600777. Accessed October 28, 2024. 17. ClinicalTrials.gov identifier NCT05878717. Accessed October 28, 2024. 18. Denton CP, et al. Ann Rheum Dis. 2023; 82 (suppl_1):1668. 19. ClinicalTrials.gov identifier NCT06572384. Accessed October 28, 2024. 20. https://www.gsk.com/en-gb/innovation/pipeline/. Accessed October 28, 2024. 21. ClinicalTrials.gov identifier NCT04585009. Accessed October 28, 2024. 22. ClinicalTrials.gov identifier NCT05677347. Accessed October 28, 2024. 23. ClinicalTrials.gov identifier NCT06405633. Accessed October 28, 2024.

Upcoming novel treatments for patients with COPD

Elizabeth Laws, Sanofi

Sanofi's current COPD and broader respiratory pipeline is illustrated in Table 3. Dupilumab is now approved for COPD in more than 30 countries (including the USA). This, plus itepekimab (Phase 3 results for which are due in 2025), covers 80% of patients with COPD. Future developments are expected from Sanofi's proprietary NANOBODY® platform that can target multiple domains in a single molecule– for example, lunsekimig targets both TSLP and IL-13 in a single molecule. Initial data suggest that these domains exert independent and synergistic effects on tissue inflammation.

*Table 3. Sanofi's current pipeline in COPD.**

COPD with Type 2	COPD in former smokers	Broader commitment
• **Dupilumab** (IL-4Ra mAb) Two positive Phase 3 trials in COPD First biologic FDA approved in COPD • **Lunsekimi**g (TSLP/IL13 Nanobody® VHH) Ongoing early development in COPD	• **Itepekimab** (IL-33 mAb) Passed Phase 3 futility analysis in COPD, Phase 3 readouts in 2025	• **PCV21 Pneumococcal vaccine** initiating Phase 3 • **RSV vaccines** initiating Phase 3 for older adults • **Nirsevimab** RSV protection across ages • **Itepekimab** development in bronchiectasis • **Amlitelimab** development in asthma & systemic sclerosis interstitial lung disease • **Lunsekimig** development in asthma & CRSwNP • **Rilzabrutinib** development in asthma • **Dupilumab** development in asthma (2-6 years old) & AFRS • **Belumosudil** ROCK2 inhibitor Phase 3 development for chronic lung allograft dysfunction • **INBRX-101** development in AATD, genetic cause of COPD

*Some assets are under clinical investigation and have not been approved for these uses by any regulatory authority. NOTE – Includes assets developed and/or owned by Sanofi alone or in collaboration with partners, including Regeneron. IL, interleukin; mAb, monoclonal antibody; COPD, chronic obstructive pulmonary disease; FDA, Food and Drug Administration; TSLP, thymic stromal lymphopoietin; VHH, single variable domain on a heavy chain; RSV, respiratory syncytial virus; CRSwNP, chronic rhinosinusitis with nasal polyps; AFRS, allergic fungal rhinosinusitis; ROCK2, Rho-associated coiled-coil kinase 2; AATD, alpha-1 antitrypsin.

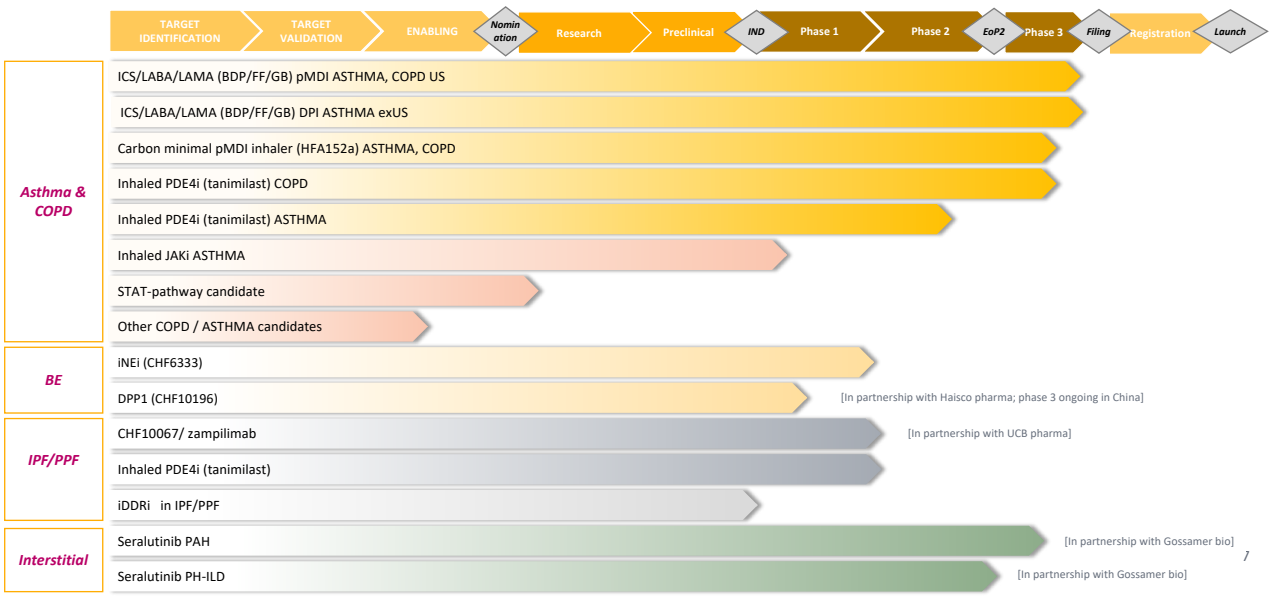
Approaching COPD systemically: Patients, pathways and planet

Diego Ardigo, Chiesi

Several mechanisms are responsible for much of the unmet need across multiple respiratory disease states, including inflammation, fibrosis, mucociliary dysfunction, vascular remodeling, and infections. Two pathways of particular interest for Chiesi are PDE4 inhibition and the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway, with other therapies in development targeting neutrophilic inflammation, fibrosis, and vascular remodeling in representative diseases (Figure 9). Tanimilast is an inhaled PDE4 inhibitor with Phase 3 in COPD and Phase 2 in asthma under way.

The effects of climate change have a substantial impact on respiratory health, with a 1°C rise increasing the risk of death six-fold in patients with a respiratory disease. Chiesi aims to be sustainable and supportive of both patients and the planet, with one action to minimize the organization's carbon footprint being the replacement of HFA-134a with HFA-152a as propellant in pMDIs.

Figure 9. The Chiesi respiratory pipeline.



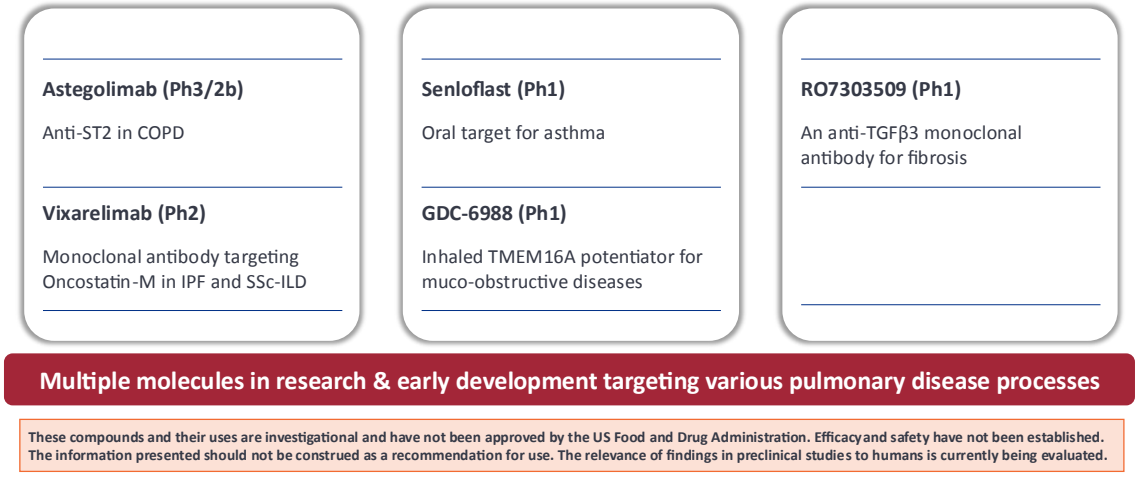
ICS/LABA/LAMA, inhaled corticosteroid/long-acting β2-agonist/long-acting muscarinic antagonist; BDP, beclomethasone dipropionate; FF, formoterol fumarate; GB, glycopyrronium bromide; pMDI, pressurized metered-dose inhaler; COPD, chronic obstructive pulmonary disease; PDE4i, phosphodiesterase 4 inhibitor; JAKi, Janus kinase inhibitor; STAT, signal transducer and activator of transcription; iNEi, inhaled neutrophil elastase inhibitor; DPP, dipeptidyl peptidase; IPF/PPF, idiopathic pulmonary fibrosis/progressive pulmonary fibrosis; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; ILD, interstitial lung disease.

Roche respiratory pipeline: Innovating for COPD

Divya Mohan, Genentech/Roche

Genentech is a member of the Roche group, which has a history of over 30 years in respiratory therapeutics, with the first approval for a cystic fibrosis drug (Pulmozyme), the first approved biologic approved for asthma (the Genentech product Xolair [omalizumab]), and one of the first approved therapies for idiopathic pulmonary fibrosis (Esbriet). The current Roche pulmonology pipeline is shown in Figure 10. This includes astegolimab, which works via the ST2/IL-33 pathway, potentially impacting both eosinophilic and neutrophilic inflammation. This is being studied in two studies (a Phase 2b and a Phase 3 study) that have recruited broad COPD populations (former and current smokers, with no limitation on eosinophil levels), and that are expected to report in 2025. A future aim is to develop targeted therapy for different COPD endotypes and phenotypes, with many molecules in research and development. In addition, the company is working on the identification and development of endpoints of relevance to respiratory patients.

Figure 10. The Genentech/Roche pulmonology pipeline.



ST2, interleukin 1 receptor-like 1; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; Ph1, Phase 1; Ph2, Phase 2; Ph3/2b, Phase 3/2b; SSc-ILD, scleroderma-associated idiopathic lung disease; TGFβ3, transforming growth factor beta 3.

References

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