Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

Journal Club–COPD2020 Update. Global Initiative for Chronic Obstructive Lung Disease 2020 Report and the *Journal of the COPD Foundation* Special Edition, Moving to a New Definition for COPD: "COPDGene® 2019"

Ron Balkissoon, MD, MSc, DIH, FRCPC[1]

Abbreviations: chronic obstructive pulmonary disease, **COPD**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; forced expiratory volume in 1 second, **FEV_1**; COPD Assessment Test, **CAT**; long-acting beta2-agonists, **LABA**; long-acting muscarinic antagonist, **LAMA**; inhaled corticosteroid, **ICS**; T-helper 2 cells, **TH-2**; forced vital capacity, **FVC**; COPD Genetic Epidemiology study, **COPDGene®**; computed tomography, **CT**

Citation: Balkissoon R. Journal club—COPD2020 update. Global Initiative for Chronic Obstructive Lung Disease 2020 report and the *Journal of the COPD Foundation* special edition, moving to a new definition for COPD: "COPDGene2019". *Chronic Obstr Pulm Dis.* 2020;7(1):64-72. doi: https://doi.org/10.15326/jcopdf.7.1.2020.0133

1 Denver, Colorado

Address correspondence to:

Ron Balkissoon, MD, MSc, DIH, FRCPC
balkissoonr@njhealth.org

Keywords

chronic obstructive pulmonary disease; COPD; Global Initiative for Chronic Obstructive Lung Disease; GOLD; COPD Genetic Epidemiology; COPDGene

Introduction

In 2001 an international expert panel published a consensus report, "Global Strategy for the Diagnosis, Management and Prevention of COPD."[1] With the backing and support of the U.S. National Heart, Lung and Blood Institute and the World Health Organization, a multi-disciplinary consortium of experts convened to review the existing chronic obstructive pulmonary disease (COPD) guidelines at the time and provide an evidence-based review of the current literature including clinical studies, epidemiology, socioeconomic and pathogenic mechanisms. Recommendations were provided with a grading of the evidence upon which the recommendations were made. This marked the formation of a network of national leaders and the beginning of the Global initiative for chronic Obstructive Lung Disease (GOLD) reports.

Since the initial report, published 18 years ago, there have been several advancements in our understanding of the pathogenesis of COPD and newer treatment options. Verinicline was introduced for smoking cessation. The phosphodiesterase type 4 inhibitor roflumilast, and the macrolide antibiotic azithromycin have been added to help reduce the frequency of exacerbations. Surgical options such as lung volume reduction and lung transplantation, and, more recently, bronchoscopic endobronchial valve lung volume reduction have been added.

The GOLD2019 report, provided greater refinement of its ABCD paradigm by revisiting the utility of combining the ABCD classification scheme (symptoms and exacerbation frequency) with a separate scale for spirometry, Grades 1-4.[2] For example, a patient with a forced expiratory volume in 1 second (FEV_1) of 25%, a COPD Assessment Test (CAT) score of 25 and 2 exacerbations in the past 12 months would be a 4-D patient and triple therapy would be recommended, whereas a patient with an FEV_1 of 30% but no exacerbations and a CAT score of 25 would be a 4-B and may warrant consideration for long-acting beta2-agonists/long-acting muscarinic antagonist (LABA/LAMA) without an inhaled corticosteroid (ICS) and

could be considered for lung volume reduction or lung transplant due to severe emphysema and or significant small airway disease and air trapping. The reintroduction of the FEV_1, as a separate scale from the ABCD paradigm, acknowledges that the FEV_1 confers greater refinement in classification of the COPD patient and their treatment options rather than simply being a surrogate measurement for risk of frequent exacerbations. It has been proposed as a means to improve the precision of determining treatment options for COPD patients.

There is also a new chart for the "Management of COPD" describing the important steps for "initial diagnosis, assessment and management" and then a separate iterative loop for the follow- up components of "Reviewing and Adjusting Therapy," as well as a treatment paradigm for the role of dual combination therapy (LABAs, LAMAs and combinations with ICSs): ICS/LABA, LABA/LAMA, LABA/LAMA/ICS). As previously, group A patients start with short-acting bronchodilators, Group B with long-acting bronchodilators or the consideration of dual bronchodilators if they are particularly symptomatic. For Group C the initial recommendation would be a LAMA. For Group D the initiating therapy could be LAMA or LAMA/LABA if the patient is particularly symptomatic or ICS/LABA if the blood eosinophil count is greater than 300 cells/MCL. "Triple therapy" is recommended when trials of dual bronchodilation and/or ICS/LABA don't adequately relieve symptoms or reduce exacerbations. Following initiating treatment, escalation or de-escalation of therapy is adjusted according to response to therapy.

In the past few years, there has been some jockeying in the placement of ICSs within the GOLD treatment paradigm. Whereas earlier versions of GOLD placed ICS/LABA as the first line of therapy for GOLD Grades 3 and 4 and (Group C and Group D), the more recent iterations have essentially reserved their use for patients where LAMA and/or LABA fail to reduce exacerbations. The rationale for this shift relates to concerns regarding ICS adverse effects, particularly, their higher association with lower respiratory tract infections,[3] in addition to evidence that LAMAs (with or without a LABA) were capable of reducing exacerbations in a subset of COPD patients who had at least 1 exacerbation in the previous 12 months.[4-12] More recent large-scale studies such as the IMPACT and FULFIL trials have revisited the role of ICSs in the reduction of exacerbations,[13-15] (suggesting the reduction is superior to LABA/LAMA or LABA/ICS in patients who have 2 or more exacerbations, but also, with respect to the IMPACT trial, reexamining the potential mortality benefit related to ICSs).[16]

The renewed interest in the last few years to the relevance of the concept of asthma/COPD overlap was in part related to trying to establish greater precision in determining those patients who might be most appropriate for ICS/LABA or ICS/LABA/LAMA therapy but also due to the development of monoclonal antibodies such as the anti-interleukin-5 ligand and interleukin-5 receptorα antagonist and the anti-interleukin-4 receptorα antagonist that block pathways important for T-helper 2 (TH-2) cell signaling. Sputum eosinophils were studied to see if they helped predict good responders to ICSs and to the TH-2 biologics[17-22] for treating patients with COPD or so-called asthma/COPD overlap. To date none of the trials with biologics have proven them to be efficacious in COPD patients.[23-26] Interestingly, the GOLD committee has decided to cease from using the "asthma/COPD overlap" term and instead states that these are separate diseases that share some common characteristics and may coexist in an individual. A new table has been added that provides a clearer outline of the decision factors to be used to decide on the use of ICSs and indicates that the strongest support is history of at least 1 hospitalization or at least 2 moderate exacerbations for COPD exacerbations or at least moderate exacerbations per year and blood eosinophil count > 300 cell/mcL and history of/or current concomitant asthma. There is moderate support for considering use for those with 1 moderate exacerbation and blood eosinophil count between 100-300 cells/mcL. Factors against the use of ICSs include if patients have repeated pneumonia events or blood eosinophil counts < 100 cells/mcL or history of mycobacterial infection.

GOLD2020 provides an updated review and list of common conditions that should be considered in the differential diagnosis of COPD exacerbations including; pneumonia, pneumothorax, pleural effusion, pulmonary embolism, pulmonary edema due to cardiac related conditions, and cardiac arrhythmias-atrial fibrillation/flutter.

The GOLD report continues to recommend initiating therapy only after patients demonstrate evidence of a threshold cutoff post-bronchodilator FEV_1 to forced

vital capacity (FVC) ratio of less than 70%. In addition to exposure and symptoms, this remains the physiologic cornerstone of GOLD's definition for the diagnosis of COPD despite the recognition in the report that there are individuals who may have structural changes such as emphysema or significant small airway disease and air trapping and even a reduced FEV_1. Yet, if a patient has a preserved FEV_1/FVC ratio, he/she is not considered for treatment within the GOLD paradigm. The rationale has been that, while these abnormalities may indicate that these individuals are susceptible to lung injury related to cigarette smoking or other injurious inhalants, (biomass fuels for example), there is little evidence that our current treatment options have much impact on their symptoms or progression of their disease. Further, there is little data as to whether a group of these patients has been fully identified and characterized and to know whether or not this group of individuals experience significant exacerbations.

The COPD Genetic Epidemiology (COPDGene®) study includes over 10,000 current or former smokers in the United States enrolled between 2008 and 2011. Baseline evaluations included pre-and post-bronchodilator spirometry, 6-minute walk test distance, inspiratory and expiratory computed tomography (CT) scans that included a quantitative assessment of airway wall thickness, emphysema and gas trapping. Participants also complete 6-month interval telephone and web-based follow-ups. In addition, a series of biomarkers were collected including fibrinogen C-reactive protein, surfactant protein D, soluble receptor for advanced plication and products, and Clara cell secretory protein. Mortality is also being tracked. There were 4615 participants who completed a 5-year follow-up with a full set of data including return visits for physiologic and radiographic assessments. With this enormous database of exposure, symptoms, CT imaging, spirometry and biomarkers, the COPDGene® investigators set out to formulate a unique and new classification scheme for COPD patients by characterizing patients based on quantitative CT and physiologic and biomarker variables.

Interestingly, 3 papers from the COPDGene® study group were published in a Special Issue of this Journal—*Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*—in November 2019.[27-29] The papers present thought-provoking data compelling us to rethink whether our current definition, diagnostic criteria, and characterization of patients with COPD is adequate to optimally care for this patient population. To date, while oxygen therapy and smoking cessation have been shown to prolong survival, there are no medications that have been definitively proven to have the ability to improve survival or to change the natural course of the disease in ways that would be considered as disease modifying. With the IMPACT trial data[16] bringing into question whether or not ICSs may indeed confer an improved survival benefit, we want to make sure we optimally characterize the spectrum of COPD patients to identify who are likely to benefit and whether such interventions have their greatest impact if they are started early. Further, as we move forward, it is hoped that we will be able to discover new medications that may be truly disease modifying for patients with COPD. The COPDGene® study has been following a large cohort of individuals with substantial smoking histories over several years and is allowing us to characterize a group of current and former smokers in a level of detail that has never been previously attempted. With the data generated from this study and the papers that are being published, we are able to more clearly phenotype individuals who have significant smoking histories and indeed, pose a compelling argument for revisiting our current GOLD definition of COPD that has been the accepted standard for almost 20 years. Ultimately, the goal of such documents is to educate health care providers and the public about the deleterious effects of cigarette smoke (and other potential harmful inhalant exposures) and lay out comprehensive strategies to prevent the development and progression of disease. Moving to a definition of COPD that incorporates not only lung function, but also structural changes noted on CT scans will enable us to select patients with greater precision for clinical trials to test these newer medicines.

The COPDGene® articles presented in this Journal Club are thought-provoking and compelling yet there are a few important issues to put in perspective. The COPDGene® cohort is highly enriched with heavy smokers (average of approximately 50 pack years) with airflow limitation and therefore the findings, including associations and projections, may not be universally applicable to those with lower cigarette, (or biomass), exposure or non-smokers who demonstrate airflow limitation. CT scanning is a high tech and expensive modality and quantitative CT is not standardized.

This will need to be further studied and standardized as far as automated algorithms for calculation of emphysema and small airway disease and its practical application globally. Studies will need to examine whether there may be other less expensive means to acquire similar information regarding small airway disease, particularly for parts of the world where there may not be access to such technology.

Since 2007 the COPD Foundation has produced a Pocket Consultant Guide to assist health care providers in caring for patients with COPD. They launched a mobile version in 2013 that was then updated in 2018 and in June of 2019 released the latest iteration that is a mobile app with a significant health care provider track and a patient track with an interactive daily action plan, activity monitoring and exercise videos. Considering the COPD Foundation endorsement of moving to a new definition of COPD, the next iteration of the COPD Foundation pocket guide is likely to reflect this transition to the COPDGene® 2019 definition.

Bottom Line

The GOLD Committee has provided an abundance of sound evidence-based recommendations for over 18 years and will continue to be a global leader and an invaluable source of information. Hopefully, they will find the work of the COPDGene® group compelling enough to incorporate their findings into an updated definition of COPD going forward. Of course, the big question that future studies will need to address is whether suggesting that a screening CT scan (with special quantitative measurement capabilities, as yet not standardized) on smokers with a certain smoking history (yet to be determined) leads to interventions that will provide significant positive outcomes that will justify the added expense to incorporate such screening. It has been proven for lung cancer; it is quite plausible it will also be found for COPD. Indeed, there will certainly be overlap and insights to gain from the lung cancer screening program to date. It will also be instructive to review how many lung cancers are serendipitously found on CT evaluations as part of COPDGene® and what are the characteristics of that cohort.

Abstract 1
COPDGene® 2019: Redefining the Diagnosis of Chronic Obstructive Pulmonary Disease

Lowe KE, Regan EA, Anzueto A, et al. *Chronic Obstr Pulm Dis*. 2019;6(5):384-399.
doi: http://dx.doi.org/10.15326/jcopdf.6.5.2019.0149

Background: Chronic obstructive pulmonary disease (COPD) remains a major cause of morbidity and mortality. Present-day diagnostic criteria are largely based solely on spirometric criteria. Accumulating evidence has identified a substantial number of individuals without spirometric evidence of COPD who suffer from respiratory symptoms and/or increased morbidity and mortality. There is a clear need for an expanded definition of COPD that is linked to physiologic, structural (computed tomography [CT]) and clinical evidence of disease. Using data from the COPD Genetic Epidemiology study (COPDGene®), we hypothesized that an integrated approach that includes environmental exposure, clinical symptoms, chest CT imaging and spirometry better defines disease and captures the likelihood of progression of respiratory obstruction and mortality.

Methods: Four key disease characteristics - environmental exposure (cigarette smoking), clinical symptoms (dyspnea and/or chronic bronchitis), chest CT imaging abnormalities (emphysema, gas trapping and/or airway wall thickening), and abnormal spirometry - were evaluated in a group of 8784 current and former smokers who were participants in COPDGene® Phase 1. Using these 4 disease characteristics, 8 categories of participants were identified and evaluated for odds of spirometric disease progression (FEV_1 > 350 ml loss over 5 years), and the hazard ratio for all-cause mortality was examined.

Results: Using smokers without symptoms, CT imaging abnormalities or airflow obstruction as the reference population, individuals were classified as Possible COPD, Probable COPD and Definite COPD. Current Global initiative for obstructive Lung Disease

(GOLD) criteria would diagnose 4062 (46%) of the 8784 study participants with COPD. The proposed COPDGene® 2019 diagnostic criteria would add an additional 3144 participants. Under the new criteria, 82% of the 8784 study participants would be diagnosed with Possible, Probable or Definite COPD. These COPD groups showed increased risk of disease progression and mortality. Mortality increased in patients as the number of their COPD characteristics increased, with a maximum hazard ratio for all cause-mortality of 5.18 (95% confidence interval [CI]: 4.15-6.48) in those with all 4 disease characteristics.

Conclusions: A substantial portion of smokers with respiratory symptoms and imaging abnormalities do not manifest spirometric obstruction as defined by population normals. These individuals are at significant risk of death and spirometric disease progression. We propose to redefine the diagnosis of COPD through an integrated approach using environmental exposure, clinical symptoms, CT imaging and spirometric criteria. These expanded criteria offer the potential to stimulate both current and future interventions that could slow or halt disease progression in patients before disability or irreversible lung structural changes develop.

Comments

It has been appreciated that there are smokers with significant symptoms of cough, shortness of breath, and mucous production who may demonstrate evidence of emphysema and/or small airways disease, (noted by gas trapping and airway wall thickening), despite having normal FEV_1 and a preserved FEV_1/ FVC ratio of greater than 70%. In the initial iterations of the GOLD guidelines such patients were considered to be GOLD 0 but this Grade was dropped in subsequent iterations of the GOLD report. There is also the group of individuals who have an FEV_1 that is reduced below 80% of predicted but have a normal FEV_1/FVC and have been labeled as preserved ratio-impaired spirometry (PRISm). This study demonstrates the utility of incorporating the 4 significant features of exposure, symptoms, CT scan characterization of emphysema and airway wall thickening and physiological measures of lung function. The study identifies that a substantial number already would meet GOLD criteria for a COPD diagnosis and a significant number would be added using the COPDGene® 2019 definition. With this data set the authors use a matrix to identify 8 groups and define the relative probability of having COPD. Using these parameters to characterize these individuals it is apparent that many individuals, up to 40 %, fall into these categories and that they do indeed progress over 5 years with similar rates of mortality as those with an FEV_1/FVC < 70%.

Abstract 2
Subtypes of COPD Have Unique Distributions and Differential Risk of Mortality

Young KA, Regan EA, Han MK, et al and the COPDGene Investigators. *Chronic Obstr Pulm Dis.* 2019;6(5):400-413. doi: http://dx.doi.org/10.15326/jcopdf.6.5.2019.0150

Background: Previous attempts to explore the heterogeneity of chronic obstructive pulmonary disease (COPD) clustered individual patients using clinical, demographic, and disease features. We developed continuous multidimensional disease axes based on radiographic and spirometric variables that split into an airway-predominant axis and an emphysema-predominant axis.

Methods: The COPD Genetic Epidemiology study (COPDGene®) is a cohort of current and former smokers, > 45 years, with at least 10 pack years of smoking history. Spirometry measures, blood pressure and body mass were directly measured. Mortality was assessed through continuing longitudinal follow-up and cause of death was adjudicated. Among 8157 COPDGene® participants with complete spirometry and computed tomography (CT) measures, the top 2 deciles of the airway-predominant and emphysema-predominant axes previously identified were used to categorize individuals into 3 groups having the highest risk for mortality using Cox proportional hazard ratios. These groups were also assessed for causal mortality. Biomarkers of COPD (fibrinogen, soluble receptor for advanced glycation end products [sRAGE], C-reactive protein [CRP], clara cell secretory protein [CC16], surfactant-D [SP-D]) were compared

by group.

Findings: High-risk subtype classification was defined for 2638 COPDGene® participants who were in the highest 2 deciles of either the airway-predominant and/or emphysema-predominant axis (32% of the cohort). These high-risk participants fell into 3 groups: airway-predominant disease only (APD-only), emphysema-predominant disease only (EPD-only) and combined APD-EPD. There was 26% mortality for the APD-only group, 21% mortality for the EPD-only group, and 54% mortality for the combined APD-EPD group. The APD-only group (n=1007) was younger, had a lower forced expiratory volume in 1 second (FEV_1) percent (%) predicted and a strong association with the preserved ratio-impaired spirometry (PRISm) quadrant. The EPD-only group (n=1006) showed a relatively higher FEV_1 % predicted and included largely GOLD stage 0, 1 and 2 participants. Individuals in each of the 3 high-risk groups were at greater risk for respiratory mortality, while those in the APD-only group were additionally at greater risk for cardiovascular mortality. Biomarker analysis demonstrated a significant association of the APD-only group with CRP, and sRAGE demonstrated greatest significance with both the EPD-only and the combined APD-EPD groups.

Interpretation: Among current and former smokers, individuals in the highest 2 deciles for mortality risk on the airway-predominant axis and the emphysema-predominant axis have unique associations to spirometric patterns, different imaging characteristics, biomarkers and causal mortality.

Comments

This study by Young and colleagues examined the differences between airway predominant and emphysema predominant CT patterns with regard to disease progression and mortality. The study once again reinforces that patients currently not identified by GOLD classification as having disease warranting pharmacologic intervention, can progress significantly over a 5-year interval. This study also pointed out the benefits of smoking cessation leading to reduced progression for patients at early stages such as GOLD 0 and GOLD 1. These findings support the concept that, for at least certain interventions, early detection and commencement of therapy may lead to better long-term outcomes rather than waiting for further progression to occur before initiating treatment. Also sobering is the fact that the combined airway predominant disease group and emphysema predominant disease group individuals progressed at the highest 5-year all-cause mortality.

Abstract 3
Pulmonary Subtypes Exhibit Differential Global Initiative for Chronic Obstructive Lung Disease Spirometry Stage Progression: The COPDGene® Study

Young KA, Strand MJ, Ragland MF, et al for the COPDGene Investigators. *Chronic Obstr Pulm Dis.* 2019;6(5):414-429. http://dx.doi.org/10.15326/jcopdf.6.5.2019.0155

Rationale: We classified individuals into pulmonary disease subtypes based on 2 underlying pathophysiologic disease axes (airway-predominant and emphysema-predominant) and their increased mortality risk. Our next objective was to determine whether some subcomponents of these subtypes are additionally associated with unique patterns of Global initiative for chronic Obstructive Lung Disease (GOLD) spirometry stage progression.

Methods: After accounting for intra-individual measurement variability in spirometry measures between baseline (Phase 1) and the 5-year follow up (Phase 2) of the COPD Genetic Epidemiology (COPDGene®) study, 4615 individuals had complete data that would characterize patterns of disease progression over 5 years (2033 non-Hispanic whites; 827 African Americans; 48% female). Individuals could express increased risk for mortality on one or both of the primary subtype axes (airway-predominant or emphysema-predominant) and thus they were further classified into 6 groups: high-risk airway-predominant disease only (APD-only), moderate-risk airway-predominant disease only (MR-APD-only), high-risk emphysema-predominant disease only (EPD-only), combined high-risk airway- and emphysema-predominant disease (combined APD-EPD), combined moderate-risk airway- and emphysema-predominant disease (combined MR-

APD-EPD), and no high-risk pulmonary subtype. Outcomes were dichotomized for GOLD spirometry stage progression from Phase 1 to Phase 2. Logistic regression of the progression outcomes on the pulmonary subtypes were adjusted for age, sex, race, and change in smoking status.

Results: The MR-APD-only group was associated with conversion from GOLD 0 to preserved ratio-impaired spirometry (PRISm) status (odds ratio [OR] 11.3, 95% confidence interval [CI] 5.7-22.1) and GOLD 0 to GOLD 2-4 (OR 6.0, 95% CI 2.0-18.0). The EPD-only group was associated with conversion from GOLD 0 to GOLD 1 (OR 2.4, 95% CI 1.2-4.6), and GOLD 1 to GOLD 2-4 (OR 2.6, 95% CI 1.0-6.9). Conversion between PRISm and GOLD 2-4 (31%-38%) occurred in both the APD-only and the MR-APD-only groups.

Conclusion: Differential conversion occurs from GOLD 0 to PRISm and GOLD 0 to GOLD 1 based on groups expressing airway-predominant disease or emphysema-predominant disease independently or in combination. Airway-predominant and emphysema-predominant subtypes are highly important in determining patterns of early disease progression.

Comments

The findings of this analysis further reinforce the findings and conclusions of the 2 other studies above. The study also highlights the need for such precision in understanding the underlying pathobiology as it is likely that targets for therapy will differ between those who have airway predominant disease only and those who have emphysema predominant disease only.

References

1. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care*. 2001;46(8):798-825.

2. Patel AR, Patel AR, Singh S, Singh S, Khawaja I. Global Initiative for Chronic Obstructive Lung Disease: the changes made. *Cureus*. 2019;11(6):e4985. doi: https://doi.org/10.7759/cureus.4985

3. Yang M, Du Y, Chen H, Jiang D, Xu Z. Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *Int Immunopharmacol*. 2019;77:105950. doi: https://doi.org/10.1016/j.intimp.2019.105950

4. Halpin DMG. The role of tiotropium+olodaterol dual bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Tuberc Respir Dis (Seoul)*. 2018;81(1): 13-18. doi: https://doi.org/10.4046/trd.2017.0098

5. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med*. 2018;6(10):747-758. doi: https://doi.org/10.1016/S2213-2600(18)30327-8

6. Deas SD. Huprikar N. Dual bronchodilator therapy for chronic obstructive pulmonary disease: evidence for the efficacy and safety of fixed dose combination treatments in the setting of recent guideline updates. *Curr Opin Pulm Med*. 2018;24(2):130-137. doi: https://doi.org/10.1097/MCP.0000000000000450

7. Wedzicha JA, Decramer M, Ficker J, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*. 2013;1(3): 199-209. doi: https://doi.org/10.1016/S2213-2600(13)70052-3

8. Calverley PMA, Anzueto A, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6(5): 337-344. doi: https://doi.org/10.1016/S2213-2600(18)30102-4

9. Wark, P. ACP Journal Club. Tiotropium reduced exacerbations more than salmeterol in moderate-to-very severe COPD. *Ann Intern Med*. 2011;155(2):JC1-3. doi: https://doi.org/10.7326/0003-4819-155-2-201107190-02003

10. Anzueto A, Miravitlles M. Efficacy of tiotropium in the prevention of exacerbations of COPD. *Ther Adv Respir Dis*. 2009;3(3):103-111. doi: https://doi.org/10.1177/1753465809338854

11. Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177(1):19-26. doi: https://doi.org/10.1164/rccm.200707-973OC

12. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med*. 2005;143(5):317-26. doi: https://doi.org/10.7326/0003-4819-143-5-200509060-00007

13. Mehta R, Pefani E, Beerahee M, et al. Population pharmacokinetic analysis of fluticasone furoate/umeclidinium/vilanterol via a single inhaler in patients with COPD. *J Clin Pharmacol*. 2018;58(11):1461-1467. doi: https://doi.org/10.1002/jcph.1253

14. Lipson DA, Criner GJ, Lomas DA. Single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;379(6):592-593. doi: https://doi.org/10.1056/NEJMc1807380

15. Halpin DMG, Birk R, Brealey N, et al. Single-inhaler triple therapy in symptomatic COPD patients: FULFIL subgroup analyses. *ERJ Open Res*. 2018;4(2). doi: https://doi.org/10.1183/23120541.00119-2017

16. Lipson DA, Barnhart F, Brealey N, et al for the IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680. doi: https://doi.org/10.1056/NEJMoa1713901

17. van den Berge M, Kerstjens HA. Blood eosinophils as a continuous variable in the treatment of COPD: impact on the guidelines. *Lancet Respir Med*. 2019;7(9):722-723. doi: https://doi.org/10.1016/S2213-2600(19)30195-X

18. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med*. 2018;6(11): 855-862. doi: https://doi.org/10.1016/S2213-2600(18)30368-0

19. Siddiqui SH, Pavord ID, Barnes NC, et al. Blood eosinophils: a biomarker of COPD exacerbation reduction with inhaled corticosteroids. *Int J Chron Obstruct Pulmon Dis*. 2018;13: 3669-3676. doi: https://doi.org/10.2147/COPD.S179425

20. Gibson PG. Variability of blood eosinophils as a biomarker in asthma and COPD. *Respirology*. 2018; 23(1):12-13. doi: https://doi.org/10.1111/resp.13200

21. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax*. 2016;71(2):118-125. doi: https://doi.org/10.1136/thoraxjnl-2015-207021

22. Barnes NC, Sharma R, Lettis S, Calverley PMA. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J*. 2016;47(5):1374-1382. doi: https://doi.org/10.1183/13993003.01370-2015

23. Sciurba FC, Bradford ES, Pavord ID. Mepolizumab for eosinophilic COPD. *N Engl J Med*. 2018;378(7):681-683. doi: https://doi.org/10.1056/NEJMc1715454

24. Long G, Wall J. Precision medicine in COPD: review of mepolizumab for eosinophilic COPD. *Breathe (Sheff)*. 2018;14(4):338-341. doi: https://doi.org/10.1183/20734735.026318

25. Dasgupta A, Kjarsgaard M, Capaldi D, et al. A pilot randomised clinical trial of mepolizumab in COPD with eosinophilic bronchitis. *Eur Respir J*. 2017;49(3):1602486. doi: https://doi.org/10.1183/13993003.02486-2016

26. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019;381(11):1023-1034. doi: https://doi.org/10.1056/NEJMoa1905248

27. Lowe KE, Regan EA, Anzueto A, et al. COPDGene 2019: redefining the diagnosis of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2019; 6(5):384-399. doi: https://doi.org/10.15326/jcopdf.6.5.2019.0149

28. Young KA, Strand M, Ragland MF, et al for the COPDGene Investigators. Pulmonary subtypes exhibit differential global initiative for chronic obstructive lung disease spirometry stage progression: the COPDGene study. *Chronic Obstr Pulm Dis*. 2019;6(5):414-429. doi: https://doi.org/10.15326/jcopdf.6.5.2019.0155

29. Young KA, Regan EA, Han MK, et al and the COPDGene Investigators. Subtypes of COPD have unique distributions and differential risk of mortality. *Chronic Obstr Pulm Dis*. 2019; 6(5): 400-413. doi: http://dx.doi.org/10.15326/jcopdf.6.5.2019.0150