

# Precision Medicine in COPD: Integrating Clinical Phenotypes, Biomarkers and Targeted Therapies

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**Abstract:** *Chronic Obstructive Pulmonary Disease (COPD) is a long-term lung disease that makes the passages in the lungs narrower and narrower and inflams the passages in the lungs. Primarily due to exposure to the harmful gases or particles for a long period of time, and the largest risk factor is from smoking cigarettes. Patients usually have symptoms such as chronic cough, coughing up sputum, wheezing and worsening breathlessness, which significantly affect their quality of life.*

*COPD management is primarily aimed at symptom alleviation, facilitation of airway flow and minimizing disease progression. Bronchodilators such as short acting beta-agonists (SABA) and long acting beta-agonists (LABA) along with anticholinergics (SAMA and LAMA) are first line of drugs that work on relaxing the airways, and thus, promote breathing. Smoking cessation, pulmonary rehab, vaccines, and lifestyle changes are essential for disease control, as well as medical treatment. Finally, both pharmacologic and non-pharmacologic interventions are important in order to reduce symptoms, exacerbations and enhance quality of life in patients with COPD.*

**Keywords:** COPD, Precision Medicine, Clinical Phenotypes, Biomarkers, Endotypes, Targeted Therapies, Personalized Medicine, Multi-omics, COPD Heterogeneity, Biomarker-Guided Therapy.

## I. LITERATURE REVIEW

Chronic Obstructive Pulmonary Disease (COPD) is no longer viewed as a one-size-fits-all disease but as a heterogeneous disease with different phenotypes and pathogenesis. Agustí et al. (2016) explains that COPD is no longer a single disease entity but rather a spectrum of different phenotypes and biological processes. He then brings in the notion of “treatable traits” for disease management, which is based on specific and measurable disease features not just on airflow limitation. Personalized medicine in COPD is based on this concept.

In support of this, Han et al. (2010) points out that COPD can be divided into clinical phenotypes comprising of emphysema-dominant, chronic bronchitis, and frequent exacerbator groups. The onset and course of the disease, as well as the response to the treatment, vary between these phenotypes. These subgroups can be used to guide the selection of more focused treatment strategies, resulting in better disease management and outcomes.

Biomarker-based classification also is important in the treatment of COPD, especially for personalization. Inhaled corticosteroid response, especially in exacerbations, has been shown to be correlated with eosinophil levels in the blood (Bafadhel et al. 2012). This would be clinically relevant for the selection of therapy as patients with elevated eosinophils have a good therapeutic response and those with low eosinophils may only benefit minimally.

Genetic factors play a key role in the susceptibility and progression to COPD. Silverman et al. (2009) refer to alpha-1 antitrypsin deficiency as a "significant genetic disorder that is linked to early-onset emphysema. A genetic abnormality can be identified, allowing for targeted therapies that have a particular benefit for this group of patients, such as augmentation therapy. This demonstrates the significance of genetic testing in personalizing COPD treatment.

For clinical practice, Vestbo et al. (2013) notes the importance of including COPD symptoms, exacerbation history and risk factors in the management of COPD, rather than just relying on spirometric values. He believes in tailored treatment options as they lead to better disease management, fewer hospitalizations and better quality of life for patients.



The literature suggests that the pillars of personalized medicine in COPD are phenotypic classification, biomarker-driven therapy and genetic profiling. The conclusions drawn from the studies by Agustí et al., 2016; Han et al., 2010; Bafadhel et al., 2012; Silverman et al., 2009 and Vestbo et al., 2013 are unequivocally that a personal approach to treatment results in more precise treatment, fewer adverse effects and better patient outcomes.

## II. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease of the lungs in which airflow in the lungs becomes too limited to be fully reversed, and the airways and lungs are chronically inflamed. It is a huge health burden, and one of the leading causes of morbidity and mortality in the world. The disease is closely linked to smoking and environmental pollution, as well as work place irritants( Vestbo et al., 2013)

Until recently, COPD was treated as a monodisease based on spirometric measurements (FEV1) for diagnosis and severity classification. Recent clinical and molecular studies, however, indicate that COPD is a complex condition with various clinical features, progression patterns and therapeutic responses (Han et al., 2010) This has resulted in a move away from broad-based treatment strategies and more individual and targeted treatment.

In this context, Agustí et al. (Agustí, 2014) suggested the so-called “treatable traits” approach, which has been proposed to guide COPD management to target specific identifiable and modifiable COPD features, including airway inflammation, symptom burden, exacerbation risk and comorbid conditions. This approach forms an important foundation for the development of personalized medicine in COPD.

Additional clinical studies have revealed that there are distinct COPD phenotypes—emphysema predominant, chronic bronchitis, and frequent exacerbator. These phenotypes are associated with different disease mechanisms, disease courses and treatment effects, and are therefore essential for tailoring treatment to the individual.(Han et al., 2010).

Biomarkers are a major step forward in personalized COPD care and inform treatment decisions. Of these, blood eosinophil count is proving to be a useful guide to response to inhaled corticosteroids, especially an acute exacerbation. This aids the clinician in determining which patients are likely to benefit from steroid therapy and which are not (Bafadhel et al., 2012).

There is also some evidence that genetic susceptibility and progression to COPD are largely genetic. Alpha-1 antitrypsin deficiency is a recognised genetic condition which is linked to early onset emphysema and if identified can guide the treatment of those with the condition. In addition, there have been further advancements in genomics and molecular biology that further increase our understanding of the heterogeneity of COPD, which also help guide the development of precision medicine approaches (Postma & Rabe, 2015; Cho et al., 2015).

## III. BIOLOGICAL, MOLECULAR AND CLINICAL BASIS FOR PERSONALIZATION IN COPD

Biological basis of personalized medicine in COPD is based on the airway inflammation heterogeneity, immune response and tissue damage, which exists between COPD patients. While the COPD inflammatory pathway was previously thought to be linear, it is now known that patients can have varying inflammatory profiles such as eosinophilic inflammatory and neutrophilic inflammatory. These differences account for variability in response to common treatments, including bronchodilators and corticosteroids, and impact severity of the disease. This diversity of biology, combined with the large number of known and unknown factors, is a powerful argument for treating each person differently, rather than using a one-size-fits-all approach (Barnes, 2008, Lötvall et al., 2011)

COPD at the molecular level is a combination of various pathological mechanisms, such as generation of oxidative stress, chronic inflammatory signaling, protease-antiprotease imbalance, and progressive structural damage of airway and alveoli tissues. Recent molecular studies have demonstrated that these mechanisms are not consistent among all COPD cases, but rather different molecular profiles are found in subgroups of COPD. This indicates that COPD is not a linear disease process but rather a set of overlapping biological processes, with specific therapeutic targets. (Agustí & Sin, 2014 , Barnes, 2008)



The understanding of COPD heterogeneity has been further enhanced by the development of omics technologies including genomics, transcriptomics, and proteomics. The use of these tools has allowed researchers to discover molecular patterns associated with progression and the risk of exacerbation, as well as patterns of response to treatment in disease. These molecular-level insights are increasingly being applied to classify COPD into biologically meaningful subgroups, which may help to inform the treatment decisions for these subgroups with greater precision and a more mechanistic approach (Agusti et al., 2011)

Clinically, COPD has been classified into several phenotypes, such as emphysema predominant, chronic bronchitis and frequent exacerbator. These clinical classifications have significance because they capture variations in exacerbation rates, lung function as well as symptom patterns. For example, exacerbators are a high-risk group and they should be managed more aggressively and proactively to prevent hospitalizations and burden of disease (Han et al., 2010, Hurst et al., 2010)

Combining clinical phenotyping with biomarker-based assessment has greatly bolstered personalized COPD management. Blood eosinophil count has become one of the most important biomarkers to predict response to inhaled corticosteroids, with some other markers like C-reactive protein and fibrinogen being investigated for their use in monitoring inflammation and risk stratification. This integrated, biological and clinical strategy enables a more individualized treatment approach (Bafadhel et al., 2012, Singh et al., 2018)

In summary, the three aspects of COPD biology, molecular, and clinical all underpin the need to shift from a generic COPD treatment model to a precision medicine approach. Personalized medicine is a more individualized and effective approach to improve outcomes in COPD patients by combining inflammatory profiles, molecular signatures and clinical phenotypes.

**Table 1: Biological, Molecular and Clinical Basis of COPD Personalization**

Level	Key components	Role in COPD
Biological	Neutrophils, macrophages, CD8+ T cells	Cause chronic Airway inflammation
Molecular	TNF- $\alpha$ , IL 6, IL 8	Promote inflammation, mucus production, airway damage
Oxidative stress	Reactive oxygen species (ROS)	Leads to protease-antiprotease imbalance and lung damage
Structural changes	Airway remodelling, alveolar destruction	Results in irreversible air flow limitation
Clinical variation	Different disease patterns in patients	Explain need for personalised treatment

#### IV. BIOMARKERS AND ENDOTYPING IN COPD

In fact, in COPD the use of biomarkers is now pivotal in the progression of personalized medicine, acting as objective biological markers that enable disease classification, prognosis and prediction of treatment responses. Biomarkers provide more insight in inflammatory activity and disease behaviour at individual level as compared to traditional spirometry assessment. This makes them very useful to design therapy based on patient-specific disease mechanisms (Agusti & Sin, 2014, Agusti, Gea & Faner, 2016)

Blood eosinophil count is one of the most popular COPD-associated biomarkers studied. Increased eosinophils are correlated with improved response to inhaled corticosteroids, especially those with frequent exacerbations. This has resulted in its application as a useful clinical tool to monitor anti-inflammatory treatment and minimize unnecessary corticosteroid exposure in nonresponsive patients (Bafadhel et al., 2012)

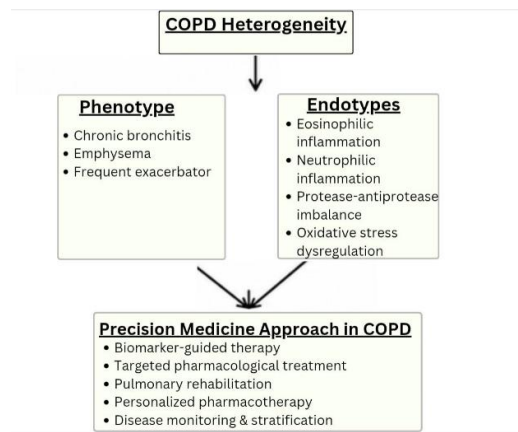
Besides eosinophils, there are several systemic inflammatory markers that have been studied for COPD severity assessment, including C-reactive protein (CRP), fibrinogen and interleukins. These biomarkers are markers of systemic inflammation and are associated with increased exacerbation risk, more rapid lung function decline and worse clinical



outcomes (Singh et al., 2018). But, the use of these in clinical practice is still a work in progress, as there are cutoff values and interpretations that vary across populations.

In addition to the individual biomarkers, new ideas are emerging on endotyping as an advanced classification approach in COPD. Endotyping is based on measurable biological and molecular mechanisms to define disease subsets as opposed to phenotyping, which is based on observable clinical features. This allows the underlying pathophysiological mechanisms underlying disease progression to be identified in each individual patient (Lötvalld et al., 2011). Other potential COPD endotypes include eosinophilic inflammatory endotype, neutrophilic inflammatory endotype, and oxidative stress – dominant endotype. These endotypes may help the clinician to go beyond symptom-focused treatment and begin to focus on certain processes that cause disease activity in specific patients (Barnes, 2008, Lötvalld et al., 2011)

The incorporation of biomarkers into endotyping approaches has greatly enhanced COPD management. The molecular information along with the clinical information can assist a clinician to better forecast the disease trajectory, pinpoint high-risk patients and choose more effective therapies. This integrated approach is a significant step towards delivering mechanism-guided and truly personalized COPD care (Agustí, Gea & Faner, 2016. Lötvalld et al., 2011)



**Figure 1. COPD is a heterogeneous disease and the concept of COPD phenotyping, endotyping and biomarker integration in COPD personalized management.**

## V. TREATABLE TRAITS FRAMEWORK AND PHENOTYPE-GUIDED MANAGEMENT

Treatable traits is a paradigm shift in COPD management, from disease label-based management, to the identification and targeting of specific clinically relevant disease characteristics. Treatment can be focused at each individual trait, and be patient-specific, rather than generalized, by doing so (Agustí et al., 2016). Agustí and his colleagues have backed this up, emphasizing the need to treat COPD according to biological and clinical characteristics instead of depending on spirometric classification. This enables clinicians to determine the major disease drivers in individual patients and choose interventions accordingly, hence increase the effectiveness of treatment (Agustí et al., 2016).

Phenotype-guided management is closely connected to the treatable traits approach, which includes classification of patients into clinically recognisable phenotypes (emphysema-dominant, chronic bronchitis and frequent exacerbator). These phenotypes have different pathological mechanisms, symptom patterns and disease trajectories that affect therapeutic decisions and clinical outcomes. (Pinto et al., 2015).

These phenotypes have different pathological mechanisms, symptom patterns and disease trajectories that affect therapeutic decisions and clinical outcomes (Han et al., 2010). For instance, frequent exacerbators are a high-risk phenotype consisting of frequent acute exacerbations of symptoms, elevated risk for hospitalization and rapid lung function decline. Identification of this group is critical, as they may need more aggressive pharmacologic treatment and preventive measures to decrease the number of exacerbations and disease burden (Hurst et al., 2010)



Likewise, chronic bronchitis phenotype can be linked to increased mucus production and chronic cough, necessitating specific treatment including anti-inflammatory drugs and/or mucolytic drugs. However, bronchodilation therapy and pulmonary rehabilitation to enhance lung mechanics and quality of life may be more useful in emphysema dominant patients.

Treatable traits integrated with the phenotype-based classification brings a more precise approach to COPD management that includes biological, clinical and functional information. The combination of these elements enables better than a traditional one-dimensional classification approach, and promotes a more holistic and individualized treatment plan (Agusti et al., 2016, Cazzola et al., 2023).

**Table 2: Personalized COPD Management Approach (Biomarkers, Phenotypes & Therapy)**

Component	Details	Clinical application
Biomarker	Blood eosinophils, CRP, Fibrinogen	Predict inflammation, exacerbations and steroid response
Endotyping	Eosinophilic, Neutrophilic, Oxidative stress types	Identifies disease Mechanism for targeted therapy
Phenotypes	Chronic bronchitis, emphysema, frequent exacerbator	Help in patient classification and treatment selection
Pharmacological therapy	Bronchodilators, inhaled Corticosteroid	Improve air flow and reviews exacerbations
Non pharmacological therapy	Smoking cessation, pulmonary rehab, exercise	Slows progression and improves quality of life

## VI. PERSONALIZED PHARMACOLOGICAL AND NON PHARMACOLOGICAL THERAPIES

Nowadays, COPD is increasingly managed according to patient phenotype and symptom burden, exacerbation risk and underlying biological characteristics, both pharmacologically and non-pharmacologically. This strategy goes beyond uniform therapy algorithms and means to tailor therapies to the individual disease characteristics to improve clinical outcomes and minimize side effects (Cazzola et al., 2023, Stolz et al., 2022)

Bronchodilators continue to be the cornerstone of COPD therapy, with long-acting  $\beta_2$ -agonists (LABA) and long-acting muscarinic antagonists (LAMA) as the backbone of maintenance therapy, from a pharmacological standpoint. Dual bronchodilation (LABA/LAMA) has been demonstrated to offer enhanced lung function benefits and symptom control to monotherapy in patients with more severe symptoms and/or persistent dyspnea. Spirometric values are no longer the only indicator of choice of therapy; there is increasing focus on exacerbation history and the severity of symptoms (Vogelmeier et al., 2017, Kaplan & Price, 2013)

Inhaled corticosteroids (ICS) are prescribed with bronchodilators, especially in patients with frequent exacerbations and high blood eosinophils count, in selected patients. This biomarker-driven method can be used to select patients that are more likely to respond to anti-inflammatory treatment and reduce the risk of side effects, including pneumonia, in patients who are not likely to respond. Triple therapy (LABA/LAMA/ICS) was only used in high-risk patients who have persistent symptoms and exacerbations despite using dual therapy ((Vogelmeier et al., 2017; Bafadhel et al., 2012).

There are also some specific pharmacologic approaches, such as the use of phosphodiesterase-4 inhibitors in chronic bronchitis phenotype with frequent exacerbations and mucolytic agents in patients who produce a lot of sputum. These therapies underscore the need to prescribe medications based on the individual's phenotype and not a common prescription plan for all COPD patients (Rennard, 2015).

Personalized COPD care will also include non-pharmacological interventions. One of the most effective strategies is pulmonary rehabilitation, which increases exercise tolerance, decreases dyspnea and improves quality of life. Degree and type of rehabilitation program can be adjusted depending on the baseline functional status and the severity of the disease (Vestbo et al., 2013; GOLD Report, 2024)



Individual behavioral counseling with pharmacotherapy has the largest impact on smoking cessation success rates and smoking cessation is the most important intervention for all COPD patients. Furthermore, dietary plans, vaccinations and patient education plans are tailored to the individual based on any underlying medical conditions and risk factors, enhancing the individualised approach to care (Vestbo et al., 2013; GOLD Report, 2024).

In conclusion, the adoption of personalized pharmacological and non-pharmacological approaches guarantees a holistic and patient-oriented approach to COPD management that aims at the control of symptoms and long-term disease modification and enhancement of quality of life.

## VII. APPLICATIONS

- **Improved Diagnostic Stratification**

Improved COPD patient diagnostic stratification is one of the most significant uses of customized medication. Traditional diagnosis based on spirometry does not adequately reflect disease heterogeneity, and together with clinical symptoms and imaging results it will facilitate the distinction between different COPD phenotypes, which are known to have different clinical behavior and outcomes, like emphysema-predominant, chronic bronchitis, and frequent exacerbator groups ( Han et al., 2010).

- Utilize phenotype and Endotype-based selection of treatment. Use Phenotype and Endotype-directed treatment selection.

- Phenotype and endotype diagnosis and treatment is an important application of personalised medicine. Airway inflammatory patterns, including neutrophilic and eosinophilic inflammation, help to determine the best drug treatment for each patient. Bronchodilator therapy may be more effective in other types of patients; inhaled corticosteroid therapy is more beneficial for patients with eosinophilic inflammation. (Bafadhel et al., 2012; Lötvall et al., 2011)

- **Ability to anticipate and prevent exacerbations.**

Predicting and preventing acute exacerbations, which are a significant contributor to COPD morbidity and mortality, is another crucial use. Patients who are more likely to experience frequent exacerbations can be identified with the use of biomarkers like blood eosinophil counts and systemic inflammatory markers (Bafadhel et al., 2012, Hurst et al., 2010). Prompt intervention of high-risk individuals by increased therapy, and increased observation, will reduce hospitalization rates and improve overall disease outcomes (Hurst et al., 2010). Early detection. One of the main benefits of precision medicine in respiratory care is this proactive management strategy

- **Imaging-Based Clinical Applications**

Advanced imaging techniques, such as high-resolution computed tomography (HRCT), have proven to be essential in providing an anatomical view of the distribution of emphysema, airway wall thickness, and small airway illness, which is essential for individual treatment of COPD. These imaging indicators help to identify disease patterns that cannot be discerned by spirometry (Cazzola et al., 2023)

Also, imaging helps to select the most appropriate therapeutic strategy, e.g. selecting people that might benefit from more sophisticated interventional procedures, or pulmonary rehabilitation. This facilitates therapy planning and enhances the accuracy of disease classification (Cazzola et al., 2023)

## VIII. CHALLENGES AND HEALTH SYSTEM CONSIDERATIONS

There are a number of hurdles in the way to applying personalized medicine in the real world for COPD, although significant strides have been made. A lack of harmonisation in the interpretation of biomarkers, particularly blood eosinophils and systemic inflammatory markers is one of the important problems. The cutoff value is different for



various studies and it is hard to adopt a common clinical decision making strategy for all groups of patients.(Singh et al., 2018; Koutsokera et al., 2013)

The cost and availability of state-of-the-art diagnostics like genetic testing, ‘omics profiling and molecular diagnostics are also a constraint. The majority of these technologies are limited to highly equipped tertiary hospitals and this limits the translation of research into clinical routine, particularly in resource-poor healthcare settings(Agustí et al., 2011; Stolz et al., 2022).

In many patients the phenotype is overlapping (chronic bronchitis and emphysema) or the exacerbation period is followed by stable periods (frequent exacerbations). This overlap decreases the accuracy of a phenotype-based approach to therapy in clinical practice (Han et al., 2010; Watz et al., 2014)

From the healthcare system point of view, trained healthcare professionals, multidisciplinary teams and advanced digital infrastructure is the requirement for implementing personalized medicine. Most healthcare systems however, continue to use standard treatment protocols based on guidelines, and do not yet employ individualized treatment strategies(GOLD Report, 2024; Stolz et al., 2022).But there are also ethical issues regarding both the use of genetic information and constant digital tracking. Patient privacy, data security, and equitable access to personalized treatments are still significant challenges that need to be resolved for the large-scale implementation of precision medicine(Stolz et al., 2022).Last, large-scale, long-term clinical trials to confirm personalized treatment strategies in a variety of populations are still lacking. Recommendations for universal clinical use are at present mostly from subgroup analysis or observations studies, therefore, the evidence is limited to the strength of the recommendation (Cazzola et al., 2023; Stolz et al., 2022)

#### **IX. FUTURE PROSPECTS**

The development of multi-omics technologies (genomics, transcriptomics, proteomics, and metabolomics) will play an important role in future personalized medicine in COPD, as they enable to gain deeper biological understanding of the heterogeneity of the disease.Such strategies enable molecular signatures to be identified for different patient cohorts that are linked to disease progression and treatment response (Postma & Rabe, 2015; Cho et al., 2015)

AI’s and machine learning’s are also becoming powerful tools in COPD management, with the ability to analyse large clinical data sets, imaging data and pattern of biomarker changes to identify exacerbations and hospitalisation risk ((Stolz et al., 2022) This allows intervention earlier and helps to move away from reactive treatment to preventive and predictive care models in COPD patients(Stolz et al., 2022).

Another area that shows potential for the future lies in the targeted use of biologic drugs based on specific inflammatory and molecular endotypes of COPD (Lötvall et al., 2011; Barnes, 2008). With ongoing research to uncover new pathways like eosinophilic inflammation, neutrophilic dominance and oxidative stress mechanisms, treatment is likely to become more and more mechanism-driven than symptom-driven

In addition, digital health technologies, like wearable devices, mobile health applications, and remote monitoring technologies are projected to be integral to the future of COPD care (Stolz et al., 2022). The tools can continually monitor patient health status and enable early detection of deterioration, helping to achieve better clinical outcomes and minimise emergency hospital admissions.

COPD personalized medicine in the next few years will turn to precision healthcare systems that fully integrate clinical phenotypes, molecular markers, genomic information and real-time digital monitoring into a single, comprehensive decision support system (Agustí et al., 2011; Stolz et al., 2022). This will allow for highly individualized treatment plannin, which will be done according to this patient’s disease profile.

But challenges including cost restrictions, privacy data concerns, and standardization of protocols, as well as unequal access to more advanced healthcare technologies (Stolz et al., 2022) will remain hurdles to successful implementation. Large clinical validation studies will also be necessary before these techniques are routinely used in the clinic.



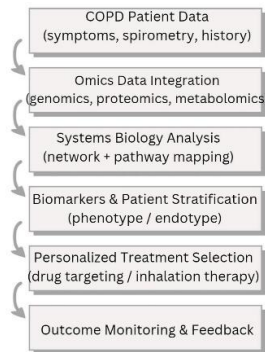


Figure 2. The potential precision medicine pathway in COPD, incorporating omics technologies, biomarkers, and tailored therapies is shown.

## X. CONCLUSION

PMP is a major paradigm change from a one-size-fits-all approach to treating COPD to a more personalized and patient-centred treatment strategy. As COPD is now known to be a multi-faceted disease with different clinical phenotypes, biological endotypes and responses to treatment, individualized care is becoming more important in contemporary respiratory care management.

Combining clinical phenotyping, biomarkers, genetic data and molecular profiling has enhanced the capability to individualize therapy based on disease features for each patient. This has resulted in a better selection of pharmacological treatments, better prediction of exacerbations and more effective utilization of non-pharmacological measures like pulmonary rehabilitation and lifestyle modification.

These improvements have not yet been translated into the broader application of personalized approaches, however, because of various obstacles including limited access to sophisticated diagnostics tools, limited budgets, and the absence of standardized clinical protocols. Other issues such as ethics and large scale validation studies also have significance and need to be addressed.

Furthermore, implementation of multidisciplinary care models will be a key determinant of the success of personalised COPD care in the future. Interdisciplinary work between pulmonary physicians, geneticists, clinical pharmacologists, and data scientists will be critical to help interpret complex patient information and help translate it into clinical care decisions. This comprehensive approach will be useful in developing more precise and productive care pathway opportunities for COPD patients.

Additionally, ongoing developments in digital health, AI, and real-world data analysis will further enhance decision-making in COPD management. The innovations will enable early diagnosis, ongoing monitoring and tailored treatment approaches that will adapt to the patient's response to treatment over time. These advances will make personalized medicine more feasible, available, and effective in helping to enhance long-term outcomes in COPD patients.

In summary, personalized medicine has the potential to meaningfully impact COPD treatment outcomes, disease burden and quality of life in COPD. It is hoped that with ongoing research and technological advances it will become a standard practice in the future.

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