

Pathogenesis, Diagnostic Advances, and Therapeutic Management of Chronic Obstructive Pulmonary Disease: A Narrative Review

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading global cause of morbidity and mortality, now recognized as a complex, heterogeneous disorder driven by environmental exposures, genetic susceptibility, immune dysregulation, and accelerated lung aging rather than solely by airflow limitation. This shift in understanding has fundamentally altered perspectives on its development and treatment. This narrative review synthesizes recent advances from 141 studies identified through a structured literature search of PubMed and Web of Science. It explores the molecular and cellular mechanisms of COPD pathogenesis and the resulting structural and functional lung changes. The review highlights innovations in diagnostics, including advanced imaging, physiological assessments, and biomarkers that enable more precise patient classification beyond spirometry. Progress in pharmacotherapy includes personalized inhaled therapies and targeted anti-inflammatory agents, while non-pharmacological approaches such as pulmonary rehabilitation and digital health technologies are increasingly integral to comprehensive management. Despite these advances, challenges persist, including inconsistent early detection, a lack of disease-modifying treatments, and significant variability in disease course and treatment response. This review provides a cohesive overview of current knowledge, identifies ongoing research needs, and outlines priorities for advancing personalized, mechanism-based care for COPD patients.

Keywords: chronic obstructive pulmonary disease, airway inflammation, emphysema, precision medicine, inhaled therapy, pulmonary rehabilitation

Introduction

Historical Evolution of Chronic Obstructive Pulmonary Disease

COPD is one of the most studied diseases that exists today, and it has had the same basic symptoms for over a hundred years, however, our perception or description of those symptoms have evolved slowly over time. In the late 1800's pathologists identified two different disease processes that they referred to as chronic bronchitis and emphysema. Both chronic bronchitis and emphysema are described as having specific physical changes and symptom characteristics. Chronic bronchitis patients would typically have a productive cough for at least three months in each year for at least two years, and their bronchial tubes contained enlarged mucus glands.¹⁻³ Patients diagnosed with emphysema would experience permanent (irreversible) increase in size of the air spaces of the lungs and destruction of the walls of the alveoli.⁴⁻⁶ Historically these two diseases were thought to be secondary to repeated infections, exposure to pollutants, occupational exposures, etc, prior to the widespread knowledge of tobacco smoking as the primary risk factor for developing COPD.

Following the increased use of cigarettes during the last half of the twentieth century, epidemiologic studies found a very significant association between cigarette smoke and chronic airflow limitation.⁷⁻⁹ As such, chronic bronchitis and emphysema became categorized as part of a single disease process known as COPD.¹⁰⁻¹² This created a broadened understanding of COPD that focused on the loss of lung function due to an irreversible narrowing of the airways of the lungs.¹³⁻¹⁵ This understanding influenced diagnosis and treatment options for decades and as such led us to overlook

other factors such as early life lung development, other types of environmental exposures (beyond smoking), and epigenetic modifications that mediate gene-environment interactions in disease pathogenesis. While rare monogenic conditions such as alpha-1 antitrypsin deficiency account for approximately 1–3% of all COPD cases and confer markedly increased susceptibility to early-onset emphysema, the vast majority of COPD cases arise from complex interactions between environmental exposures and epigenetic regulatory mechanisms.¹⁶ The historical view of COPD as a single disease entity contributed to a delay in recognizing the biological complexity of COPD and thus hindered the development of new treatments that could potentially modify the course of the disease. Importantly, the predominant etiological drivers of COPD differ markedly between geographic and socioeconomic contexts, with significant implications for disease phenotype and underlying molecular biology. In high-income Western countries, cigarette smoking remains the primary risk factor for COPD and has shaped much of the existing mechanistic understanding of the disease.¹⁷ In contrast, in low- and middle-income countries, household air pollution from biomass fuel combustion for cooking and heating constitutes the dominant cause of COPD.¹⁸ Biomass smoke-associated COPD exhibits distinct clinical and pathophysiological features compared to cigarette smoke-induced COPD, including a slower decline in lung function, greater airway involvement with less emphysematous destruction, and a different inflammatory signature.¹⁹ These differences underscore that COPD is not a uniform disease entity but rather a syndrome whose biological underpinnings are shaped by the nature of the inciting environmental exposure, necessitating context-specific approaches to both research and clinical management.

Contemporary Understanding of Pulmonary Structure and Functional Decline

Advancements in respiratory physiology and lung biology have transformed our understanding of how normal pulmonary structure supports both effective ventilation and gas exchange, and how these processes are disrupted in COPD. The coordination among conducting airways (small), alveoli, extracellular matrix scaffolds and the vascular system is critical to maintaining low resistance flow through the lung, and adequate matching between ventilation and perfusion.^{20–22} Additionally, the structural integrity of the alveolar walls provides the necessary elasticity for recoil of the lungs, while the intact epithelial layers and mucociliary clearance mechanisms serve as a protective barrier to insult from inhaled pathogens.^{23–25}

In COPD, these carefully regulated systems are progressively and unevenly damaged. Early in the course of the disease, small airway pathology develops with inflammation, thickening of the walls of the airways, and narrowing of their lumen occurring before destructive loss of the alveoli occurs.^{23–25} Loss of structural support of the alveolar unit as a result of degradation of the extracellular matrix results in an increase in size of the alveolar unit, and therefore impaired gas exchange.^{26,27} Importantly, recent imaging and physiological studies have shown that this does not occur equally across all lung regions or in all individuals. Therefore, the variability in the extent of damage across the lung explains the significant difference in symptom burden and disease progression experienced by two individuals with similar levels of spirometry impairment, which further underscores the need for diagnostic methods that go beyond measurement of global lung function.

Evolution of Pathophysiological Concepts

Research on the pathophysiology of COPD has greatly increased beyond the initial focus on chronic inflammation only.²⁸ Research initially focused on the effects of toxic inhalation exposures (such as cigarette smoke), resulting in neutrophilic inflammation and subsequently in airway injury and mucus hypersecretion. However, today researchers understand that inflammation represents only one aspect of the many interconnected biological pathways involved in COPD.

Presently, research into the pathophysiology of COPD continues to show that there are complex immune system abnormalities at both the innate and adaptive levels.²⁹ The persistent activation of macrophages, neutrophils, and lymphocytes results in tissue injury; however, due to a failure in resolution mechanisms of inflammation, inflammation persists even after removal of the original insult.³⁰ Oxidative stress has been identified as another key molecular mechanism, allowing for the linkage of environmental insults to DNA damage, altered cellular signaling and to corticosteroid resistance.³¹ Additionally, the disruption of the protease-antiprotease balance results in disruptions of the homeostatic equilibrium of the extracellular matrix thereby creating conditions which promote emphysematous destruction and loss of mechanical integrity of lung parenchyma.³²

Recent developments have further broadened the existing framework for the pathogenesis of COPD by implicating defects in epithelial repair, mitochondrial dysfunction, and cellular senescence in COPD.^{33–36} These findings provide evidence that COPD may not only be characterized by chronic injury, but also by a failure in the normal regenerative capacities of the lung, suggesting that COPD is a model for the process of accelerated lung aging. The finding that the lung microbiome has been disrupted and that there are host-microbiome interactions, which can influence each other in a bidirectional manner, provides another level of complexity to the study of COPD, emphasizing that the relationship between the airway environment and immune responses are interactive. Overall, these expanding concepts of COPD highlight how a multitude of mechanisms interact across molecular and cellular scales to support the chronicity of the disease.

Advances in Therapeutic Approaches and Clinical Management

While treatment options have progressed in sync with increased knowledge of COPD's pathology, it is crucial to underscore that smoking cessation remains the single most effective intervention capable of altering the natural history of the disease and slowing the accelerated decline in lung function. Building on this foundation, management techniques have transitioned from strictly symptomatic treatments using short acting bronchodilators and supportive care (eg, oxygen, pulmonary rehabilitation) to include evidence based, clinically proven treatments such as long acting bronchodilators and combinations of inhaled agents which have greatly improved symptoms, exercise capacity and reduced frequency of exacerbations.³⁷ Additionally, advancements in inhaler design and formulation have further optimized the delivery of medication to the peripheral lung parenchyma.

The shift toward personalized or individualized management has been supported by recognition of the importance of patient specific factors including phenotypic characteristics and inflammatory profiles. For example, it is now recognized that the primary population that derives a benefit from inhaled steroids are patients who exhibit chronic inflammation.³⁸ This represents a paradigmatic shift in the direction of “precision” medicine. Concurrently, an increasing emphasis on non-pharmacologic interventions has emerged as the appreciation grows that pharmacotherapy alone will never be able to adequately manage the entire scope of the disease burden associated with COPD. Pulmonary rehabilitation, ventilator support, nutritional counseling, and psychological and social support services have become important components of comprehensive care for patients with COPD, highlighting the systemic nature of the disease.³⁹

Current Clinical Significance

Although significant progress has been made with regards to COPD as a public health issue; it still presents an immense challenge for global health. COPD affects approximately 350 million people worldwide and ranks as the third leading cause of death globally, accounting for 3.7 million deaths annually.⁴⁰ Over half of all cases and approximately 68% of COPD-related deaths and disability-adjusted life-years occur in low- and middle-income countries, where diagnostic resources and access to care remain severely limited.⁴¹ The global prevalence among individuals aged 40 years and older is estimated at 12.64% (95% CI: 10.75–14.65%).⁴² Furthermore, the absolute number of cases, deaths, and disease burden is projected to continue rising through 2045, driven largely by population aging and growth.⁴³ It is often under-diagnosed, especially in early stages of disease, which would allow for interventions that could have the greatest benefit. Late-stage diagnoses lead to irreparable structural damage and will limit the therapeutic effects of available treatments. Additionally, there is a large variability in how the disease progresses, how symptoms are expressed and how patients respond to treatments, all of these factors contribute to decision-making for clinicians, and highlight the remaining gaps between the ability to stratify patients based on prognosis and severity of disease.

Currently, no treatment exists that can reliably halt or reverse structural lung destruction and many existing therapies provide minor benefits that include relief from symptoms and/or reducing the number of exacerbations. In addition, comorbidities further complicate the management of the disease, as they add to functional limitations, increase healthcare utilization and contribute to increased risk of mortality. The recent COVID-19 pandemic underscored the heightened vulnerability of COPD patients to viral exacerbations and poor outcomes. Retrospective analyses from high-burden regions such as Punjab, Pakistan, have demonstrated that patients with COPD who contract SARS-CoV-2 face a significantly increased risk of mortality and prolonged recovery times.^{44,45} These studies further identified that clinical symptoms such as cough, lower respiratory tract infection, and body aches serve as independent predictors of adverse

outcomes in this patient population during the pandemic. These ongoing unmet needs emphasize the need for continued research into earlier detection of the disease; therapies directed at the mechanisms involved in disease pathology and delivery of comprehensive care models that address both the pulmonary and systemic manifestations of the disease.

Rationale of the Review

As new research emerges rapidly across molecular, clinical, and translational fields, it is both imperative and timely that there be an overall synthesis of the most recent developments in COPD as they relate to disease mechanisms, diagnostic innovations, drug development, and support services. This review will synthesize these recent findings into an integrated and cohesive model for understanding COPD. This review will assess critically all of the available evidence and identify the key challenges and future directions for COPD research and practice; the ultimate goal is to create a structured base from which to improve, through the creation of more efficient, personalized, and equitable treatment strategies for patients with COPD.

Cellular and Molecular Mechanisms Underlying COPD Progression

COPD is a multilevel pathologic continuum resulting from the translation of molecular perturbations into cellular dysfunction, tissue remodeling, and irreversible structural and functional changes of the lung, rather than a linear disease process. COPD development is influenced by the cumulative effects of genetic susceptibility, environmental injury, immune dysregulation, and impaired repair mechanisms at molecular, cellular, tissue, and organ-system scales. A comprehensive multi-scale perspective is necessary to understand disease heterogeneity and variable responsiveness to treatment.^{46–48}

Oxidant-rich environmental stimuli, primarily cigarette smoke and airborne pollutants, initiate and maintain COPD at the molecular level. The oxidative stress generated by these stimuli overwhelms the body's endogenous antioxidant systems (eg, superoxide dismutase, catalase, and glutathione) and introduces high concentrations of reactive oxygen and nitrogen species into the airway microenvironment. The oxidative stress directly damages DNA, lipids, and proteins; leads to genomic instability, altered protein folding, and dysfunctional signaling cascades; and activates redox-sensitive transcription factors (eg, NF- κ B and AP-1), which regulate the expression of pro-inflammatory genes and support chronic inflammation.⁴⁹

The molecular disturbances produced by oxidative stress lead to significant cellular dysfunction. Airway epithelial cells were previously viewed as passive structural components, but are now recognized as central contributors to COPD pathogenesis. Injury to the airway epithelium disrupts tight junctions, increases epithelial permeability, and facilitates pathogen invasion.^{50,51} Chemokines, cytokines, and alarmins released from injured epithelial cells recruit and activate immune cells and impair mucociliary clearance.^{50,52} Goblet cell hyperplasia and altered epithelial differentiation contribute to mucus hypersecretion and promote airflow obstruction and bacterial colonization.^{53–55}

Innate immune cells are responsible for the amplification of the inflammatory response in COPD(23). Alveolar macrophages in COPD exhibit abnormal polarization states characterized by increased pro-inflammatory activity and decreased ability to phagocytose pathogens.⁵⁶ Dysfunctionally polarized macrophages secrete TNF- α , ILs, and matrix-degrading enzymes and are unable to efficiently remove apoptotic cells, referred to as defective efferocytosis. Large numbers of neutrophils are recruited to the airway lumen, releasing proteases, myeloperoxidase, and neutrophil extracellular traps (NETs), further enhancing tissue injury and oxidative stress.⁵⁷ Collectively, the abnormalities in innate immunity result in an ongoing inflammatory environment that does not resolve.

Adaptive immunity also contributes to the progression of disease in COPD by causing prolonged lymphocytic infiltration into the lungs and disrupting immune homeostasis.^{58,59} Elevated numbers of cytotoxic CD8⁺ T-cells infiltrate the airways and alveoli, inducing apoptosis of epithelial and endothelial cells via mechanisms involving perforin and granzymes.⁶⁰ The Th1 and Th17 CD4⁺ T-cell responses are skewed towards pro-inflammatory phenotypes, whereas the number of regulatory T-cells is reduced, decreasing immune tolerance and the capacity to resolve inflammation.^{61,62} Advanced disease is characterized by the formation of ectopic lymphoid follicles, indicating that the adaptive immune system contributes to the persistence of disease in COPD.

A key interface between inflammation and structural destruction of the lung in COPD is the balance between proteases and antiproteases. Activated neutrophils and macrophages release proteolytic enzymes that degrade

elastin and collagen within the extracellular matrix, compromising the integrity of the alveolar wall.⁶³ When the antiprotease defense mechanism is insufficient, progressive emphysema occurs, characterized by dilated airspaces and a reduction in elastic recoil. Matrix degradation caused by proteolytic enzymes disrupts cell-matrix signaling, impairs mechanotransduction, and limits tissue repair.⁶⁴ Ultimately, the combined effect of these processes results in a fragile lung structure that is susceptible to mechanical stress and declines in function.

Impaired regeneration in addition to inflammation and proteolysis has been identified as another hallmark of COPD. Cellular senescence accumulates within various lung cell types, including epithelial cells, fibroblasts, and endothelial cells. Cells undergoing senescence exhibit irreversible growth arrest accompanied by a senescence-associated secretory phenotype that promotes chronic inflammation and matrix degradation. Impaired mitochondrial function contributes to this process by decreasing cellular energy availability and increasing reactive oxygen species production, thus reinforcing oxidative stress and senescence pathways.^{27,65} As such, aging-related mechanisms linking COPD progression to accelerated lung aging have been identified.⁶⁶

In addition to the processes described above, accelerated aging mechanisms have emerged as central to COPD pathogenesis. COPD is now widely recognized as a disease of premature lung aging, driven in part by telomere dysfunction and immunosenescence.⁶⁷ Telomeres, the protective nucleoprotein structures at chromosomal ends, shorten with each cell division and under oxidative stress. In COPD patients, leukocyte telomere length is significantly reduced compared with age-matched controls, reflecting accelerated biological aging at the cellular level.⁶⁸ Telomere attrition contributes to genomic instability and limits the replicative capacity of lung progenitor cells, thereby impairing normal tissue repair and regeneration. Concurrently, immunosenescence, the age-related decline in immune function, further compounds the inflammatory burden. In COPD, immunosenescence is characterized by diminished anti-infection capacity, heightened activation of neutrophils and macrophages, T cell infiltration, and aberrant B cell activity, all of which perpetuate airway inflammation and lung injury.⁶⁹ Beyond these aging-related changes, epigenetic alterations provide a critical mechanistic link between environmental exposures and persistent gene expression changes in COPD. Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, regulate gene activity without altering the underlying DNA sequence.⁷⁰ Exposure to environmental stressors such as cigarette smoke and biomass fuel combustion disrupts normal epigenetic regulation in structural and immune cells of the lung, giving rise to aberrant DNA methylation patterns and altered histone acetylation. These modifications disturb the precise control of gene expression governing inflammatory signaling, the protease–antiprotease equilibrium, and tissue repair mechanisms.⁷¹

Finally, the molecular and cellular abnormalities described above converge to cause characteristic structural changes in tissues and organs of the lung. Fibrosis of small airways, smooth muscle remodeling and luminal narrowing of small airways, and destruction of alveolar units due to emphysema decrease gas exchange surface area and increase airflow resistance.^{72,73} Additionally, vascular remodeling and endothelial dysfunction reduce pulmonary perfusion, contributing to ventilation-perfusion mismatch and hypoxemia. The structural changes identified above occur clinically as progressive dyspnea, limited exercise capability, and susceptibility to acute exacerbations.

There is emerging evidence that alterations in the composition of the respiratory microbiome impact disease expression across the aforementioned scales. Reduced microbial diversity and over-representation of pathogenic taxa enhance inflammatory signaling and disrupt host-microbe homeostasis, especially during exacerbations. Interactions between the microbiome and immune system can modulate both innate and adaptive immune responses, suggesting a reciprocal relationship between the ecological status of the microbiome and inflammatory phenotypes of the host. The integration of these molecular, cellular, and macroscopic mechanisms is summarized in [Figure 1](#).⁷⁴

Advances in Diagnostic Strategies and Disease Phenotyping

Beyond Spirometry: Expanding Physiological Characterization and Early Detection

Although spirometry has remained fundamental in establishing whether there has been chronic airflow limitation; however, the degree to which spirometry assesses the full biological and clinical spectrum of COPD remains limited.⁷⁵ Spirometry's forced expiratory measurements represent diverse structural and inflammatory pathologies within a singular global measure, thus potentially failing to capture early small-airway pathology, differentiating between the

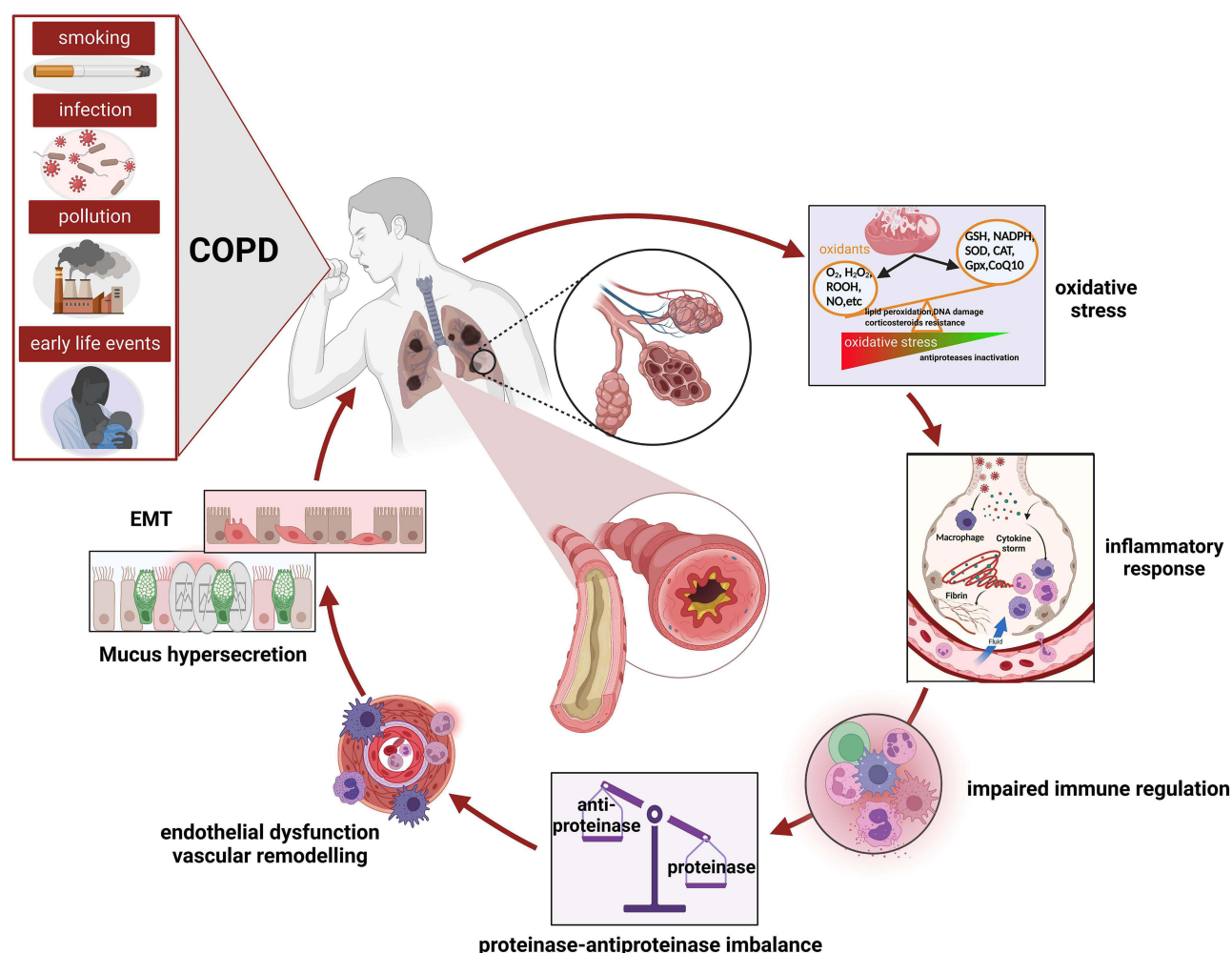


Figure 1 Mechanisms underlying COPD development. Multiple risk factors including cigarette smoke and other irritants activate alveolar macrophages and epithelial cells in the respiratory tract leading oxidative stress followed release of multiple inflammatory mediators. These inflammatory mediators, particularly chemokines, attract neutrophils and monocytes as well as T helper cells. The activated alveolar macrophages and epithelial cells also release proteases such as neutrophil elastase and matrix metalloproteinase-9 (MMP-9), which damage the lung parenchyma resulting in lung vascular remodeling, alveolar wall destruction and mucus hypersecretion. In addition, the activated macrophages and epithelial cells release fibrogenic mediators, such as TGF β which causes EMT and eventually small airway fibrosis.

most common mechanisms responsible for obstructing airflow and failing to account for the large proportion of patients' symptom burdens. This deficit is notably evident in those who are symptomatic with preserved or near-preserved spirometry, where dyspnea and exercise limitation may result from small-airway dysfunction, dynamic hyperinflation, gas-exchange impairments or cardiopulmonary interactions instead of a notable reduction in the patient's forced expiratory volume.^{76–78} Therefore, contemporary physiological evaluations increasingly aim to establish physiologically identifiable, treatable functional defects that predict outcome and help direct individualized management beyond traditional spirometric staging of COPD.

Assessment of lung volume and static and dynamic hyperinflation have taken center stage in the development of this broader physiological assessment strategy. Static hyperinflation refers to an increase in the end-expiratory lung volume at rest, while dynamic hyperinflation refers to an additional increase during physical activity as a result of expiratory flow limitation and decreased expiratory time.⁷⁹ Both conditions increase the mechanical load of breathing, flatten the diaphragm and reduce the patient's inspiratory capacity resulting in exertional dyspnea that may be out of proportion to the degree of spirometric impairment.^{80,81} The use of plethysmographic assessment of residual volume, functional residual capacity and total lung capacity provides important mechanistic data on air-trapping and mechanical restriction relevant to patient symptoms and exercise intolerance.⁸² Additionally, these measurements demonstrate utility in

assessing the patient's response to bronchodilator therapy, lung-volume reduction therapy, and rehabilitation interventions as increases in inspiratory capacity can correlate with clinical improvement even when changes in forced expiratory volume are minimal.

The additional dimension provided by gas-transfer testing assesses the integrity of the alveolar-capillary interface and the degree of pulmonary microvascular involvement. A reduced diffusing capacity can be indicative of emphysematous destruction of surface area, capillary bed rarefaction, ventilation-perfusion mismatch or pulmonary vascular disease each of which may have unique implications regarding long-term prognosis.⁸³ The extension of gas-transfer testing by exercise oximetry and cardiopulmonary exercise testing allows for the assessment of ventilatory inefficiency, dynamic hyperinflation during exercise and the relative contribution of ventilatory, cardiovascular and peripheral muscle limitation.^{84–86} Assessments such as these are being utilized to better understand complex symptom profiles, to differentiate between respiratory and non-respiratory factors contributing to limitation, and to identify patients that would be ideal candidates for targeted interventions.

Small-airway dysfunction represents one of the earliest substrates of COPD and is increasingly assessed using methods that measure peripheral airway resistance and ventilation heterogeneity.^{87,88} Impulse oscillometry and other forced-oscillation techniques assess the frequency-dependent changes in resistance and reactance measured during expiration that may indicate peripheral airway narrowing and loss of elastic recoil.⁸⁹ In addition to impulse oscillometry, multiple breath washout and other measurements of ventilation distribution are providing increasing sensitivity to early airway disease and are able to detect subtle ventilation inhomogeneities prior to significant spirometric abnormality. Together, these expanded physiological assessments are changing how diagnosis and phenotyping occur by identifying functional patterns of disease - hyperinflation-dominant, gas transfer-limited, ventilation heterogeneity-dominant or mixed - thereby allowing for the establishment of mechanistic anchors for subsequent imaging and molecular profiling.

Structural Imaging and Quantitative CT: From Visual Descriptors to Measurable Phenotypes

Structural imaging has changed how clinicians assess COPD through the ability to visually examine the anatomic bases of airflow obstruction and impaired gas exchange.⁹⁰ Structural imaging through high resolution computerized tomography (HRCT) provides details on the spatial distribution and severity of emphysema, as well as the degree of airway wall thickening, luminal narrowing, and evidence of loss of small airways. The advantage of HRCT lies in its ability to directly visualize the heterogeneity of COPD; emphysema can predominate in the upper lobes, airway remodeling can occur in central or segmental airways and small airway pathology can be present throughout but invisible to spirometry. Through the use of HRCT imaging clinicians are able to map out the heterogeneity of COPD and support disease subtyping and improve the clinico-pathological correlation.⁹¹

The application of quantitative imaging techniques converts the qualitative data from HRCT into quantitative data that can be compared and correlated with patient symptoms, risk of future exacerbations, and progression of disease.^{92,93} Quantitative imaging of the lungs using densitometry provides a measure of emphysema burden and allows for longitudinal measurement of parenchymal loss.⁹⁴ Morphometric analysis of the airways allows clinicians to quantify the caliber of the lumen and the thickness of the walls. The combination of the two measurements allow clinicians to differentiate between patients with predominant emphysema from those with predominant airway involvement and identify patients who have mixed forms of the disease and therefore may require different treatment emphases. In addition to providing a method of classification, quantitative imaging has shown that small airway loss and remodeling can occur prior to significant emphysematous damage, suggesting a pathophysiological model where early small airway pathology leads to subsequent irreparable parenchymal changes.⁹⁵ This finding has significant implications for developing new methods of early detection and understanding why some patients with similar spirometric values demonstrate different rates of disease progression.

Imaging based phenotypes also provide mechanistic explanations for the presence of symptoms and functional impairments associated with COPD.⁹⁶ Phenotypes characterized by predominance of emphysema often correlate with reductions in diffusing capacity and the presence of exercise-induced desaturation, while those characterized by

predominance of airway disease often correlate with chronic bronchitis symptoms and increased susceptibility to exacerbations.⁹⁷ The regional distribution of emphysema influences candidacy for surgical interventions such as lung volume reduction surgery and the potential benefits of surgical intervention.⁹⁸ Furthermore, imaging provides information relevant to evaluating comorbidities by identifying the presence of coronary artery calcification, pulmonary artery dilatation and interstitial disease that can affect the outcome of therapies and guide their selection.^{99,100}

While structural imaging has many advantages, there are several factors that will affect the interpretation and integration of structural imaging data into clinical decision-making. These include variability in acquisition protocol, reconstruction parameter and image segmentation methods that result in differences in quantitative output. As a result, standardized protocols will be required for both research and clinical applications. Additionally, structural imaging requires radiation exposure and carries a cost, which limits its application to all patients with COPD. Finally, imaging findings must be placed in the appropriate clinical context to avoid misinterpreting normal variants or age-related changes as indicative of disease. Despite the limitations and challenges presented by structural imaging, it has become a fundamental tool in defining phenotypes due to its ability to link anatomy to physiology, provide measurable end points for longitudinal assessments and facilitate the integration of advanced computational approaches.

Functional Imaging and Regional Mechanics: Capturing the Dynamics of Airflow Obstruction

Although structural imaging shows anatomically abnormal areas of the lungs, functional imaging examines how those anatomical irregularities result in regional variations in ventilation and airflow behavior during breathing.¹⁰¹ It is this difference which is important since, in many cases, symptoms of COPD and the risk of experiencing acute exacerbations result from dynamically changing respiratory behaviors (eg, air trapping during exhalation, ventilation heterogeneity during physical activities, etc.) rather than the anatomically abnormal structures themselves. As such, functional imaging provides a way to bridge the gap between pathological findings and physiological events through creation of “function maps” showing the regional “function” of the lungs in relation to symptoms and predicting clinically significant outcomes.¹⁰²

One of the major contributions of functional imaging has been the separation of emphysematous destruction from functional small-airway disease in situations where both types of disease exist simultaneously.¹⁰³ Techniques comparing the inspiratory and expiratory CT images will show the area(s) of air trapping and altered density changes indicating small-airway obstruction. This is important, as small-airway disease represents an early or potentially reversible form of disease whereas established emphysema indicates irreversible loss of lung tissue. Practically, separating these components of disease allows for better mechanistic phenotyping and may provide guidance on the direction of therapeutic emphasis, ie, focusing on bronchodilators and inhaled drug delivery strategies directed toward distal airways when there is significant functional small-airway disease.¹⁰⁴

The use of regional imaging techniques demonstrates the patchwork nature of the mechanical dysfunction of COPD. Ventilation may occur normally in certain parts of the lungs while being severely impaired in other parts; this produces ventilation-perfusion mismatches and limits exercise performance, even when global indices indicate a relatively stable condition of lung function.¹⁰⁵ The regional heterogeneity of lung function explains why some individuals with mild spirometric impairment experience extreme shortness of breath due to localized air trapping and hyperinflation resulting in mechanical constraints to inspiratory capacity and increased ventilatory demands.¹⁰⁶ Therefore, functional imaging can be used to help explain apparent discrepancies between clinical presentations and test results.

In addition, functional imaging techniques are increasingly recognized as having the capability for longitudinal monitoring. Changes in regional indices of air trapping and ventilation inhomogeneity over time may not be reflected in spirometric values and could serve as markers of disease progression or responses to treatment. These measurements are particularly useful in research studies in order to provide physiologically relevant endpoints for mechanistic trials.¹⁰⁷ Clinically, functional imaging has the potential for selecting patients who would most benefit from treatments that target specific regional aspects of lung mechanics, eg, volume reduction procedures and targeted bronchoscopic interventions; however, the use of functional imaging for routine selection of patients remains limited.

There are several limitations to standardizing functional imaging including differences in how subjects are coached regarding their breath holds, differences in the lung volumes present at the time of image acquisition, and differences in the algorithms employed to analyze the data. However, the conceptual implications of using functional imaging are considerable; they create a framework for assessing COPD as a disease of dynamic obstruction and mechanical constraint of the lungs, connecting anatomical damage to functional consequences and establishing a basis for developing a unifying model of COPD that incorporates biomarkers and clinical phenotypes based upon mechanisms.

Biomarkers and Molecular Endotyping: From Inflammation Signatures to Mechanism-Linked Stratification

COPD biomarker research has extended beyond COPD anatomical and physiological phenotypic characteristics and has provided an opportunity for the molecular characterization of disease mechanisms. The primary goal is to develop measurable indicators of disease process which can provide insight into the biological basis of the disease, allow clinicians to predict when clinical events will occur, and assist in the selection of the most effective treatments for each individual patient's disease mechanism.¹⁰⁸ There is now growing evidence that COPD is not characterized by a uniform inflammatory response; different individuals with COPD may exhibit distinctly different immune responses, remodeling pathways, and systemic effects on their body systems that are likely to affect their risk of experiencing an exacerbation of the disease and how they respond to available treatments.^{109,110}

One of the first practical biomarkers to emerge was blood eosinophil counts. Blood eosinophil counts have been used in a number of settings to serve as an indicator of eosinophil-related inflammation and help clinicians determine whether an individual with COPD is likely to derive benefit from use of an inhaler containing an inhaled corticosteroid in the proper clinical context.¹¹¹ However, eosinophils are just one aspect of the complex biology of COPD and therefore their ability to predict outcomes is influenced by variability in the biology of each individual, comorbidities, and the presence of multiple types of inflammation in the same individual. Other biomarkers that are part of the larger landscape of biomarkers include systemic inflammatory markers, indicators of oxidative stress, and proteins related to the remodeling of tissues and the breakdown of extracellular matrix. Some of the biomarkers in this category have been found to be associated with increased risks of exacerbations, higher levels of symptoms, and the presence of comorbidities; however, many biomarkers in this category suffer from limitations such as a lack of specificity, a high degree of overlap with biomarkers of other chronic inflammatory diseases, and variable consistency in their performance across different populations.¹¹²

Another type of biomarker that offers greater proximity to lung processes is airway-derived biomarkers. Biomarkers derived from sputum cytology, inflammatory mediators in sputum, and analyses of exhaled breath can capture the presence of inflammation in the airways, signs of infections in the airways, and oxidative chemistry more closely than biomarkers obtained through blood samples. Breath condensate analysis and volatile organic compound (VOC) analysis of exhaled breath provide non-invasive methods of performing molecular phenotyping; however, both VOC and breath condensate analyses require additional study regarding variability in methods and the need for standardization before either technique can be used widely.¹¹³ Airway-based approaches to biomarker development may be especially relevant to the identification of chronic bronchitic inflammation, signals of microbial dysbioses in the airways, and high-risk exacerbation biology.

The advent of high-dimensional molecular profiling has created opportunities for the development of endotypes—classification of disease based on shared mechanisms of disease progression rather than solely on the clinical presentation. Transcriptomic, proteomic, and metabolomics analyses have identified molecular signatures that are associated with susceptibility to exacerbations, severity of emphysema, systemic inflammation, and impaired repair processes.¹¹⁴ Molecular signatures have also distinguished biological subgroups within COPD that do not correlate well with the degree of obstruction measured by spirometry, providing support for a precision medicine model that identifies predominant mechanisms of disease and directs therapies accordingly.¹¹⁴ However, for these signatures to be translated into clinical practice, they must demonstrate reproducibility, lower costs, and feasibility of simplification into assays that retain their predictive capability. Another factor to consider in developing endotypes is the potential for molecular signatures to change over time due to factors such as changes in smoking status, infections, treatment exposures, and aging, suggesting that endotypes may need to be dynamically reassessed rather than assigned at one point in time.

A potentially more effective approach to biomarker development in COPD is the use of multimarker panels, combining multiple biomarkers that measure complementary aspects of disease mechanisms.¹¹⁵ This approach recognizes that the progression of COPD results from the interplay of multiple biological pathways and that few, if any, single biomarkers explain sufficient variance in disease outcome.¹¹⁶ Furthermore, the combination of biomarkers with data from imaging and physiologic assessments can enhance the strength of mechanistic phenotyping, improve the accuracy of predictions of risk, and facilitate the selection of therapies that target specific disease mechanisms as they become increasingly available.^{108,117,118}

Clinical Phenotypes and Integrated Multidimensional Models: Toward Actionable Precision in Practice

The use of clinical phenotyping translates complex biology and structure into practical classifications used to guide management decisions. Traditional staging of COPD using spirometry alone does not provide adequate information regarding symptom burden and exacerbation risk, which are the primary predictors of outcome; contemporary approaches to defining COPD phenotypes include symptom burden and exacerbation history, comorbid conditions, and treatment response patterns to characterize the clinically relevant phenotype groups including frequent exacerbators, chronic bronchitic presentations, emphysematous predominant disease, and eosinophil associated inflammatory patterns. These phenotypes have relevance in terms of their prediction of differing trajectories of illness and differing therapeutic needs; however, these phenotypes are increasingly being recognized as dynamic states rather than static entities.^{119,120}

One of the major insights from recent research is that COPD phenotypes exhibit considerable variability over time. Changes in the rate of exacerbations with optimized therapy, smoking cessation, changing levels of infection exposure, and evolving comorbidities; and changes in symptom burden due to physical deconditioning, mood disorders (eg, depression, anxiety), cardiac disease, and worsening hyperinflation are all potential sources of variation. Thus, longitudinal phenotyping, ie, repeated assessment of symptom patterns, risk of exacerbations, physiology, and biomarkers over time, will be required to provide a comprehensive description of an individual's disease state, and to move beyond the use of a single point-in-time classification.¹²¹

In this context, the treatable traits approach to the diagnosis and management of COPD has gained popularity as a conceptual framework. Instead of assigning patients to one of several rigid subtypes of COPD (based upon symptoms and/or physiological findings), clinicians will identify multiple “modifiable” traits of disease that are present in the patient, such as eosinophilic inflammation, chronic bronchitic mucus production, a tendency to experience frequent exacerbations, deconditioning, anxiety, or hypoxemia, etc.; and, apply evidence-based treatments to reduce the presence and impact of each identified trait.¹²²

Multidimensional indices that measure multiple aspects of COPD disease are superior to unidimensional indices for predicting the future course of disease in patients, since they account for the multifactorial nature of both disability and mortality. Multidimensional models of COPD disease are developed by combining various measures of physiological impairment, symptom burden, exercise capacity, and body composition, to reflect the systemic nature of COPD.¹²³ Future generations of multidimensional models will also include additional types of data including quantitative imaging measurements and biomarker panels, and will be designed to link clinical decision-making directly to the underlying pathophysiology of the disease. This integration is facilitated by computational techniques that enable the use of high dimensional data sets and identification of relationships between variables that may not be evident through standard analytical techniques. As a result, there is increasing potential for these approaches to predict the likelihood of future exacerbations of COPD, to identify individuals who are at higher risk of progressing rapidly, and to match patients with specific therapies that are most likely to lead to positive health outcomes; provided that these models are validated in diverse populations and remain easily interpretable for clinical use.

Table 1 identifies the diagnostic modalities and emerging biomarker classes that form the basis of contemporary phenotyping, describes what each tool captures mechanistically, and outlines the main constraints that limit their current utility.

The combination of contemporary diagnostic methods and phenotypic assessment is an example of a shift from single-dimension (airflow) evaluation to multi-dimensional (physiology, structure, region, biology) evaluations, as such

Table 1 Contemporary Diagnostic Tools and Biomarker Domains Supporting COPD Phenotyping

Domain	Representative Tool or Measure	Mechanistic Signal Captured	Primary Clinical Value	Principal Constraint
Spirometry ¹²⁴	Post-bronchodilator airflow indices	Global expiratory flow limitation	Diagnostic confirmation; severity staging	Insensitive to early small-airway disease; limited mechanistic specificity
Lung volumes ¹²⁵	Residual volume, inspiratory capacity, hyperinflation indices	Air trapping and mechanical constraint	Explains dyspnea; tracks response to bronchodilation and volume-targeted interventions	Requires specialized equipment; interpretation influenced by technique and comorbid restriction
Gas exchange ¹²⁶	Diffusing capacity and exertional desaturation	Alveolar-capillary integrity and vascular involvement	Identifies emphysema-predominant or vascular-complicated disease; prognostic utility	Affected by anemia, pulmonary vascular disease, and technical variability
Small-airway function ¹²⁷	Oscillometry; ventilation heterogeneity measures	Peripheral airway resistance and elastic recoil loss	Early detection; mechanistic phenotyping when spirometry is nondiagnostic	Limited standardization and availability; normative thresholds vary
Structural imaging ¹²⁸	Quantitative CT emphysema and airway metrics	Parenchymal destruction; airway remodeling; regional heterogeneity	Phenotype definition; progression monitoring; procedural selection support	Radiation, cost, protocol dependence, and analytic variability
Functional imaging ¹²⁹	Regional air trapping and ventilation mapping	Functional small-airway disease versus emphysema contribution	Links regional mechanics to symptoms; supports mechanistic trials	Standardization challenges; limited routine clinical implementation
Blood biomarkers ¹³⁰	Eosinophils; systemic inflammatory panels	Inflammatory milieu and systemic activation	Risk stratification and therapy alignment in selected contexts	Biological variability; overlap with non-COPD inflammation; limited specificity
Multi-omics ¹³¹	Transcriptomic/proteomic/metabolomic signatures	Pathway-level endotypes and repair/remodeling biology	Mechanism-based stratification and therapeutic targeting research	High cost, complexity, and evolving signatures over time

a shift will allow for better stratification of both clinical risk and response to treatment, however, this will require standardized and scalable tools that will convert current advanced phenotyping into standard medical practices without expanding health disparities.

Pharmacological Innovations and Precision Therapeutics

Pharmacologic treatments for COPD continue to evolve from a general, symptom-oriented approach to a more individualized, mechanism-based strategy. As the understanding of COPD as a multi-faceted, biologically heterogeneous disease progresses, so too does the goal of current pharmacologic treatments, which include not only alleviating symptoms, but also modulating the risk of exacerbations, improving function and selecting treatments based upon inflammatory and structural phenotypes.

Bronchodilators are the cornerstone of COPD treatment, and produce their primary effect through the relaxation of airway smooth muscles and a reduction in dynamic hyperinflation. Long acting muscarinic receptor antagonists (LAMAs) inhibit bronchoconstriction mediated by acetylcholine, while long acting beta-2 agonists (LABAs) increase cyclic AMP levels to induce sustained bronchodilation. The synergistic combination of LAMAs and LABAs acts on different pathways, producing greater improvement in lung function and symptom burden when used in combination, compared to either agent when used alone. Bronchodilators may also reduce air-trapping and improve inspiratory capacity, both of which are likely responsible for the reduction in exertional dyspnea and increased exercise tolerance observed in some individuals treated with bronchodilators.¹³² Therefore, the physiologic effects of bronchodilation provide evidence of its utility, independent of changes in forced expiratory volumes.

A prime example of how precision pharmacology is being applied in COPD is through the refined use of inhaled corticosteroids (ICS). ICS were previously widely prescribed in COPD, but their use is now more selective due to the recognition that ICS have varying degrees of benefit dependent upon the presence or absence of eosinophilic inflammation in the airway. Clinical evidence supports the use of ICS in preventing future exacerbations in patients with eosinophilic inflammation, and this is consistent with the overlap between COPD and asthma of type 2 immune pathway involvement. In contrast, patients who do not have eosinophilic inflammation derived little benefit from ICS treatment while continuing to be at risk for adverse effects such as pneumonia and systemic side effects.¹³³ The inclusion of blood eosinophil counts in clinical decision making for the initiation of ICS therapy serves as an example of how biomarker research can be translated into routine clinical practice and demonstrates the trend towards biologically directed therapy selection.

Systemic anti-inflammatory agents have also been developed to address specific pathogenic mechanisms of COPD, outside of the inhaled therapies listed above. Phosphodiesterase-4 (PDE4) inhibitors prevent the degradation of intracellular cyclic adenosine monophosphate (cAMP), and as a result decrease the release of inflammatory mediators from immune cells.¹³⁴ The clinical application of PDE4 inhibitors appears greatest in patients with chronic bronchitis phenotypes who experience frequent exacerbations; in these patients, inflammation is not limited to the airway lumen, but extends into the systemic compartment. However, the relatively small degree of benefit and the potential for dose limiting adverse effects related to the gastrointestinal and neuropsychiatric systems highlight the difficulty in treating systemic inflammation in a chronic disease that is caused by immune imbalance rather than immune hyperactivity.

Biologic therapies, which target specific components of the inflammatory cascade in COPD, offer another advancement in the application of precision medicine in COPD.¹⁰⁸ However, the role of biologics in COPD is significantly less defined than it is in asthma. Monoclonal antibodies targeted against cytokines involved in eosinophilic and type 2 inflammation have produced variable results across clinical trials, suggesting that there is both biologic variability and variability in patient selection across studies. Together, these observations suggest that only a portion of patients with COPD will have inflammatory pathways that are amenable to cytokine-targeted therapies. Early failures of biologic therapies for COPD have nonetheless provided insight into the endotyping of disease and reinforce the need for robust biomarkers to identify responsive populations.

There is increasing focus on developing pharmacotherapeutic modalities to treat oxidative stress and dysfunctional cellular homeostasis in COPD. Oxidative injury is an overarching mechanism that links environmental exposures to inflammation, corticosteroid resistance, and tissue destruction.¹³⁵ A number of pharmacologic approaches to restore redox balance in COPD have included antioxidant supplementation and agents that target pathways involved in oxidative

signaling. To date, clinical benefits have been inconsistent. However, ongoing advances in the molecular targeting of drugs and drug delivery systems may ultimately allow for more effective modulation of oxidative stress in selected patient populations.

While there have been significant advances in pharmacologic treatments for COPD, there remain significant limitations to the effectiveness of pharmacologic treatments for COPD. Variability in treatment response, limited impact of treatments on disease modification, and the challenge of identifying reliable surrogate endpoints for clinical trials are just a few examples of the challenges that exist in the pharmacologic treatment of COPD. Despite these limitations, the trajectory of pharmacologic innovation reflects a progressive alignment of pharmacologic treatment with biological mechanisms, clinical phenotypes, and patient-specific characteristics. This evolving precision-based approach to the pharmacologic treatment of COPD represents a necessary step in the development of comprehensive COPD care that incorporates pharmacologic treatments with non-pharmacologic and supportive interventions.

Non-Pharmacological and Supportive Interventions in Contemporary COPD Care

Non-pharmacologic and supportive interventions are essential components of a complete, comprehensive COPD management plan. Additionally, there is increasing recognition that non-pharmacologic interventions are a key factor in achieving long term outcomes in patients with COPD. Since COPD affects multiple body systems and extends beyond airflow limitation to include skeletal muscle dysfunction, metabolic disturbances, psychological distress, and decreased social participation, addressing each of these factors is necessary to develop effective interventions. Recent research has strengthened the biological and clinical rationale for developing individualized care pathways that include supportive strategies, regardless of the degree of irreversible structural lung damage present in the patient.

Pulmonary rehabilitation represents the most validated form of non-pharmacologic intervention for patients with COPD, regardless of stage. Pulmonary rehabilitation programs utilize a combination of structured aerobic and resistance training, patient education, and behavioral interventions to help reduce the effects of physical deconditioning and symptom-related anxiety.¹³⁶ Exercise training improves the oxidative capacity of skeletal muscle, increases the efficiency of mitochondria, and optimizes peripheral oxygen utilization, resulting in reduced ventilatory demands during exertion. Improved exercise tolerance, reduced dyspnea, and improved health-related quality of life are the clinical manifestations of these adaptations. In addition, pulmonary rehabilitation has consistently demonstrated a reduction in hospitalizations due to acute exacerbations, including those occurring in patients with advanced COPD. Emerging evidence also suggests that initiating pulmonary rehabilitation prior to the development of severe disease may slow the rate of decline in functional capacity and potentially prevent disability.

Recent innovations in the delivery of pulmonary rehabilitation have made it possible to expand access to this beneficial intervention to larger segments of the population and make it more adaptable to different settings. Studies have demonstrated that home-based and remotely supervised pulmonary rehabilitation programs can be as effective as center-based models of pulmonary rehabilitation in selected populations, especially when they are provided with structured protocols and digital monitoring. Both types of pulmonary rehabilitation programs provide solutions to several of the barriers that exist for individuals who wish to participate in a pulmonary rehabilitation program, including limited mobility, geographic location, and the availability of healthcare resources.

Wearable sensors and activity monitors will enable “precision pulmonary rehabilitation” through tailored exercise prescription, objective monitoring of compliance, and continuous adjustment of training intensity. As such, wearable devices and activity monitors will represent an advancement of pulmonary rehabilitation toward precision health.¹³⁷ Long term oxygen therapy is a core component of supportive care for patients with chronic hypoxemia; it has a well established survival benefit in severe resting hypoxemia and thus represents a clear example of when a physician must transition from a symptom based approach to one that is individualized and based upon physiology. The advent of new portable oxygen delivery systems has significantly enhanced patient mobility, and, therefore, adherence, and real world effectiveness.¹³⁸ Non-invasive ventilation (NIV) is becoming an increasingly important treatment option in advanced COPD, especially in chronic hypercapnic respiratory failure, in which nocturnal use has been shown to improve gas

exchange, reduce the work of breathing, enhance sleep quality, and decrease hospital readmission rates.¹³⁹ In addition, there is evidence of decreased respiratory muscle fatigue and systemic inflammation with nocturnal NIV in advanced COPD. Tobacco cessation continues to be the most effective intervention for changing the course of disease and decreasing mortality associated with COPD. Tobacco cessation using a combination of behaviorally based strategies (counseling) and pharmacologically based strategies, in addition to multiple forms of counseling, and/or digital platforms, results in higher rates of sustained tobacco abstinence than single modality interventions.¹⁴⁰ Malnutrition, sarcopenia, and weight loss all have adverse effects on prognosis in COPD and thus both nutrition and metabolic interventions are essential components of comprehensive COPD management. Individualized nutritional support combined with resistance training can improve muscle strength. Psychological and psychosocial support are additional components of comprehensive COPD management that address anxiety, depression, and social isolation, which have a significant effect on perceived symptoms, compliance, and overall quality of life in COPD. Digital health technology integrates these various supportive strategies through remote monitoring and predictive analytics and enables the early identification of impending clinical deterioration and proactive intervention and, ultimately, the definition of the long-term impact of digital health technology on COPD outcomes.

Table 2 provides a summary of the primary non-pharmacologic and supportive interventions, their mechanism(s), and clinical implications, and highlights their complementary roles in an integrated management plan.

Both non-pharmacologic and support interventions collectively address those factors contributing to COPD burden beyond the lung function impairment aspect of COPD. The combination of non-pharmacologic and pharmacologic approaches are necessary to provide a comprehensive, patient-centered, multi-dimensional approach to improve both functional status and health-related quality of life for individuals living with COPD today. The multidimensional nature of non-pharmacological and supportive interventions is illustrated in Figure 2, which depicts an integrated model of comprehensive COPD management encompassing rehabilitation, ventilatory support, behavioral interventions, and digital health integration.¹⁴¹

Limitations, Challenges, and Future Research Directions

Although there has been considerable advancement in the understanding and management of COPD, the potential for continued meaningful disease modification and equalizing care delivery continues to be impeded by many existing issues. The most significant of which continues to be the underdiagnosis and delayed diagnosis of COPD. Many people are diagnosed with COPD when irreversible airflow limitation and structural lung damage have already occurred. The reason for this delay includes; the dependency on symptomatic presentation, limited access to spirometry in many regions and incorrect attribution of early respiratory symptoms to the natural aging process or other related comorbidities. Therefore, many opportunities for early intervention and preventing disease progression are lost.

Another fundamental issue is the heterogeneity of COPD. COPD is a complex condition that encompasses a broad range of biological processes, clinical manifestations and patterns of disease progression. However, current classification systems only marginally account for the diversity of COPD. Phenotypic and endotypic frameworks have enhanced our conceptualization of the complexity of COPD, however, these frameworks remain inadequately standardized and are not universally applied in daily clinical practice. Many COPD phenotypes are dynamic, changing in response to environmental exposures, age-related changes, and treatments. This variability makes it difficult to develop effective strategies to categorize patients, reduces the generalizability of clinical trial results and results in inconsistencies in treatment responses.

Additionally, therapeutic development is also being limited due to the absence of reliable disease modifying endpoints. Although commonly used measures including lung function decline, frequency of exacerbations and symptom based measures provide important clinical information, they do not reliably reflect the underlying pathological progression of COPD. Lung function decline can be slow and irregular, exacerbation frequency is influenced by factors including access to healthcare services and how exacerbations are reported, and symptom based measures exhibit large inter individual variability. The lack of validated surrogate markers for disease in the small airways, progression of emphysema and impaired repair mechanisms represents a major impediment to both the development of drugs and the long term assessment of treatment outcomes.

Table 2 Major Non-Pharmacological and Supportive Interventions in COPD

Intervention Domain	Primary Mechanisms	Clinical Benefits	Key Limitations
Pulmonary rehabilitation ¹³⁶	Improved muscle oxidative capacity, reduced ventilatory demand	Enhanced exercise tolerance, reduced dyspnea, fewer hospitalizations	Limited access, variable referral rates
Home-based and tele-rehabilitation ¹³⁷	Remote supervision, personalized exercise monitoring	Improved accessibility, sustained functional gains	Requires digital literacy and infrastructure
Long-term oxygen therapy ¹³⁸	Correction of chronic hypoxemia	Improved survival in severe hypoxemia	Limited benefit outside defined indications
Non-invasive ventilation ¹³⁹	Reduced respiratory muscle load, improved gas exchange	Fewer admissions, improved quality of life	Patient tolerance, need for careful selection
Smoking cessation support ¹⁴⁰	Elimination of ongoing toxic exposure	Slowed disease progression, reduced mortality	High relapse rates without sustained support

Chronic Obstructive Pulmonary Disease: A Narrative Synthesis of Its Hallmarks for Palliative Care Clinicians

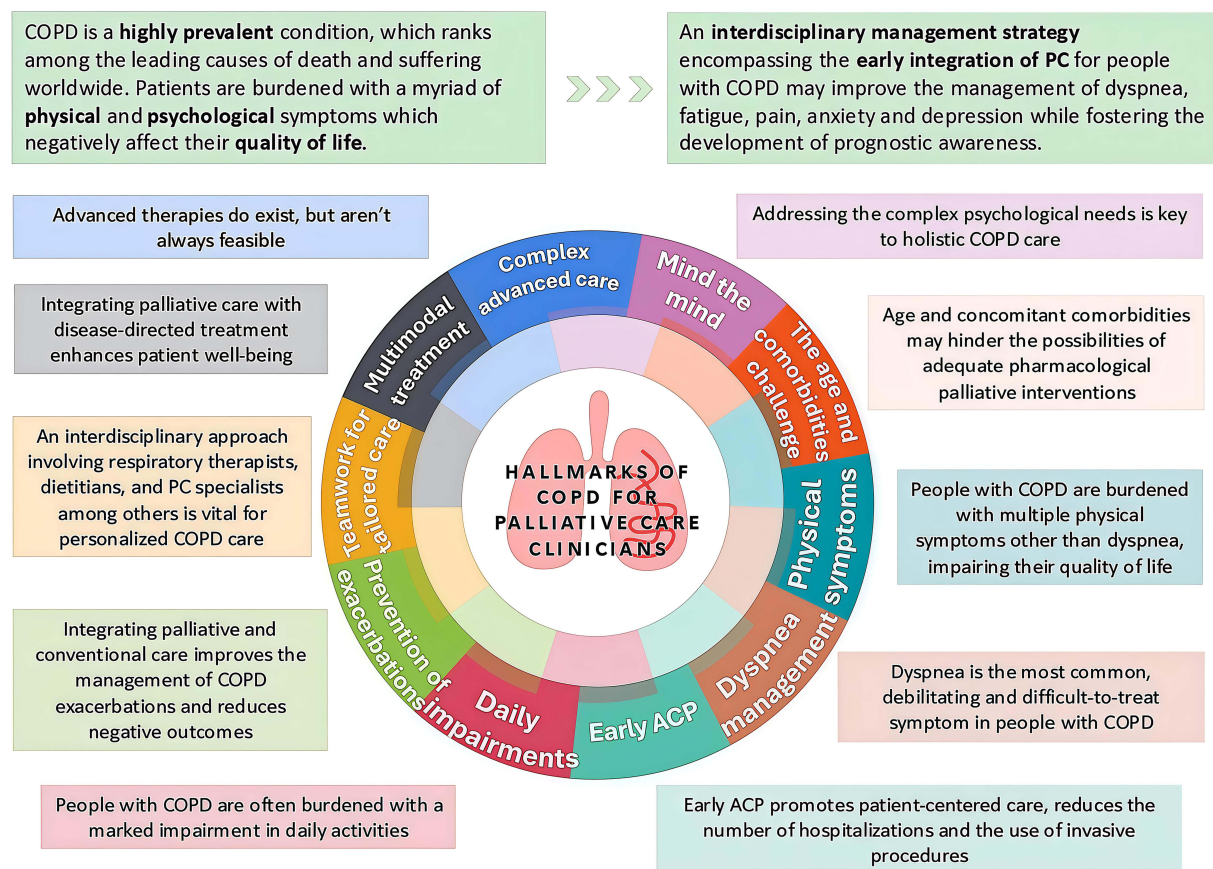


Figure 2 The hallmarks of COPD for palliative care clinicians caring for people with COPD. Visualization of the narrative review including background, its conclusions, and the featured hallmarks of chronic COPD, alongside practical tips for palliative care clinicians caring for these patients.

Abbreviations: PC, palliative care; ACP, advanced care planning.

Imaging and molecular profiling have provided significant advancements in characterizing COPD through the application of new technologies. However, the integration of these new technologies into clinical practice is restricted by many factors. While quantitative imaging technologies provide detailed structural and functional information about COPD, variability exists in the acquisition protocols, analytical methods and interpretive standards for quantitative imaging technologies limiting its widespread use. Additionally, although molecular and omics based profiling provides promising avenues for identifying biologically relevant endotypes for COPD, high costs, technical complexities and limited availability currently restrict these approaches from being used in everyday clinical practice. A critical area of need is to bridge the technology development gap to make these new technologies accessible in the clinical environment.

While pharmacologic development has increased in sophistication and produced significant improvements in treating COPD, the overall impact of these new treatments on the long-term trajectory of disease in most patients remains limited. Many treatments target downstream consequences of airway obstruction and inflammation rather than the underlying causes of disease, such as impaired lung development, disrupted epithelial integrity and accelerated cellular aging. Even targeted treatments produce benefits in relatively narrow subpopulations of patients, emphasizing the need for precise patient stratification while raising concerns regarding the accessibility of these treatments. In order to maximize the impact of new treatments, parallel advancements in early detection and patient stratification will be required.

Finally, the presence of comorbid diseases adds a layer of complexity to the management of COPD. Patients with COPD experience a disproportionate burden of cardiovascular disease, metabolic disorders, skeletal muscle dysfunction, osteoporosis, anxiety and depression. These diseases often share common inflammatory and pathophysiologic pathways

with each other and with COPD, however, they are usually treated independently of each other. In addition to reducing the effectiveness of both respiratory and non-respiratory interventions, fragmented care models highlight the need for developing comprehensive and interdisciplinary approaches to addressing COPD as a systemic disorder.

Healthcare inequities and implementation barriers are two additional challenges that are limiting progress in the management of COPD. The prevalence and severity of COPD are disproportionately higher in populations exposed to biomass fuel combustion, occupational pollutants and socioeconomic disadvantage. In addition, the availability of diagnostic tools, inhaled medications, pulmonary rehabilitation programs and long term supportive therapy programs varies widely between and within countries. As new diagnostic and therapeutic options become available for COPD, there is a risk that disparities in the availability of these resources will increase unless equity focused implementation strategies are developed and implemented concurrently with the development of new scientific innovations.

Therefore, future research efforts should focus on shifting the paradigm of COPD toward earlier identification, mechanism-based stratification and prevention of irreversible structural damage. Key areas for research include the development of scalable risk-based screening strategies, clinic ready multimodal endotyping tools, and validated biomarkers that reflect disease activity and progression. Longitudinal studies, adaptive trial design and the utilization of real world evidence will all be essential to capturing the complexity of COPD and the effectiveness of treatment across different patient populations. Ultimately, the success in improving the outcomes of patients with COPD will depend on the alignment of biological discovery, clinical innovation and health system implementation to produce sustainable improvement in patient outcomes.

Conclusion

COPD is an evolving and multifaceted clinical disorder involving the interplay of different processes at various levels including molecular, cellular, structural and systemic. The modern scientific approach has transitioned from a view of COPD as a single cause of airflow limitation to an appreciation for COPD as a heterogeneous disorder driven by multiple pathological pathways, life course influences, and environmental exposures. This conceptual model provides greater clarity in distinguishing among the biological mechanisms and clinical presentations of COPD, and thus provides better insight into disease onset and progression.

Mechanistic studies have established the role of chronic inflammation, oxidative stress, proteolytic – antiproteolytic balance, defective repair of the epithelium and premature aging of the lungs in causing permanent structural damage. These findings have led to a redefinition of COPD as a disorder of failure of resolution and regeneration, as well as simply a disorder of persistent injury. There has been a parallel advancement in the development of diagnostic strategies. Spirometry-based assessments are now recognized as being inadequate for capturing the heterogeneity of disease and for guiding personalized care, while the use of integrative assessment methodologies (ie, physiological measures, imaging and biomarkers) provide more accurate assessment of the spectrum of disease severity in patients with COPD.

Pharmacologic treatment options for COPD have also advanced to be more closely aligned to the phenotypic and inflammatory profile of each patient, and there has been improvement in drug delivery and digital integration. Non-pharmacologic treatment modalities have emerged as equally important components of treatment for COPD. In addition to addressing the physical deconditioning associated with COPD, non-pharmacologic treatment modalities address both the psychosocial burden and systemic dysfunction that significantly impact both morbidity and quality of life in patients with COPD. Collectively, these advancements highlight the need for a comprehensive and patient-centered model of management of COPD that extends beyond solely airway-directed treatments.

Notwithstanding these recent advancements, several areas of unmet need remain. There are few disease modifying agents available to treat COPD, and early diagnosis continues to be inconsistent; there continue to be inequities in access to care for patients with COPD. Meeting these unmet needs will require continued integration of mechanistic discovery, translational research and implementation science. Ultimately, future advancements in the treatment of COPD will depend upon the ability to successfully translate biological insights into scalable diagnostic tools, targeted interventions and equitable pathways to care that can alter the long-term prognosis for individuals with COPD worldwide.

Abbreviations

COPD, chronic obstructive pulmonary disease; HRCT, high-resolution computed tomography; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-2 agonist; ICS, inhaled corticosteroids; PDE4, phosphodiesterase-4; NIV, non-invasive ventilation; MMP-9, matrix metalloproteinase-9; EMT, epithelial-mesenchymal transition; NETs, neutrophil extracellular traps; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, activator protein-1; VOC, volatile organic compound.

Data Sharing Statement

As this research is a review, we did not generate or analyze primary datasets. All data presented here are retrievable from PubMed and Web of Science.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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