1 Introduction and Definition of Chronic Obstructive Pulmonary Disease COPD

Key Points
1. Chronic obstructive pulmonary disease (COPD) is a syndrome, a constellation of historical findings, clinical signs and symptoms, physiologic derangements, and radiologic abnormalities.
2. There is not a single test that can establish a diagnosis of COPD or exclude other similar processes.
3. Recent findings suggest multiple different COPD phenotypes which may have different clinical courses and responses to treatment.
4. COPD is usually characterized by airflow obstruction that does not fully normalize (return to predicted levels) with diverse pulmonary and extra-pulmonary manifestations including variable clinical symptoms, natural history and longevity, physiology, imaging, and responses to therapy.
5. Most commonly, airflow obstruction/limitation is measured by spirometry by demonstrating a reduced FEV₁:FVC ratio (Forced Expiratory Volume in one second : Forced Vital Capacity) [GOLD (Global initiative for chronic Obstructive Lung Disease) advocates a fixed ratio < 0.7, whereas others utilize a ratio < LLN (lower limit of normal, the 5th percentile of the population distribution of FEV₁/FVC among nonsmokers with no clinical lung disease)].
6. Occasionally, COPD is diagnosed based upon radiographic findings of emphysema in the absence of airflow obstruction.
7. Definitions of COPD include:
   - GOLD Definition: COPD, a common, preventable, and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.
   - ATS/ERS (American Thoracic Society/European Respiratory Society) Definition: Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.


1.1 Definition of Chronic Obstructive Pulmonary Disease (COPD)

The definition of COPD has evolved over the past several years. The most recent definitions of COPD by national and international groups are presented in Table 1.1. Key words in each of these definitions include: *preventable, progressive, treatable, airflow obstruction that is not reversible* [persistent], *inflammation, lung/pulmonary, and exacerbation*.

1.1.1 Preventable

As presented in Chapter 2, Epidemiology and Economic Consequences of COPD, and Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD, tobacco smoke inhalation is the greatest risk factor for the development of COPD; approximately 75–90% of all individuals with COPD have been or are smokers, but only 20–50% of all smokers develop COPD. The factor(s) that place this subgroup of smokers at risk for the development of COPD are not known. Up to one quarter of individuals with COPD are non-smokers (Zeng, 2012). Other risk factors for the development of COPD include history of asthma or tuberculosis, exposure to traffic, outdoor pollution, and biomass smoke. Refraining from or quitting smoking (see Chapter 7, Smoking Cessation), and mitigating or avoiding chemical, dust, and fume exposure will prevent many individuals from developing COPD.

1.1.2 Progressive

Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD, presents the longitudinal time course of lung function from birth to death. In healthy individuals, maximal physiologic function is achieved in the early 20’s and is followed by a slow reduction in flow rates measured by spirometry. COPD is characterized by an increased rate of decline in airflow. Although this accelerated decline is marked by parenchymal and airway derangements (including loss of lung tissue in emphysema, excessive airway mucous and inflammatory cell accumulation in chronic bronchitis), COPD can also be considered pulmonary physiologic progeria. This concept is captured by the term “lung age” (Reviewed in Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction). Lung age is the physiologic age of the lungs extrapolated from the normal predicted values of lung function based upon age and is compared with an individual’s chronologic age to illustrate the accelerated decline in lung function that occurs with COPD. For example, a 60 year old individual with significant airflow limitation might have spirometry (forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)) that would be normal for a 90 year old; thus, this person has a lung (physiologic) age of 90 but is only 60 years old chronologically. The progressive loss of lung function is heterogeneous and the
rate of decline is variable (Vestbo, 2014). (See Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD for a discussion of lung development and the natural history of COPD.) Some interventions, especially early smoking cessation, may be associated with improvement in lung function and a reduction of the loss in years of life that occurs with persistent smoking (Jha, 2013). The effect of exacerbations on lung function decline appears to be less than previously thought, only 2 ml/yr/exacerbation in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, whereas the mean rate of decline in the FEV1 among participants with COPD was 33 ml/yr (Vestbo, 2011). In addition, ECLIPSE showed that not everyone with COPD experiences progressive decline in lung function measured by FEV1; approximately 15% of participants with COPD had improvements in FEV1, averaged over 3 years. All ECLIPSE participants were treated for COPD so it remains unclear whether the disease management affected the measured rate of decline or contributed to the improvement in lung function in these patients.

### 1.1.3 Treatable

As reviewed in Chapters 14, 16, and 17 Management of Stable COPD, Outpatient Management of COPD Exacerbations, and Inpatient Management of COPD Exacerbations, COPD is a treatable disorder. Current treatments have significant salubrious benefits

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<tr>
<th>Source</th>
<th>Reference</th>
<th>Definition</th>
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<tr>
<td>GOLD</td>
<td><a href="http://www.goldcopd.org">www.goldcopd.org</a></td>
<td>a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients</td>
</tr>
<tr>
<td>WHO</td>
<td><a href="http://www.who.int/respiratory/COPD/definition/en/">www.who.int/respiratory/COPD/definition/en/</a></td>
<td>a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible</td>
</tr>
<tr>
<td>ATS/ERS</td>
<td><a href="http://www.thoracic.org/clinical/copd-guidelines">www.thoracic.org/clinical/copd-guidelines</a></td>
<td>a preventable and treatable disease state characterized by airflow limitation that is not fully reversible</td>
</tr>
<tr>
<td>ACP/ACCP/ATS/ERS</td>
<td>(Qaseem, 2011)</td>
<td>a slowly progressive disease involving the airways or pulmonary parenchyma (or both) that results in airflow obstruction</td>
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and reduce the frequency and severity of exacerbations, improve the quantity and quality of life by reducing mortality, decreasing healthcare utilization, and improving health related quality of life. Previously many clinicians and patients had a nihilistic approach to COPD and considered it a self-inflicted, untreatable condition; this approach to COPD has changed dramatically in recent years. Individuals with COPD who receive optimal management can and do live longer with better quality of life.

1.1.4 Airflow Obstruction That Is Not Reversible [Persistent]

Airflow limitation is a reduction in expiratory airflow that occurs due to increased resistance to flow and reduced lung parenchymal elastic recoil. Airflow limitation is measured by spirometry (see Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction).

1.1.5 Major Point of Confusion: “Reversibility”

The term reversible has caused significant confusion among clinicians and has muddled the distinction between asthma and COPD. During pulmonary function testing, a response to bronchodilators is often termed “reversible airflow obstruction”. Bronchodilator responsiveness is determined by a ≥12% and ≥200 ml increase in either the FEV₁ or the FVC (ATS criteria, see Table 1.2). The intraday variation in FEV₁ and FVC is minimal in individuals with no lung disease and a change greater than 5–10% is considered significant (Dawson, 1965; Rozas, 1982). In patients with obstructive lung disease, the daily variation is greater and a significant change is 8–17% (Rozas, 1982; Pennock, 1981; Nickerson, 1980). [Interestingly, although the minimal clinically important difference for a change in FEV₁ in individuals with COPD is not known, a FEV₁ change of 100 ml can be perceived by most patients with COPD (Donohue, 2005).]

“Reversibility” is not a normalization or return to predicted levels of either the FEV₁ or FVC but simply a measured response (an increase in either FEV₁ or FVC) to a bronchodilator that exceeds the defined threshold. In individuals with COPD, airflow obstruction may improve after treatment with a bronchodilator but measures of airflow, FEV₁ and FVC, do not improve to a normal or predicted level. Depending upon the definition of bronchodilator responsiveness or “reversibility”, underlying lung function, the dose, type, and route of bronchodilator administration, between 38% and 73% of individuals with COPD may respond to bronchodilators with increases in FEV₁ or FVC (Hanania, 2011). Thus, COPD is characterized by airflow limitation that may improve after treatment with a bronchodilator but does not improve to a normal or predicted level. In contrast, in asthma, one expects measures of airflow to return to normal or predicted levels in all patients except for that subset of asthmatics
who have developed fixed airflow limitation. Spirometry testing in this group of asthmatics is indistinguishable from patients with COPD. A response to a bronchodilator should not be equated with normalization of lung function.

Table 1.2: Key terms related to the response to bronchodilators

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition/Clarification</th>
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<tr>
<td>Bronchodilator responsiveness</td>
<td>a &gt;12% and &gt;200 ml increase in either the FEV1 or the FVC after inhalation of a bronchodilator (usually a short acting beta agonist)</td>
</tr>
<tr>
<td>Normalization of airflow limitation</td>
<td>a return to predicted levels of FEV1 or FVC</td>
</tr>
<tr>
<td>“Reversibility”</td>
<td>a confusing term which should not be used</td>
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</table>

Thus, although bronchodilator response has been used in the past to distinguish COPD and asthma, recent evidence and the large proportion of patients with COPD who respond to bronchodilators demonstrate that the acute spirometric response to bronchodilators cannot be used to distinguish asthma from COPD (Chhabra, 2005). The response to bronchodilators is used to define a subgroup (phenotype) of individuals with COPD who may respond better to inhaled corticosteroids (see Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD).

1.1.6 Inflammation

COPD is characterized by an inflammatory reaction within the lung to inhaled particles or gases and this response may be triggered by activation of both innate and adaptive immune responses (Angelis, 2014; Rovina, 2013). Inflammatory markers are present both systemically as well as within the lung. Chapter 6, COPD Pathogenesis: Etiology and Systemic Inflammation, discusses the etiology and pathophysiologic pathways that are activated in COPD. Recent studies have shown that the inflammation in COPD is not limited to the lungs but occurs systemically and may play a role in the multisystemic manifestations of COPD (see Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations). However, the presence of systemic inflammation does not occur universally among individuals with COPD. The ECLIPSE study showed that about one third of participants with COPD never demonstrated systemic inflammation, 16% had persistent elevation of systemic inflammatory markers, and most participants had evidence of variable systemic inflammation (Agusti, 2012). The regulatory mechanisms that control the development of pulmonary and systemic inflammation in individuals with COPD are not well defined presently. These inflammatory processes are the subject of intense study to develop new therapeutics that interdict the development and consequences of inflammation in COPD.
1.1.7 Lung/Pulmonary

COPD is classically considered a pulmonary disorder; however, recent evidence over the past 10 years shows that COPD pathophysiology may extend beyond the lungs and affect other organ systems (see Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations). COPD is also associated with significant psychosocial manifestations that may intensify an individual’s reaction to the sensation of breathlessness and profoundly influence their disease manifestations and course (Reviewed in Chapter 13, COPD’s Effects on Psychosocial Functioning and Familial Interactions). The breathlessness and exertional limitations caused by COPD may increase the reliance upon others while simultaneously restricting and diminishing familial and social interactions for patients with COPD. Finally, COPD affects other systems including the pulmonary vasculature (see Chapter 12, COPD and Pulmonary Vasculature) and sleep (see Chapter 11, COPD and Sleep: Overlap Syndrome).

1.1.8 Exacerbation

The clinical course of COPD is punctuated by exacerbations, episodes of symptom worsening beyond their normal day to day variation that occur after a period of recovery from a prior exacerbation (Triqueros, 2013). COPD exacerbations are often triggered by respiratory infections and are the leading cause of healthcare utilization and cost in the management of COPD (see Chapters 16 and 17 on the management of COPD in the outpatient and inpatient settings). One of the major advancements in COPD management over the past two decades has been the development of treatments that reduce the number and severity of COPD exacerbations.

1.2 Diagnostic Criteria

Until recently, the sine quo non for the diagnosis of COPD has been the presence of airflow limitation, a reduction in the flow of air from the lungs during exhalation due to increased airway resistance and dynamic airway collapse (see Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction). How airflow limitation is defined, measured, and quantified have evolved over the past several decades. Airflow limitation is currently measured by the ratio of FEV\textsubscript{1} to FVC and is defined when this ratio is less than a threshold value. The two most common thresholds are an absolute value of 0.7 and the lower limit of normal, the 5\textsuperscript{th} percentile of the distribution of the FEV\textsubscript{1}/FVC ratio in a nonsmoking population with no clinical evidence of lung disease. Because the ratio of FEV\textsubscript{1}/FVC decreases with age, use of an absolute threshold may be overly sensitive and may over-diagnose airflow obstruction in older individuals and under-diagnose younger people (see
Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction.) More individuals with airflow obstruction defined by fixed ratio have emphysema and gas trapping than those who have airflow obstruction defined by the lower limit of normal (Bhatt, 2014).

Recent findings suggest that some individuals with radiographic evidence of emphysema, gas trapping, regional ventilation derangements, and airway alterations may not have airflow limitation on physiologic testing (Coxson, 2014), (see Chapter 5, Radiology: Use of lung imaging to help in the identification of patients with COPD.) Recently developed advanced pulmonary imaging techniques such as x-ray computed tomography, magnetic resonance imaging, and use of hyperpolarized noble gases provide structural as well as functional assessments of the lungs that may detect earlier and more subtle changes than can be measured by spirometry. Thus, although the presence of physiologic airflow limitation is currently a critical criterion for the diagnosis of COPD, it may not be essential as newer lung imaging techniques are developed and become more universally available.

1.3 Staging Disease Severity

Traditionally COPD has been categorized and staged based upon spirometry measurements. Airflow severity is determined by the comparison between the measured FEV₁ and the predicted FEV₁, the FEV₁% of predicted value, and is segregated into several categories ranging from mild to very severe (see Chapter 4, Pulmonary Function Testing: Spirometry: Presence and Severity of Airflow Limitation/Obstruction). These divisions are artificial as the reduction in lung function is a continuum from normal to severely deranged.

Previous COPD staging schemes were based solely upon airflow severity. With the realization that airflow severity does not correlate well with disease course, clinical outcomes, health status, or disease management, multivariate staging methods have been proposed (Jones, 2009). One of the more recent and widely adopted schemes is the GOLD staging classification which utilizes three variables: airflow severity, respiratory symptoms measured by the COPD Activity Test or mMRC (modified Medical Research Council) dyspnea scale, and the number of COPD exacerbations within the previous year (see Chapter 14, Management of Stable COPD). Other multifactorial indices include BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity), ADO (Age, Dyspnea, and airflow Obstruction), and DOSE (Dyspnea, Obstruction, Smoking, and Exacerbation) (Celli, 2004; Puhan, 2009; Jones, 2009). The goals of these multivariate staging classifications are to provide COPD categories that are more clinically useful and assist with disease management and prognostication (see Chapter 19, Integrating Supportive, Palliative, and End of Life Care for COPD).
1.4 COPD is a Syndrome

Historically, COPD has been considered an overlapping dyad of pulmonary disorders characterized by airflow obstruction and different clinical, radiographic, and physiologic manifestations: chronic bronchitis and emphysema, that are distinguished from asthma, the other major cause of airflow obstruction (Table 1.3).

Table 1.3: Definitions of Chronic Bronchitis and Emphysema

<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Chronic bronchitis</td>
<td>the presence of a productive cough for at least 3 consecutive months in 2 consecutive years</td>
</tr>
<tr>
<td>Emphysema</td>
<td>an abnormal enlargement of the air spaces distal to the terminal bronchioles accompanied by destruction of their wall and without obvious fibrosis pathologically or radiographically</td>
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More recent COPD studies have focused on further refinement and definition of COPD categories or phenotypes (see Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD). The ECLIPSE study is a 3 year prospective investigation of 2,164 patients with clinically stable COPD, 337 smokers with normal lung function, and 245 never smokers that has provided valuable insights into the heterogeneity of COPD and its variable and not always progressive course. Among the COPD phenotypes identified in ECLIPSE are frequent (≥ 2 yearly) exacerbators and infrequent (<2 yearly) exacerbators, those experiencing a more rapid decline in FEV\textsubscript{1} (continued smokers, CT defined emphysema, and bronchodilator responsiveness), greater loss of lung density/parenchyma (smokers and women), bronchodilator responsiveness (more frequent exacerbators, although bronchodilator responsiveness was variable throughout the study), and systemic inflammation (approximately one third of patients with COPD never demonstrated evidence of systemic inflammation and 16% had persistent systemic inflammation with a 6-fold increase in overall mortality) (Augusti, 2012; Vestbo, 2014).

1.5 Genetic Factors

Only a minority of tobacco smokers develop COPD and the genetic risk factors for the development of COPD are not known. Mutations in the alpha-1-antitrypsin gene are associated with the development of emphysema and have been well characterized and replacement therapy is available. More recently, large multicenter investigations have used genome-wide association studies of populations that are clinically,
physiologically, and radiographically well characterized to identify potential genetic loci associated with the development of COPD and with different COPD phenotypes (Chen, 2013; Cho, 2012; Bosse, 2012; Berndt, 2012). Other studies have focused on epigenetics (heritable variations that alter gene expression but do not change the DNA sequence) such as DNA methylation, histone alteration, and RNA-associated silencing, and their role in the development of COPD (Mortaz, 2011).

### 1.6 Clinical Symptoms and Differential Diagnosis

The three major symptoms associated with COPD are breathlessness, cough, and sputum production (see Chapter 3, COPD Recognition and Diagnosis: Approach to the Patient with Respiratory Symptoms, and Chapter 14, Management of Stable COPD.) Breathlessness is a subjective sensation of shortness of air that is normally experienced by everyone during vigorous or strenuous activity. With COPD, the initial manifestations may be subtle; an inability to maintain the pace when walking with peers or increased sensation of breathing while doing routine activities to overt wheezing and gasping for breath during activities. Cough is the forceful exhalation of air to clear the airways from irritating or obstructing material. Cough may be nonproductive or productive of phlegm. These symptoms are neither sensitive nor specific for the diagnosis of COPD and must be interpreted in conjunction with the clinical history and laboratory and radiographic findings (see Chapter 5, Radiology: Use of lung imaging to help in the identification of patients with COPD).

The differential diagnosis of COPD includes asthma, congestive heart failure, bronchiolitis, pulmonary infections, and bronchiectasis. Some distinguishing features between COPD and asthma are presented in Table 1.4. Thus, even though COPD and asthma are characterized by airflow limitation, they are distinct disorders with very different pathophysiologic mechanisms that lead to different and distinct treatment regimens. Nevertheless, in some patients it may not be possible to distinguish asthma and COPD despite extensive evaluation and this undifferentiated group is now classified as asthma COPD overlap syndrome. Many other

<table>
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<tr>
<th>Characteristic</th>
<th>Asthma</th>
<th>COPD</th>
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<tr>
<td>Anatomic Distribution</td>
<td>Small airways</td>
<td>Small airways</td>
</tr>
<tr>
<td></td>
<td>Parenchyma</td>
<td></td>
</tr>
<tr>
<td>Cells</td>
<td>Eosinophil predominant</td>
<td>Neutrophil predominant</td>
</tr>
<tr>
<td>cytokines</td>
<td>CD4 Th2: IL-4, IL-5, IL-9, IL-13</td>
<td>CD8 Th1: IFN γ</td>
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disorders may occur concurrently with COPD and it may be difficult to discern the primary process. See Chapter 3, COPD Recognition and Diagnosis: Approach to the Patient with Respiratory Symptoms, for a detailed discussion of the differential diagnosis of COPD and assessment of patients presenting with breathlessness, cough, and sputum production.

1.7 Imaging

The chest x-ray may demonstrate hyperinflation with reduced peripheral vascular markings, flattening of the diaphragms, and a central and narrowed cardiac silhouette in individuals with emphysema. Although these findings are sensitive for the presence of COPD, they are not specific (Washko, 2012). Chest CT provides more detailed images of the lung parenchyma, airways, and vasculature. Chest CT imaging is commonly used for the diagnosis of emphysema and may be quantified by various densitometric analyses that demonstrate the loss of lung parenchyma. In addition, chest CTs may be used to measure central and peripheral small airway wall thickness, caliber, and number. More recent studies using micro-CT techniques have demonstrated that COPD is associated with reduced numbers of airways as well as pulmonary vessels in the lung parenchyma (Washko, 2012). Chapter 3 presents a more detailed review of the radiographic findings in COPD.

1.8 Treatment

Recent advances in the management of COPD have led to reductions in respiratory symptoms, improvements in quality of life, fewer exacerbations and less hospitalizations, and better survival for individuals with COPD. Chapter 8, Fostering Patient Self-Management of COPD reviews how providers may approach patients with COPD and encourage them to participate actively in their disease management; Chapter 7, Smoking Cessation, discusses smoking cessation, the single most important intervention for the prevention and management of COPD; treatment of stable COPD and exacerbations are reviewed in Chapters 14, 16, and 17, Management of Stable COPD, Management of Outpatient COPD Exacerbations, and Management of Inpatient COPD Exacerbations. Optimal COPD management is interdisciplinary and the role of primary care providers and their interaction with other providers is discussed in Chapter 18, Primary Care and Interaction with Specialty Care for the COPD Patient. Finally, advanced care planning is presented in Chapter 19, Integrating Supportive, Palliative, and End of Life Care for COPD.
1.9 Conclusion

COPD is a complex disorder with protean manifestations that are not limited to the lungs. Although, COPD has been classified historically as chronic bronchitis, emphysema, or a combination of these two processes, more recent research has identified a plethora of COPD phenotypes with varying clinical, radiographic, genetic, and biochemical characteristics with distinct prognostic and therapeutic implications. Thus, COPD is clearly a universe of different disorders that we are just beginning to understand and differentiate. The clinical application of these phenotypes and their use in management has begun with the utilization of classification and management guidelines that extend beyond the physiologic characterization of patients to include symptom severity and exacerbation risk. Further studies will identify other clinical, biochemical, physiologic, and radiographic variables that are critical to the characterization and classification of COPD and to better and more precisely directed management strategies.

1.10 Summary Points

1. The definition of COPD has evolved and continues to change with further clinical, genetic, biochemical, and radiologic studies.
2. Although COPD has historically been defined by airflow obstruction measured by spirometry, physiologic impairment is only one aspect of this disorder and does not correlate perfectly with disease severity, quality of life, or management.
3. COPD is a plethora of diverse phenotypes that are becoming better defined and characterized; these phenotypes are beginning to define more specific treatment regimens.

References


References


