Contribution of the Environment and Comorbidities to Chronic Obstructive Pulmonary Disease Phenotypes

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Keywords

Chronic obstructive pulmonary disease (COPD) is a syndrome characterized by significant disease heterogeneity.[1] Whereas the presence of airflow obstruction that is not completely reversible is a hallmark of the disease, in the individual patient this obstruction may be caused by airway inflammation and remodeling, emphysema, or both. Clinicians have identified 2 basic subtypes of COPD: "pink puffers" characterized by emphysema, significant dyspnea, hyperinflation, and weight loss but with adequate oxygenation; and "blue bloaters" characterized by chronic bronchitis, hypoventilation, and obesity. It is likely that many other phenotypes exist in COPD but their relevance has not been adequately validated.[2] To provide some clarity, a recent consensus group defined COPD phenotypes as, "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)."[2] The validation of phenotypes will ultimately require an iterative process (Fig. 1) so that groups of patients may initially be identified either by similar clinical outcome, radiologic or physiologic characteristics, biological or molecular signature, or response to therapy. Ultimately, the hope is that these patient subgroups share similar pathophysiologic processes, so that specific therapies can be developed. The goal of this article is to highlight the accumulated data regarding environmental and host factors, in particular comorbid diseases, that may help to identify and refine patient phenotypes in COPD.

ENVIRONMENT

Tobacco is the principal risk factor and environmental toxin responsible for the development of the disease in most patients with COPD. Most of what we know about the natural history of COPD is in tobacco smokers. The prevalence of COPD in smokers is approximately 20% as compared with 4% in nonsmokers.[3] This association is supported by the acceptance of the preventive effects of smoking cessation. The Lung Health Study, an interventional smoking cessation study in smokers with COPD with mild airflow obstruction, demonstrated that the decline in the rate of forced expiratory volume in 1 second (FEV_1) was greatest in patients

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who smoked the most and least in those who achieved sustained smoking cessation.[4] However, the fact that only one in five smokers develops COPD, points towards additional factors that contribute to its development. The importance of second-hand smoke exposure, also known as environmental tobacco smoke (ETS), should not be overlooked. Higher cumulative lifetime ETS at home and work has been associated with increased risk of COPD, even after adjustment for personal smoking history and occupational exposure.[5]

The prevalence of COPD in nonsmokers in the United States, according to data from the Third National Health and Nutrition Epidemiologic Survey is approximately 6.6%.[6] Worldwide figures for nontobacco related COPD vary around 20% to 25% of all COPD cases, with estimates as high as 40% to 50% in countries such as Colombia and South Africa.[7] The risk factors associated with COPD in nonsmokers are numerous and incompletely understood, but a history of asthma or tuberculosis, exposure to traffic and outdoor pollution, and exposure to biomass smoke show the strongest associations.[8,9] How disease presentation and course differs by risk factor is not well described. One study has suggested that life expectancy for nonsmokers with COPD is only modestly reduced (0.7 years for the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 patients, and 1.3 years for GOLD stages 3–4) compared with substantially reduced life expectancy in current smokers with COPD (2.2 years for GOLD stage 2, and 5.8 years for GOLD stages 3–4) and former smokers with COPD (1.4 years for GOLD stage 2 and 5.6 years for GOLD stages 3–4).[10]

Whereas it has been estimated that COPD attributable to cigarette smoking is between 80% and 90%, COPD attributed to occupational exposures (vapors, gas, dust, or fumes) is close to 15%.[11] Whereas specific industries, such as coal mining, have been related to the development of airflow obstruction, increasing data from across various industries and occupations are being collected.[11] Outdoor air pollution also probably contributes to the development of COPD. A 1958 study of postmen in the United Kingdom documented the prevalence of COPD to be higher in those working in more polluted areas, independent of personal smoking history.[12] Data from other population studies of individuals living close to roads with heavy motor vehicle traffic also support these findings.[13]

In the developing world, exposure to smoke from biomass fuels is an important cause of COPD, particularly in women who use biomass fuels for cooking.[14] It is unclear whether the phenotype of COPD in this group of nonsmokers differs from that of tobacco-exposed individuals, although studies of women exposed to biomass fuel smoke suggest that disease presentation and mortality are similar to those with COPD attributable to tobacco smoking.[15]

Nutrition may also be an important factor that influences the development of COPD. Vitamin D levels, in particular, demonstrate an inverse relationship with pulmonary function in COPD.[16] Genetic polymorphisms in vitamin D metabolic pathways have also been associated with COPD.[17] An association has also been described between higher levels of vitamin C in plasma and protection against incident COPD.[18] Similar information has been reported between vitamin A intake and prevalence of COPD.[19] Lately, a protective function has been attributed to a diet high in cereal fiber.[20] Further studies of the relationship

between nutritional factors and COPD may offer mechanistic insights into the pathogenesis and treatment of this disease.

HOST FACTORS

Gender is an important factor that also may affect disease phenotype.[14] Conflicting data exist on whether women are more susceptible to developing COPD for a similar amount of tobacco smoke exposure.[14] However, women with COPD report more dyspnea, similar degrees of cough, but less sputum compared with men with similar degrees of airflow obstruction.[21] It has been suggested that women are more likely to display a chronic bronchitic phenotype of COPD whereas men display a more emphysematous phenotype.[14] Radiologic data from the National Emphysema Treatment Trial among patients with severe emphysema supports this hypothesis whereby women demonstrated less overall emphysema, particularly in the peripheral portions of the lung.[22] Histologic data from the same study revealed that the bronchioles of women have significantly thicker airway walls and smaller lumen than the bronchioles of men.[22] Recent data also suggest that COPD exacerbations are more frequent in women but it is unknown whether this represents a difference in disease biology or reporting patterns.[23,24]

Whereas genetic and epigenetic contributions to COPD are discussed in more detail elsewhere, genetics must also play a role in disease phenotype. The best known genetic risk factor for development of COPD is alpha-1 anti-trypsin (AAT) deficiency, whereby patients are more likely to develop lower lobe predominant emphysema patterns compared with patients without AAT deficiency, who are more likely to present with upper lobe emphysema. More data in this regard are likely to come from the ongoing COPDGene Study, a genome-wide association study of more than 10000 subjects, with the goal of identifying the genetic determinants of specific disease phenotypes (http://www.copdgene.org). Information derived from such studies may help determine the reason for these phenotypic expressions of the disease and their clinical relevance.

Another host factor that probably contributes to the COPD phenotype but is often overlooked is the lung microbiome. Alteration in the lung and the gut microbiomes has been associated with the development of asthma.[25–27] This leads to the consideration of the role of the microbiome in COPD, wherein bacterial colonization has been associated with FEV_1 decline and increased rates of acute exacerbations of COPD (AECOPD).[28] Recent data also support a similar process with the genesis of emphysema and airway structural abnormality.[28,29] Although investigations of COPD using advanced, culture-independent techniques are limited, a predominance of Pseudomonas species in patients with more impaired lung function in COPD has been reported.[30]

COMORBIDITIES

Accumulating data suggest that comorbidities must be included in the assessment of patients with COPD. Some comorbid conditions, such as cardiovascular disease and osteoporosis, are more common in patients with COPD compared with the general population. Although comorbidities such as obstructive sleep apnea may not be more prevalent in COPD, they are important because they may modify the course of the disease.[31] Because comorbid

conditions can alter the course of the disease or the need for specific therapies in COPD, they remain important considerations in the development and refinement of COPD phenotypes. Systemic inflammation may be pathogenically related to many comorbidities seen in COPD including cardiovascular disease, osteoporosis, metabolic syndrome, and depression.[32,33] There is not enough confirmatory data to support the specific treatment of systemic inflammation in patients with COPD but current studies aimed at capturing the nature and extent of the importance of this pathobiological mechanism, may lead to the development of specific therapy for patients presenting with this phenotype.

Cardiovascular Disease

Ischemic cardiovascular disease continues to be a leading cause of death in COPD.[34] Whereas shared risk factors, such as tobacco use, contribute to this association, epidemiologic evidence suggests that impaired lung function itself is an independent risk factor for increased cardiovascular mortality. Data from the National Health and Nutrition Examination Survey demonstrated that patients in the lowest FEV_1 quintile had the highest risk of cardiovascular mortality (risk ratio [RR] of 3.36), even after adjustment for pertinent risk factors including smoking status, blood pressure, body mass index (BMI), and diabetes.[35] In a meta-analysis of studies relating cardiovascular mortality to reduced FEV_1 adjusted for smoking status, the RR of death for patients with COPD was 1.77 (95% confidence interval [CI], 1.46–1.97).[35] In the Lung Health Study, cardiovascular events accounted for 42% of first hospitalizations and 48% of second hospitalizations in patients with mild to moderate COPD.[36] An inverse relationship between FEV_1 and the presence of atherosclerosis has also been documented. [37] In addition to the degree of airflow obstruction in COPD, the actual rate of FEV_1 decline is also an independent predictor of cardiovascular mortality.[38,39]

Because atherosclerosis, like COPD, is a disease of systemic inflammation,[40] an increase in systemic inflammation may explain the association between the two diseases. Elevated C-reactive protein (CRP) levels correlate not only with the presence of COPD but also with the presence of exacerbations, severity of lung function, and risk for hospitalization and death.[41] The interaction between COPD and cardiovascular disease may also have important therapeutic implications. In one study, the withdrawal of inhaled steroids in patients with COPD with moderate-to-severe disease was associated with a 71% increase in serum CRP levels.[42] Subsequent treatment with inhaled corticosteroids resulted in a 50% reduction in CRP levels (95% CI, 9%–73%); prednisone-treated patients had a reduction of CRP levels of 63% (95% CI, 29%–81%) whereas the patients receiving placebo experienced no significant change in CRP levels. Medications used to treat cardiovascular disease may affect COPD outcomes. In an analysis of a large Canadian database of patients with COPD, the combination of statin and either angiotensin-converting inhibitor or angiotensin receptor blocker therapy was associated with a reduction in hospitalization (RR 0.66; 95% CI, 0.51–0.85) and total mortality (RR 0.42; 95% CI, 0.33–0.52).[43] A separate cohort study also found that statin therapy in COPD was associated with reduced risk of death, (hazard ratio 0.57; 95% CI, 0.38–0.87).[44] Although beta-blockers have been used with caution in obstructive lung disease, a retrospective analysis of a COPD cohort recently reported that

there was a 22% overall reduction in all-cause mortality in patients with COPD using beta-blockers.[45]

Musculoskeletal Disease

Although prevalence estimates vary, low BMI is clearly associated with COPD, and in particular with disease severity.[46] Low BMI is also an important independent prognostic factor for increased mortality in patients with COPD.[47] A relationship between low fat-free mass index (FFMI) and increased mortality in COPD has been demonstrated, even in subjects with a normal BMI, after controlling for age and spirometric severity.[48] The prognostic effect of the BMI is further supported by its importance in the calculation of the BMI, obstruction, dyspnea, exercise capacity (BODE) index, one of the best mortality prediction indices in COPD.[49]

Low BMI has been recognized as a distinguishing feature of pink puffers for many years and several studies correlating low BMI with greater extent of emphysema on high resolution computed tomography (HRCT) help to confirm this association.[50] The fat-free mass index (FFMI) has also been demonstrated to have an inverse association with extent of emphysema on HRCT, the six minute walk test distance, and CRP levels.[51] In contrast to the observed association between low BMI and emphysema, the presence of chronic bronchitis has been statistically associated not only with higher BMI but also with HRCT indicators of airway disease.[52] Different mechanisms have been postulated for the loss of body mass in COPD including systemic inflammation and oxidative stress, tissue hypoxia, disuse atrophy, energy imbalance, hormone insufficiency, and genetic factors but no definitive explanation has been identified.[53] There have been several attempts to reverse the cachexia observed in a significant proportion of patients with COPD. The results have been disappointing with nutrition-based interventions, the use of nocturnal ventilation to decrease energy expenditure, and the use of growth-hormone releasing factors.[53] However, there are data supporting the capacity of COPD patients with low FFI (<17 kg/m^2) to remodel muscle and improve cachexia in response to exercise training.[54]

Whereas estimates vary, the prevalence of osteoporosis is increased in patients with COPD. Estimates ranging between two- and fivefold increase have been made for patients with COPD compared with age-matched controls without airflow obstruction. [55,56] The frequency of osteoporosis also seems to be correlated to the severity of airflow obstruction. Vertebral fractures are more prevalent as the severity of spirometrically-defined COPD increases.[55,57] Whereas there are multiple shared-risk factors such as the use of oral steroids, smoking, and low BMI that may contribute to osteoporosis in COPD, these risk factors do not appear to completely explain the association, as several studies have documented lower bone mineral density (BMD) even in the absence of systemic steroids.[57,58]

As with low BMI, osteoporosis and low BMD also seem to be more strongly related to the presence and severity of emphysema but not related to the severity of chronic bronchitis or airway wall thickness as assessed by HRCT.[59] Whereas an adequate understanding of this association at the cellular and molecular level is incomplete, better insights could lead to novel diagnostic and therapeutic interventions. Although matrix metallopeptidase-9 (MMP-9), interleukin-6 (IL-6) and adipokines have all been implicated, no clear causal link

has emerged.[60–62] Participation in pulmonary rehabilitation is an option to improve the functional status of patients with advanced COPD. Whereas exercise programs have not been demonstrated to increase BMD in COPD, they may diminish the risk of fracture by decreasing the risk of falls.[63]

Diabetes

Diabetes is another frequent comorbidity in COPD. Many studies have reported a relationship between increased risk of the development of diabetes and the presence of COPD. Lung function impairment, measured either by a low FEV_1 or a low forced vital capacity (FVC), has been associated with the coexistence of the metabolic syndrome, the development of insulin resistance, and development of diabetes.[64–66] The association between lung-function impairment and metabolic syndrome remains, even after adjustment for BMI and smoking history. The independent risk for metabolic syndrome conferred by a low FEV_1 was estimated to be 1.28 (95% CI, 1.20–1.37) in a study of more than 121,000 cases.[64] In the Nurse's Health Study, the RR of incident diabetes among participants with COPD was 1.8 (95% CI, 1.1–2.8),[67] a value very similar to that reported in the Women's Health Study cohort, wherein the relative risk of incident diabetes after a diagnosis of COPD was 1.38 (95% CI, 1.14–1.67).[65]

The link between COPD and diabetes is not clear. Certainly the role of therapies, such as inhaled corticosteroids (ICS) frequently used by patients with COPD, must be considered. At least two independent studies point toward the existence of a dose-dependent association between the use of ICS and diabetes control or new-onset diabetes,[68] but this is unlikely to be the sole explanation responsible for the association. Certain inflammatory mediators, Interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in particular, have been implicated in both bronchial inflammation and insulin resistance. In a study of the HRCT characteristics of patients with COPD who experienced exacerbations, a higher prevalence of diabetes was associated with an airway-disease-predominant COPD phenotype compared with an emphysema-predominant disease phenotype.[69] Not surprisingly, patients with predominant airway disease also demonstrated higher BMI and less frequent osteoporosis. These data support a possible relationship between certain metabolic pathways and COPD phenotypes, although the exact pathways and potential therapeutic implications are yet to be defined.

Anemia

Because COPD is a disease of chronic inflammation, it is not surprising to find that anemia is another common comorbidity. The prevalence of anemia in COPD has been reported to be between 7% and 17% in outpatients,[70,71] 12% in patients receiving long-term oxygen therapy,[72] and 23% in hospitalized patients.[73] Anemia in COPD patients has significant implications, and is particularly associated with increased health-care related costs.[71,74] Anemia also has an independent impact on 3-year survival[72] and all-cause mortality.[74] The pathophysiology of anemia in COPD patients is probably similar to that of other chronic inflammatory diseases.[75] The mediators responsible for the airway and pulmonary parenchymal inflammation, especially IL-6, can interfere with the intestinal absorption of iron.[75] Interleukin 1 (IL-1) and TNF-α have been implicated in abnormalities in the

production and peripheral effect (or resistance) of erythropoietin.[75] There are no specific recommendations for the treatment of the anemia seen in patients with COPD.

Gastroesophageal Reflux Disease

The association between gastroesophageal reflux disease (GERD) and COPD has been long recognized. In cross-sectional studies using validated questionnaires, the prevalence of heartburn, regurgitation, and dysphagia have been found with higher frequency in patients with COPD compared with controls.[76,77] In one series using 24-h continuous esophageal pH monitoring, acid reflux was recorded in 62% of patients with COPD compared with 19% of controls.[78] This study highlighted the fact that the actual proportion of reflux in the COPD patient population was probably higher than estimates based on symptoms alone. However, even GERD detected by symptoms in the COPD patient population has been associated with poorer outcomes. Both cross-sectional and longitudinal studies have reported associations between the presence of reflux and poor quality of life in COPD.[79] GERD has also been identified as a risk factor for COPD exacerbations[23,80] and seems to be specifically associated with the chronic bronchitic phenotype in COPD.[52]

One hypothesis attempting to explain the association between GERD and COPD is that aspiration may lead to persistent airway inflammation resulting in bronchial remodeling. In support of this hypothesis is human data demonstrating a relationship between elevated C-reactive protein levels and swallowing dysfunction in patients with COPD.[81] An association between lower exhaled breath condensate pH, and GERD symptoms in COPD has also been documented.[77] Whether COPD precedes GERD or vice versa is still open to debate, although epidemiologic evidence supports the idea that a diagnosis of COPD is a risk factor for the development of GERD.[82] Whereas robust evidence that GERD treatment alters COPD outcomes is lacking, in a small, randomized, single-blind, study the proton pump inhibitor lansoprazole reduced the risk of COPD exacerbations and adjusted the odds ratio of 0.23, $P = .004$.[83] Thus, common sense suggests that GERD should be suspected in patients with COPD and once diagnosed it should be treated because there are effective treatments for this condition.

Neuropsychiatric Disorders

Like patients afflicted with other chronic diseases, patients with COPD tend to have a significant burden of coexistent depression and anxiety. Assessments of the prevalence of neuropsychiatric disorders demonstrate wide variation, given the difficulty of exploring this sensitive issue in large population samples, the diversity of the instruments available for assessment, and variations in the severity of the disease detected in different surveys.[84] Conservative estimates suggest that the prevalence of anxiety and depression is at least 10% in the nonhospitalized, general, COPD patient population. Higher estimates have been reported of the prevalence of symptoms of depression (37%–71%) and anxiety (51%–75%) in patients with severe COPD.[85]

Factors associated with increased risk for depression in COPD include disease severity, limited mobility, low body mass, coexistent comorbid conditions, and the need for supplementary oxygen therapy.[86,87] Women are particularly susceptible, with the frequency

of depression and anxiety being nearly two times greater in women compared with men.[88] More importantly, depression and anxiety have also been associated with poorer disease outcomes in patients with COPD. Anxiety has been associated with lower functional capacity measured by the six minute walk test[89] Anxiety and depression are also associated with greater dyspnea at rest, worse scores in quality of life questionnaires, and reduced exercise performance at both the beginning and end of pulmonary rehabilitation.[90] Anxiety has been associated with increased risk for COPD exacerbations and greater mortality.[91] Depressive symptoms have been associated with two to three times greater risk of death in COPD.[92,93] Unfortunately, only a small proportion of COPD patients with anxiety and depression receive effective treatment.[86] Specific note should be made that pulmonary rehabilitation can also improve symptoms of anxiety and depression, although its effects beyond the treatment period are not well defined.[86]

A frequently overlooked comorbidity in COPD is cognitive dysfunction. Data on the prevalence of cognitive dysfunction in COPD is limited by methodological issues, including the need for normative data, the use of different cognitive evaluation instruments, and the interaction of shared risk factors. Even with these limitations, the finding of abnormal cognitive function in COPD has been consistent and includes decreased cognitive performance (story recall, addition tests) compared with healthy controls, lower scores on the Mini-Mental State Examination, slower reaction time, and impaired verbal and logical thinking.[94–96] Common factors associated with cognitive dysfunction in cross-sectional studies of patients with COPD include low FEV1, coexistent cardiovascular disease, diabetes, depression, and also obstructive sleep apnea (OSA), hypoxemia, and hypercapnia, all with the potential to affect the cerebral metabolism. [97] COPD exacerbations may also affect cognitive dysfunction, in particular those requiring mechanical ventilation.[97] The mechanisms behind cognitive dysfunction probably vary with each of these associations; some studies have demonstrated that participation in rehabilitation programs and the use of supplementary oxygen in patients with hypoxemia may decrease the risk of cognitive abnormalities.[94,98]

Obstructive Sleep Apnea

The coexistence of COPD and OSA, commonly described as overlap syndrome, has gained significant attention in recent years. Poor sleep quality, decreased sleep efficiency, and difficulties in initiating and maintaining sleep have been reported in more than 40% of patients with COPD.[99] The frequency of sleep-disordered breathing in the general population has been estimated to be 9% for women and 24% for men.[100] In patients with COPD, the prevalence of OSA been estimated to be about 16%.[101] In general, COPD patients with OSA are more severely hypercapnic, demonstrate more profound and frequent nocturnal oxygen desaturation, and have higher risk of pulmonary hypertension.[102] Untreated OSA is also a risk factor for poor quality of life, development of AECOPD, and increased all-cause mortality.[31,103] COPD and OSA share some pathophysiological characteristics and risk factors, including hyper-inflation with parenchymal destruction and increased traction on the upper airway, the presence of systemic inflammation, particularly TNF-α, IL-6 and Interleukin-8 and increased oxidative stress.[102] The importance of OSA assessment in COPD is underscored by the recent finding that continuous positive airway

pressure (CPAP) therapy during sleep in patients with overlap syndrome, was associated with both decreased risk of death (RR 1.79; 95% CI, 1.16–2.77) and decreased risk of severe AECOPD leading to a hospitalization (RR 1.70; 95% CI, 1.21–2.38).[31]

PROGRESS IN DISEASE PHENOTYPES

Only a few of the proposed phenotypes in COPD meet the premise that these phenotypes relate to clinically relevant outcomes or response to therapy. One such example is the subgroup of patients with upper-lobe-predominant emphysema and low exercise tolerance. This unique group benefits from lung-volume-reduction surgery with significant improvements in functional status, quality of life, and survival, although the mechanism of benefit in this specific group is not well understood.[104] Another phenotype is composed of patients with frequent exacerbations who produce significant sputum at baseline. These patients specifically demonstrate reduction of exacerbation in response to the phosphodiesterase-4 inhibitor, roflumilast.[105] The premise that combinations of comorbid conditions help define disease phenotypes is supported by the data presented here. Two general patterns of clinical features and comorbidities that share some association include (1) emphysema, low BMI and osteoporosis and (2) chronic bronchitis, airway disease, high BMI, OSA, and diabetes. It remains unknown whether these associations are related to specific mechanistic pathways that will lead to the development of targeted therapies.

SUMMARY

- COPD is a heterogeneous disease, modified by environmental and intrinsic host factors. The interaction between COPD and its comorbidities is complex and bidirectional.

- It has been estimated that the proportion of patients with COPD caused by cigarette smoking is between 80% and 90%. Risk factors associated with COPD in nonsmokers are numerous and incompletely understood, but a history of asthma or tuberculosis, exposure to traffic and outdoor pollution, and exposure to biomass smoke show the strongest associations. Other factors that may contribute to COPD phenotypes include gender, genetics, and the lung microbiome.

- Certain comorbid conditions, such as cardiovascular disease and osteoporosis, are more common in the COPD patient population. Other comorbidities, such as overlap syndrome, the coexistence of COPD, and obstructive sleep apnea may not be as prevalent in COPD but are important because they may modify disease course.

- Systemic inflammation may be pathogenically related to many comorbidities seen in COPD including cardiovascular disease, osteoporosis, metabolic syndrome, and depression.

- Based on the data presented here, two general patterns of clinical features and comorbidities that share some associations are (1) emphysema, low BMI and osteoporosis and (2) chronic bronchitis, airway disease, high BMI, OSA, and diabetes.

- The classification of patients with COPD into subgroups with shared characteristics and outcomes offers the potential for specific interventions. New research tools from the fields of epidemiology, immunology, imaging, and data analysis will be helpful in accomplishing this goal.

Acknowledgments

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KEY POINTS

- The heterogeneity implicit to COPD suggests that a wide variety of influences including environmental and biologic factors likely contribute to an individual's disease presentation and progression.

- Certain comorbid conditions such as cardiovascular disease and osteoporosis also contribute to the heterogeneity of the patient population.

- Systemic inflammation may be pathogenically related to many of the comorbidities seen in COPD including cardiovascular disease, osteoporosis, metabolic syndrome and depression.

- New research in COPD using large patient populations with extensive clinical and biologic characterization along with advanced analytic methods will hopefully further expand our potential to identify disease phenotypes such that targeted therapies can be developed.
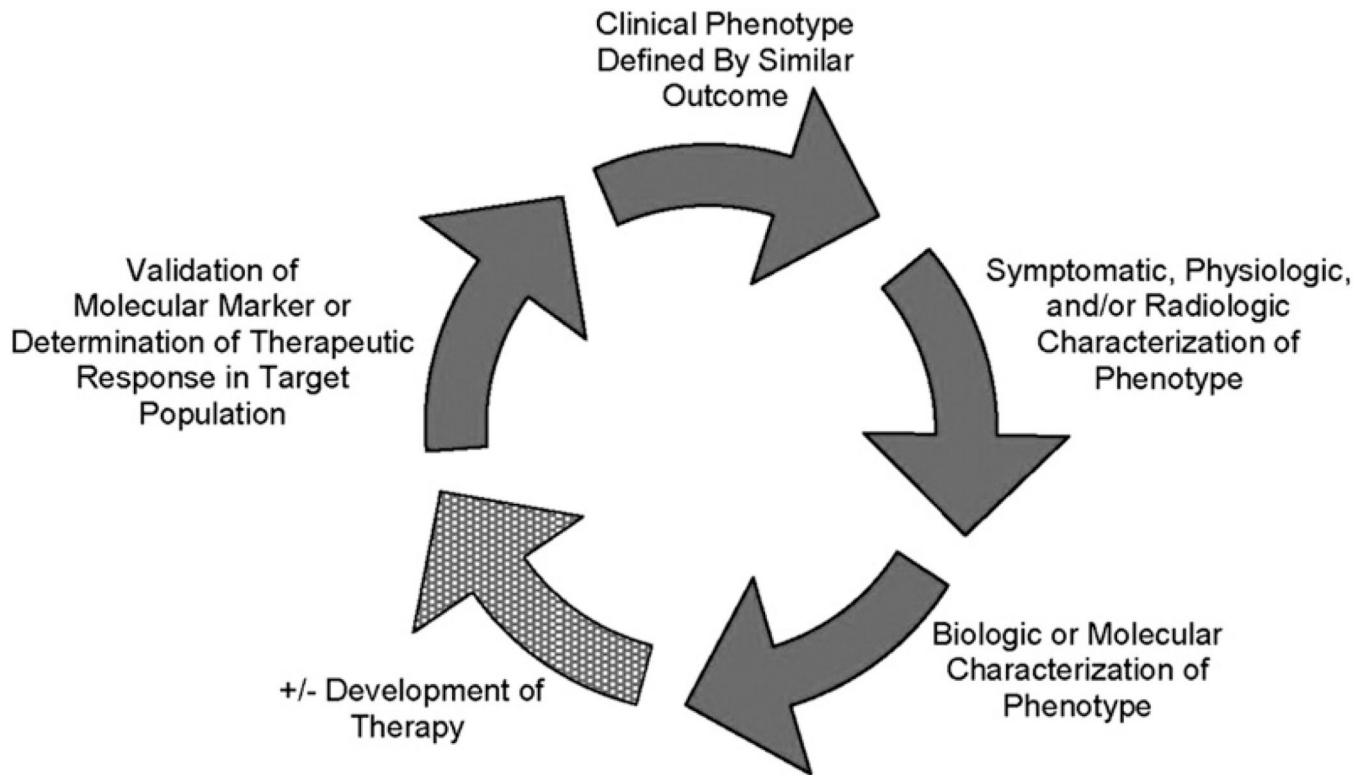
Clinical Phenotype Defined By Similar Outcome

Symptomatic, Physiologic, and/or Radiologic Characterization of Phenotype

Biologic or Molecular Characterization of Phenotype

+/- Development of Therapy

Validation of Molecular Marker or Determination of Therapeutic Response in Target Population

Fig. 1.
Ideal phenotyping construct wherein candidate phenotypes are validated once their relevance to clinical outcomes is established. There are multiple potential points of entry into this iterative process of phenotype identification. For instance, similar clinical outcomes may define a subpopulation that leads to the identification of a biologic target and focused therapy. Alternatively, the process might begin with the differentiation of subgroups based on a biologic marker that is then validated by similar clinical response within subgroups. (*From* Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182(5):598–4; with permission.)