Clinical Commentary

Chronic Obstructive Pulmonary Disease Phenotypes
The Future of COPD


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Significant heterogeneity of clinical presentation and disease progression exists within chronic obstructive pulmonary disease (COPD). Although FEV1 inadequately describes this heterogeneity, a clear alternative has not emerged. The goal of phenotyping is to identify patient groups with unique prognostic or therapeutic characteristics, but significant variation and confusion surrounds use of the term “phenotype” in COPD. Phenotype classically refers to any observable characteristic of an organism, and up until now, multiple disease characteristics have been termed COPD phenotypes. We, however, propose the following variation on this definition: “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).” This more focused definition allows for classification of patients into distinct prognostic and therapeutic subgroups for both clinical and research purposes. Ideally, individuals sharing a unique phenotype would also ultimately be determined to have a similar underlying biologic or physiologic mechanism(s) to guide the development of therapy where possible. It follows that any proposed phenotype, whether defined by symptoms, radiography, physiology, or cellular or molecular fingerprint will require an iterative validation process in which “candidate” phenotypes are identified before their relevance to clinical outcome is determined. Although this schema represents an ideal construct, we acknowledge any phenotype may be etiologically heterogeneous and that any one individual may manifest multiple phenotypes. We have much yet to learn, but establishing a common language for future research will facilitate our understanding and management of the complexity implicit to this disease.

Keywords: prognosis; mortality; decline; therapy; outcomes

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Significant heterogeneity of clinical presentation and disease progression exists within chronic obstructive pulmonary disease (COPD). Although FEV1 inadequately describes this heterogeneity, a clear alternative has not emerged.

What This Study Adds to the Field

We propose that COPD phenotypes should be associated with clinically meaningful outcomes. This more focused definition allows for classification of patients into distinct prognostic and therapeutic subgroups for both clinical and research purposes. Establishing a common language for future research will facilitate our understanding and management of this disease.

The diagnosis, assessment and management of chronic obstructive pulmonary disease (COPD) are currently facing an important dilemma. On the one hand, COPD is defined by the presence of airflow limitation that is not fully reversible, and its treatment is mostly guided by the severity of this limitation (1). On the other hand, it is now widely recognized that COPD is a complex syndrome with numerous pulmonary and extrapulmonary components. Importantly, significant heterogeneity exists with respect to clinical presentation, physiology, imaging, response to therapy, decline in lung function, and survival. As a result, there is consensus that FEV1 by itself does not adequately describe the complexity of the disease and that FEV1 cannot be used in isolation for the optimal diagnosis, assessment, and management of the disease. However, a clear alternative has not yet been defined. Considering that almost all we currently know about pathophysiology, mechanism, and response to treatment is regarding COPD caused by or associ-
ated with cigarette smoking, the discussion that follows relates only to COPD observed in smokers.

The identification and subsequent grouping of key elements of the COPD syndrome into clinically meaningful and useful subgroups (phenotypes) that can guide therapy more effectively is a potential solution to this dilemma. Caution, however, is warranted when clustering patients with similar symptoms and clinical manifestations, as phenotyping in COPD is still a relatively young endeavor as compared with other fields. The novelty of COPD phenotyping is illustrated by the fact that a MEDLINE search revealed just over 400 phenotyping papers published in the field of COPD, whereas, for instance, it identifies more than 5,000 in breast cancer. Moreover, there is significant variation, confusion, and uncertainty surrounding use of the term phenotype in COPD. A common language for future research should facilitate our understanding of the heterogeneity implicit to this disease and help us design better alternatives for the prevention and management of the disease. This article discusses and refines the concept of phenotyping in COPD and presents a possible schema that can serve as a framework for future research.

**COPD PHENOTYPES: AN OPERATIONAL DEFINITION**

The classic definition of a phenotype reflects the observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment: the interactions between “nature” and “nurture” (2). Although this definition has been historically useful in a variety of contexts (3), in medicine in general, and in COPD in particular, we believe this concept must be refined to more efficiently fulfill the following clinical and research goals. From a clinical and patient-centered perspective, a COPD phenotype should be able to classify patients into distinct subgroups that provide prognostic information and allow us to better determine appropriate therapy that alters clinically meaningful outcomes. From a research standpoint, phenotyping should allow us to select a uniform group of patients and assess the most important outcome measures in that group for therapeutic clinical trials. Phenotypes can also form the basis for biological mechanistic investigations. Hence the ultimate goal of phenotyping in medicine is to allow the identification of patient groups with unique prognostic or therapeutic characteristics. In COPD until now, disease characteristics and/or disease severity have frequently been termed COPD phenotypes (3).

Accordingly, we propose the following variation on the traditional definition of a phenotype: “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).” In other words, it is proposed that phenotypes in COPD should have real predictive value. It follows, therefore, that any proposed phenotype must be prospectively validated and refined for each of the outcomes to which it relates. Identifying the outcome is important as certain descriptors appear to have independent prognostic value either as sole measures or as components of the body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity (BODE) Index (6). Similarly, depression and anxiety have been independently associated with an increased frequency of hospital admissions and COPD exacerbation relapses (7, 8).

**POTENTIAL PHENOTYPES**

Here we discuss how disease attributes fit within the phenotyping framework we have proposed. As patient outcomes are a key component of the operational definition of phenotype proposed above, potential phenotypes are discussed within the clinical outcomes to which they relate.

**Clinical Manifestations**

Age, smoking history, sex, and ethnicity may all significantly impact disease presentation and progression. For example, lung function declines with increasing age (4). Female sex appears to be associated with worse quality of life (QOL) and higher rates of depression and anxiety; data suggest female sex may also be associated with higher susceptibility to the toxic effects of smoking (5). Women may also differ from men in the extent and distribution of airway abnormality and emphysema (5), which in themselves are not clinically relevant outcomes, but may relate to clinically relevant outcomes (see Radiologic Characterization section below). Body composition and dyspnea can be assessed with various instruments, and both descriptors appear to have independent prognostic value either as sole measures or as components of the body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity (BODE) Index (6). Similarly, depression and anxiety have been independently associated with an increased frequency of hospital admissions and COPD exacerbation relapses (7, 8).

**Physiological Manifestations**

Spirometric indices, including FEV₁, FVC, and their ratio, are used to define the presence and severity of disease. Unfortunately, these features explain less than 10 to 25% of the disease impact on patient symptoms, QOL, and exercise performance (9–11). Rapid physiologic progression as indicated by change in
FEV₁, however, may indicate a distinct phenotype. Rapid decline in FEV₁ is not only predictive of morbidity, mortality, and hospitalization rates (12) but has also been linked to distinct plasma biomarker signatures (13). Bronchodilator reversibility and airway hyperresponsiveness are highly variable in patients with COPD from patient to patient, and also within a given patient when measured serially over time, and thus have limited sensitivity or specificity in distinguishing COPD from asthma (14, 15). Airway hyperresponsiveness has been associated with a greater longitudinal decline in lung function; bronchodilator reversibility defined as change in FEV₁ may be less common with an emphysema-dominant phenotype (14, 16). Hyperinflation may also define patient groups associated with varying mortality or functional impairment (17, 18). Similarly, diffusing capacity impairment is an independent predictor of the magnitude of radiologic emphysema (19), presence of resting hypoxemia, exercise-induced arterial oxygen desaturation (20), and functional impairment (21). Although we cannot say with certainty, this may reflect unique biologic processes (22). Other physiologic measures, such as hypercapnia, physiologic exercise impairment, or even measures of physical activity derived from actigraphy, may also reflect unique biological processes and consequently potential opportunities for unique therapeutic interventions (23, 24).

Radiologic Characterization
Quantitative assessment of emphysema by computed tomography (CT) scanning offers an objective measure of parenchymal disease that correlates well with histopathologic findings and is predictive of the degree of expiratory airflow obstruction (25). Objective measures of proximal airway wall thickening obtained via CT are inversely correlated with lung function and relate to a subject’s burden of small airway disease (26) and exacerbation frequency (27). More recent work suggests that the correlative strength between CT measures of airway wall thickening and lung function increase when examining more distal fourth- and fifth-generation airways (28), although such structures approach the limits of accurate measurement using most currently available CT imaging reconstruction protocols and should therefore be used with caution.

Whether or not the presence of specific lung structural abnormalities (including emphysema, airway wall thickening, and/or bronchiectasis) predict meaningful clinical outcome is an area of current research interest (29, 30). Increasing emphysema severity as defined by CT has been associated with worse health status (27) and increased mortality (31). The National Emphysema Treatment Trial provides the most compelling evidence supporting distinct CT-based phenotypes in defining an increased risk of mortality in patients with homogenous emphysema and impaired FEV₁ or diffusing capacity of carbon monoxide undergoing LVRS, whereas upper lobe–predominant emphysema and a low postrehabilitation exercise capacity identify a group of emphysema patients who experience a mortality and functional benefit from LVRS (16). These compelling data strongly support that a combination of CT imaging and physiological testing can clearly impact therapeutic decision making, thus validating its value as a phenotype according to our operational definition.

COPD Exacerbations
Within the framework we have proposed, an acute exacerbation of COPD (AECOPD) could be viewed as outcome or, in the context of describing a “frequent exacerbator,” a phenotype. AECOPD is currently defined as: “A sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD” (32). This general description poses numerous operational challenges for use in clinical phenotyping. It remains unclear if these changes are quantitative or if there is also a qualitative element. Similarly, the normal variation in symptoms in patients with COPD remains relatively unexplored; how long changes in symptoms must be sustained before being characterized as an exacerbation varies according to study. Sputum color is a marker of bacterial-infective exacerbations that has validity in populations of patients (33). Although the consensus definition states: “necessitates a change in regular medication,” the criteria invoked by health-care providers to judge when to alter medication remains unclear. Importantly, patient-recorded increases in symptoms that appear to be exacerbations outnumber those that cause them to present for medical attention (34). In addition, events with worsening symptoms that do not lead patients to seek additional care may, nevertheless, impact prognosis.

Despite limitations in defining AECOPDs, numerous investigators have highlighted the negative implications of these events in patients with COPD. Reviews of the published data confirm that AECOPDs exert significant short- and long-term negative effects on health-related QOL in patients with COPD (35). AECOPD episodes also result in modest, yet measurable, acute effects on pulmonary function (36). Perhaps most importantly, repeated AECOPDs have also been suggested to result in negative effects on longitudinal lung function (37) and can be identified by previous history of AECOPD (38), suggesting that patients with COPD with recurrent AECOPDs may reflect a distinct phenotypic group. This subgroup may be particularly relevant in consideration as a phenotype because it appears to be responsive to therapy with inhaled bronchodilators either alone or in combination with inhaled corticosteroids (39). Furthermore, a chronic bronchitic subgroup with sputum production and prior exacerbation history has recently identified a COPD cohort who experience improvement with the novel phosphodiesterase 4 inhibitor roflumilast (40). Here we have an example of targeting a drug for a specific COPD subpopulation that was identified by post hoc analysis of prospectively collected data from well-conducted clinical trials. This methodology may have value when considering variables not defined by therapeutic responses and is analogous to the widely adopted approach of identifying and then confirming genotypic information in replicate data sets. Post hoc analysis of well-done, prospective, placebo-controlled clinical trials conducted in patients with COPD with a range of disease severity and symptoms may be a fertile area in which to conduct responder analyses. This method of retrospective analysis may help to uncover patient attributes that indicate differential responses to treatment and may lead to the discovery of separate COPD clinical phenotypes potentially linked with molecular fingerprints of disease pathogenesis.

Systemic Inflammation
The presence of systemic inflammation may represent a unique COPD phenotype.

If defined by the presence of elevated biomarkers (including C-reactive protein, serum amyloid A, proinflammatory cytokines IL-6 and IL-8, tumor necrosis factor α, and leukocytes), systemic inflammation does not appear to be present in every patient with COPD (41, 42). In fact, the prevalence of systemic inflammation in COPD appears to vary significantly depending on the particular marker (or combination of markers) chosen. Evidence of systemic inflammation can also be detected in
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patients who appear otherwise clinically stable (41, 42) but with evidence of further increase during exacerbations (43). Additionally, the presence of systemic inflammation does not appear to be unique to COPD but also occurs in other chronic diseases and even during normal aging. As it relates to phenotyping, thus far no clear relationship between systemic inflammation and a particular aspect of COPD (such as the severity of airflow limitation or the presence of emphysema, airway colonization, arterial hypoxemia, comorbidities, or symptoms), has clearly emerged. Thus, at this point in time it is unclear what mechanisms drive the presence, type, and/or severity of systemic inflammation in any given patient. It is also unclear whether therapy aimed at optimizing pulmonary function in COPD results in a reduction of systemic inflammation in these patients (44, 45) or whether the direct targeting of systemic inflammation influences the natural history of COPD.

Comorbidities

Patients with COPD often present with comorbid diseases, including cardiovascular disease, metabolic syndrome, osteoporosis, depression, and skeletal muscle wasting and dysfunction (46, 47). Systemic inflammation may contribute to the development of comorbid conditions and these disorders can be seen as manifestations of COPD or vice versa (48). Accelerated aging is a further process that could account for both the local lung effects of COPD and its comorbidities (49). Aging is characterized by a progressive, generalized impairment of function and amplification of the inflammatory response (50) that results in an increased vulnerability to environmental challenge and an increased risk of disease. The presence of many of these comorbidities appears to have a deleterious effect on several outcomes in COPD (51). In particular, diabetes, hypertension, cardiovascular disease, and cancer increase the risk of death in COPD (51). However, whether treatment of comorbid conditions alters the natural history of COPD or whether treatment of COPD is altered by the presence of a concomitant comorbidity awaits further study.

MULTIDIMENSIONAL INDICES

Recently several multidimensional indices have been described for prognostic purposes in COPD. Perhaps best well known of these is the BODE Index to predict mortality, which incorporates dyspnea, BMI, FEV1, and exercise capacity as measured by 6-minute walk distance (6MWD). Modifications of the BODE index have also been described, including the mBODE (replaces 6MWD with VO2) (52), e-BODE (BODE plus exacerbations) (53), and BODE-x (substitution of exacerbations for exercise capacity) (53), as well as the ADO index (dyspnea, FEV1, and age), which are all better predictors of mortality in COPD than FEV1 alone (6, 54). Other indices that have been described include the COPD Prognostic Index (QOL, FEV1, age, sex, BMI, exacerbation history, cardiovascular disease history) (55) that predicts mortality, hospitalization, and exacerbation frequency, the SAFE Index (QOL, FEV1, 6MWD) (56) to predict exacerbation frequency, and the DOSE Index (dyspnea, smoking status, FEV1, and prior exacerbation history), which also predicts exacerbations (57). From the standpoint of clinical phenotyping, such multidimensional indices are useful in their ability to group patients in terms of clinically relevant outcomes. However, from a research standpoint, a note of caution is warranted. Although it is possible that the seemingly diverse measures included in a multidimensional index actually relate to a shared latent variable responsible for the clinical presentation, it is also possible that by grouping patients in this fashion we may be blurring distinct features of the disease that may hamper our understanding of the biologic or physiologic basis for the shared outcome.

WHERE DO WE GO FROM HERE?

The identification of COPD phenotypes will require an iterative validation process in which candidate phenotypes are identified before their relevance to clinical outcome is determined (Figure 1). As research is currently advancing on all fronts simultaneously, there are multiple points of entry into this process of phenotype identification (see Figure 1). Borrowing from the field of breast cancer, initially hormone-based therapies were tested in the general breast cancer population, but it was ultimately determined that that the presence of estrogen and progesterone receptors within the tumor determined the response to therapy (58). In asthma, cellular phenotypes of asthma (eosinophilic, neutrophilic, and paucigranulocytic) were identified by analyses of sputum and subsequently used to direct the successful application of mepolizumab (anti–IL-5) therapy (59). In COPD, roflumilast was initially studied in a general COPD population, but it was ultimately determined that it is a subgroup of patients (FEV1 < 50% predicted, chronic cough, and sputum production) who demonstrate the greatest clinical response. Mechanistic studies, however, will be needed to understand the biologic basis for response in this subgroup.

From a practical standpoint, validation of phenotypes in COPD will require longitudinal data collection in carefully characterized patient populations. Studies such as Evaluation

Figure 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.
of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), Subpopulations and intermediate outcome measures in COPD (SPIROMICS), and COPDGene that are systematically gathering clinical, physiologic, radiologic, biologic, and genetic data on COPD subjects will aid in this regard. Additionally, advanced statistical techniques may also prove useful in identifying candidate phenotypic subgroups. One such example is cluster analysis, which has a basis both in mathematics and biology and is a technique for data exploration. Cluster analysis encompasses a number of different algorithms for grouping subjects without an a priori hypothesis. A related statistical technique, factor analysis, may also prove useful in COPD phenotyping. Although the goal of cluster analysis is to reduce the number of observations or cases by grouping them into a smaller set of clusters, the goal of factor analysis is to reduce the number of variables by grouping them into a smaller set of factors. Cluster and factor analysis have been used in conjunction in COPD to identify key variables on which to select clusters of related patients (60–63). These types of analyses would still, however, require longitudinal validation to determine how such clustered subjects differ with respect to important clinical outcomes. In addition, such analyses may or may not ultimately be useful in defining specific biologic pathways or therapies.

The suggested schema for phenotype identification, however, represents an ideal construct, as almost every outcome measure other than death displays inherent difficulties with measurement. Furthermore, for every phenotype, a specific therapy may not be ultimately identified. An individual’s phenotype may not ultimately be useful in defining specific biologic pathways or therapies.
companies and entities supported by tobacco companies were terminated in 2007. F.C.S. received $1,001–5,000 from Pfizer in consultancy fees, $1,001–5,000 from GlaxoSmithKline, $1,001–5,000 from AstraZeneca, $1,001–5,000 from Boehringer Ingelheim, $1,001–5,000 in advisory board fees, and more than $100,001 from GlaxoSmithKline, more than $100,001 from Pfizer, and more than $100,000 from Boehringer Ingelheim in industry-sponsored grants. E.K.S. received $10,001–50,000 from GlaxoSmithKline and $10,001–50,000 from Pfizer in consultancy fees; $1,001–5,000 from Bayer in lecture fees; and more than $100,000 from GlaxoSmithKline in industry-sponsored grants. J.V. received $10,001–50,000 from GlaxoSmithKline, $1,001–5,000 from Boehringer Ingelheim, $1,001–5,000 from Naunheim KGaA in consultancy fees; $1,001–5,000 from GlaxoSmithKline, $5,001–10,000 from AstraZeneca, and $1,001–5,000 from Bayer in lecture fees; and more than $100,000 from Naunheim KGaA in industry-sponsored grants. E.K.S. received $10,001–50,000 from GlaxoSmithKline, $10,001–50,000 from Boehringer Ingelheim, $1,001–5,000 from Naunheim KGaA in consultancy fees; and more than $100,000 from GlaxoSmithKline in industry-sponsored grants for the ECLIPSE study and HP-He substudy. G.R.W. received $1,001–5,000 from MedImmune in consultancy fees. E.F.M.W. received $1,001–5,000 from Nycomed in advisory study and HP-He substudy. G.R.W. received $1,001–5,000 from Talecris in lecture fees; and more than $1,001–5,000 from Nycomed, and $1,001–5,000 from Hoffman LaRoche in industry-sponsored grants. E.K.S. received $10,001–50,000 from GlaxoSmithKline and $10,001–50,000 from Pfizer in consultancy fees, and more than $100,000 from Hoffman LaRoche in consultancy fees; and more than $100,000 from GlaxoSmithKline, more than $100,000 from Pfizer, and more than $100,000 from Boehringer Ingelheim in industry-sponsored grants; F.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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