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Chronic Obstructive Pulmonary Disease Biomarkers

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Abstract

Despite significant decreases in morbidity and mortality of cardiovascular diseases (CVD) and cancers, morbidity and cost associated with chronic obstructive pulmonary disease (COPD) continue to be increasing. Failure to improve disease outcomes has been related to the paucity of interventions improving survival. Insidious onset and slow progression halter research successes in developing disease-modifying therapies. In part, the difficulty in finding new therapies is because of the extreme heterogeneity within recognized COPD phenotypes. Novel biomarkers are necessary to help understand the natural history and pathogenesis of the different COPD subtypes. A more accurate phenotyping and the ability to assess the therapeutic response to new interventions and pharmaceutical agents may improve the statistical power of longitudinal clinical studies. In this study, we will review known candidate biomarkers for COPD, proposed pathways of pathogenesis, and future directions in the field.

Keywords: Biomarker, chronic obstructive pulmonary disease, emphysema, fibrinogen, smoking

INTRODUCTION

Research regarding chronic obstructive pulmonary disease (COPD) biomarkers has been hindered because of the slow clinical progression of COPD. COPD progression is considered to be related to inflammatory responses to inhaled particles and gases in genetically susceptible individuals that continue to persist even after the source of inflammation has been removed. Smoking is a causative factor for most cases of COPD in developed countries; however, in developing areas of the world, biomass fuels and air pollution cause a significant proportion of COPD. Despite smoking cessation, airway mucosal inflammation persists and is implicated in a self-perpetuating mechanism leading to abnormalities that do not allow the lungs to completely repair.

Because much of the associated mortality is due to the systemic manifestations of COPD, biomarkers that target the affected organs and extend beyond the correlations with lung function decline hold promise (1). COPD is a heterogeneous disorder and likely requires different biomarkers for its phenotypes. Most traditional biomarkers of the disease activity have been related to lung function decline. The forced expiratory volume in one second (FEV_1) and its relationship to forced vital capacity (FVC) that is expressed as a ratio (FEV_1/FVC) has been traditionally considered as a biomarker because it defines the disease. However, neither FEV_1 nor FEV_1/FVC adequately measure COPD severity. FEV_1 has a weak correlation with symptoms (2), and although FEV_1 has been linked to poor outcomes, it requires expensive and prolonged studies to detect a measurable longitudinal result that is expressed as the FEV_1 decline slope.

Unfortunately, few better alternatives exist. Importantly, the rate of FEV_1 decline is higher in the intermediate stages of the disease when most of the patients remain underdiagnosed. Attempts to make a diagnosis when FEV_1 can have a measurable change are hampered by the lack of studies that demonstrate that an early diagnosis changes outcomes. More longitudinal studies are required because COPD diagnosis at early stages is not currently a target of most public health initiatives (3). The search for a better test to detect early COPD continues. The goal of this study is to investigate COPD biomarkers that may simultaneously improve patient care and outcomes, assist in developing new therapies, and decrease soaring COPD costs.

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Biomarker Definition and Desired Qualities

A biomarker is an objectively measured characteristic that indicates normal or pathogenic biological processes. For a biomarker to have clinical relevance, it should change with treatment responses to relevant therapeutic interventions (4). Biomarkers should be linked to outcomes. They are used to establish diagnosis and measure the disease severity, progression, and treatment effect (5). Patient care and patient-related outcomes should be improved by appropriate use of a biomarker. The biomarker could be diagnostic indicator (present as a dichotomous variable: present/absent or be measured as a continuous variable with an established threshold value).

Biomarker development is a very prolonged process and at a minimum includes several stages. Discovery, qualification, and verification are the initial steps of the process. These are followed by research assay optimization, biomarker validation, and commercialization. Unfortunately, most potential biomarkers are destined to end their utility at the discovery stage. Diagnostic accuracy studies are difficult to conduct, and a Standards for Reporting of Diagnostic Accuracy statement was developed to improve the reporting and quality of these studies (6). An ideal biomarker should possess the qualities listed in Table 1. Important goals of the biomarker include the early detection of a subclinical disease, thus enabling timely and effective therapeutic interventions, stratifying risk, selecting therapies, and monitoring disease progression and response to interventions. For any biomarker to have relevance in COPD, it must strongly correlate with disease outcomes. Candidates that meet this requirement might be physiological, radiographical, or more traditional serum biomarkers. If a biomarker is used in lieu of a known outcome, it is termed as a surrogate biomarker. In many disease states, specifically the multisystemic ones, composite biomarkers play significant roles.

COPD Phenotypes

Chronic obstructive pulmonary disease is a preventable and treatable disease that is characterized by not completely reversible airflow limitation and multiple systemic manifestations. The airway obstruction can occur through many mechanisms. Obstruction may be related to emphysematous destruction of the lung parenchyma with loss of elastic recoil, injury and/or remodeling of small airways, obstruction from mucus, bronchospasm, or a combination of these heterogeneous processes. There is a significant heterogeneity in the disease (7); both chronic bronchitis and emphysema (widely accepted phenotypes) can be present or overlap. Moreover, some patients with asthma develop poorly reversible airflow limitation and may be indistinguishable from patients with COPD as has been described in the asthma–COPD overlap syndrome (ACOS) (8).

Table 1. Qualities for the ideal biomarker

Relevance	Relation to specific disease
Sensitivity	Ability to detect clinically relevant differences
Specificity	Non-influenced by confounders
Reliability	Consistent performance in different settings
Consistency	Similar instruments produce similar results
Repeatability	Change is present only with change in the disease
Interpretability/ clinical utility	Clinical meaningfulness
Simplicity	Feasibility in routine clinical practice
Cost-effectiveness	Cost is lower than the savings it generates
Clarity	Non-ambivalent
Practicality	Ease of use
Generalizability	Applicable to patients with a specific disease
Biological credibility	Implicated in pathogenesis

The observed heterogeneity of COPD manifestations and its associated outcomes led to the description of COPD phenotypes (Table 2, Figure 1) (9). A phenotype results from a clinical observation that unique disease features have prognostic and therapeutic characteristics that may be related to its pathogenesis. Most COPD phenotypes are not yet validated and will require further studies to confirmits relationship with clinically meaningful outcomes. Phenotyping is a complex process because some individuals may have features that are applicable to several phenotypes. Once established, the identification of specific phenotypes should enable individualized prognosis, targeted treatment, and personalized medicine.

Systemic Inflammome in COPD

Both pulmonary and systemic inflammation play an integral role in COPD pathogenesis (10). The term systemic inflammome refers to the complex network of systemic inflammatory processes in COPD that might cause the development of comorbidities. Low-grade systemic inflammation is commonly observed with moderate and severe airflow obstruction and is associated with an increased risk of cardiac injury. This may explain the high rates of cardiovascular complications in COPD (11) and worse outcomes with comorbid conditions. The mechanism by which COPD results in a persistent systemic inflammatory response is unknown.

Inflammation and recovery processes are both complicated events. Injury to the airways and subsequent tissue repair may participate in the re-modeling of the small airways. Autoimmunity to modified connective tissue matrix elements may also have a role in COPD pathogenesis (12).

An ideal drug to treat any systemic inflammatory disease should be directed to one or both of the following two targets: inhibiting the inflammatory response and/or assisting the resolution process. Most COPD therapies are directed to the lung. Although broadly impacting a number of inflammatory pathways, inhaled corticosteroids (ICS) with long-acting beta-2 adrenergic agonists do not reduce C-reactive protein CRP or interleukin-6 (IL-6) levels in the serum of patients with COPD over 4 weeks. Other serum biomarkers associated with systemic inflammation, such as surfactant protein-D are downregulated by ICS (13). Therefore, drugs that will target systemic inflammation in COPD would be predicted to affect generalized biomarkers of systemic inflammation in COPD.

Traditional COPD Biomarkers

The purpose of a COPD biomarker is to improve or establish an early diagnosis, monitor disease activity and progression, evaluate therapeutic response, predict outcomes, and provide a guided therapy for different phenotypes of the disease. Although all clinical trials require a primary endpoint, many traditional biomarkers appear as secondary or exploratory endpoints. Although easily measured, mortality is rarely a primary endpoint in clinical trials because of the difficulty in achieving adequate power. Therefore, validation studies should determine if short-term changes in biomarkers are useful surrogate markers of long-term patient-centered outcomes. In COPD management and research, a number of physiological markers and

Table 2. Proposed COPD phenotypes

Recognized phenotypes	Characteristic	Targets for interventions
Chronic bronchitis	Clinical definition of productive cough in 3 months in 2 successive years	Anti-inflammatory therapies, airway clearance
Emphysema	Lung parenchymal destruction observed best on CT	Preservation of lung connective tissue matrix, anti-proteases, bron choscopic LVR interventions
AATD	Familial aggregation due to a genetic cause	Alpha-1 antitrypsin augmentation, targeting of Z polymer formation and transport
Asthma/COPD overlap	Independent features of fixed obstruction and history of asthma or bronchial hyper-responsiveness.	ICS, bronchodilators
Frequent exacerbator (two or more per year)	Strongest link to mortality. Poorer outcomes with respect to quality of life and higher co-morbidity rates	Antibiotics, ICS, anti-inflammatory therapy affecting PMN trafficking and activation
Newly considered phenotypes	**Characteristic**	**Targets for interventions**
Comorbidities	Increased incidences of CAD, CHF, DM, arthritis, cancer, renal disease, and osteoporosis	Evaluate for and treat, same guidelines apply
COPD in never smokers	Usually induced by lung injury early in life or exposure to dust or fumes	Genetic testing to rule out hereditary causes
Deconditioned	Poor muscle function compromises functional capacity	Pulmonary rehabilitation, muscle mitochondrial activity, electrical muscle stimulation
Eosinophilic airway inflammation	Sputum/airway eosinophilia is present instead of neutrophilic disease observed in most patients with COPD	Targeted IL-5 therapies (benralizumab)
Inflammome (10)	Several inflammatory biomarkers present, associated with an increased risk for cardiovascular disease	Anti-inflammatory therapies, screen and treat cardiovascular disease
Malnourished	Cachexia and low BMI have poor prognosis and may be induced by unique metabolic pathways	Nutrition assessment and recommendations
Obese	Underappreciated impact on COPD outcomes in the very obese population with BMI of>35	Weight loss, leptin signaling, anti-inflammatory therapies
Out of proportion hypoxemia	Pulmonary vascular injury out of proportion to airway disease or emphysema. This may also be observed with COPD/ILD overlap	Oxygen, oxygen transport (e.g., almitrine)
Out of proportion PH	Pulmonary vascular disease out of proportion to degree of emphysema sometimes observed in COPD/OSAS overlap	PAH specific therapies, diagnose and treat OSAS
Premature or early severe airflow limitation	Genetic or lung developmental abnormalities. Also observed in prenatal disease and associated with prematurity	Genetic testing to rule out hereditary causes. Early diagnosis and prevention for adults with history of prematurity

AATD: Alpha-1 antitrypsin deficiency; BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CT: computed tomography; DM: diabetes mellitus; ICS: inhaled corticosteroids; ILD: interstitial lung disease; LVR: lung volume reduction; OSAS: obstructive sleep apnea syndrome; PAH: pulmonary arterial hypertension; PD15: percentile density at 15%; PH: pulmonary hypertension; PMN: polymorphonuclear leukocytes

patient-related outcomes are utilized (Table 3). Some represent composite measurements and most are longitudinally followed.

FEV_1

Individuals with COPD considerably vary in disease severity, progression rate, and extrapulmonary systemic manifestations. Clinical outcomes are best measured by a marker that reflects the presence, severity, disease stage, or end-result of therapeutic interventions. The most widely accepted COPD biomarker, FEV_1, has been used for three decades and possesses most of the qualities of a good biomarker. However, it has limitations. It has a poor correlation with COPD manifestations of weight loss, dyspnea, exercise tolerance, and cough. In addition, it is poorly sensitive early and late in the disease process with both ceiling and floor effects.

BODE

In 2004, Celli et al. (14) developed a multidimensional grading system utilizing BMI, degree of spirometric obstruction, dyspnea score, and

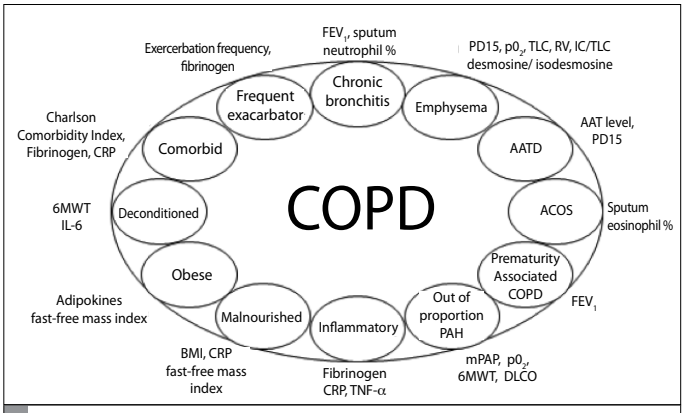

Figure 1. Optimal biomarkers should target specific phenotypes in COPD
AAT: Alpha-1 antitrypsin; BMI: body mass index; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 second; IC/TLC: inspiratory capacity/total lung capacity; IL-6: interleukin-6; mPAP: mean pulmonary arterial pressure; PD15: percentile density at 15%; pO_2: partial pressure of oxygen; RV: residual volume; TLC: total lung capacity; TNF-α: tumor necrosis factor alpha; 6 MWT: 6-min walk test

exercise capability that was measured by a 6-min walk test, known as the BODE index. BODE is better than FEV_1 at predicting all cause- and respiratory-related mortality among patients with COPD. Out of these four components, FEV_1 is the most difficult to alter and/or reverse. The COPD co-morbidity Test (COTE) index when added to the BODE index was found to be complimentary and significantly improved outcome predictions (15). COTE includes comorbidities that have an impact on survival in patients with COPD (16). A total of 79 comorbidities were observed in the study cohort and 12 of them had the strongest association with increased risk for death. Oncologic comorbidities included lung, pancreatic, esophageal, and breast cancer. Cardiac conditions were prevalent (13%–30%) and included atrial fibrillation/flutter, congestive heart failure, and coronary artery disease. Pulmonary fibrosis, diabetes with neuropathy, anxiety, gastric/duodenal ulcers, and liver cirrhosis are also included.

Non-traditional Cellular and Molecular Biomarkers

Various proteins implicated in COPD pathogenesis are dysregulated in this disease (Table 4). It has been proposed that the imbalance between pro-inflammatory and anti-inflammatory proteins might be useful surrogate biomarkers. Unfortunately, the measurements of oxidant stress and antioxidant protection and protease injury and anti-protease protection have been explored for many years with limited advances. The protease–anti-protease theory of emphysema has a long history that was initiated with alpha-1 antitrypsin deficiency (AATD). Because local inflammatory events in the lung interstitium or alveolus have proteolytic pathways that are activated in general COPD, much study has been conducted to measure these pathways in disease pathogenesis. Unfortunately, many of the local events in the airways or lung parenchyma can only be accessed through invasive tests. Lung biopsies, exhaled breath condensates, sputum, or bronchoalveolar lavage can provide an insight into the disease pathogenesis (17). However, serum or plasma biomarkers will be necessary to become universally accessible for COPD.

Antioxidants and Lung Health

A current theory of COPD pathogenesis includes dysregulation of oxidant–anti-oxidant activity leading to progressive destruction and abnormal repair of the lung tissue. There is substantial literature regarding the association between diet; exercise; and cardiovascular disease prevention, development, and progression. Biomarkers that are associated with systemic redox potentials require more study with respect to COPD.

Table 3. Physiological biomarkers and patient-related outcomes in COPD

FEV_1	Physiological outcome of airway flow
DLCO	Physiological outcome related to the integrity of pulmonary capillary bed
RV, TLC, and RV/TLC	Physiological outcomes related to hyperinflation
6 MWT	Functional outcome that integrates pulmonary, cardiac, and muscle functioning and correlates with quality of life
Frequency of exacerbations (EXACT instrument)	Patient-related outcome that correlates with quality of life and cost
BMI	Extremes of high or low values associated with worse outcomes and different comorbidities
Fat-free mass index	Low muscle mass impacts outcomes
Frequency of hospitalization	Important outcomes related to cost and mortality
Dyspnea	Patient-related outcome
Quality of life tools (e.g., SGRQ, SF-36)	Patient-related outcome
COPD specific questionnaires (CAD, COPD severity score)	Patient-related outcome
Mortality	Patient-related outcome
CT measurements of emphysema, bronchiectasis	Imaging outcomes that directly measure lung anatomy

BMI: Body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CT: computed tomography; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 second; RV: residual volume; SF-36: short form 36 health survey; SGRQ: St. George's respiratory questionnaire; TLC: total lung capacity; 6 MWT: 6-min walk test

Fibrinogen

Fibrinogen is the most promising COPD biomarker that has been extensively studied and was recently certified by the United States Food and Drug Administration (US FDA) as a biomarker that is sufficient for regulatory purposes. It is a glycoprotein by structure, is an acute-phase protein with levels reflecting the degree of inflammation, and is important in coagulation. An abundance of research demonstrates that fibrinogen is associated with various chronic diseases that have a low-grade systemic inflammation. This acute-phaseprotein has serum levels that vary with the degree of inflammation. It has been variably associated with disease progression and mortality after adjusting for confounding factors such as age, smoking status, and degree of lung function impairment (18). Literature from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) revealed that elevated fibrinogen levels were associated

Table 4. Subgroups of most promising and studied biomarkers in COPD

Biomarker	Comments
Cellular biomarkers	
Eosinophil count	Can be measured in the blood, sputum, or BAL. May be helpful to stratify into allergic or idiopathic eosinophilic bronchitis phenotypes and to direct corticosteroid therapy in COPD (36)
Leukocyte count	Can be measured in the blood, sputum, or BAL. Very non-specific in blood. Weak associations with systemic inflammation, exacerbations, comorbidities, and mortality
Sputum neutrophils	Increased in individuals whosmoke and individuals with COPD
Protease/anti-protease biomarkers	
Neutrophil elastase	Very short-lived protease that requires bronchoscopy for analysis of NE inhibitory capacity and complexed forms
Desmosine/isodesmosine	Breakdown products of elastin that can be measured in the blood or urine (37). Most helpful in emphysema phenotypes. Increases with disease progression in both AATD and usual COPD
Alpha-1 antitrypsin	Serum level defines severe deficiency. It is an acute-phase reactant and has limited utility as a COPD biomarker
Matrix metaloproteinases/ Tissue inhibitors of matrix metaloproteinases	Implicated in homeostasis of elastin and collagen; MMP-9 is associated with cough and FEV_1 decline in cohort study
Biomarkers to measure systemic inflammation	
Fibrinogen	Linked to FEV_1, exacerbations, comorbidities, hospitalization risks, and mortalities (38). It is sensitive to intervention with inhibitors of p38 mitogen-activated protein kinase (39). Recently certified by the US FDA as a biomarker sufficient for regulatory purposes
IL-6	Measurement of systemic inflammation, associated with mortality and worse physical performance in individuals with COPD (18)
CRP	Measurement of systemic inflammation. Association with FEV1, exacerbations, comorbidities, hospitalization risks, and mortalities (19, 40-42)

Table 4. Subgroups of most promising and studied biomarkers in COPD (continued)

Biomarker	Comments
Exhaled nitric oxide	NO collected in exhaled gas is a measurement of pulmonary specific inflammation. Used as an outcome for some studies in asthma. Also increased in COPD, particularly unstable disease (43)
IL-8	Upregulated in many inflammatory diseases, therefore, likely to be a non-specific measure of neutrophil activation
TNF-α	Elevated in individuals who smoke, individuals with COPD, and associated with other inflammatory biomarkers (10)
Serum amyloid A protein	Increased during acute exacerbation (44)
Leptin	Obesity gene product, levels are lower in individuals with COPD and are implicated in cachexia
Adiponectin	Increased risk of respiratory mortality. It is not affected by smoking. Associated with iproved cardiovascular outcomes in COPD (45)
Leptin/adiponectin	Lower ratio is correlated with lung function decline in patients with COPD (46)
Tumor markers	
CEA, CA-125	Increased and associated with increased inflammatory biomarkers (WBC, CRP), and the disease severity in COPD (47)
Endothelial dysfunction markers	
VEGF	In exacerbations correlated with systemic inflammatory markers (CRP, fibrinogen), in stable patients with COPD, levels correlated with FEV1 (48)
Von Willebrand factor	Levels increased in acute exacerbations
Microalbuminuria	Present in acute exacerbations
Lung specific biomarkers	
Surfactant protein-D	Good predictor of cardiovascular morbidity and mortality (49). Sensitive to CS administration (13)
CC-16	Best biomarker of disease progression in ECLIPSE (50)

AATD: Alpha-1 antitrypsin deficiency; CA-125: cancer antigen-125; CC-16: Clara Cell protein-16CS: corticosteroids; CEA: carcinoembryonic antigen; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; IL-6: interleukin-6; MMP: matrix metalloproteinases; NO: nitric oxide; TIMP: tissues inhibitors of metalloproteinases; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor

with an increased risk of exacerbations in those with moderate to severe COPD, and it was useful to isolate frequent exacerbators (two or more per year) from those with none. Furthermore, fibrinogen was found to be longitudinally robust and associated with symptoms, exercise capacity, exacerbation, BODE score, and mortality. A large meta-analysis by Danesh et al. (19) encompassed over 150,000 patients and evaluated over 30 prospective studies. A strong association was found between fibrinogen level and the risk of COPD-specific mortality. Similar data have been reported in separate cohorts (18, 20). Substantial literature confirms the association between fibrinogen levels, exacerbation risks, exacerbation frequencies, and COPD-related hospitalizations.

Other Candidate Biomarkers in COPD

- Magnesium has been implicated in predicting the frequency of COPD exacerbations (21).
- Von Willebrand, microalbuminuria, and fibrinogen levels were found to be increased in acute exacerbations and in patients with COPD compared with those of controls (22). These findings may represent a possible pathophysiological mechanism underlying the increased vascular morbidity of patients with COPD. It may also indirectly detect the endothelial dysfunction as a manifestation of systemic outcomes because of COPD.
- Relatively higher levels of bilirubin were associated with a lower risk of pulmonary disease and all-cause mortality (23). Bilirubin possesses anti-oxidant, anti-inflammatory, and anti-proliferative effects (24).
- Pulmonary and activation-regulated chemokine/CCL-18 is another pneumo protein found in the serum. Similar to CC-16, the PARC/CCl-18 levels were found to be associated with an increased risk of mortality in ECLISPSE; however, a relatively low repeatability index will limit its use.
- The p38 mitogen-activated protein kinase pathway is activated by different extracellular stimuli (in COPD particularly cellular stress and inflammatory cytokines) and plays a role in various cellular responses, including proliferation and apoptosis (25).
- Receptor for advanced glycation end (RAGE) products play a role in COPD pathogenesis and contribute to airway inflammation that is triggered by cigarette smoke. A recently published study suggested a positive feedback involving RAGE and its ligands as an inciting mechanism for tobacco-induced airway inflammation in COPD (26).

ECLIPSE

Substantial literature regarding COPD biomarkers is from ECLIPSE. This large 3-year observational, controlled, multicenter international study defined clinically relevant subtypes of COPD and identified novel biomarkers along with genetic factors. The study produced over 50 original publications and a review summarizing the main biomarker findings (27). ECLIPSE clearly documented COPD heterogeneity and found weak correlations between clinical measurements, health status, functional outcome, and large variability in circulating biomarkers and proteomic features.

ECLIPSE investigators chose to explore 34 protein biomarkers with prior hypotheses implicating pathogenetic value. Each biomarker assay was validated in "the ECLIPSE biomarker cohort" and then explored in the whole study cohort. The associations among biomarkers, age, gender, smoking status, clinical characteristics, and outcomes were investigated. Some of the proteins studied in ECLIPSE are listed in Table 4.

Composite Scores

Unfortunately, single biomarkers may have sufficient confounders to prevent translation to clinical use. Therefore, panels of biomarkers are sometimes able to be more sensitive and specific for research. A panel of six inflammatory biomarkers (WBC, CRP, IL-6, IL-8, TNF-alpha, and fibrinogen) in ECLIPSE demonstrated that the inflammome that was induced by smoking was different from that associated with COPD. In addition, individuals with an inflammation had higher all-cause mortality and more exacerbations compared with patients without an inflammation despite similar pulmonary abnormalities (10). Fewer individuals without COPD (16%) who smoked had persistent systemic inflammation (two or more abnormal biomarkers present at baseline and in 1 year follow-up) versus 30% of the COPD cohort. Mortality was six-times higher in those having an inflammation with double the exacerbation rate.

Perhaps creating a composite biomarker similar to the BODE index using serum biomarkers could serve as a good tool for COPD diagnosis, staging, management, and outcome prediction. An optimal composite biomarker should have components that are independent of each other and that reflect differing aspects of the disease pathogenesis. In a study, the addition of a panel of selected serum biomarkers improved the ability of established clinical variables to predict mortality in COPD (18). However, composite biomarkers are not often accepted by regulatory authorities because additional validation steps are necessary to prove that multiple biomarkers add value to a single biomarker in disease outcomes.

Computed Tomography and COPD

Over the years, computed tomography (CT) has become the most comprehensive imaging modality for lung disease. Concerns exist regarding radiation exposure, high cost, and unnecessary imaging prompting further radiological follow-up, particularly for lung nodules. Nevertheless, the results of CT chest imaging change pulmonary diagnoses in approximately 50% of cases. CT imaging of the chest in COPD also appears to have value. Accurate phenotyping is paramount in COPD because it is a very heterogeneous disorder. Because emphysema is diagnosed by lung biopsy or by CT imaging, studies regarding emphysema progression require CT. The widely used and accepted measure to define emphysema progression on CT imaging is the percentile density at 15% (PD15). This is the Hounsfield Unit in which 15% of the lung is more lucent on the voxel histogram.

PD15 is an accepted biomarker for large multicenter, international studies in AATD confirming the value of augmentation therapy in this rare disease (28). Calibration and following standards of acquisition are extremely important because emphysema calculations are dependent on lung volumes. All longitudinal studies apply a lung volume correction factor to their analysis (29).

Unfortunately, CT density decline was not as robust in the ECLIPSE cohort (30). The COPD Gene study analyzed CT density of emphysema, bronchial wall thickness, and its association with COPD exacerbations. Not surprisingly, the findings were independent of the severity of airflow obstruction (31).

Open-access Biorepository for COPD

A few open-access biorepositories for COPD are now available from worldwide. These are required to provide researchers with biosamples to continue studying this heterogeneous disorder. Many basic science studies use animal models. Although animal models can help pulmonary research, human samples are eventually required to confirm the disease pathways. In the past year, some disease groups have sought biorepositories linked to a registry to accelerate research. Ideally, the biorepository would contain quality blood, cell,

lung, and other samples that are uniformly collected, well annotated, easily accessible to researchers and that are linked to longitudinal clinical phenotyped data (32).

Future Directions

Traditionally, investigators targeted a disease pathway with apriori hypotheses to identify potential new biomarkers. However, the genetic revolution has enabled an integrated analysis of thousands of genes, gene expression signals, and proteins correlated with the clinical outcome of interest. For example, protein microarray platform technology can be useful in the process of biomarker discovery in COPD (33). This gel-free approach is rapid and enables simultaneously efficient studying of multiple proteins.

If the question being asked and the population being studied are specific enough, biomarkers might be discovered without a hypothesis-generating background. The high-risk, high-reward research for biomarkers is hampered by the lack of standardization in data acquisition, processing, and statistical approaches to reduce false discovery rates. This type of study depends on collaborative group science and multiple well-phenotyped disease cohorts to establish consistent results.

Recently, collaborative efforts of the US FDA, COPD Foundation, United States National Heart Lung and Blood Institute, and scientists from both academia and the pharmaceutical industry initiated the COPD Biomarker Qualification Consortium. The overarching purpose of this consortium is to address the problem of drug development tools for COPD by developing biomarkers to serve as regulatory tools in clinical trials.

The COPD Foundation organized two COPD Biomarkers Qualification Workshops in 2010 and 2011. These conferences enabled academia, regulatory bodies, patients, and the pharmaceutical industry to advance the best science for new drug development. Different stakeholders usually have different expectations for biomarkers. For example, financers may want cost-effectiveness, whereas scientists may want the best specificity, sensitivity, and reliability that is linked with a biological credibility (34). The goal of the process is to qualify biomarkers for specific "contexts of use". The ultimate goal is to improve drug development and reduce the time required to develop a new therapeutic intervention with good results.

CONCLUSION

Much more research regarding COPD needs to be conducted to identify and validate biomarkers (35). Although many biomarkers appear to be promising, none has been validated sufficient to guide a clinical practice. The next generation of biomarker research should provide insights into disease pathogenesis through integrated "omics" approaches. Biomarkers may assist in the discovery of pathways in COPD, leading to a better disease phenotyping. The ultimate goal is to enable research to discover novel therapies potentially phenotype specific to allow patient-centered care.

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