Biomarkers, the control panel and personalized COPD medicine

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ABSTRACT
Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease, so its clinical management needs to be personalized as much as possible. ‘Complex’ means that COPD has several components with non-linear dynamic interactions, whereas ‘heterogeneous’ indicates that not all these components are present in all patients or, in a given patient, at all time points. This complexity and heterogeneity explains and justifies the need for personalizing the assessment and treatment of patients with COPD. We propose here that the implementation of a ‘control panel’ will facilitate the deployment of personalized COPD medicine in clinical practice. Such a control panel should provide the practicing clinician complementary and relevant information on treatable clinical characteristics in a single patient at a given time point. For the purpose of this discussion, we consider these variables to be ‘biomarkers’. Which treatable clinical characteristics should the COPD control panel include has not yet been formally validated. The review below suggests and discusses which ones might be considered in the future and should be viewed as a working proposal.

Key words: chronic bronchitis, emphysema, inflammation, network analysis, smoking.

Abbreviations: 6MWD, 6-min walk distance; ADAM19, metallopeptidase domain 19; ADO, age, dyspnoea and obstruction; AGER, advanced glycosylation end product-specific receptor; BICD1, bicaudal D homolog 1; BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnoea and exercise capacity; BPI, body mass index; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; CC16, chemokine (C-C motif) ligand 18 (pulmonary and activation regulated); CHRNA3, cholinergic receptor, nicotinic, alpha 3 (neuronal); CHRNA5, cholinergic receptor, nicotinic, alpha 5 (neuronal); COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; CYP2A6, cytochrome P450, family 2, subfamily A, polypeptide 6; DBH, dopamine beta-hydroxylase (dopamine beta-monooxygenase); EBC, exhaled breath condensate; ECLIPSE, evaluation of COPD longitudinal decline; FAM13A, family with sequence similarity 13, member A; FEV1, forced expiratory volume in 1 s; FFG7, fibroblast growth factor 7; FTO, fat mass and obesity-associated; FVC, forced expiratory capacity; GOLD, global initiative for chronic obstructive lung disease; GWAS, genome-wide association studies; HHIP, hedgehog interacting protein; IL-13, major histocompatibility complex, class I; IC/TLC, inspiratory to total lung capacity ratio; IREB2, iron-responsive element binding protein 2; LABA, long-acting b2 agonists; LAMA, long-acting anti-muscarinic bronchodilators; miRNA, mitochondrial DNA; miRNA, microRNA; mMRG, modified Medical Research Council Dyspnoea Scale; NIH, National Institutes of Health; ncRNA, non-coding RNA; PaO2, arterial oxygen pressure; SCGB1A1, secretoglobin, family 1A, member 1; SFTPD, surfactant protein D; sRAGE, soluble form of receptor for advanced glycation end products; VOC, volatile organic compound; WBC, white blood cell counts.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is the end result of a complex set of interactions between the environment and the genetic background of the individual (Fig. 1). As a result, it is often stated that...
COPD is a complex and heterogeneous disease. Yet, the meaning of the terms ‘complex’ and ‘heterogeneous’ in this setting might not be immediately obvious. In our view, ‘complex’ means that COPD has several components with non-linear dynamic interactions, whereas ‘heterogeneous’ indicates that not all these components are present in all patients or, in a given patient, at all time points. This complexity and heterogeneity explains and justifies the need for personalizing the assessment and treatment of patients with COPD.

It has been proposed that a first step towards personalized COPD medicine is the identification of homogeneous groups of patients (i.e. clinical phenotypes) with similar characteristics and outcomes. This approach (the so-called stratified medicine) is probably correct in a research setting, where the investigation of mechanisms of disease or response to therapy necessarily requires the study of homogeneous groups of patients. However, it may be difficult to implement in the clinic because these clinical phenotypes may overlap in the same patient, and the presence of one does not necessarily exclude the presence of a second (or a third) one. Likewise, the same clinical phenotype could result from different biological mechanisms (i.e. endotypes) (Fig. 1).

An alternative approach for the implementation of personalized COPD medicine in clinical practice is the use of a ‘control panel’ (Fig. 2). ‘This approach proposes to use a number of biological and clinical variables (organized in ‘modules’) that can provide the practicing clinician complementary and relevant information for the proper management of the individual patient, either because of its prognostic implications and/or requirement for specific therapeutic intervention. In other words, the control panel provides information on treatable clinical characteristics in a single patient at a given time point.

These treatable clinical characteristics have not yet been formally validated. The review below discusses which ones might be considered in the future. For the purpose of this discussion, we consider these variables to be ‘biomarkers’. Although biomarkers are generally considered to be substances rather than physiological or imaging measurements, according to the definition endorsed by the National Institutes of Health (NIH) in the USA, a biomarker is ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions’, so we use the term biomarker here in this broader sense (albeit we discuss in greater detail the more traditional ‘biological’ biomarkers). Likewise, we organize the discussion below using the three ‘modules’ proposed originally in the description of the ‘COPD control panel’: severity, activity and impact (Fig. 2).

**SEVERITY MODULE**

The severity of any disease (including COPD) relates to the ‘extent of functional impairment of the target organ(s)’. The ‘severity’ of COPD has been traditionally determined by the degree of airflow limitation (assessed by measuring forced expiratory volume in the 1 s (FEV1)). FEV1 is a good estimate of the pulmonary functional impairment, although other physiological measurements such as the inspiratory capacity (IC) to total lung capacity (TLC) ratio, arterial blood gases and exercise capacity provide complementary information that also reflects the severity of COPD. Importantly, these are ‘treatable traits’ because they can be improved by the use of one or two long-acting bronchodilators, long-term oxygen therapy, chronic non-invasive ventilation and/or rehabilitation, respectively.

More recently, to account for the complexity of the disease, a number of composite indexes have been proposed, including among others the BODE (body mass index (BMI), airflow obstruction, dyspnoea and exercise capacity) and ADO (age, dyspnoea and obstruction). They are also measurements of disease severity and are probably better than the FEV1 in order to establish the prognosis of a given patient. However, in order to guide therapy in clinical practice, they necessarily need to be deconstructed into their original, treatable components.

Finally, although the previously mentioned definition of severity refers to the main target organ (the lungs in the case of COPD) it is also important to consider that comorbidities are extremely frequent in these patients (cardiovascular and metabolic diseases in particular) that they may have a profound impact in their health status and prognosis and that they seem to share molecular pathways with COPD. Hence, although not strictly indicators of the severity of the ‘pulmonary component’ of COPD, we propose that their presence should be noted and treated appropriately, as the GOLD document recommends specifically.

**ACTIVITY MODULE**

The ‘activity of a disease’ (please note that we are not referring here to the ‘activities of daily living’ of the patient) relates to the ‘level of activation of the
biological processes that drive disease progression'.

Although this concept is well established in other diseases (e.g. tuberculosis or rheumatoid arthritis), so far it has not been well defined in COPD. Yet, it is likely that the treatment of a patient with a very ‘active’ disease (as discussed below) should be very different from that of a patient with a ‘stable’ disease. For instance, consider the case of tuberculosis. If your patient suffers ‘active’ tuberculosis, pharmacological treatment for several months would be indicated, whereas if, after appropriate diagnostic assessment, you conclude that he/she has ‘latent’ disease, treatment would not be indicated.

Importantly, activity and severity do not necessarily run in parallel. For instance, consider now the case of rheumatoid arthritis. In the early stages of the disease, activity may be high but severity mild. Under these circumstances, the rheumatologist will likely try to use the most appropriate treatment to reduce the activity of the disease and prevent joint deterioration. By contrast, in advanced disease there may be severe joint deformities but low disease activity due to the spontaneous and/or therapeutically induced down-regulation of the biological mechanisms that caused it. Under these alternative circumstances, the management of the patient is likely to be different. To date, we are not considering these circumstances in the management of our COPD patients.

This is, in part, because we have not really thought carefully enough about this and, in part, because what is/are the most appropriate markers of disease activity in COPD are not resolved. Yet, several ‘clinical’ candidate biomarkers of disease activity in COPD can be conceived. For instance, the rate of FEV₁ decline or the rate of progression of emphysema are obvious candidates, because recent research has shown FEV₁ decline rate (and emphysema progression) varies greatly among patients with COPD. Likewise, given that smoking is the major COPD risk factor, current smoking may also be considered a marker of disease activity. Another potential clinical marker of disease activity may be the frequency of exacerbations because they can occur at any level of airflow limitation. Likewise, unintentional weight loss is associated with poor prognosis in COPD and could therefore be also considered a clinical marker of disease activity. On the other hand, the identification and validation of ‘biological’ biomarkers in COPD has generated a great deal of interest over the past decade or so. Table 1 presents a number of them, as reviewed recently. Main findings can be summarized as follows.

### Cellular biomarkers

Despite that sputum neutrophilia is a relatively stable biomarker in COPD, it does not seem to be a major surrogate of clinical or pathophysiological abnormalities in COPD, hence limiting its potential clinical application. High circulating leukocyte number is weakly associated with frequent exacerbations and mortality both in COPD and in the general population. Other cellular biomarkers, such as the percentage of circulating eosinophils, merit further investigation.

### Protein biomarkers

Plasma fibrinogen is relatively stable over time and it is significantly associated with symptoms, exercise capacity, exacerbation rate, the BODE index and mortality. It is currently being considered a potential candidate for regulatory qualification as a prognostic biomarker. Club-cell 16 (CC16) is weakly associated with lung function decline, emphysema and depression in COPD, and it has been recently reported to have a protective role in COPD. Surfactant protein D (SP-D) was also weakly related with exacerbations and, interestingly, it seems to respond to oral and inhaled corticosteroid
Table 1  Summary of different COPD31 ‘biological’ biomarker studies published using the ECLIPSE database. Reproduced with permission from Faner et al. (2014)32

<table>
<thead>
<tr>
<th>Type of biomarker</th>
<th>Main findings</th>
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<tbody>
<tr>
<td><strong>Cellular biomarkers</strong></td>
<td></td>
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<tr>
<td>Sputum neutrophils</td>
<td>3.5% variability at 1-year follow up33</td>
</tr>
<tr>
<td>Sputum neutrophils</td>
<td>Weak/absent association with FEV1%, SGRQ, emphysema, systemic inflammatory markers, exacerbation frequency or lung function decline33</td>
</tr>
<tr>
<td><strong>Circulating WBC</strong></td>
<td>Associated with persistent systemic inflammation,34 frequent exacerbations28 and mortality35</td>
</tr>
<tr>
<td><strong>Blood protein biomarkers</strong></td>
<td></td>
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<tr>
<td>Fibrinogen</td>
<td>Significantly associated with symptoms, exercise capacity, exacerbation rate and the BODE index.36,38 Currently undergoing a regulatory qualification process32</td>
</tr>
<tr>
<td>CC16</td>
<td>Weakly associated with lung function decline, emphysema and depression23,26,38,39</td>
</tr>
<tr>
<td>SP-D</td>
<td>Weak association with COPD exacerbations29,36 sensitive to treatment with oral and inhaled corticosteroids40</td>
</tr>
<tr>
<td>CCL18 (PARC)</td>
<td>Increased risk of cardiovascular hospitalization or mortality41</td>
</tr>
<tr>
<td>sRAGE</td>
<td>Lower circulating sRAGE levels are associated with emphysema severity, and genetic polymorphisms in the AGER locus are associated with circulating sRAGE levels42</td>
</tr>
<tr>
<td>Inflammome</td>
<td>Patients with persistent systemic inflammation (16%) had higher mortality and exacerbation rate than non-inflamed patients (30%).34 Systemic inflammation was also associated with heart disease, hypertension and diabetes43</td>
</tr>
<tr>
<td>Adipokines</td>
<td>Leptin and adiponectin levels were (+) and (−) related to CRP, respectively; BMI and gender were the strongest determinants of both adipokines44</td>
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<tr>
<td>Vitamin D</td>
<td>Low levels of vitamin D were related to emphysema, 6MWD, airways reactivity and CC-16 levels45</td>
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<tr>
<td><strong>Gene studies</strong></td>
<td></td>
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<tr>
<td>Smoking history</td>
<td>Suggestive associations identified for age at smoking initiation (chromosomes 2q21 and 6p21), lifetime mean number of cigarettes per day (CHRNA3/CHRNAS and CYP2A6), current number of cigarettes smoked per day (CYP2A6) and smoking cessation (DBH)46</td>
</tr>
<tr>
<td>COPD susceptibility</td>
<td>Several genomic regions associated with COPD susceptibility (FAM13A, HHIP, CHRNA3/CHRNAS/IREB2 and a region on chromosome 19). Other (ADAM19, FGF7, and SP-D) need replication in other populations</td>
</tr>
<tr>
<td>COPD subtypes</td>
<td>CHRNA3/5 significantly associated with pack-years, emphysema and airflow limitation;47 HHIP not associated with pack-years, but related FEV1/FVC, lean body mass and exacerbations47</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Borderline genome-wide significant association with BICD116</td>
</tr>
<tr>
<td>Cachexia</td>
<td>Suggestive association of BMI and FFMI with FTO gene.49 The latter also related to FEV149</td>
</tr>
<tr>
<td>Blood biomarkers</td>
<td>Genome-wide significant associations identified only for CC16 (chromosome 11) and SP-D (SFTPD and SNP on chromosomes 6 and 16)50</td>
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<tr>
<td><strong>Sputum transcriptomics</strong></td>
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<tr>
<td>Airflow limitation</td>
<td>277 genes associated with the severity of airflow limitation (GOLD grade)51</td>
</tr>
<tr>
<td>Emphysema</td>
<td>198 genes associated with the presence of emphysema51</td>
</tr>
<tr>
<td>Blood biomarkers</td>
<td>SNP affecting circulating CC16 protein levels were significantly associated with sputum mRNA expression of SCGB1A1, the CC16 coding gene on chromosome 1150</td>
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<tr>
<td>COPD susceptibility</td>
<td>An integrative genomics approach located potential functional variants in two genes located within a COPD GWAS locus on chromosome 15 (CHRNA5 and IREB2) and one locus in the HLA-C region on chromosome 652</td>
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<tr>
<td><strong>Serum metabolomics</strong></td>
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<tr>
<td>Serum profile</td>
<td>Results indicate that:53,54 (i) there is increased protein turnover in all COPD patients; (ii) increased protein degradation in individuals with emphysema and cachexia</td>
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<tr>
<td>Exhaled breath condensate pH</td>
<td>Lower pH in COPD and smoking controls, but not related to FEV1, or sputum leukocyte counts, and not responsive to steroid treatment55</td>
</tr>
<tr>
<td>Adenosine/purines</td>
<td>Increased concentrations in COPD patients, and adenosine levels correlated with FEV156</td>
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6MWD, 6-min walk distance; ADAM19, ADAM metallopeptidase domain 19; AGER, advanced glycosylation end product-specific receptor; BICD1, bicaudal D homolog 1 (Drosophila); BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnoea and exercise capacity; CC16, Club-cell 16; CCL18, chemokine (C-C motif) ligand 18 (pulmonary and activation regulated); CHRNA3, cholinergic receptor, nicotinic, alpha 3 (neuronal); CHRNA5, cholinergic receptor, nicotinic, alpha 5 (neuronal); COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CYP2A6, cytochrome P450, family 2, subfamily A, polypeptide 6; DBH, dopamine beta-hydroxylase (dopamine beta-monooxygenase); ECLIPSE, evaluation of COPD longituinde to identify predictive surrogate end-points; FAM13A, family with sequence similarity 13, member A; FEV1, forced expiratory volume in 1 s; FFMI, the fat-free mass index; FTO, fat mass and obesity-associated; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; GWAS, genome-wide association studies; HHIP, hedgehog interacting protein; HLA-C, major histocompatibility complex, class I, C; IREB2, iron-responsive element binding protein 2; SCGB1A1, secretoglobin, family 1A, member 1; SFTPD, surfactant protein D; SGRQ, St George’s Respiratory; SNP, single nucleotide polymorphisms; SP-D, surfactant protein D; sRAGE, soluble receptor for advanced glycation end products; WBC, whole blood counts.
and blood CC-16 levels. Finally, lower circulating levels of vitamin D in blood were related to the increased risk of cardiovascular hospitalization and treatment. Serum CCL18 was associated with increased risk of cardiovascular hospitalization and mortality. A combined panel (‘inflammome’ of four ‘biological’ biomarkers (circulating leukocytes, C-reactive protein, fibrinogen and interleukin-6) identified a group of COPD patients in the evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE) study with persistent inflammation (16% of the cohort studied) who had a six times higher mortality during 3-year follow up as compared with those who were persistently non-inflamed (30% of the cohort studied). The consideration of these biomarkers improved the ability of well-established clinical variables to predict mortality in COPD. These results are in keeping with those of other studies that have also reported an association between systemic inflammation and heart disease, hypertension and diabetes. The two main adipokines (leptin and adiponectin) appear to be abnormally regulated in COPD and related to systemic inflammation, BMI and gender. In ECLIPSE, low levels of vitamin D in blood were related to the presence of emphysema, exercise capacity (as determined by the 6-min walk distance), airways reactivity and blood CC-16 levels. Finally, lower circulating levels of the soluble receptor for advanced glycation end products (sRAGE) were associated with emphysema severity and a genetic polymorphisms in the advanced glycosylation end product-specific receptor (AGER) locus (the gene coding for RAGE). In summary, several systemic ‘biological’ biomarkers, alone or in combination, have potential relevance for the enrichment of clinical trials aimed at validating future therapeutic interventions.

Genetic biomarkers

As Figure 1 illustrates, COPD is the end result of complex gene–environment interactions. It is not surprising, therefore, that over the last several years there had been a great interest in studying and understanding the genetics of COPD (Table 1). These studies have actually investigated the genetic basis of a number of different but relevant aspects of COPD, such as its relationship with smoking habits (the main risk of COPD), the susceptibility to develop the disease among smokers (only a proportion of them develop the disease) and/or the phenotypic heterogeneity of COPD. Main results (Table 1) are discussed below.

Genes associated with smoking

Genome-wide association studies (GWAS) in four independent cohorts including more than 3000 ever-smoking COPD patients failed to definitely identify genomic regions (as assessed by single nucleotide polymorphisms (SNP) analysis) associated with smoking intensity or behaviour. However, suggestive association were found for several loci associated with age at smoking initiation (chromosome 2q21 and chromosome 6p21), lifetime mean number of cigarettes per day (cholinergic receptor, nicotinic, alpha 3 (neuronal)/cholinergic receptor, nicotinic, alpha 5 (neuronal) and cytochrome P450, family 2, subfamily A, polypeptide 6), current number of cigarettes smoked per day (CYP2A6) and smoking cessation (SNP rs3025343 in DBH locus), strongly supporting a genetic basis for smoking initiation, maintenance and cessation.

Genes associated with susceptibility to develop COPD in smokers

Several genomic regions are strongly associated with the risk of developing COPD among smokers. These include family with sequence similarity 13, member A, hedgehog interacting protein, cholinergic receptor, nicotinic, alpha 3 (neuronal)/cholinergic receptor, nicotinic, alpha 5 (neuronal), iron-responsive element binding protein 2 (FAM13A, HHIP, CHRNA3/CHRNA5/IREB2) and a region on chromosome 19. Other genomic regions, including ADAM19, FGF7 and SP-D, require replication in other studies.

Genes associated with different COPD subtypes

The potential genetic contributions to the phenotypic heterogeneity of COPD are unclear, but recent studies are beginning to illuminate them although, admittedly, many reported associations require replication in additional cohorts. With this caveat in mind, CHRNA3/5 has been associated with cumulative smoking exposure (pack-years), presence of emphysema and severity of airflow limitation. HHIP is not associated with pack-years, but it is related to the FEV1/forced vital capacity ratio, with body composition and COPD exacerbations in ECLIPSE. There is a borderline genome-wide significant association between the presence of bicaudal D homolog 1 (Drosophila) (BICD1) SNP and emphysema. Given that variants in BICD1 are associated with telomere length, this suggests that accelerated ageing can be a potential pathogenic mechanism of emphysema. A SNP (rs8050136) located in the first intron of the fat mass and obesity-associated (FTO) gene is associated with the BMI and the fat-free mass index (FFMI) and, interestingly, with the severity of airflow limitation. Likewise, several genetic determinants of the circulating levels of the protein biomarkers discussed above have also been identified. Significant genome-wide significant associations were identified for the blood-stream levels of CC16 (SCGB1A1 on chromosome 11, and another one located more than 20 Mb away on the same chromosome) and surfactant protein D (SP-D) (several SNP near its coding gene (SFTPD)). In addition, SNP on chromosomes 6 and 16 also demonstrated genome-wide significant associations with SP-D serum levels. Finally, very recently, it has been shown that COPD patients with different b2-adrenergic receptor (ADRB2) polymorphisms may respond differently (at least in terms of reduction of exacerbations) to treatment with long-acting b2 agonists (LABA) or long-acting anti-muscarinic bronchodilators (LAMA). If confirmed prospectively, this may have implications for the personalized treatment of COPD. Likewise, resistance to steroids has been shown to be associated with activation of a number of different kinases, which in turn may be the consequence of phosphatase gene down-regulation.
Epigenetic biomarkers
Epigenetic biomarkers, including histone methylation and miRNAs, have also been investigated in COPD. It has been reported that gene promoters are hypo-methylated in COPD patients as compared with non-smokers or smokers with normal spirometry. Likewise, both in lung tissue and plasma of COPD patients, expression changes in specific miRNAs acting on inflammatory mediators have been also described, albeit clearly more work is required in this area to validate and contextualize these observations.

Sputum and systemic transcriptomic biomarkers
Integrative genomics approach of sputum transcriptomics has the potential to identify potential COPD susceptibility loci. As shown in Table 1, sputum transcriptomics studies in the ECLIPSE cohort identified: (i) 277 genes associated with airflow limitation and 198 with emphysema; and, (ii) an association of mRNA expression of CC16 and several SNP influencing its circulating levels. Similarly, a gene expression signature in frequent exacerbators has been reported in circulating leukocytes, which may be useful to help in understanding the molecular pathogenesis of COPD exacerbations.

Serum metabolic biomarkers
Several ECLIPSE studies investigated the serum metabolomic profile of patients with COPD (Table 1). Main results indicate that: (i) there is increased protein turnover in all COPD patients, particularly in those with emphysema and cachexia; and, (ii) whereas there are some promising metabolomic signals detected in the serum of certain subtypes of COPD patients, replication in other cohorts is required.

Exhaled breath condensate and electronic nose biomarkers
Despite initial enthusiasm for the exhaled breath condensate (EBC) as a potential source of valid COPD biomarkers, results have been mostly disappointing. Except for the pH value of EBC, which was significantly lower in patients with COPD and smoking controls than in non-smokers (albeit not related to airflow limitation or sputum neutrophils, using conventional methodology, investigators in the ECLIPSE study were not able to reliably measure protein biomarkers in EBC. They found, however, that the relative concentrations of adenosine and adenosine monophosphate were elevated in COPD patients, the former being correlated with airflow limitation severity.

On the other hand, exhaled breath contains a complex mixture of volatile organic compounds (VOC), some of which could potentially represent biomarkers for lung diseases. In fact, very recent studies suggest that an electronic nose, a novel non-invasive technology capable of distinguishing VOC breath prints can identify the presence of airway bacterial colonization in clinically stable patients with COPD.

IMPACT MODULE
The impact of any disease depends on how the patient perceives both the severity and the activity of the disease (as defined above) and how the patient modifies the ‘activities of daily living’ (please note that we are not talking here about the ‘biological activity’ of the disease, discussed above). This perception varies substantially in patients with asthma and is therefore likely to do the same in patients with COPD, although this has not been formally demonstrated to our knowledge. On the contrary, somewhat naively, we have traditionally assumed that mild COPD (as assessed by the severity of airflow limitation) has a minor impact on the patient, whereas the impact is much greater in severe disease. Yet, the systematic use of instruments that measure such an impact, like the St George’s Respiratory Questionnaire, has clearly shown that this assumption was wrong, because the relationship between FEV1 and health status is poor and individual variability is enormous (Fig. 3). In fact, it is precisely because of this variability that it is recommended in the GOLD 2011 document to determine the level of symptoms as a key component of the current assessment of COPD patients. Similar arguments can be applied to other relevant domains of COPD, such as exacerbations because a number of patients suffer frequent exacerbations, other apparently have ‘unreported exacerbations’ and others have severely impaired lung function and, nevertheless, do not apparently have exacerbations. All in all, these observations suggest that as described in asthma, it is likely that the perception of symptoms vary in different COPD patients. This hypothesis deserves specific research because of its potential therapeutic implications, particularly in frequent exacerbators. It is also worth mentioning that activities of daily living are impaired in some, but not all, patients with COPD, and that objectively measured physical activity is a strong predictor of all-cause mortality in patients with COPD. Considering all of the above arguments, we propose the need of an impact module in the control panel (Fig. 2), albeit what are the optimal questionnaires and activity monitor to use requires validation.

TOWARDS PERSONALIZED COPD MEDICINE: THE CONTROL PANEL AS A WAY TO MOVE FORWARD
A recent symposium held in Barcelona reviewed the critical steps required to move forward towards personalized respiratory medicine. To address the biological complexity of COPD (Fig. 1), these include, among others, the use of network analysis and an extremely close collaboration between basic, clinical and computer scientists. The potential for
translation of all this new knowledge to clinical practice is illustrated in Figure 4 (right column). A better understanding of the genetic level will identify (as discussed above) genetic markers that can help clinicians to better determine the future risk of a given patient (risk of deterioration of the disease and/or development of complications and/or response to a given therapy). The biological level will eventually provide relevant information on ‘biological’ markers (also as discussed above) that can help clinicians in their assessment and monitoring of a given patient. A deeper understanding of the relationships between different comorbidities at the clinical level can facilitate better strategies for integrated care, the development of so-called Clinical Decision Support Systems (CDSS), a generic name for the COPD control panel discussed here and, eventually, the development of a network of guidelines that facilitate the assessment and treatment of COPD patients. Finally, the ‘exposome’ (a term that describes the ‘totality of human environmental exposures, from conception onwards’) also forms a complex network that merits further research and, eventually, intervention.

We propose that the ‘COPD control panel’ provides a way to visualize the complexity of COPD and that the combined assessment of the severity, impact and

**Figure 3** The relationship between the severity of airflow limitation (forced expiratory volume in 1 s, FEV₁) and health status (as assessed by St George Respiratory Questionnaire) is statistically significant at the population level but individual variability is enormous, indicating that health status cannot be predicted from the FEV₁ value in a single patient. Reproduced with permission from Agusti et al. (2010). For further explanations, see text.

**Figure 4** Diagram illustrating the network relationships and different levels of complexity of chronic obstructive pulmonary disease (COPD; environment, clinical, biological and genetic), as well as the potential outcomes of clinical relevance (right-hand column) that each of these levels can be envisaged to deliver when properly understood. Each level only shows some of its potential components in order to illustrate the concept (the diagram is not intended to be comprehensive). Likewise, links between the different elements of the network are drawn for illustrative purposes also and do not necessarily reflect evidence-based relationships. For further explanations, see text. CVD, cardiovascular disease; GWAS, genome-wide association studies; miDNA, mitochondrial DNA; miRNA, microRNA; ncRNA, non-coding RNA. Reproduced with permission from Agusti and Vestbo (2011). For further explanations, see text.
activity can best inform the physician on the most appropriate management strategies for an individual patient based on the ‘treatable traits’ present in this particular patient at this specific time point. Need-toless to say that this proposal needs prospective research and validation because there are a very large number of possible factors that can be included into this model of disease characterization with the potential to inform clinical care. Hence, it is important to avoid redundancy and duplication so such a comprehensive system will eventually be cut down into its critical components. To this end, systems biology, network analysis and computer modellers are likely to be of great use. Importantly, the control panel can be customized to the needs of the patient and the resources available locally (e.g. rural vs urban health care centres; primary vs specialized care).

CONCLUSIONS

There is no such thing as ‘the’ COPD biomarker. Different biomarkers will be needed to assess different components of this complex and heterogeneous disease. Combining them in a ‘control panel’ has the potential to facilitate their translation to clinical practice. By doing so, this strategy has the potential to move COPD management towards personalized (precision) medicine.

Acknowledgements

The authors thank Dr. W. MacNee (Professor of Respiratory and Environmental Medicine/Honorary Consultant Physician, University of Edinburgh, MRC Centre for Inflammation Research) and the numerous colleagues who, over the past few years, have contributed with their ideas and criticisms to the development and refinement of the concept of a ‘COPD control panel’. This study was supported, in part, by Instituto de Salud Carlos III (PI12/01117), Recercaixa-2012 (AA084096), SEPAR (PI065/2013, PI192/2012), FUCAP 2012 and SAF-2011-26908.

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APPENDIX I: GLOSSARY OF TERMS

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<th>Term</th>
<th>Definition</th>
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<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Variables providing relevant information on (treatable) clinical characteristics.</td>
</tr>
<tr>
<td>Clinical phenotypes</td>
<td>Groups of patients with similar characteristics and outcomes (stratified medicine).</td>
</tr>
<tr>
<td>Control panel</td>
<td>Biological and clinical variables that provide complementary and relevant information for the management of the individual patient.</td>
</tr>
<tr>
<td>Modules</td>
<td>Group of related variables. Treatable traits related to the extent of functional impairment of the lung and the presence of comorbidities.</td>
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<tr>
<td>Severity module</td>
<td>Treatable traits related to the level of activation of the biological processes that drive disease progression, including clinical and biological biomarkers.</td>
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<tr>
<td>Impact module</td>
<td>Patient’s perception of severity and activity modules.</td>
</tr>
<tr>
<td>Exposome</td>
<td>Totality of human environmental exposures, from conception onwards.</td>
</tr>
</tbody>
</table>