From systemic effects of COPD to COPD as pulmonary component of multimorbidity

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) was originally defined as a chronic disease of the airways due to an abnormal inflammatory response to tobacco smoking. However, although primarily a pulmonary disease, the systemic consequences of COPD have been subject of intensive research for more than two decades. Extrapulmonary manifestations and/or comorbidities are invariably present in COPD and contribute significantly to morbidity and mortality. These observations warrant a strategy in which COPD should be seen as the pulmonary component of chronic multimorbidity that develops in a patient in response to a spectrum of risk factors. Specific multimorbidity combinations are associated with specific COPD phenotypes, suggesting that lung and other organ disease trajectories are entangled from an early disease state onwards. The management of the patient with multimorbid COPD should include an active search for the most impactful comorbidities and a patient-tailored multidisciplinary shared-decision treatment plan embedded in clinical pathways with supportive informatics. (BRN Rev. 2020;6(2):161-78)

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INTRODUCTION AND HISTORICAL PERSPECTIVE

Approximately 20 years ago, Alvar Agustí suggested moving away from the concept of chronic obstructive pulmonary disease (COPD) as just a pulmonary disease characterised by irreversible airflow limitation due to chronic bronchitis and/or emphysema, and rather view it as a pulmonary disease with systemic effects due to the consequences of an excessive pulmonary inflammatory response to tobacco smoking. The theory was that the pulmonary inflammation was not only causing emphysema and bronchitis but, being associated with systemic inflammation, might be responsible for the simultaneous development of systemic effects, most notably the loss of skeletal muscle mass. Thus, the suggestion was that smoking could cause pulmonary inflammation and that the spill-over of this inflammation could have systemic consequences.

Several years later, Fabbri and Rabe further developed this concept and suggested that tobacco smoking could cause not only pulmonary inflammation but simultaneous systemic inflammation, thus directly causing the various chronic diseases, including the cardiovascular and metabolic diseases, as well as cancer, that often occur together with COPD. Similarly, smokers with non-pulmonary chronic diseases are at increased risk of developing COPD.

Today, we know that the concept of systemic inflammation in COPD and its association with comorbidities is much more complex. Indeed, although systemic inflammation is seen in patients with COPD as well as in those with cardiovascular and metabolic diseases, including diabetes, the causative mechanism has not been established. There are a number of arguments for the absence of a unifying role of systemic inflammation in COPD and its multimorbid spectrum. First, Agustí et al. showed that persistent systemic inflammation (defined as repeatedly increased markers of inflammation with a one-year interval) was only present in 16% of patients with COPD in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort, with persistent systemic inflammation detectable in only a minority of those with moderate-to-severe disease. Also, within COPD, multiple studies have shown a lack of association between serum inflammatory markers and, for example, the presence of cardiovascular disease. Furthermore, one study in patients with stable COPD found no association between pulmonary and systemic inflammation, challenging the theory that inflammation is generated in the lungs and spills over to the blood to induce pathology in other organs.

Despite this, comorbidities are the rule rather than the exception in COPD. Furthermore, the presence of comorbidities has a negative impact on health care utilisation, quality of life and survival in patients with COPD. Divo et al. showed that some of the comorbidities of COPD were tightly linked to the increased risk of death, and developed the concept of a “comorbidome.” The high level of underdiagnosis of multiple comorbidities in COPD is therefore worrying. In this context, Vanfleteren et al. showed that the frequency of comorbidities of COPD depends on whether they are actively searched for, or are just assessed through medical records. This highlights the importance of a structured and
active search for the most common comorbidities as, although they are highly prevalent and impactful, they remain commonly undiagnosed. Indeed, the prevalence of comorbidities in COPD depends on the definition, method of assessment and population studied (Fig. 2)\textsuperscript{12–21}.

Comorbidity describes the burden of illness co-existing with a particular disease of interest. The term multimorbidity is commonly understood to be the coexistence of multiple health conditions in an individual\textsuperscript{22}. Given that COPD is almost invariably associated with comorbidities, COPD should be considered as the pulmonary component of multimorbidity. Indeed, Vanfleteren previously described COPD as COmorbidities with Pulmonary Disease\textsuperscript{23}. This concept, which can be applied to many chronic diseases, has been clearly emphasised in the first guideline on multimorbidity, published by the United
Kingdom National Institute for Health and Care Excellence (NICE) in 2016 \(^{24-26}\). Since the complex interactions between various chronic conditions obviously cannot be determined from a simple count of conditions, NICE suggests a pragmatic definition of multimorbidity as “people with multiple conditions where these present significant problems to everyday functioning or where the management of their care has become burdensome to the patient and/or involves a number of services working in an uncoordinated way”. From this perspective, the problems faced by patients may be due to the severity or nature of their chronic conditions but may also relate to the fragmented organisation of healthcare or a combination thereof, which is particularly relevant for patients with COPD, resulting in increasing complexity of care needs and impact (Fig. 3).

The recognition of the importance of co- and multimorbidity in patients with a chronic respiratory diagnosis followed the development of similar concepts in other chronic diseases. This highlighted the increasing importance and complexity of multimorbidity, and its impact on medicine, health systems, prevention and management \(^{27-33}\). The increased lifespan of the population has led to a marked increase in the prevalence of elderly patients with multiple concomitant chronic illnesses, estimated as a mean of 2.6 comorbidities per person in the general population aged > 65 years and

![Diagram](image-url)
3.6 in those > 85 years\textsuperscript{27}, rising to > 7 per person in hospitalised patients > 75 years of age\textsuperscript{27,34}.

### COMORBIDITIES OF COPD

As previously mentioned, although the lung is usually the primary target organ in COPD, smoking greatly affects other organs since tobacco smoke exposure leads to generalised endothelial injury in multiple organ systems\textsuperscript{35–38}, thus resulting in coincident chronic injury to different organs. It is possible that in patients with COPD, changes caused by (or linked to) COPD \textit{per se} (such as hypoxaemia, chronic systemic inflammation, and increased oxidative stress levels) contribute to organ injury through endothelial injury\textsuperscript{39,40}. Some of these changes arise independently of COPD, whereas others may be causally related, either with shared risk factors or by one disease increasing the risk or compounding the severity of the other. For example, pulmonary hypertension and right heart failure (HF) might be the consequence of severe COPD and hypoxia\textsuperscript{41}, and a \textit{post-hoc} analysis of the Study to Understand Mortality and Morbidity in COPD (SUMMIT) showed a ten-fold increased risk of cardiovascular incidence after a hospitalisation for an exacerbation of COPD\textsuperscript{42}. It is possible that features of COPD are shared with other diseases, and as such represent a mechanism linking COPD with some of its
comorbidities\textsuperscript{2,3,30}. The most frequent chronic diseases that are more prevalent in patients with COPD, and that have an impact on severity and prognosis are listed in Table 1.

The prevalence and impact of these chronic conditions have been reviewed in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document\textsuperscript{43}, in review articles\textsuperscript{44–47} and a monograph\textsuperscript{48}. All these documents highlight that concomitant chronic diseases are often misdiagnosed or undiagnosed in patients with COPD – and are thus untreated.

This concept was firstly reported for chronic HF by Rutten et al. 15 years ago, who found 20.5\% of comorbid undiagnosed chronic HF in patients with COPD\textsuperscript{49}; similar results have been observed in other cohorts\textsuperscript{10,50,51}.

Whether or not COPD and comorbid diseases are related, management of patients with COPD must include identification and treatment of comorbidities. Importantly, comorbidities with symptoms that are also associated with COPD may be overlooked, including HF and lung cancer (breathlessness), depression,

\begin{table}
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Cardiovascular diseases} & \textbf{Chronic respiratory diseases} \\
\hline
Hypertension & Asthma \\
Chronic heart failure & Bronchiectasis \\
Ischaemic heart diseases & Obstructive sleep disorders \\
Arrhythmias & Lung cancer \\
Peripheral artery disease & Interstitial lung diseases \\
Stroke and transient cerebrovascular ischaemia & Pulmonary hypertension \\
Thromboembolism & Tuberculosis \\
\hline
\textbf{Metabolic diseases} & \textbf{Endocrine diseases} \\
\hline
Metabolic syndrome & Diabetes \\
Obesity & Osteoporosis \\
Nutritional disorders & Hypothyroidism \\
\hline
\textbf{Central nervous system disorders} & \textbf{Gastrointestinal diseases} \\
\hline
Respiratory disorders during sleep & Gastrooesophageal reflux \\
Anxiety and depression & Inflammatory bowel diseases \\
Psychiatric diseases & Chronic liver diseases \\
Cognitive impairment & \\
Degenerative disorders & \\
\hline
\textbf{Kidney/genitourinary} & \textbf{Haematological disorders} \\
\hline
Chronic kidney failure & Anaemia \\
Benign prostatic hypertrophy & \\
Erectile dysfunction & \\
\hline
\end{tabular}
\caption{Chronic diseases that have been reported to be more prevalent in patients with COPD, and that have an impact on severity and prognosis.}
\end{table}
(fatigue and reduced physical activity), and sleep disorders (fatigue)\textsuperscript{52}. In addition, comorbidities are common at any severity of COPD\textsuperscript{53}, and the differential diagnosis can often be difficult. For example, in a patient with both COPD and HF, an exacerbation of COPD may be accompanied by worsening of HF or vice versa\textsuperscript{54,55}.

**COPD as comorbidity of other frequent chronic diseases**

Although COPD is negatively impacted by multiple comorbid diseases, COPD itself is one of the most important comorbid conditions adversely impacting the outcome of other disorders. For example, patients hospitalised with congestive HF or undergoing cardiac procedures such as coronary artery bypass grafting have greater morbidity and mortality when COPD is present compared to when it is absent\textsuperscript{56}. In addition, patients with COPD have greater mortality after hospitalisation for hip fracture, with 1-year mortality 3–5 times greater in individuals with COPD compared to controls\textsuperscript{57}. Due to the aforementioned mechanisms, patients with COPD are at increased risk of a range of chronic conditions, including cardiovascular disease, with reduced lung function independently associated with an increased risk of chronic HF, ischaemic heart disease (IHD), myocardial infarction (MI), atrial fibrillation (AF), peripheral artery disease, and stroke\textsuperscript{56}.

COPD is frequent and often undiagnosed (and hence untreated) among patients with chronic HF, at rates of 13 to 39\%\textsuperscript{56}. Moreover, COPD is associated with higher mortality in patients with chronic HF\textsuperscript{58}. Similarly, the prevalence of COPD is high among patients with established IHD, but, as in chronic HF, is grossly underdiagnosed\textsuperscript{56,59}. In the largest study to date, among patients undergoing percutaneous coronary intervention, those with concomitant COPD had a 30\% increased risk of death and 20\% higher rate of repeat revascularisation at one year compared with patients with IHD who did not have comorbid COPD\textsuperscript{60}. COPD prevalence estimates in patients with AF ranges from 10 to 15\%, reaching 23\% in patients older than 65 years\textsuperscript{56}. As always, the prevalence of COPD in patients with AF varies widely depending on the population studied\textsuperscript{61}.

Systemic arterial hypertension is highly prevalent in elderly populations\textsuperscript{62} and is possibly the most prevalent comorbidity of COPD. Indeed, while it is well known that arterial hypertension occurs in more than 50\% of patients with COPD who are diagnosed at a primary health care level, the prevalence of COPD among patients with arterial hypertension, a disease often diagnosed and managed by primary health care providers, has been poorly investigated. In one study, the prevalence of airflow limitation in a group of patients with arterial hypertension identified at the primary care level was 12–17\%\textsuperscript{63}.

Although both prevalence and incidence of stroke are increased in patients with COPD, the weight of evidence does not support the hypothesis that COPD is an independent risk factor for stroke. The possibility remains that COPD is causal in certain subsets of patients with COPD and for certain stroke subtypes\textsuperscript{64}. However, even if little is known about the prevalence and impact of COPD in patients with stroke, patients with COPD have a significantly
higher risk of cerebral microbleeds (even after excluding those with a history of stroke)\textsuperscript{65}, which could, in turn, increase the risk and severity of haemorrhagic stroke.

Comorbid obesity or metabolic syndrome are common in COPD\textsuperscript{66}. A link between metabolic syndrome and lung disease has been observed in several cross-sectional and longitudinal studies\textsuperscript{67–70}. However, the recognition that the metabolic syndrome affects the lung is relatively new. Individual components of metabolic syndrome have been independently associated with changes in pulmonary function or lung disease\textsuperscript{71}. There is, however, uncertainty as to the relative contribution of each metabolic factor, and it is unclear how much of the lung effects of the metabolic syndrome occur independently of obesity. Despite these epidemiological limitations, the proposed mechanistic pathways strongly suggest that this association is likely to be causal\textsuperscript{71}.

Increased prevalence of airflow limitation and/or COPD have been reported also in patients with the human immunodeficiency virus\textsuperscript{72}, chronic kidney disease\textsuperscript{45}, rheumatoid arthritis\textsuperscript{73}, and psoriasis\textsuperscript{74}.

FROM LUNG FUNCTION TO MULTIMORBIDITY TRAJECTORIES IN COPD

Since the pivotal paper of Lange et al. on lung function trajectories leading to COPD\textsuperscript{75}, there has been increasing interest in lung function development and its early determinants. In these analyses, approximately half of COPD cases were in those with low maximally attained lung function during early adulthood, demonstrating that accelerated decline of forced expiratory volume in one second (FEV\textsubscript{1}) is not needed for development of COPD\textsuperscript{75}. These findings have been confirmed in several longitudinal studies\textsuperscript{76,77}. A normal lung function trajectory throughout life has three phases: a growth phase from birth to early adulthood; a plateau from around 20 years of age; and decline resulting from normal ageing of the lungs. All these phases can be altered by environmental, clinical and genetic factors. A recent review pointed to the fact that some of the trajectories may have substantial implications for morbidity and mortality\textsuperscript{76}. Indeed, Agustí et al. showed that low lung function in early adulthood was associated with higher incidence of respiratory, cardiovascular, and metabolic diseases later in life\textsuperscript{78}. This interesting study gives fuel to the hypothesis that abnormal lung function development, or the aetiology behind it, influences development of diseases in other organ systems. These findings were also supported by another observational study, where low FEV\textsubscript{1} in young adulthood predicted the risk of premature cardiovascular mortality\textsuperscript{79}. The causative mechanisms behind these associations remain to be elucidated.

Previous studies have shown that in utero and early life factors, including low birth weight and alterations in insulin response\textsuperscript{81,82}, and abnormal acquisition of body fat and peak bone mass\textsuperscript{83}, may influence the development of comorbidities later in life. Low attained lung function in childhood and adolescence may affect exercise capacity and cardiovascular fitness, which are themselves risk factors for development of comorbid diseases later in life\textsuperscript{84}. Furthermore, established risk factors for disease such as tobacco smoking, ageing and
sedentary lifestyle probably play an important role in both suboptimal lung function trajectories and development of other diseases. It is clear that patients with COPD therefore follow not only a lung function trajectory, but also a trajectory of multimorbidity. This concept has been described by Hu et al. (Fig. 4)\(^80\). Patients will follow trajectories in the multimorbidity space during their lifetime as they receive new diagnoses or are cured or treated for other diseases. Germline variation, somatic mutations and environmental effects can influence such transitions, and can be either detrimental or protective. Environmental effects can include drugs, changes in lifestyle and exposure to a pathogen.\(^80\)

In patients with COPD, the co-occurrence of different comorbidities have shown not to be random but seem to cluster in subgroups. Some of these subgroups are common, and so might even be characteristics of specific COPD phenotypes, in which the pulmonary phenotype might also be different. Obesity, insulin resistance, and different disease expressions of atherosclerosis are associated with less severe COPD, whereas low body-weight, muscle wasting, osteoporosis, and arterial stiffness are linked to the emphysematous phenotype. Therefore, it is crucial to understand the underlying biology, i.e. the endotypes or subtypes of a clinical disorder defined by a distinct pathophysiological mechanism that relate to clinical phenotypes.
of COPD (characterised by specific constellations of comorbidities) as well as how the different organ disease trajectories interact in the context of multimorbidity (Fig. 5)\textsuperscript{30}.

Endothelial dysfunction and pulmonary hypertension (which is a major cause of morbidity and a predictor of mortality in COPD\textsuperscript{89}), may explain some of the clustering tendency of COPD and cardiovascular disease. Interestingly, vascular changes in COPD have also found to be present in mild and early cases, indicating that this could be an early marker of certain COPD phenotypes\textsuperscript{90}. Whether this is caused by shared risk factors or a common underlying disease mechanism remains uncertain. Interestingly, emerging evidence surrounding body composition and fat distribution, circulating levels of adipokines such as leptin and adiponectin, and their influence on lung function trajectories remains an interesting field for further studies\textsuperscript{91}.

COPD has been viewed as a disease of early ageing. The main hallmarks of ageing include alterations in transcription, metabolism and cellular processes\textsuperscript{92}, and it is possible that, in susceptible individuals, premature or rapid ageing could influence the development of both lung function decline and other
comorbidities. Alterations of developmental pathways including Notch, sonic hedgehog and Wnt signalling are found to be susceptibility factors for COPD through the regulation of stem cells\textsuperscript{89}. Altered transcription, including telomeric attrition, may be more predominant in certain COPD phenotypes; however, a recent study found that accelerated ageing was present across comorbidity clusters in COPD, although the study might have been underpowered\textsuperscript{93}.

The ability to identify individuals at risk of developing low maximally attained lung function early in life may provide an opportunity for early intervention and the prevention of the development of not only COPD but also multimorbidity.

**PHARMACOLOGICAL AND NONPHARMACOLOGICAL MANAGEMENT OF COPD AND CONCOMITANT CHRONIC DISEASES**

Twenty-five percent of the UK and US populations have chronic multimorbidity, with the prevalence increasing to at least two thirds in those over 65 years\textsuperscript{31}. The increasing prevalence of multimorbidity is a major challenge to all health-care systems because these patients are heavy users of services. In the US, people with multimorbidity account for more than two-thirds of total health spending\textsuperscript{31}.

The approach to the pharmacological treatment of patients with COPD and concomitant chronic diseases has so far been to treat the individual diseases according to separate guidelines, with the simple message of, for example, treating each disease in patients with COPD as you would treat that disease in patients without COPD\textsuperscript{43}. This approach is the only one possible according to evidence-based medicine, as it is supported by data from randomised clinical trials that have typically been conducted without considering concomitant chronic diseases – and often excluding patients with more severe comorbidities. As a consequence, patients can be prescribed numerous drugs and lifestyle changes\textsuperscript{31,94,95}. An increasing number of publications and guidelines have highlighted the need to improve the management of patients with multimorbidity, and in particular recommending regular comprehensive reviews of patients’ needs, paying specific attention to patients’ quality of life, function and disease control, and to the risk-benefit balance of treatment, whilst promoting self-management and a personalised care plan\textsuperscript{96–98}. Unfortunately, the number of studies performed according to these suggestions have been few and often incomplete\textsuperscript{99}. In the largest study to date based on a patient-centred care model, and which implemented strategies recommended in international multimorbidity guidelines\textsuperscript{24}, there was no improvement in patients’ quality of life, or perceived illness or treatment burden, although there were significant improvements in measures of patient-centred care\textsuperscript{31}. The authors of this study updated a previous Cochrane review\textsuperscript{99}, and suggested that more comprehensive approaches to management of multimorbidity are needed. Furthermore, they advocated health systems and medical and general education should change and adapt to face this increasingly important challenge. Pulmonary rehabilitation is such a comprehensive intervention, which is designed to improve the physical and psychological condition of patients with chronic respiratory disease and to
promote the long-term adherence to health-enhancing behaviours\textsuperscript{100}. It is of note that patients referred to pulmonary rehabilitation are commonly multimorbid, but importantly, comorbidity does not prevent them from benefiting from this intervention\textsuperscript{101}. Pulmonary rehabilitation can even positively influence the presence and severity of certain comorbidities. For example symptoms of anxiety and depression, sarcopenia, and cardiovascular risk factors (e.g., arterial stiffness) can respond to pulmonary rehabilitation in patients with COPD\textsuperscript{5,102–104}. Interestingly, video-assisted telehealth rehabilitation has recently been shown to reduce re-hospitalisation after a hospitalised COPD exacerbation\textsuperscript{105}.

It is crucial to understand not only the harms of a drug for COPD on comorbid outcomes (or vice versa), but also the potential benefits. A good example is the use of phosphodiesterase-4 inhibitors (such as roflumilast), which have been shown to reduce the risk of COPD exacerbations and hospital admissions in patients with chronic bronchitis who have frequent exacerbations\textsuperscript{106,107}. Weight loss (about 2 kg in the first 6 months of treatment) is a common side effect of roflumilast, whilst an improvement in glucose homoeostasis and metabolism has been shown in patients with newly diagnosed type 2 diabetes (but without COPD)\textsuperscript{108}. A specific role for these drugs should be considered in the phenotype of patients who are overweight, and have insulin resistance, chronic bronchitis and frequent COPD exacerbations.

Pleiotropic effects on COPD outcomes, and specifically in preventing exacerbations, have been suggested in observational studies for both statins and selective beta-1 blockers. However, these studies are subject to immortal time bias and residual confounding\textsuperscript{109}. The Simvastatin in the Prevention of COPD Exacerbations (STATCOPE) study randomised 885 patients with COPD to receive placebo or simvastatin\textsuperscript{110}, and the Beta-blockers for the prevention of acute exacerbations of Chronic Obstructive Pulmonary Disease (BLOCK) study randomised 532 patients with COPD to receive placebo or extended-release metoprolol\textsuperscript{111}. Both studies were designed to show that, in patients who had no guideline indication for statins or beta-blockers, respectively, short-term pleiotropic effects were absent in terms of lung-specific processes underlying exacerbations. However, both trials were prematurely stopped because of futility, and thus, there so far is no pulmonary-centred indication to prescribe statins or beta-blockers in patients with COPD.

**IMPORTANCE OF EARLY RECOGNITION AND MANAGEMENT OF COPD AND MULTIMORBIDITY**

There is increasing interest in the concept that diagnosis and management of COPD and concomitant chronic diseases at an early stage in life might provide an opportunity to prevent evolution to more severe diseases later in life\textsuperscript{112}. The most important cause of COPD is tobacco smoking\textsuperscript{43}, and smoking cessation is the only intervention to has been shown to prevent COPD progression\textsuperscript{112}. Furthermore, COPD, in common with all components of chronic multimorbidity, is associated with a range of risk factors in addition to smoking, including premature birth and early events, premature ageing, inactivity, alcohol consumption, overweight/obesity, and exposure to air pollution.
to outdoor, indoor, and occupational pollution and other tobacco products\textsuperscript{33,113,114}.

All the above suggests that future research should take into account that early COPD is almost invariably associated with one or more concomitant chronic diseases either early or in the overt stage, and thus that these conditions should be researched simultaneously; for the same reason, interventions in early COPD should include management of concomitant multimorbidity.

\textbf{ORGANISATION OF CARE TO MEET THE NEEDS OF THE MULTIMORBID PATIENT}

As discussed earlier, in most studies in COPD comorbidities are treated as risk factors and not included in the study protocols as treatable traits, even though evidence is accumulating that better treatment of comorbidities has a profound impact on quality of life and survival for patients with COPD\textsuperscript{30}. Hence, we rely on information that is commonly single-disease oriented. Therefore, structured and planned diagnosis and management (process-oriented care) for patients with multimorbidity can increase in complexity if treatment plans for multiple diseases and multiple goals are joined. Successful and efficient support for a patient with COPD with comorbidity requires health care to be organised to meet the challenges of continuity, quality and resource efficiency. Chronic multimorbidity is optimally met with continuity of care in terms of treatments, recommendations and other care efforts. Such continuity in care can, with proper local organisation, be met in primary care, where the patient sees the same doctor at every visit – especially in those with a mild-to-moderate disease burden. However, this traditional expert model, where decisions are made with a single medically responsible doctor, yields a high variability in care decisions (Fig. 6)\textsuperscript{115}.

Patients with increasing disease severity and complexity are typically referred to secondary care. The specialisation of health care is not optimal for the patient with multi-morbid COPD, and it is recommended that health care is organised as a multidisciplinary team that coordinate care interventions with an individual patient’s aims and ambitions\textsuperscript{24}. Such a model for organisation of care is potentially very costly and cumbersome unless proper tools for information sharing are available. The electronic medical record was originally created for documentation of medical and billing reasons and not for support of the patient along the care trajectory with planning. Also, as it is a professional’s record, it has a low degree of standardisation. Hence, when the single doctor continuity is broken, the knowledge transfer to the next care instance is often of low quality.

Patient involvement and continuity in planning require information tools that can handle both the legally required documentation and can also convey plans of future care events and data collection (e.g., patient-related outcome measures [PROMS]). In order to reduce variability in such plans, structured standard care pathways are recommended\textsuperscript{116}. Such pathways can include planning support, logistical support, and directives on which data are needed to systematically build knowledge on a patient, and potentially support for decision making. Standard pathways
promise an increase in safety and efficiency – and importantly can lead to better planning of which data should be recorded as indicators of treatment, results, and progression of the disorders. Importantly, such standard care plans cover the recommended aspects of care in multimorbidity, such as information on goals and treatable traits, list advice on decisions and recommended clinical observations and laboratory and other tests and provide logistical information. Standard care pathways can therefore reduce the variability in diagnostical procedures and recommendations, something that is very important in multimorbidity. However, the co-organisation of care in COPD and concurrent diagnoses with team-based care run the risk of becoming very complex.

The way forward is continuous development of standard clinical pathways that support decision making. Properly planned clinical pathways can support the collection of medical and other information at the right time and in a fully structured format. Such information may be aggregated in real time and support the professional decision making along the care pathway (a clinical dashboard at the level of the individual patient). Our experience is that, in a multi-professional care

Figure 6. In the traditional model the physician iteratively prescribes treatments and follow up. The patient has a low amount of information on what will happen. Data are collected in an unstructured fashion in the electronic medical record. A standard clinical pathway (yellow) provides guidance both in the early diagnosis and phenotyping phase as well as in the treatment and follow-up phase. The clinical path (green) is guided, with data collected in a structured fashion (including from the patient). In addition to collection of data into the electronic medical record, a dashboard for local guidance of the multidisciplinary team is available. EMR: electronic medical record.
pathway, all professionals need access to clear and standardised data aggregation that reflect all aspects of the diagnosis and treatments, including the patient agreed treatment goals. This suggested model for knowledge sharing could be seen as a real-time dashboard that is continuously accessible for all involved professionals. The perspective change from a single diagnosis of a patient who has COPD with a number of co-morbidities, to COPD as the pulmonary component in multimorbidity entails a change in perspective that should be reflected also in the way knowledge and information is shared.

**CONCLUSION**

In conclusion, while COPD was originally defined as a chronic pulmonary disease, there is now strong evidence that patients with COPD almost invariably have concomitant chronic diseases, suggesting that we should move from the concept of comorbidities of individual chronic diseases to the concept of chronic multimorbidity, i.e., a condition characterised by the simultaneous development of several chronic diseases in response to similar risk factors. In this respect, COPD both at an early stage (early COPD) and when diagnosed in the adult/elderly, should be considered just as the pulmonary component of chronic multimorbidity and managed accordingly.

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