COPD stands for complex obstructive pulmonary disease

Sarah Houben-Wilke[1,8], Ingrid M. Augustin[2,8], Jan H. Vercoulen[3],
Dirk van Ranst[4], Eline bij de Vaate[5], Johan B. Wempe[6], Martijn A. Spruit [2,7],
Emiel F.M. Wouters[2,7] and Frits M.E. Franssen [2,7]

Affiliations: [1]Dutch Lung Centers, Horn, The Netherlands. [2]CIRO+, Horn, The Netherlands. [3]Radboud University Medical Center, Nijmegen, The Netherlands. [4]Revant, Breda, The Netherlands. [5]Merem, Hilversum, The Netherlands. [6]University Medical Center Groningen, Groningen, The Netherlands. [7]Dept of Respiratory Medicine, Maastricht University Medical Center, Maastricht, The Netherlands. [8]Both authors contributed equally.

Correspondence: Sarah Houben-Wilke, CIRO+, Hornerheide 1, 6085 NM, Horn, The Netherlands.
E-mail: sarahwilke@ciro-horn.nl

ABSTRACT Chronic obstructive pulmonary disease (COPD) has extensively been reported as a complex disease affecting patients' health beyond the lungs with a variety of intra- and extrapulmonary components and considerable variability between individuals. This review discusses the assessment of this complexity and underlines the importance of transdisciplinary management programmes addressing the physical, emotional and social health of the individual patient.

COPD management is challenging and requires advanced, sophisticated strategies meeting the patient's individual needs. Due to the heterogeneity and complexity of the disease leading to non-linear and consequently poorly predictable treatment responses, multidimensional patient profiling is crucial to identify the right COPD patient for the right treatment. Current methods are often restricted to general, well-known and commonly used assessments neglecting potentially relevant (interactions between) individual, unique "traits" to finally ensure personalised treatment. Dynamic, personalised and holistic approaches are needed to tackle this multifaceted disease and to ensure personalised medicine and value-based healthcare.

Introduction

Chronic obstructive pulmonary disease (COPD) has extensively been reported as a complex disease affecting patients' health beyond the lungs with a variety of intra- and extrapulmonary components and considerable variability between individuals [1–6]. Unfortunately, current reductionist approaches of COPD often ignore this complexity and heterogeneity [7, 8].

The complexity of COPD has already been highlighted, for instance by FREY and SUKI [8] who critically reviewed reductionist approaches "whereby researchers isolated and identified specific mechanisms from the complex web of interacting subsystems" and suggested a multidimensional, complex systems approach also considering the unpredictable nature of COPD. During recent years, multidimensional assessment of COPD has been increasingly studied as well as (trying to be) incorporated in clinical practice [9–11]. Unfortunately, methods are often restricted to general, well-known and commonly used assessments, which

are easily performed, interpretable and comparable between individuals or groups (*e.g.* questionnaires) but which neglect potentially relevant (interactions between) individual, unique "traits" (*i.e.* underlying explanatory mechanisms) to finally ensure personalised treatment.

Looking back

Given our increasing understanding of COPD as a heterogeneous and complex disease, it is important to accentuate that, in this context "complex" means that COPD has a number of intrapulmonary and extrapulmonary components whose dynamic interactions over time are not linear, whereas "heterogeneous" indicates that not all of these components are present in all individuals at any given time-point [12]. An overview of methods assessing and involving this heterogeneity and complexity will be discussed below and are illustrated in table 1.

Global Initiative for Chronic Obstructive Lung Disease

To honour the 20th anniversary of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), RODRIGUEZ-ROISON *et al.* [13] recently summarised the key differences of the major revisions of the GOLD documents (2001–2017) clearly demonstrating a shift from a solely spirometric staging system to a more extensive classification.

The 2006 GOLD statement classified COPD patients into four groups (GOLD stages I to IV), exclusively based on the degree of airflow limitation [22]. Since this parameter is only poorly to moderately associated with disease activity, progression and prognosis, the 2011 GOLD strategy started classifying patients into four new groups (GOLD groups A to D) based on the combination of the degree of airflow limitation and the number of exacerbations and the severity of symptoms [23]. The latest 2017 GOLD strategy separated spirometric assessment from symptoms and risk evaluation aiming to facilitate tailored treatment to the needs of the individual patient and proposed patients' symptoms and exacerbation history alone to assign patients to ABCD categories [9]. However, exacerbation history as a decisive parameter has not been validated; a recent study showed that exacerbation frequency is highly variable over time, while the frequent exacerbator phenotype (two or more exacerbations every year) was the most uncommon one [24]. Extrinsic factors might further impact exacerbation occurrence making these events difficult to predict [24]. Furthermore, variations may occur in the pathophysiology of exacerbations over time in an individual patient, which is a currently unexplored topic and adds to the complexity of COPD. Finally, the choice of symptom measure and/or cut-off point used impacts the classification of patients with COPD into GOLD A/C or B/D groups which can result in misclassification and, consequently, different treatment recommendations [25].

Multidimensional indices

During the past decade, multidimensional indices including medical, pathophysiological, symptomatic and/or psychological parameters have been developed as screening instruments [11, 15] or prognostic markers for COPD [10]. Prognostic performance of multidimensional indices providing composite scores (*e.g.* the BODE (body mass index, airflow obstruction, dyspnoea and exercise) index [14]) is moderate to good, but it is still unknown if they improve COPD disease management or patients' health [10]. Another example of providing a more detailed patient profile is the Nijmegen Clinical Screening Instrument which is an empirically composed battery of existing instruments providing a detailed picture of 21 dimensions of an individual patient's integrated health status and thus guides individualised treatment [15, 26]. It has been suggested that, on the one hand, multidimensional indices might be useful in grouping patients in terms of clinically relevant outcomes; and on the other hand, it is also possible that by grouping patients this way distinct features of the disease might be grouped, blurring the heterogeneity and understanding of the disease [27]. Indeed, it has been suggested that prognostic indices cannot identify or substitute groups or phenotypes since patients sharing a similar prognosis based on a single score might not be considered as belonging to the same phenotype [28]. As further clarified, they are not risk factors or phenotypes but useful measures of disease severity to establish prognosis [29].

Phenotypes

A phenotype has been defined as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)" [27].

In the 1960's, the terms "blue bloater" and "pink puffer" came up to describe patients with chronic bronchitis and emphysema, respectively [30], marking the very beginning of phenotyping COPD. Commonly used phenotypes are often based on pulmonary disease characteristics like the presence of emphysema, chronic bronchitis, overlap asthma-COPD and/or (in)frequent exacerbations [31]. MIRZA and BENZO [32] recently described several "easily identifiable" and "clinically meaningful" COPD phenotypes

TABLE 1 Overview of strategies to classify, assess or group patients with chronic obstructive pulmonary disease (COPD)

	Goal	Advantages	Shortcomings	Heterogeneity	Complexity
GOLD	Classification of COPD based on the degree of airflow obstruction (up to 2011), in combination with symptoms/ exacerbations (2011– 2017), or symptoms/ exacerbations only (2017)	From an FEV1 centric view to a more extensive approach and a more prominent role of symptoms/individual measures [13]	Parameters assessing COPD severity still very limited; ignoring variability and unpredictability of symptoms/exacerbations/ hospitalisations; proposed cut-off points for symptom measures mostly expert driven	Separation of airflow limitation from clinical parameters (GOLD 2017) [9] clarifies what is being evaluated and ranked and might facilitate more precise treatment	Not addressed
Multidimensional indices	Prognostic indices to predict survival; screening instruments	As prognostic markers: useful in grouping patients in terms of clinically relevant outcomes [14]; as a screening instrument: multidimensional assessment of COPD [11, 15]	Identification of substitute groups or phenotypes only by selected variables included in the respective index; consist of a limited number of variables; have not been developed to guide future treatment [16]	Multidimensional assessment, including, for example, medical, pathophysiological, symptomatic [14] and/or psychological [15] parameters	Not addressed
Phenotypes	Grouping patients based on certain characteristics	From "blue bloater" and "pink puffer" to complex cluster analyses identifying existing and novel phenotypes	Cluster analyses only moderate reproducibility, clinical application disputable [17], considerable overlap between phenotypes for some specific attributes	As a screening instrument: differentiating between individuals by assessing/ clustering various characteristics	Not addressed
COPD control panel	Assessment of different elements of the disease	Assessing at least three dimensions (severity, activity and impact), can be customised to the need of the patient [18]	Unclear which characteristics should exactly be assessed, which methods, cut-off points, *etc.* should be used	Multidimensional assessment; might serve as a "clinical decision support system" (by selecting/classifying patients)	Not addressed
Treatable traits	Label-free, precision medicine approach	COPD management based on individual treatable characteristics (intra- and extrapulmonary treatable traits, treatable behaviour/ lifestyles (including patients' environment)) [19]	Separate assessment of treatable traits results in fragmented treatment; frequency of assessment and inter-relationships between traits unknown	Assessing heterogeneity by individual unique traits	Not addressed
Pulmonary rehabilitation	Personalised, holistic approach of treatable traits	Comprehensive intervention based on a thorough assessment taking into account the combination and interaction between the (treatment of) individual treatable traits [20]	Applicability in routine clinical practice (dependent on organisational structure, facilities, workforce, funding, *etc.*) is challenging; poor referral and compliance; not all traits are always addressed (yet); mostly non-pharmacological generic interventions	Assessing heterogeneity by individual unique traits	Assessment of complex interactions of physical, psychological, social and environmental factors by dedicated, transdisciplinary teams being able to respond flexibly as well as accept unpredictability and non-linear outcomes [21]

GOLD: Global initiative for chronic Obstructive Lung Disease; FEV1: forced expiratory volume in 1 s.

and added the upper lobe-predominant emphysema phenotype, rapid decliner phenotype, comorbid COPD phenotype, physical frailty phenotype and emotional frailty phenotype with the purpose of guiding personalised and effective care.

Using phenotypes to classify and/or screen patients might be an interesting alternative to currently used criteria for recruiting patients in clinical trials [28] and might help optimising (non)pharmacological integrated treatment [33], but the application into routine clinical practice and to facilitate personalised medicine is questionable since phenotypes still group patients and therefore potentially ignore individual characteristics. Indeed, the same clinical phenotype could result from different endotypes [34].

Clustering patients

Cluster analysis has been defined as a group of analysis techniques that aim to organise information so that heterogeneous subjects can be classified into homogeneous subgroups (*i.e.* clusters) which may further identify novel phenotypes [35]. To identify phenotypes, clinical features, imaging, pulmonary function, exercise tests, biomarkers and comorbidities may be used [28].

However, the current understanding of phenotypes might be biased since there is a significant heterogeneity in the selection of subjects and statistical methods used, as well as a lack of information about different COPD populations (including women, never-smokers and those with mild disease) which challenges the clinical application of the defined phenotypes [28, 36]. Indeed, a recent study assessing the reproducibility of COPD clustering subtypes concluded that identical clustering analyses across multiple COPD cohorts showed modest reproducibility [17]. Furthermore, it is known that subtypes (phenotypes) might change over time [37], underlining the need for continuous evaluation of a given phenotype. Finally, a systematic review showed that the number of phenotypes ranged from two to five [36], which seems rather limited for personalised approaches. Nonetheless, phenotyping and/or clustering patients might be a useful screening procedure differentiating between individuals; further validation of statistical clustering techniques is needed to refine and elaborate (existing) clusters.

The COPD control panel

AGUSTI and MACNEE [18] suggested to use a "control panel" including at least three dimensions (severity, activity and impact) to assess different elements of the disease (in a single patient at a given time-point) to visualise the complexity of COPD and to move COPD management towards personalised medicine. These three modules containing biological and clinical variables can provide complementary and relevant information for the proper management of the individual patient. It can be customised to the needs of the patient and the available resources (*e.g.* rural *versus* urban healthcare centres and primary *versus* specialised care) [38]. The "control panel" may further serve as a clinical decision support system [39]. However, which treatable clinical characteristics should exactly be assessed and which methods and cut-off points should be used has not yet been formally validated. Furthermore, a control panel does not reveal any complex interactions, possibly resulting in fragmented treatment [7].

Treatable traits

Based on the control panel, the appellation "treatable traits" has recently been introduced which refers to a "label-free, precision medicine approach to the diagnosis and management of chronic airway diseases" [19], while precision medicine is defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" [40].

As suggested earlier, patients with COPD should be assessed and treated according to their individual treatable characteristics, which is further likely to improve clinical outcomes [41]. Management of airway diseases based on individual treatable traits present in each subject has been suggested: "these traits can be 'treatable' based on 'phenotypic' recognition (and thereby probabilistic evidence based on positive and negative predictive values) or on deep understanding of the critical causal pathways (*e.g.* true 'endotypes')" [19]. The authors suggested a variety of treatable traits (which can coexist) summarised into three groups: pulmonary treatable traits, extrapulmonary treatable traits and treatable behaviour/lifestyle risk factors. Remarkably and importantly, the patients' environment (family and social support) has been included as a distinct treatable trait [19]. Assessing "treatable traits" has been suggested as a way to facilitate precision medicine, although individual variability in genes is not part of this disease treatment. Furthermore, this approach focusses on the assessment of several separate traits [18, 19], while integrated holistic approaches are needed to tackle the complexity of every unique patient. Furthermore, a global outline of treatable traits consequently rather leads to general treatment recommendations without the suggested "deep understanding of the critical causal pathways" [19] than facilitates personalised medicine understanding evident complexity of the disease. Finally, besides the assessment of specific traits, the evaluation of

outcomes and reassessment of treatable traits during follow-up, including readjustment of treatment as well as new outcome assessment, are essential.

In summary, the multidimensional approaches illustrated above are assessing the heterogeneity of the disease, rather than tackling the complexity of the disease. One tool can neither guarantee a personalised approach nor provide a patient profile enabling individualised treatment [42]. A control panel or treatable traits approach is largely driven by disease characteristics, resulting in fragmented treatment of identified traits [7]; a list of variables does not reveal complex interactions consequently leading to patient-tailored treatment.

Looking forward

Complex goals need complex solutions [43]. Personalised medicine or treatment strategies require personalised assessment including pulmonary and extrapulmonary as well as personal, social and environmental factors. As shown by a factor analysis including 16 demographic and clinical characteristics (*i.e.* age, body mass index, pre-bronchodilator forced expiratory volume in 1 s (FEV1), pre-bronchodilator FEV1/forced vital capacity or FEV1/vital capacity, FEV1 reversibility, St Georges' Respiratory Questionnaire total score, months since first COPD symptoms, systolic and diastolic blood pressure, pulse, morning peak expiratory flow (PEF), PEF variability, scores of breathlessness, cough, sleep disturbance and reliever use), six factors of characteristics explained ∼60% of COPD heterogeneity [44], resulting in 40% which still remained unexplained. Other relevant characteristics (*e.g.* functional performance, personal or social factors and biomarkers) are missing in this analysis and might explain part of the remaining variance. Thus personalised and holistic approaches are needed to facilitate a full understanding of (the impact of) the disease.

Towards personalised and holistic approaches

When personalisation is viewed as "tailoring medicine to patient preferences, further work is needed regarding: revealed preferences, *e.g.* treatment (non)adherence; stated preferences, *e.g.* risk interpretation and attitude; consideration of heterogeneity in preferences; and the appropriate framework to incorporate non-health benefits" [45]. Personalised approaches require holistic approaches; an integrated, all-embracing understanding of the disease, since COPD is the end result of a complex set of interactions between the environment, the genetic background of the individual and biological networks [38]. Indeed, "personalised medicine must consider human beings as composed of and operating within multiple interacting and self-adjusting systems where illness arises from the dynamic interaction within and between these systems" [7].

Below, we will discuss three examples of complex interactions of (and within) disease characteristics demonstrating the (underlying mechanisms of) individual, unique "traits".

Example 1: functional status

Patients with COPD report a variety of problematic activities in daily life [46, 47] of which walking is most frequently reported [46]. Field-based walking tests are the most commonly used and reported tests. However, these tests are a quantitative identification of the patient's walking abilities rather than a qualitative description of the individual's performance. Generally, these tests do not consider problems or inconveniences patients perceive during the particular activity. Research has shown that patients with COPD are at increased risk for frailty [48], have an impaired balance [49] and an altered gait pattern compared to controls [50, 51]. Thus, understanding the individual's limitations would enhance the possibilities for a personalised approach, *e.g.* sophisticated gait analyses.

Alternatively, for instance, the Canadian Occupational Performance Measure (COPM) might be used to assess functional performance [20]. The COPM is an individualised scale assessing patients' problematic activities of daily life. Patients have to rate the perceived performance as well as satisfaction for relevant problematic activities [52], which may provide a better understanding of the individual physical limitations as well as abilities. A qualitative study revealed social barriers (lack of time, overprotective family members) and enablers (social support) and a variety of personal barriers and enablers (figure 1) that limit and encourage, respectively, participation in physical activity in patients with COPD. The authors conclude that "it is important to understand the patient-specific social cognitive influences on physical activity participation" which might consequently facilitate individually tailored management planning [53]. This study clearly demonstrates the necessity to detect and understand underlying individual factors to finally enable personalised medicine and respond to the individual patient's needs.

Example 2: patients' social network

As already illustrated in figure 1, patients' physical activity can be affected by their social network [53], *i.e.* by their resident loved ones. Indeed, patients with an active loved one are also more active themselves [54].
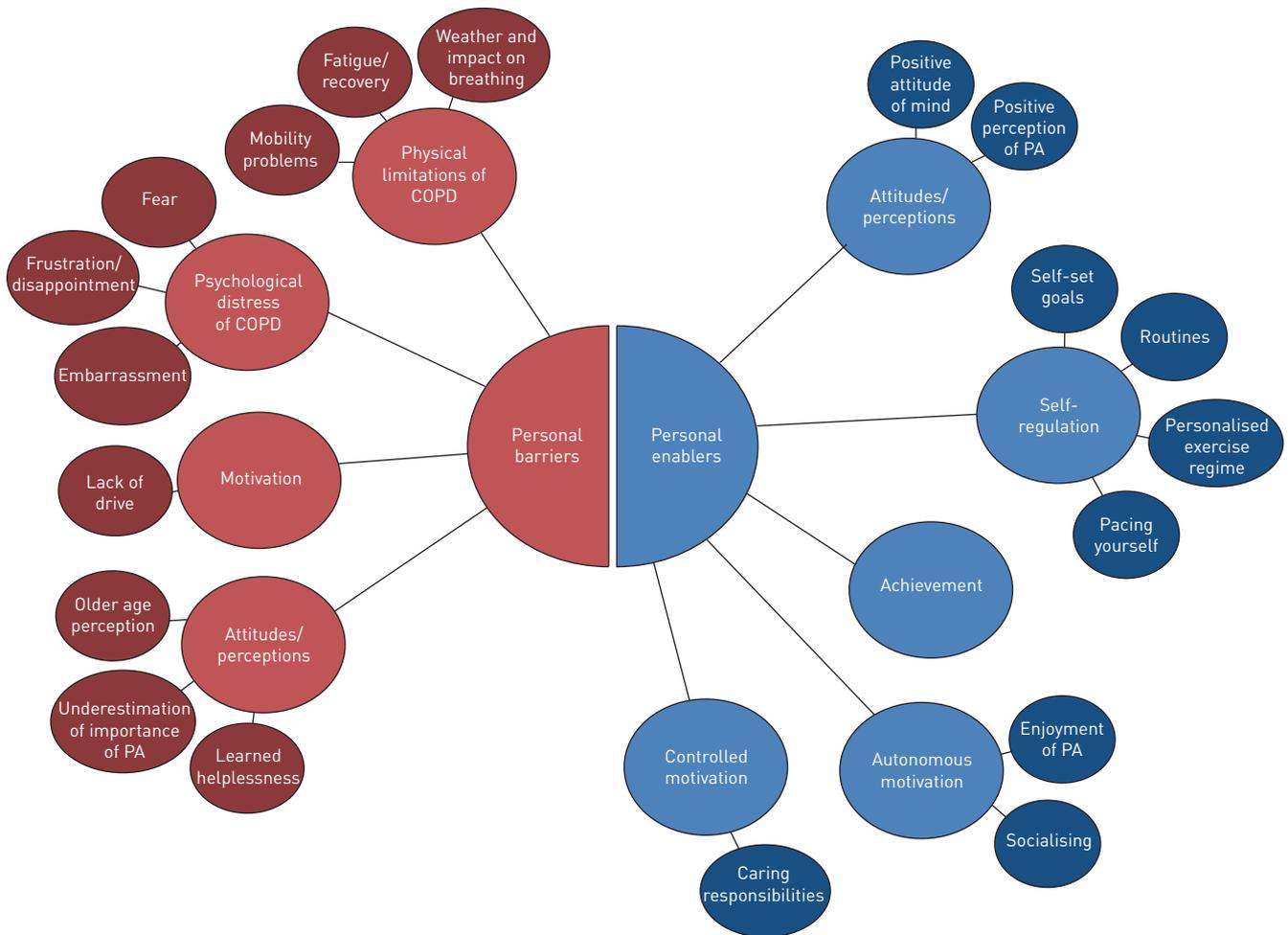
FIGURE 1 Examples of personal barriers and enablers that both encourage and limit participation in physical activity for patients with chronic obstructive pulmonary disease (COPD). PA: physical activity. Reproduced from [53] with permission.

A recent study demonstrated that structural support (*e.g.* living status, having a partner, having a caregiver) is associated with higher levels of physical activity and greater participation in pulmonary rehabilitation in patients with COPD while higher functional support was associated with, for instance, lower odds of smoking [55]. Furthermore, patients with more perceived social support experienced fewer depressive symptoms through the use of problem-oriented coping strategies [56]. Thus, the patients' home environment plays an important role in the process of disease management emphasising the need to include it as a relevant part for treatment strategies [57]. However, the process of informal caregiving is complex [58]. For instance, partners were often not able to identify patients' most important problematic activities [59] and are often current smokers and have (undiagnosed) morbidities [60]. Unfortunately, caregivers often feel unsupported and are often overlooked as important members of the interdisciplinary treatment team [61]. Thus, patients, caregivers, healthcare providers and society are all engaged in managing life with COPD [62], emphasising the need for holistic models considering patient's family and social context [63].

Example 3: patient-reported outcomes
Facilitating personalised disease management requires the assessment of individual parameters, as outlined above. Patient-Reported Outcome (PRO) is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [64]. The importance of PRO's in clinical practice as well as research will substantially increase in the coming years [65].

Linking to example 2, patients with more perceived social support experienced fewer depressive symptoms [56]. Anxiety and depression have been identified as one of the most important COPD-related comorbidities [66]. However, anxiety and depression are most commonly assessed and consequently most commonly

reported (to define psychological impairment) raising the interest and need to assess other underlying mechanisms or individual psychological factors which may play a central role in COPD management. For instance, patients with symptoms of anxiety and depression reported a lower use of active confronting coping (*i.e.* actively seeking information, solutions and/or support) [67]. A qualitative study revealed that patients are struggling with acceptance of their disease which even precludes patients from progress during their pulmonary rehabilitation programme [68]. Indeed, acceptance of the disease is associated with behaviour change [26]. Furthermore, acceptance of the diagnoses and limitations, having a realistic disease understanding and developing a rational response to the disease are ways of enabling taking control [69]. Another considerable outcome is emotional intelligence, *i.e.* the capacity to understand and manage personal thoughts and feelings, as well as to positively influence interpersonal communication and social well-being, which has been shown to be associated with self-management abilities and health status [70].

Furthermore, health status measurement has previously been described as an essential process which is "no more 'soft' or 'touchy-feely' than any well taken clinical history" [71], supporting health status as an increasingly important PRO in the assessment of COPD [9]. Indeed, health status has been shown to be associated with exacerbations, hospitalisations and dying [72]. Also fatigue has been shown to be associated with hospitalisation risk [73]. Although fatigue is a common and important symptom in patients with COPD [74, 75], it is often assessed related to exercise testing. Furthermore, it is still underdiagnosed and consequently undertreated [76]. As it has been described as a "central driver of functional disability, to the same extent as dyspnoea" [77] (linking to example 1), recent studies emphasise the importance of assessing fatigue as a separate outcome [77, 78].

The patient's (unbiased) experiences and expectations about the patient's own life, values and preferences play a central role in healthcare, since they are the ones living with the disease and are ultimately responsible for their lives. Indeed, as suggested by a Dutch report, key concepts of future healthcare are encouraging patients' functionality and independency, adaptability and flexibility as well as control, autonomy and self-management [79]. Thus, Patient Reported Experience Measurements assessing the beneficial values for the patient are becoming relevant outcome parameters [80]. Indeed, rating and understanding patients' satisfaction and interpreting their feedback (co-creation) provides important insights and outcomes to finally improve healthcare services [81].

The non-linear and consequently poorly predictable treatment responses caused by the disease [3] further support the dynamic interactions as demonstrated above. SPRUIT *et al.* [3] demonstrated that responses to regular outcomes in patients with COPD completing pulmonary rehabilitation are differential and concluded that "choosing only one or two outcomes as key performance indicators seem to ignore the clinical complexity of rehabilitating patients with COPD". It is not about severity but complexity of the disease.

Pulmonary rehabilitation

Pulmonary rehabilitation has been defined as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education, behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" [20]. The overall goal of pulmonary rehabilitation is "to return the patient to the highest possible capacity and to contribute to achieve the individual's maximum level of independence and functioning in the community" [21]. Pulmonary rehabilitation, suggested as a future cornerstone of COPD management [82], provides an appropriate setting tackling the complexity outlined above by offering a personalised, holistic approach which was initially discussed more than 40 years ago. In 1974, the American College of Chest Physicians defined pulmonary rehabilitation as an individually tailored, multidisciplinary programme through accurate diagnosis, therapy, emotional support and education [83]. In 1994, the National Institute of Health defined pulmonary rehabilitation as a multidimensional continuum of services for the patient and family supplied by an integrated team of specialists in complementary disciplines [84].

Pulmonary rehabilitation is a dynamic, individualised, integrated intervention requiring the full range of (medical) expertise, technical skills and specialised facilities addressing carefully identified treatable traits. It is offered by a dedicated team which works within, as well as across, disciplines to realise the individual goals of the unique patient. Figure 2 demonstrates the core process of pulmonary rehabilitation. Appropriate patient selection and an integrated assessment is crucial for successful treatment. Careful identification of treatable traits and treatment goals must form the start of every pulmonary rehabilitation programme. Based on the degree of complexity, a modular treatment programme is composed. Each individualised programme is followed by an outcome measurement of the different domains as described [21].
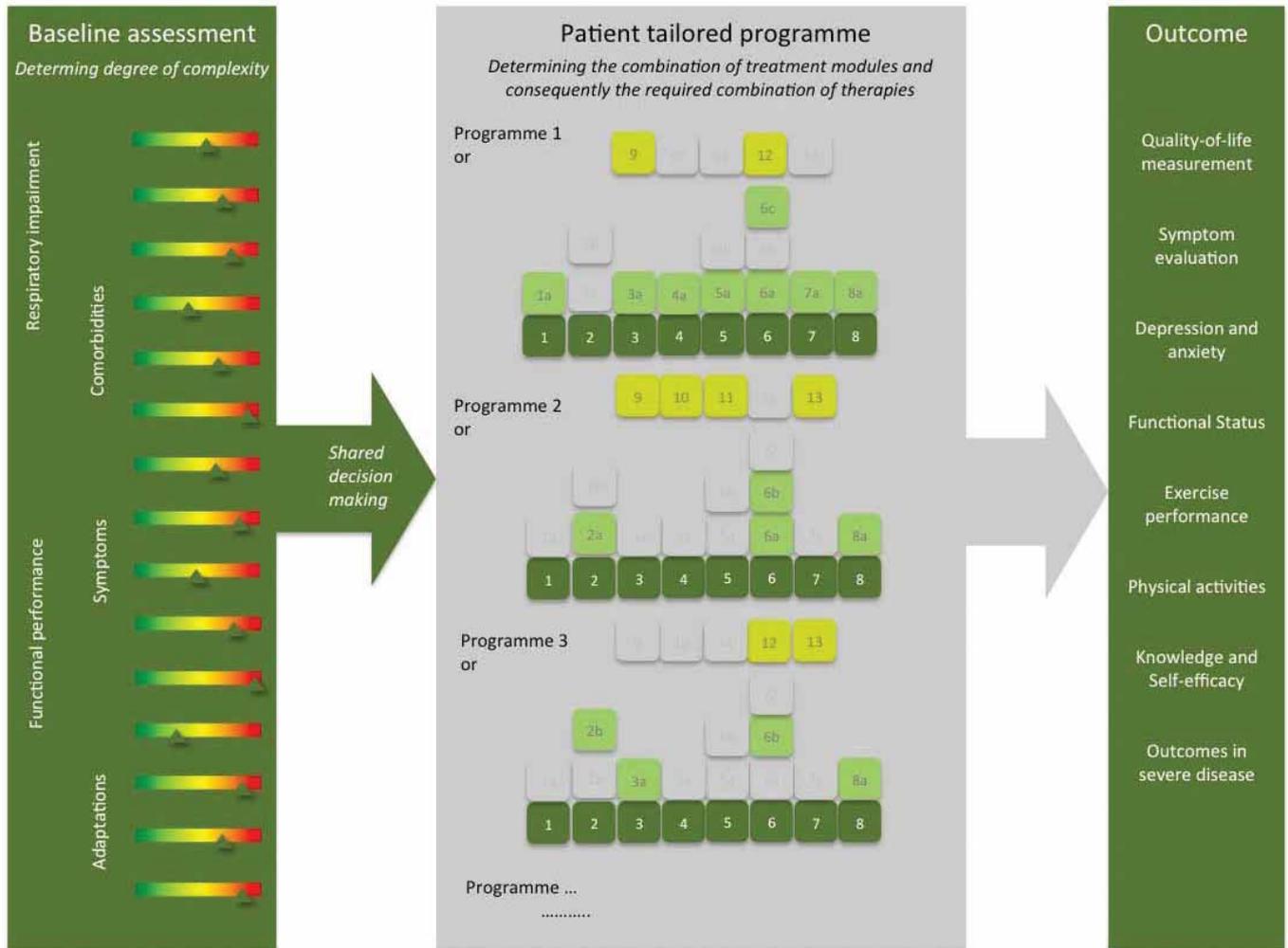
FIGURE 2 The process of a patient-tailored programme including the three core processes (baseline assessment, tailored treatment and outcome assessment). An integrated baseline assessment identifying the complexity of the disease is followed by a treatment programme composed of at least all basic modules. Depending on the complexity, specific burden-driven modules can be added. Each individualised programme is followed by an outcome measurement. Examples of adaptations include degree of self-management and coping. Reproduced from [21] with permission.

Focus: the unique patient

Pulmonary rehabilitation emphasises and relies on the central role of the patient [21]. Especially in chronic diseases, the patient, as a specialist of his own life [85], is an important member of the treatment team: it is not about curing, it is about life-long caring and learning to live with the disease, handling symptoms and accepting limitations. Indeed, enhancing self-management and empowering patients as well as achieving the individual's maximum level of independence are important goals of pulmonary rehabilitation [20, 21, 86]. Self-management, as also included in the definition of health [87], supports the concept of "positive health" [88], emphasising possibilities instead of limitations. We need to qualify patients' abilities instead of quantify their harm.

Healthcare providers involved in the management of COPD must be encouraged to target the unique needs and abilities reflecting the individual complexity of every patient (consequently) stimulating anticipation [42] and to consider the patient's social/home environment [89]. In future, and to enhance self-management, healthcare providers are expected to be competent coaches and advisors with compassion and humanity as key elements in their daily work [80].

In pulmonary rehabilitation, tailored treatment goals are composed not only in collaboration with other professionals but, probably even more importantly, in discussion with the patient [21]. Shared decision making as "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences" plays a crucial role in personalised treatment approaches. Due to the visual presentation of

the results to the health professional as well as the patient, the Nijmegen Clinical Screening Instrument might support the process of shared decision making [26].

Furthermore, a recent study showed that patients were not willing to accept the burden of treatments where they perceived minimal benefit [90], demonstrating the importance of clear information about benefits and impact of a given treatment. Indeed, in case of complex adaptive systems, a small change can have a large effect in behaviour [91]. Importantly, patients' behaviour is partly determined by unique and adaptive responses to environmental stimuli [91] underlining the importance of creating a safe and realistic environment for disease management strategies.

Yet, there are also some relevant limitations. Pulmonary rehabilitation is mostly a non-pharmacological generic intervention underlining the necessity to integrate medicine and pulmonary rehabilitation by, for instance, implementing optimal treatment of comorbidities in relevant subgroups, applying noninvasive ventilation during exercise training in patients with hyperinflation and exercise-induced desaturation, using anabolic steroids in the treatment of cachexia and/or combining pulmonary rehabilitation with lung volume reduction intervention in eligible patients. Thus, pulmonary rehabilitation is a dynamic, individualised, integrated intervention tackling respiratory and non-respiratory treatable traits. This concept of pulmonary rehabilitation is far away from the eroded approach of pulmonary rehabilitation described in some guidelines, limiting pulmonary rehabilitation to exercise training and self-management instructions [92, 93].

Conclusion

COPD management is challenging and requires advanced, sophisticated strategies meeting the patient's individual needs. Due to the heterogeneity and complexity of the disease leading to non-linear and consequently poorly predictable treatment responses, multidimensional patient profiling is crucial to identify the right COPD patient for the right treatment [3]. Transdisciplinary management programmes realising real benefits by integrating concepts of adaptive systems need to address the physical, emotional and social condition of the individual patient [94]. Dynamic, personalised and holistic approaches, *i.e.* pulmonary rehabilitation, are needed to tackle the multifaceted disease starting from the patient's perspective to finally ensuring personalised medicine and value-based healthcare: "to cope with escalating complexity in healthcare, it is necessary to abandon linear models, accept unpredictability, respect autonomy and creativity, and to respond flexibly to emerging patterns and opportunities" [21].

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