Published in : European Respiratory Journal(2017) 50, pp. 1701655
DOI: 10.1183/13993003.01655-2017
Status : Postprint (Author's version) Source Sans Pro -8

PRECISION MEDICINE IN AIRWAY DISEASES: MOVING TO CLINICAL PRACTICE

Alvar Agusti[1,2], Mona Bafadhel[3], Richard Beasley[4], Elisabeth H. Bel[5], Rosa Faner[2], Peter G. Gibson[6], Renaud Louis[7], Vanessa M. McDonald[6], Peter J. Sterk[5], Mike Thomas[8], Claus Vogelmeier[9] and Ian D. Pavord[3,10], on behalf of all participants in the seminar[11]

[1]Respiratory Institute, Hospital Clinic, Institut d'Investigacions Biomédiques August Pi i Sunyer IIDIBAPS], Universitat de Barcelona, Barcelona, Spain.
[2]Centro de Investigacion Biomédica en Red de Enfermedades Respiratorias (CIBERES], Spain.
[3]Dept of Respiratory Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, UK.
[4]Medical Research Institute of New Zealand, Wellington, New Zealand.
[5]Dept of Respiratory Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands.
[6]The Centre of Excellence in Severe Asthma, Priority Research Centre for Healthy Lungs, The University of Newcastle and Hunter Medical Research Institute, Newcastle, Australia.
[7]Pneumology Dept, CHU Liege, GIGA I3 research group, University of Liege, Liege, Belgium.
[8]Primary Care and Population Sciences, University of Southampton, Aldermoor Health Centre, Southampton, UK.
[9]University of Marburg, Member of the German Center for Lung Research (DZL], Marburg, Germany.
[10]Oxford NIHR Biomedical Research Centre, University of Oxford and Oxford University Hospitals NHS Foundation Trust, Oxford, UK.
[11]A full list of the seminar participants can be found in the Acknowledgements section

ABSTRACT

On February 21, 2017, a European Respiratory Society research seminar held in Barcelona discussed how to best apply precision medicine to chronic airway diseases such as asthma and chronic obstructive pulmonary disease. It is now clear that both are complex and heterogeneous diseases, that often overlap and that both require individualised assessment and treatment. This paper summarises the presentations and discussions that took place during the seminar. Specifically, we discussed the need for a new taxonomy of human diseases, the role of different players in this scenario (exposome, genes, endotypes, phenotypes, biomarkers and treatable traits) and a number of unanswered key questions in the field. We also addressed how to deploy airway precision medicine in clinical practice today, both in primary and specialised care. Finally, we debated the type of research needed to move the field forward.

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Many common human diseases are still diagnosed as if they are homogeneous entities, using criteria that have hardly changed in a century ...

... the treatment for diseases that are diagnosed in this way is generic, with empiricism as its cornerstone

KOLA and BELL [1]

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the two most prevalent human airway diseases [2]. Surprisingly, well into the 21st century, they are still diagnosed following 19th century approaches, which are fundamentally based on their clinical presentation and associated lung function abnormalities [3, 4], both of which are nonspecific. As a result, asthma and COPD are often treated similarly and, potentially, suboptimally [2, 5]. Furthermore, it can be questioned whether they are clearly separate entities or, alternatively, they may represent a heterogeneous spectrum of airway diseases that are linked to an array of biological deviations from what is considered a healthy state well adapted to its environment [1].

Recently, the term "precision medicine" has been proposed to define "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" [6]. Inherent in this definition is the "goal of improving clinical outcomes for individual patients and minimizing unnecessary side effects for those less likely to have a response to a particular treatment" [6]. In essence, therefore, the concept of precision medicine relates to the likelihood of responding (or not) to a given therapeutic intervention and/or suffering (or not) undesired side-effects (figure 1) [7]. In the context of chronic airways diseases, precision medicine can therefore be a promising strategy to improve their management [8]. Needless to say, physicians always try to be as precise as possible in relation to the needs of individual patients. The present step change, however, is based on the integrated assessment of the complex clinical and biological status of individual patients, which until recently was beyond reach [9].

On February 21, 2017, the European Respiratory Society convened a research seminar in Barcelona aimed at discussing how to best apply precision medicine to airway diseases and specifically to asthma and COPD. This perspective summarises the discussions and presents the conclusions and proposals from the seminar.

Full presentations from the seminar can be downloaded from: http://www.ers-education.org/events/research-seminars/precision-medicine-in-airway-diseases.aspx.

Setting the stage, or where we are coming from

We need a new taxonomy (classification] of human diseases

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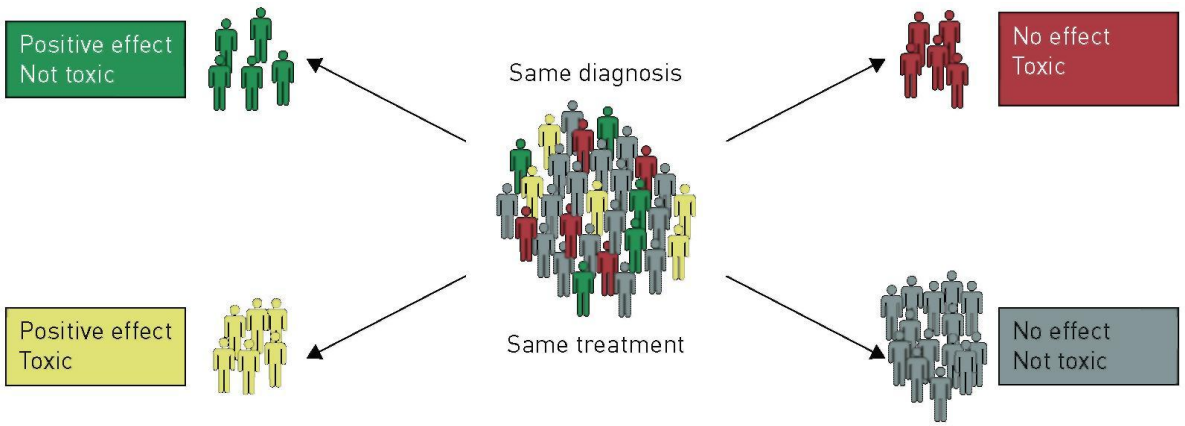
Human diseases are still classified on the basis of the principal organ system in which symptoms and signs manifest, and in which gross anatomical pathology and histopathology are correlated [10]. This so-called Oslerian paradigm, to honour Sir William Osier by whom it was first proposed, has been useful for clinical practice because it establishes a limited number of syndromic patterns to consider in daily practice. A syndrome is a set of medical signs and symptoms that commonly occur together and may be related to each other without necessarily tying them to a single identifiable pathogenesis [11]. Yet, this Oslerian paradigm over generalises pathological states (COPD and asthma, for instance, are terms that most probably include common as well as unique features), does not include susceptibility states or preclinical disease manifestations, and is of limited value to individualise precise diagnosis and therapy [12, 13]. As pointed out in the introductory quote from KOLA and BELL [1], the taxonomy of human diseases is outdated and requires a profound reconsideration that leverages the most up-to-date and integrated biological knowledge we currently have [1, 10, 12, 14],

The traditional, physiology-based classification system of airway disease that we use today does not represent the state of the art. We now know that there is a heterogeneous mix of distinct cellular and molecular mechanisms that go beyond the traditional physiological mechanisms of pulmonary disease, and that extrapulmonary comorbidities, psychosocial, behavioural and environmental factors significantly impact the health status and risk of morbidity and mortality of these patients. Therefore, there is an urgent need to rethink and disseminate the way we classify and manage airway diseases.

FIGURE 1 *Principles of precision medicine that illustrate the heterogeneity of any human disease and the potential impact of stratifying the population appropriately. Adapted from Chakma Justin [Journal of Young Investigators, 2009, Vol 16]*



The players: exposome, genes, endotypes, phenotypes, biomarkers and treatable traits

Figure 2 illustrates the current multilevel understanding of the different biological players in this scenario. The interaction between our genetic background (genome) and the cumulative

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environmental exposures an individual encounters throughout life (exposome) [15, 16], *via* a complex set of biological networks [20], determines the emergence of a number of cellular and molecular mechanisms that eventually contribute to the phenotype that we phenomenologically observe [20], this being a given disease or, more often, a specific clinical manifestation of a complex disease [17]. In this setting, several aspects require detailed discussion. 1) The traditional concept of a phenotype (an observable characteristic of an organism [20]) has been modified to provide a meaningful clinical framework. Hence, a clinical phenotype is "a single or combination of disease attributes that describe differences between individuals ... as they relate to clinically meaningful outcomes" [21]. It is their relationship with meaningful outcomes *(e.g.* symptoms, health status, death, exacerbations) that confer clinical utility to the concept; otherwise, it would remain a useless observational exercise. 2) The term endotype, a contraction of endophenotype, has been defined as "subtype of a disease defined functionally and pathologically by a molecular mechanism or by treatment response" [18]. This approach is radically different from the traditional Oslerian paradigm discussed earlier, which was (and still is) based mostly on the phenotypic presentation. Further, the beauty of the endotype concept is that, according to the definition of precision medicine presented above [6], it is a first step towards its implementation in clinical practice [7]. Yet, to date, it is still, by and large, a theoretical construct since we still do not understand the vast majority of biological mechanisms *(i.e.* endotypes) underlying different clinical presentations *(i.e.* phenotypes). 3) Given the key role played by biological networks in health and disease [22], novel analytical techniques (such as network analysis [23]) capable of integrating this multilevel complexity (exposome, genome, endotypes and phenotypes) are needed to unravel and understand the pathobiology of most human diseases, including chronic airway diseases. Such improved understanding should allow the identification and adequate validation of biomarkers *(i.e.* a biological, functional, imaging and/or clinical characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or biological responses to a therapeutic intervention [19]). This is an absolute requirement to move towards precision medicine of airway diseases [7, 24].

Key questions in the management of airway diseases

During the seminar, it was agreed that the following questions need to be answered (by appropriate research and/or consensus) to move precision medicine of airway diseases forward.

Should we continue using the traditional diagnostic labels "asthma", "COPD", "bronchiolitis" and/or asthma-COPD overlap? Which assumptions go with these labels? What are the advantages/ disadvantages of using them?

Diagnostic labels have many advantages: they are useful to discriminate grossly defined groups of patients, they form the basis for teaching students, they are easy to explain to patients, they are easy (but appropriate?) to use in interventional studies *(i.e.* randomised controlled trials (RCTs)) and they can be used to convince authorities to fund medications. In clinical practice, they are also useful to identify a syndrome (defined earlier) [11], but this will probably lead to

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empirical (imprecise) management. The implicit assumption that goes with these traditional diagnostic labels is that these diseases are homogeneous in terms of their pathobiology and, therefore, that they need the same treatment in all patients. This is wrong, and if the labels are to remain, it needs to be clear that assumptions of pathophysiology should not be made. Thus, the labels represent the start of the assessment process, not the end. It was agreed that we need validated biomarkers (figure 2) that allow the clinician to build-up a clearer picture of the main drivers of morbidity, allowing provision of the right treatment, at the right time to the right person (figure 1).

Would it be more helpful to deconstruct airway disease into components that can be measured and potentially modified (treatable traits)?

As discussed above the terms "asthma" and "COPD" actually correspond to syndromes that comprise overlapping disorders/clinical phenotypes [25]. Participants in the seminar agreed that a treatable traits-based strategy was a first appropriate step towards the deconstruction of these terms into their individual treatable components and, as a result, towards precision medicine of chronic airway diseases. A treatable trait is a therapeutic target identified by "phenotype" or "endotype" recognition through validated biomarker(s) [8]. Table 1 lists a number of potential pulmonary, extrapulmonary and behavioural/lifestyle treatable traits to consider in patients with chronic airway diseases, and their specific therapeutic recommendations as per current international recommendations [3, 4]. Again, several aspects of this proposal require discussion. 1) Treatable traits are independent of the traditional, syndromic diagnostic "labels" used to date *(i.e.* they can occur in both patients with "asthma" or "COPD"). 2) Treatable traits can coexist in the same patient and can change within patients over time. These concepts are not captured adequately by the traditional phenotype concept (figure 3), and are therefore important for the clinician to understand. 3) Finally, this treatable trait approach requires prospective validation, as discussed in detail later in this perspective. Identifying (currently) nontreatable traits *(e.g.* airway remodelling) would also be of relevance since it can foster specific research to fill the gap.

Can available biomarkers identify different phenotypes or endotypes of airway disease? The serum level of α1antitrypsin in α1 antitrypsin deficiency is a well-established biomarker of a trait that may be treatable [27]. Other biomarkers that have been proposed in the context of chronic airway diseases include the following.

1) A level of circulating eosinophils >3-4% or >300 cells-□L^{-1} appears to identify a subpopulation of patients with asthma or COPD, both when clinically stable as well as during an exacerbation of their disease, that are at higher risk of exacerbations and respond better to corticosteroid treatment [28-32], Furthermore, COPD patients with a persistent eosinophilic phenotype (about a third of the total COPD population [33]) have accelerated forced expiratory volume in 1 s decline, and a recent reanalysis of the ISOLDE study suggests that this is prevented by inhaled corticosteroid (ICS) treatment [34]. Finally, it is of note that there are different subtypes of eosinophils [35] which merit further research in patients with chronic airway diseases.

2) Exhaled nitric oxide fraction (FeNo) is associated with eosinophilic airway inflammation and raised airway concentrations of type-2 cytokines (so called type-2 inflammation),

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particularly interleukin-13 [36], It also appears to identify accelerated lung function decline in asthmatics [37], as do bronchial CD8, CD4 and CD3 cell infiltrates [38].

3) High IgE is often viewed as a treatable trait, although it is a disappointing biomarker of response to type-2 targeted treatments, including omalizumab [39-42],

4) Airway bacterial colonisation and, eventually, changes in the airway microbiome can also be considered a treatable trait [43]. Sputum cultures and even sputum colour are useful biomarkers to detect airway bacterial colonisation and antibiotics are a validated treatment for this [44-47].

5) Persistent systemic inflammation occurs in a subset of patients with COPD [48] and asthma [49], and these patients have worse outcomes (in terms of mortality and exacerbations) [48]. A pilot study in patients with stable COPD that targeted systemic inflammation showed positive clinical benefits [50].

This is only the tip of the iceberg. We need more validated biomarkers to predict response to treatment (including adverse effects) (figure 1), monitor treatment effects and/or predict clinically relevant outcomes (mortality, exacerbations and lung function decline) [51-54]. Participants in the seminar agreed that by addressing these questions airway disease management will move into a new, more precise, better and safer era. To do so, however, it was also acknowledged that, in addition to a deeper knowledge of the biological basis of airway diseases, large, prospective, long-term interventional studies across the whole spectrum of airway diseases are needed, probably leveraging on new experimental designs ("master protocols") [55], which are discussed later in this perspective.

FIGURE 2 *Schematic of the relationships between the exposome and the genome [via complex biological networks], the emergence of endotypes and phenotypes, and the possibility of identifying them through validated biomarkers of treatable traits. For further explanation see the main text.*

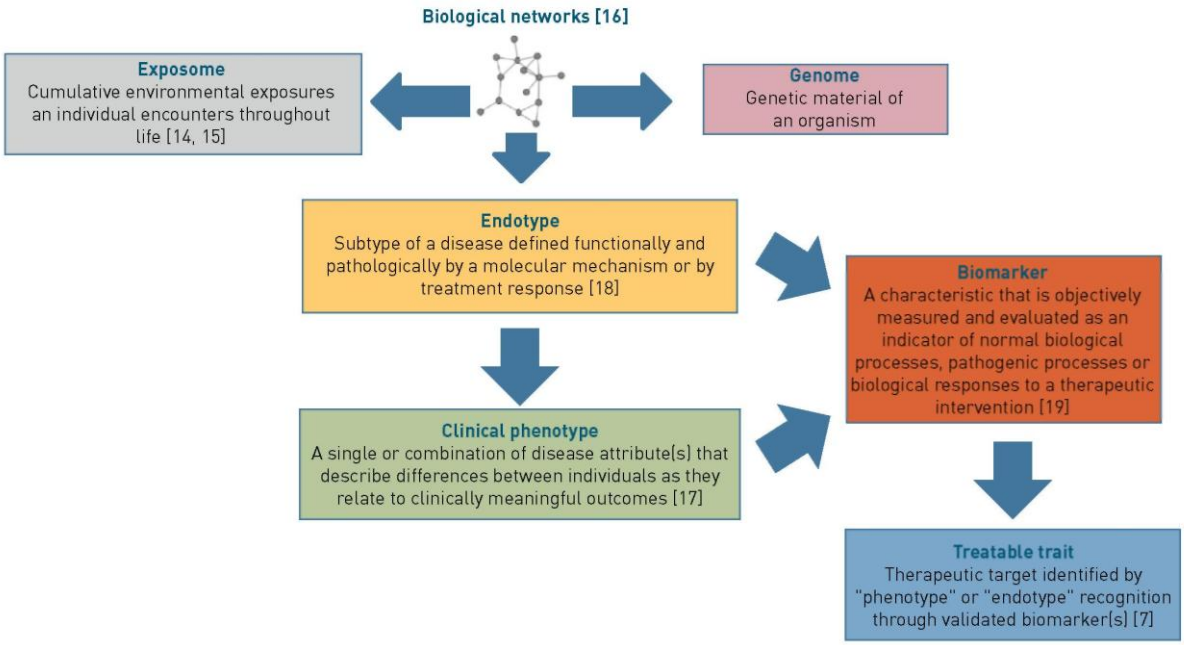

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TABLE 1 List of potential pulmonary, extrapulmonary and behavioural/lifestyle treatable traits to consider in patients with chronic airway diseases

Trait	Treatment
Pulmonary treatable traits	
Airway smooth muscle contraction	Bronchodilators
Eosinophilic airway inflammation	Corticosteroids/Type 2 biologies
Chronic sputum production	Smoking cessation, macrolides, PDE4 inhibitors
Bacterial colonisation	Macrolides, tetracyclines
Bronchiectasis	Macrolides, tetracyclines, nebulised antibiotics/aminoglycosides
Cough reflex hypersensitivity	Gabapentin, P2X3, speech pathology intervention
Chronic respiratory failure	Oxygen/NIV/lung transplant
Pulmonary hypertension	Oxygen/NIV/lung transplant
Emphysema	Lung volume reduction/transplant
Extrapulmonary treatable traits	
Rhinosinusitis	Topical steroids/surgery
Deconditioning	Rehabilitation
Cachexia	Diet/physical activity
Obesity	Diet/physical activity/bariatric surgery
Cardiovascular disease	ACE inhibitors/diuretics/β-blockers
Vocal cord dysfunction	Speech pathology therapy
Depression	Cognitive and behavioural therapy
Anxiety	Anxiolytics
Systemic inflammation	Statins?
Treatable behavioural/lifestyle factors	
Poor inhalation technique	Education
Nonadherence to treatment	Reassurance/education/periodic check-up
Smoking	Cessation support
Exposure to sensitising agents	Avoidance/desensitisation
Side-effects of treatments	Treatment optimisation
Polypharmacy	Medication review
Poor family and social support	Family therapy education/self-management support

PDE4: phosphodiesterase-4; P2X3: P2X3 receptor antagonist; NIV: noninvasive ventilation; ACE: angiotensin-converting enzyme.

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Deployment of airway precision medicine in clinical practice, or where we are now

THE PROBLEM

Current clinical management of patients with chronic airway diseases is guided by national and international guidelines and recommendations, which, in turn, are based on group mean data from RCTs and do little to recognise individual heterogeneity, although they are slowly evolving in this direction [3, 4]. Despite this, it is fair to recognise that this guideline-based approach had progressively improved outcomes up until the past 15 years or so. Yet, in many developed countries improvements in outcome have stalled [56]. There have been no further decreases in hospitalisations or mortality despite steadily increasing pharmacy costs and increasing use of combination inhalers [57]. Real-life surveys repeatedly reveal that suboptimal control is common, and frequently show that potentially preventable factors occur in many deaths, hospitalisations and in most quality of life impairments [58]. This emphasises the need of better dissemination and implementation strategies, as well as novel and more effective (precise) management strategies.

FIGURE 3 *a] Pictorial representation of chronic obstructive pulmonary disease (COPDl heterogeneity. Each node represents one patient, and each colour represents different clinical characteristics, b] The approach to COPD complexity based on similar clinical presentations (colours], so-called phenotypes. c] Given that phenotypes can coexist in the same patient, an approach based on treatable traits has been proposed more recently [8]. Reproduced from [26] with permission.*

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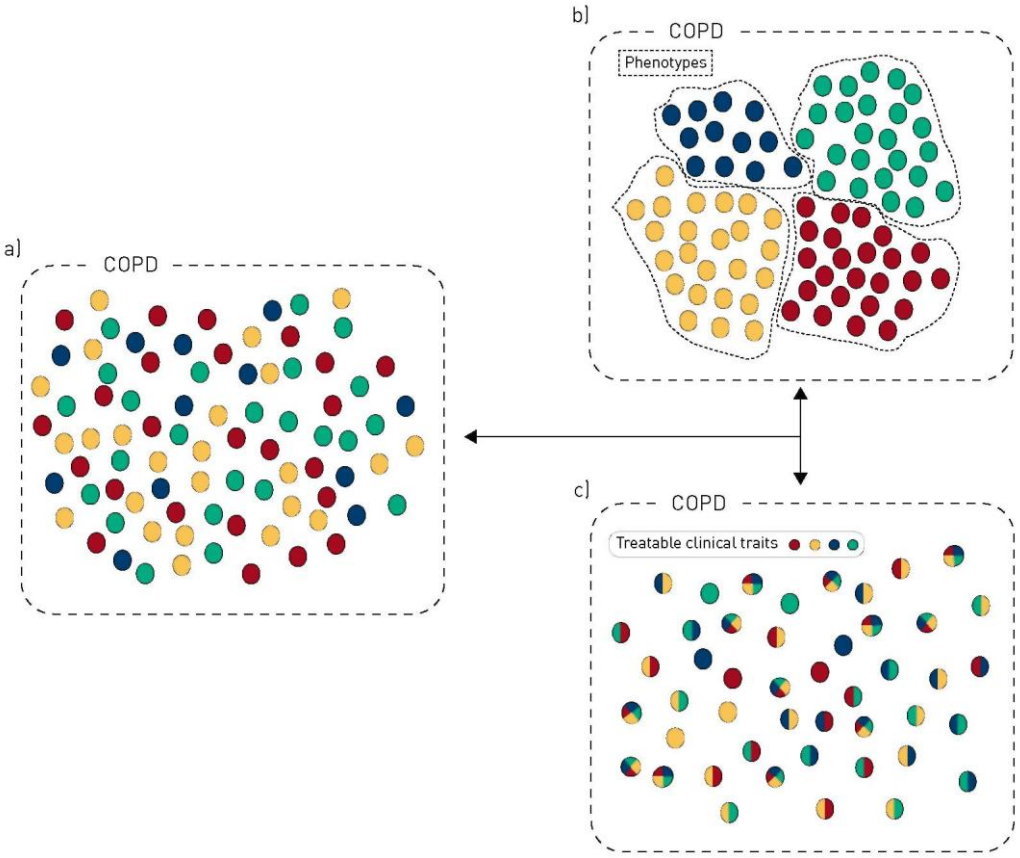

ARE WE READY TODAY?

The challenge is to develop simple algorithms that enable the identification of potential treatable traits, which may be contributing to poor respiratory health in a patient with airway disease (table 1). And, yes, despite the uncertainties discussed earlier surrounding endotypes, phenotypes and biomarkers, there are a few relatively simple things that we can do today that will probably improve the management of patients with chronic airway diseases. As shown in figure 4, the first proposed step would be to determine if the patient "really" has airway disease [8]. To answer this question a simple strategy that combines standard clinical history, assessment of potential risk factors for airway diseases (smoking, allergies, occupation, family history and early life events) and measurement of spirometry, FeNO and blood eosinophils can be conceived, both in primary and specialised care. The results of this assessment may determine the probability (high or low) of airway disease being present. If there is a high probability of airway disease, therapy should be based upon the treatable traits present in that individual patient (table 1), which, importantly, are not mutually exclusive [8]. By contrast, if the clinical history is atypical, no risk factors of airway disease can be identified and the results of these tests are normal, alternative diagnoses should be considered [8]. Needless to say, once the patient has been diagnosed and treated for airway disease according to this treatable traits strategy, follow-up needs to consider (as recommended by current international recommendations [3, 4]): adherence with treatment, inhalation technique, response to therapy [59], and risk of future events [60]. The concept of "control" has been basically applied to asthma, but some recent alternatives have also been proposed for COPD [61]. Although there is

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evidence to support the investigation and management of the individual components of this strategy, this prototype schema (and future modified versions) will need to be assessed by RCTs to provide scientific evidence of their effectiveness and safety in clinical practice. Likewise, alternative systems by which precision medicine might be delivered in clinical practice should also be investigated as a priority. Eventually, complex bio-clinical traits will need to be approached by machine learning and artificial intelligence, which provide very powerful computational models for potentially predicting clinical course and treatment responses [62, 63],

PRIMARY VERSUS SPECIALISED CARE?

The majority of new diagnoses and the routine management of mild and moderate chronic airway diseases occur in primary care. Although the impetus to precision medicine has come from difficult to control airway diseases, typically seen in tertiary care centres, the concepts of complexity and heterogeneity are equally relevant in patients with milder disease treated in the community, because individual patients are different and the reasons for poor control are heterogeneous. The era of precision medicine of airway diseases is dawning, and primary care should be involved. Individualised therapy based on assessment of the two dominant treatable traits, eosinophilic airway inflammation and airflow limitation, would be well within the scope of nonspecialist clinicians and would be an important step in this direction.

FIGURE 4 *Proposed diagnostic strategy for an adult with symptoms, signs or events suggestive of airway disease (without any further "traditional diagnostic labelling"]. For further explanation see the main text. FeNO: exhaled nitric oxide fraction. #: smoking, allergies, sputum production, occupation, lung development and growth; ¶: see tables 1-3 in [8]; +: see tables 2 and 3 in [8]. Reproduced and modified from [8] with permission.*

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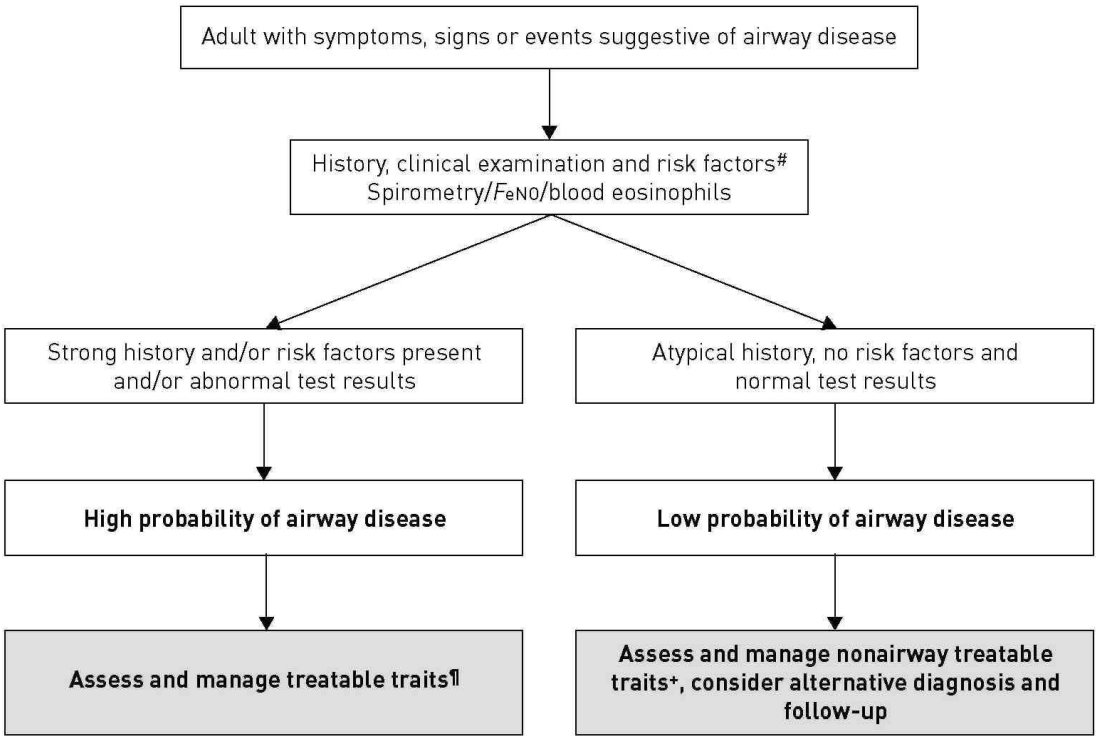

How to move the field forward through research *Prior experiences*

SINGLE BIOMARKER STUDIES

Early trials of targeted management of chronic airway diseases focused on single inflammatory biomarkers. RCTs conducted using sputum eosinophil counts as a biomarker to guide treatment decisions showed reduced exacerbations *versus* guideline-based therapy both in asthma [64] and COPD [65]. Other trials used FeNO to guide treatment decisions and a meta-analysis of these studies indicated superior outcomes over an approach focused on asthma symptoms [66]. Finally, the use of bronchial hyperreactivity as a biomarker also showed efficacy and lead to a more effective control of asthma while alleviating chronic airways inflammation, indicating that the concept goes beyond inflammatory markers [67]. All in all, these studies support the paradigm of precision medicine when treatment is targeted to a specific pathway. Importantly, they show the benefit of a precision medicine approach across the asthma severity spectrum. This means that precision medicine of airway disease need not be restricted to severe or refractory disease (as it has been in current guidelines), but can benefit people with mild disease as well [68].

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MULTIPLE BIOMARKER STUDIES

Precision medicine, however, extends beyond a single biomarker/treatable trait, since an individual patient can have multiple potentially treatable traits. To date, only a few studies have attempted to apply a multidimensional assessment followed by individualised management in patients with chronic airway diseases. MCDONALD *et al.* [50] tested this strategy in a proof-of-concept study in a COPD population, where the multidimensional assessment involved the evaluation of airways, comorbidities, risk factors and behavioural traits, as well as the measurement of several systemic inflammatory markers ("inflammometry"). The results showed that this precision medicine approach led to a highly clinically significant improvement in health status [50]. These observations have been reproduced very recently in patients with severe asthma [69]. While the results of these trials are promising, we acknowledge that this is a complex approach to trial design and execution that raises questions in terms of whether the observed effects are related to any one intervention in particular or are the result of a "stacked approach", that is additive effects of multiple interventions [55]. Thus, in the future different study designs need to be considered, as discussed later in this perspective [55]. Likewise, it is conceivable that precision medicine will more and more rely on the fast, on-site ("point of care") assessment of multiple biomarkers derived from high-throughput "omic" platforms [70-72].

A treatable traits study proposal

There was consensus that the treatable traits strategy [8] was a potentially feasible approach to deploy precision medicine of airway diseases in clinical practice. However, there was also consensus that it required formal, prospective and controlled validation, most probably in an international multicentre, multicomponent interventional setting [55]. However, it was acknowledged that this will be complex, so the following issues were specifically discussed.

TRIAL DESIGN

Traditional RCTs are designed to test a single treatment in a homogeneous population. As a result, only a small proportion of patients with asthma or COPD are included in the major RCTs for asthma or COPD that, importantly, form the basis of current guideline recommendations despite their reduced generalisability [58, 73]. Furthermore, this approach is not adequate to test multicomponent interventions in heterogeneous populations. Likewise, it is not an effective way to test a biomarker driven treatment algorithm in airway disease [74],

The so-called "master protocols" leverage from novel experimental designs and are better suited for these purposes [55]. A master protocol has one overarching protocol designed to answer multiple questions, which may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classifications, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype [55]. There are several types of master protocols, including the so-called "umbrella", "basket" and "platform" trials [55, 75, 76]. "Umbrella" trials study multiple targeted therapies in the context of a single disease; "basket" trials study a single targeted therapy in the context of multiple diseases or disease subtypes; and

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"platform" trials (figure 5) study multiple targeted therapies in the context of a single disease, with therapies allowed to enter or leave the platform on the basis of an agreed decision algorithm [55]. At the seminar, it was agreed that, in order to test the efficacy and safety of a treatable traits strategy for the management of airway disease in practice, a platform trial design (figure 5) would be probably adequate, because it is precisely designed to identify the optimal "set of treatments" in conditions where management involves multiple therapies delivered concurrently, which have the potential to have independent or interacting effects on outcome. Table 2 contrasts the main characteristics of a platform trial *versus* traditional RCTs. However, it was also acknowledged that the design and statistical methods involved in a platform trial are complex, and that they would require appropriate knowledge and expertise. Finally, it was agreed that such a trial will create the opportunity to generate a multicentre biobank [78] to store biological samples for future studies.

INTERVENTION(S)

A crucial component of the study will be the standardisation of both the multidimensional assessment and a tailored treatable traits plan. This should be greatly facilitated by a care coordinator, as the proposed intervention is a treatable traits strategy, rather than an individual single component intervention that targets a specific trait. As such it is likely to require multiple health behaviour changes from the patients' perspective and significant coordination from a healthcare perspective. The care coordinator or case manager will ensure that the overall treatment plan is implemented. Early trials with a similar design support this approach [50, 69].

Complex interventions in healthcare comprise a number of separate elements which seem essential for the proper functioning of the intervention, although "the" active ingredient(s) of the intervention is (are) often difficult to identify [55]. It is possible that the "stacked" approach, that is multiple traits being treated simultaneously with a measurable and additive benefit to each intervention, leads to a larger than expected improvement [79]. In addition, the impact of treating multiple traits may have effects not only on the intended outcome(s) but may also benefit multiple other domains. For example, treating obesity in COPD not only improves body composition, but also improves exercise tolerance, cardiovascular outcomes and depression [79]. This, combined with pharmacotherapy or pulmonary rehabilitation, may in fact increase the final effect size. A large trial should therefore be able to have enough power to perform regression/ mediation analysis of subgroups receiving particular interventions to determine what it is that is having the greatest impact. A final consideration that emerged during the discussion of this particular topic was that "no intervention" is, in fact, "an intervention" and this should be actually considered when designing the appropriate studies and subgroup analyses. For instance, it may be of interest to identify individuals in whom the active treatable traits strategy resulted in a particular treatment decision that would have been different with "usual care", and where possible compare outcomes with similar individuals from the control group treated using diagnosis-driven guidelines.

OUTCOMES

The choice of outcome measure(s) in a treatable traits trial is also of paramount importance. The primary outcome in such a study should be valid and responsive to each of the treatments used.

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Established outcomes, such as severe exacerbations, hospital admissions or death, are likely to be the preferred primary "hard" outcomes, particularly in high-risk groups. However, because the interventions will target different pathways, it is also necessary to have trait-specific outcomes that demonstrate efficacy of the intervention on each pathway. For example, a type 2 anti-inflammatory intervention needs to show benefit in reducing type 2 inflammation, such as eosinophils or FeNO. However, this may not be suitable as the primary study outcome, since it would not be responsive to non-type 2 traits, such as treatment for depression. In this situation, a more global outcome measure is needed, and health status should not be dismissed albeit it is usually considered a "soft" outcome. Health status is the single outcome that best encompasses the overall impact of disease on an individual's life. Therefore, it is of high importance from the patient perspective, particularly in light of previous data that indicates that for each additional trait there is a clinically significant decrement to quality of life [80]. Perhaps a composite outcome may be ideal, incorporating health status with other outcomes. Also, it cannot be excluded that, in addition to such measures of individual well-being, particular biomarkers or biomarker profiles can provide complementary information on therapeutic outcome of a treatable traits strategy.

Finally, provided the results of the trial are positive, other outcomes that will facilitate its eventual deployment in clinical practice relate to the inclusion of: 1) health economists to design and execute a robust health economics analysis (cost-effectiveness analysis) in the context of value-based healthcare; 2) consumers in the development of the study, since it is likely to be complex and this advice may lead to better patient adherence; and 3) some sort of qualitative evaluation to determine patient and clinician experiences and attitudes surrounding the treatable traits approach *(i.e.* acceptability, adoption, appropriateness and sustainability), which can help develop a better understanding of the intervention characteristics.

FIGURE 5 *Evolution of a platform trial over time. In this example, three interventions (A, B, and C] and their combinations (AB, BC, and AC] are assessed in a population of patients that includes three subtypes of the disease (indicated by the colours blue, red and yellow], a] When the study is started, randomisation is balanced between all possible treatments and all patient subtypes are treated similarly. After a period of time it appears that BC is having a greater effect than the other treatments and, to a lesser extent, so are B, C and AC. Thus, subsequent randomisation enriches the number of patients assigned to receive BC (indicated by the larger font] as well as B, C and AC (panel b). c] After the trial continues further, analysis reveals that treatment A and its combinations are not effective in any subgroup and the "yellow" subgroup is not effectively treated in any arm, so patients are no longer randomised to receive any combination including treatment A and the "yellow" subgroup is discontinued from further enrolment. At the end of the trial (not shown in the figure] the combination treatment BC may graduate from the trial, based on evidence of benefit in the "blue" subtype of disease, to be recommended for clinical use or for further evaluation in a separate phase III trial. Reproduced from [75] with permission.*

Published in : European Respiratory Journal(2017) 50, pp. 1701655
DOI: 10.1183/13993003.01655-2017
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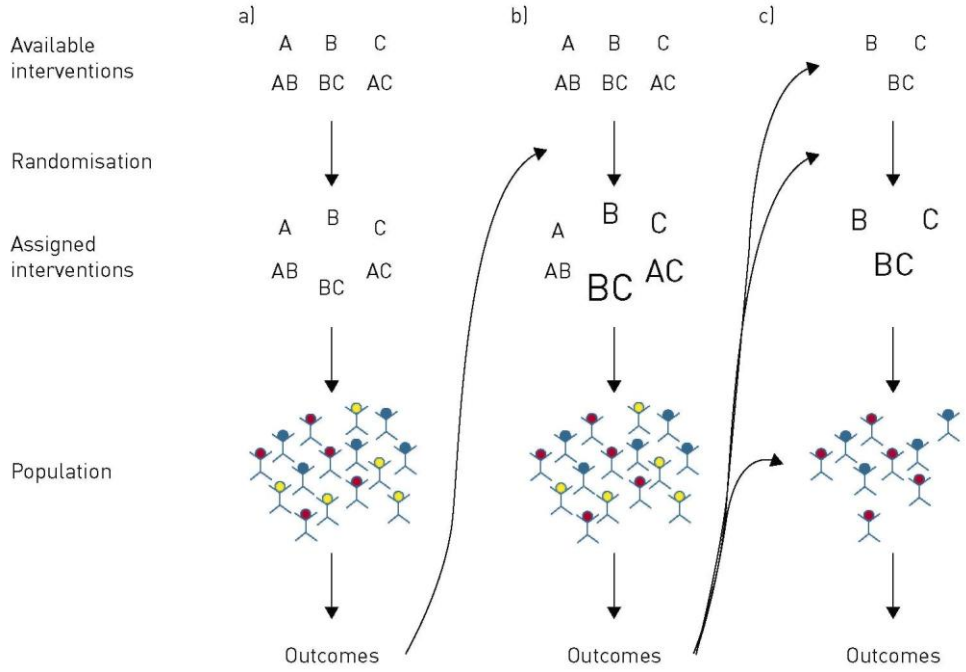

TABLE 2 *Comparison of the main features of traditional versus platform randomised controlled trials (RCTs)*

	Traditional RCTs	**Platform RCTs**
Intervention	Single public health or therapeutic intervention	Various interventions or combinations of interventions New treatments might be added during the trial
Population	Homogeneous (high risk]	Homogeneous or heterogeneous Subgroups defined by clinical phenotypes or biomarkers; might be changed over time
Allocation	Fixed randomisation	Response-adaptive randomisation
Duration	Finite with option of extending duration of follow-up	Potentially long term, extended if novel treatments need assessment
Stopping rules	Trial might be stopped early for success, failure or futility	Individual treatments might be stopped, but trial might be continued with new interventions
Statistics	Standard in-house methods	Complex, Bayesian, continuous analysis, often needing a specialised statistical team
Funding	Government or pharmaceutical company sponsorship	Scope for sponsorship from both government and pharmaceutical companies
Collaboration	Single centre or multiple centres, similar populations	Multicentre, international, from diverse populations

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Conclusions

There was unanimous agreement in the seminar that to improve the current management of complex airway diseases like asthma and COPD a precision medicine approach was required, and that to achieve this in practice the best available alternative was the one based on the treatable traits strategy. However, this consensus needs prospective, formal validation. Several key aspects of such a trial, including design (platform trial), interventions (multidimensional assessment and tailored treatable trait intervention) and outcomes (hard and soft), were discussed. We now hope that independent umbrella organisations such as the European Respiratory Society take on the challenge of promoting and facilitating the prospective testing of whether the adoption of a treatable traits strategy as a first step toward precision medicine of airway diseases improves the outcomes and safety of these patients. The European Organisation for Research and Treatment of Cancer (http://www.eortc.org) does exactly this for cancer. As one of the anonymous reviewers of this paper (to whom we are thankful) suggested, we can do something similar (EORTA: a European Organization for Research and Treatment of Airway diseases) to generate concerted actions to investigate novel treatments and strategies in COPD, asthma, asthma-COPD overlap and bronchiectasis. All of the participants in the seminar (listed in the Acknowledgements section) certainly look forward to doing so.

Acknowledgements

Author contributions: All authors contributed important intellectual content and approved the final manuscript.

Registered participants in the ERS Research Seminar: Amany Abd Al-Aziz, Natia Adamia, Abdelilah Benslimane, Irina Bobolea, Ioannis Bonovolias, Carlos Celis, Aleksandra Chwist-Nowak, Renata Da Palma, Denitsa Dimitrova, Nino fessielito Doydora, Gunnar Einvik, Ramcés Falfàn Valencia, Laura Fregonese, Judith Garcia-Aymerich, Gareth Hynes, Truls Ingebrigtsen, Neves Joao, Alexandra Lopez Giraldo, Flavia Mafia De Lima, Anke-Hilse Maitland-Van Der Zee, Stoilka Mandadzhieva, Dora Marinova, Alexander Mathioudakis, Eduard Monso, Oxana Munteanu, Marta Oliveira, Gloria Pérez-Rubio, Martin Petrek, Emilio Pizzichini, David Ramos Barbon, Roberto Rodriguez-Roisin, Alizaman Sadigov, Sabina Schmitt-Grohé, Ulla Seppala, Rahul Shrimanker, Eman Sobh, Kseniia Sytnyk, Susanne Vijverberg

The authors thank ERS for organising and supporting this research seminar, and all the audience for their active participation. Special thanks to Soraya Barazin and Hanna Michalek (ERS, Lausanne, Switzerland) for outstanding logistical support.

Published in : European Respiratory Journal(2017) 50, pp. 1701655
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