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Review article

Moving towards a Treatable Traits model of care for the management of obstructive airways diseases

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent chronic airways diseases. Both are complex and heterogeneous. Traditionally, clinical guidelines have advocated a stepwise approach to pharmacotherapy of asthma and COPD, but there is increasing realization that both require a more personalized and precise management approach. To this end, a management strategy based on the so-called Treatable Traits has been proposed. Emerging evidence suggests that this model improves relevant outcomes in patients with chronic airway diseases but further research is needed to guide implementation. This review discusses the challenges, opportunities, and hurdles that its implementation will have to face.

"When one begins as a young doctor, one's head is still full of clinical pictures and diagnoses. In the course of the years, impressions of quite another kind accumulate. One is struck by the enormous diversity of human individuals, by the chaotic profusion of individual cases, the special circumstances of whose lives and whose special character produce clinical pictures that, even supposing one still felt the desire to do so, can be squeezed into the straitjacket of a diagnosis only by force." (Carl Jung) [1].

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the two most prevalent chronic airways diseases. Both contribute a high

Abbreviations: CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; DLCO, diffusing capacity of carbon monoxide; FeNO, fractional exhaled nitric oxide; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IL, interleukin; IRR, incidence rate ratio; LABA, long-acting β-2 adrenergic bronchodilator; OCS, oral corticosteroid; RCT, randomized controlled trial; SpO_2, saturation of peripheral oxygen; TT, Treatable Traits.

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disease burden globally, with considerable impact on patients, carers, and healthcare systems [2,3]. Traditionally, clinical guidelines for asthma and COPD, based on the best scientific evidence available at the time, have advocated a stepwise approach to pharmacotherapy, where uncontrolled patients are escalated to higher doses or a combination of medications (Fig. 1A). Adoption of these guidelines has significantly improved the quality of life and prognosis of patients with these two diseases [4]. However, there is increasing realization that both asthma and COPD are complex and heterogeneous, so both require a more personalized and precise management approach.

To this end, a strategy based on the so-called 'Treatable Traits' (TTs) has been proposed [5]. It is based on traits that can be readily identified and targeted in the management of individual patients [5–9] (Fig. 1B). These TTs are assessed in three different domains [5,9]: 1) pulmonary (*e.g.* airflow limitation or emphysema), 2) extrapulmonary (*e.g.* cardiovascular morbidity) and 3) behavioral/lifestyle (*e.g.* smoking, treatment adherence). To an extent, this is already in place for some TTs, including the provision of oxygen in patients with chronic respiratory failure or lung volume reduction surgery for certain patients with emphysema [5,7,9] (Table 1). TTs may coexist and vary over time due to disease progression/evolution or treatment response [5–7,9]. TTs are recognizable and measurable by a validated 'trait identification marker' [9], which is a combination of objective measures of clinical or functional features (phenotypes), such as airflow limitation, or biological mechanisms (endotypes), such as type 2 inflammation [5–9]. Of note, some identifiable traits may not be currently treatable but may guide research into new therapeutic targets, for example neutrophilic airway inflammation [7,9]. It is also important to recognize that the current list of

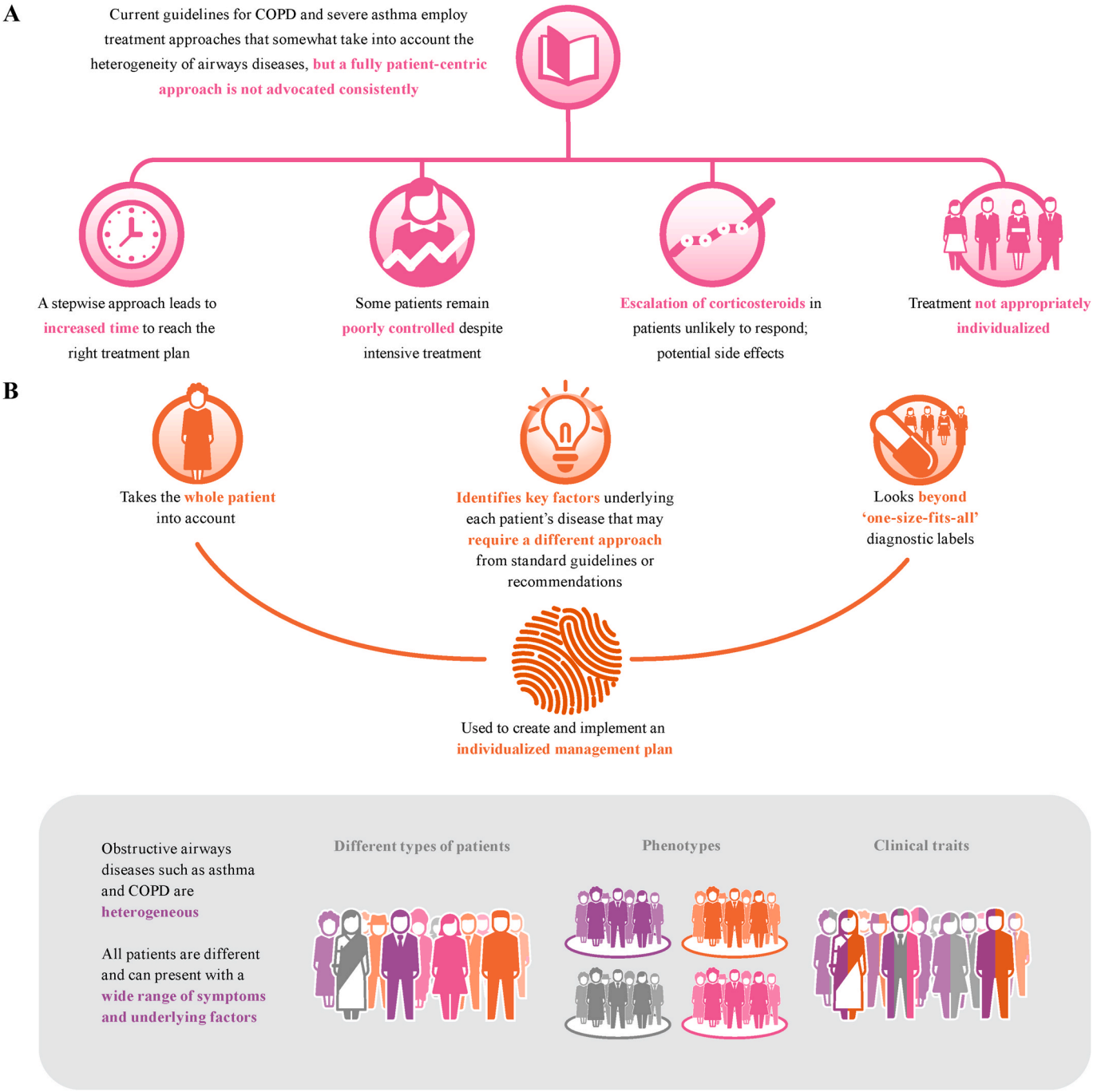

Fig. 1. The current treatment approach (A) [10–14] and the Treatable Traits concept (B) [5–9]. COPD: chronic obstructive pulmonary disease.

Table 1
Proposed guided treatment for some of the most prevalent Treatable Traits in patients with chronic airway diseases in three different domains (pulmonary, extrapulmonary, and lifestyle/behavioral factors) [5,75]. Please note that the list is not exhaustive.

Trait	Identification marker	Recommended treatment
Pulmonary domain		
Airflow limitation	Spirometry	Bronchodilators (long- and short-acting)
Eosinophilic airway inflammation	FeNO, blood eosinophils, sputum eosinophils	Inhaled/oral corticosteroids, biologics
Emphysema	Chest CT, DLCO, measurement of lung compliance	Lung volume reduction, alpha-1 antitrypsin replacement (for patients with confirmed deficiency)
Arterial hypoxemia	Arterial blood gas measurement (oxygen saturation), SpO_2	Supplemental oxygen
Bronchiectasis	Chest CT	Physiotherapy (chest clearance), nebulized antibiotics
Extrapulmonary domain		
Impaired exercise tolerance	6-min walk distance, cardiopulmonary exercise testing	Pulmonary rehabilitation, regular physical activity
Obesity/cachexia	Body mass index, body composition measures	Dietary management, physical activity
Gastroesophageal reflux disease	Gastrointestinal endoscopy, symptoms, pH monitoring	Proton-pump inhibitors, surgery
Anxiety/depression	Questionnaires, psychological assessment	Cognitive behavioral therapy, pharmacotherapy
Lifestyle/behavioral factors		
Smoking	Patient history, exhaled CO concentration, cotinine levels	Smoking cessation counseling, pharmacotherapy
Poor inhaler technique	Observation	Education, frequent assessment of technique, optimization of device types
Treatment non-adherence	Direct questioning, prescription refill rate, smart inhalers	Education, medication optimization (smart inhalers), self-management support
Health literacy/self-management ability	Patient interview, questionnaires, observations	Education

traits is not fixed; new traits will likely be identified in the future, along with treatments. Finally, it should be noted that this TT strategy is not restricted to a single airway disease (asthma or COPD or others) and can potentially be applied to any patient irrespective of the traditional diagnostic labels of asthma or COPD [4].

To make the case for a TT model of care in the management of obstructive airways diseases, below we review and discuss: 1) the currently available evidence for a TT-based care model in asthma and COPD; 2) the challenges and hurdles that the implementation of such a model will likely face for the clinical management of these patients; and 3) potential future considerations and directions in the field.

2. Available evidence for a TT-based care model

2.1. Asthma

2.1.1. The traditional stepwise management approach

Current treatment strategies for asthma are based on a stepwise symptom-directed management approach [10–14] (Fig. 1A). Using this model, which lacks objective assessment of underlying biological processes, there is the potential for treatment to be escalated to higher doses, or further treatments added in, without full consideration of alternative explanations for symptoms in a patient-centric manner [11,15–17]. This can expose patients to adverse side effects from potentially ineffective or potentially harmful treatments, such as high doses of inhaled corticosteroids (ICS) or oral corticosteroids (OCS), particularly in patients with low type 2 inflammation markers or with misattributed symptoms (*e.g.,* vocal cord dysfunction); this 'chasing' of non-responsive symptoms may adversely impact treatment adherence and engagement with the healthcare practitioner. Step-wise treatment can also reduce cost-effectiveness [5,6,15–17] and lead to increased time to reach the best treatment option, since each step up or down may take weeks or months to assess effectiveness [11,13]. Finally, both patients and healthcare professionals tend to overestimate the level of asthma control [18] due to lack of symptom perception or acceptance that symptoms are a part of life, but symptom-based definitions of control may also be overly rigid compared with patients' views. Basing treatment on tightly defined, symptom-based definitions of control risks overtreating some patients, and undertreating others who do not perceive the importance of the underlying inflammation that puts them at risk of acute attacks [17,19].

2.1.2. Previous experience with targeted treatments in asthma

Initial studies demonstrated that ICS and long-acting β-2 adrenergic bronchodilators (LABAs) target different traits in asthma, with ICS having a greater effect on prevention of acute attacks and LABAs on lung function and symptom scores [20–22]. More recently, the Clinical study in Asthma Patients receiving Triple therapy in A single INhaler (CAPTAIN) study in moderate/severe asthma showed that increasing ICS led to significant improvements in lung function (forced expiratory volume in 1 s) and reduced rates of moderate-to-severe attacks only in patients with higher baseline fractionated exhaled nitric oxide (FeNO) and blood eosinophil counts, with no such gains seen in those who had lower levels [21]. This is also the case for the use of regular ICS in mild asthma [23]. However, several studies have shown that the use of ICS plus a rapid onset LABA 'as-needed' as rescue medication reduces symptoms and exacerbation irrespective of baseline markers of type 2 inflammation [8,11,12,24–26]. This approach is also likely to improve adherence, since patients who have infrequent asthma symptoms may be resistant to taking daily controller medication [24]. A logical approach to asthma management is therefore to start with as-needed ICS plus rapid onset LABA but to escalate beyond this to regular treatment in a TT-directed way [27]. This strategy may be more precise and effective than the stepwise usual practice and it will align well with the established personalized approach to use of biologic therapies in severe asthma.

2.1.3. Towards a TT strategy in asthma

Several studies have now shown that systematically assessing and treating potential contributing TTs results in better outcomes in patients with asthma [28–30] including improved health-related quality of life, and asthma control, and a reduced number of acute primary care visits [31,32]. The potential of this approach to improve important outcomes was first shown by Green et al. [33], who demonstrated that asthma attacks were reduced by 70% in patients with moderate and severe asthma whose therapy was directed by an objective measure of type 2 airway inflammation (induced sputum eosinophil count) compared to symptoms. Similar findings were later reported by Powell et al. [34] with FeNO directed management in pregnant women with asthma. More

recently, a randomized controlled trial (RCT) in a severe asthma patient population compared the efficacy of a TT model of care to usual care in a tertiary severe asthma clinic [31]. Traits from the pulmonary, extra-pulmonary and behavioral/lifestyle domains were identified using a multidimensional assessment and then treatments were targeted to only those traits present in that individual. In people with severe asthma a mean ± standard deviation of 10.4 ± 3.0 traits were present and targeting treatment to these traits using a comprehensive TT approach supported by a case manager to facilitate implementation of the plan, and to improve patient acceptance and adherence, resulted in significant improvements in asthma quality of life, asthma control and unscheduled primary care visits compared with usual care [31]. Another RCT of 301 patients with severe asthma tested a composite biomarker algorithm (blood eosinophils, FeNO, periostin) to guide treatment decisions with the primary aim of optimizing inappropriate corticosteroid dose [35]. The primary outcome of this study was not significant [35]. Yet, in the *per* protocol analysis there was a significantly higher proportion of individuals on lower dose of corticosteroid at 48 weeks in the active, compared with the control group whose treatment decisions were made using symptoms and recent exacerbation history [35]. The main reason people were not included in the *per* protocol analysis was that they did not follow advice to adjust treatment and notably the exacerbation rate was higher in patients not following treatment advice [35]. This study illustrates the difficulty in reducing inappropriately high treatment in symptomatic patients and why getting treatment correct at an early stage is critical. It also highlights the need to include behavioral traits such as adherence, self-management ability and health literacy in these novel approaches, as well as supportive interventions, for example case management [36]. Finally, certain TTs have been associated with an increased risk of exacerbations in asthma, for example, depression, inhaler polypharmacy, and vocal cord dysfunction (Fig. 2) [32,37]. As a result, several current asthma guidelines have already evolved towards a TT model of care and recommend the evaluation and management of specific traits [12,38,39].

2.2. Chronic obstructive pulmonary disease

2.2.1. The traditional stepwise management approach

Like in asthma, the traditional approach to the management of COPD also followed a stepwise strategy originally based on the severity of airflow limitation [40]. In 2011, it was empirically recognized that the pharmacological treatment of COPD should be best determined by the level of symptoms and risk of future exacerbations [40]. This gave rise to the now well-known A, B, C and D groups [40]. In 2019, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommended use of these four groups to guide only the 'initial' pharmacological treatment of COPD patients but to move into a TTs strategy to adapt it during follow-up according to the response elicited [41].

2.2.2. Previous experience with targeted treatments in COPD

Exacerbations of COPD are associated with lung function decline and increased mortality [8,11,14]. The previous patient history of exacerbations is the best predictor of future exacerbations in COPD [31,37,42] and, as such, it can be considered a TT [43]. How to reduce this risk is, however, controversial. Several recent studies, reviewed by Agusti et al [44], have now shown that patients with history of multiple or severe

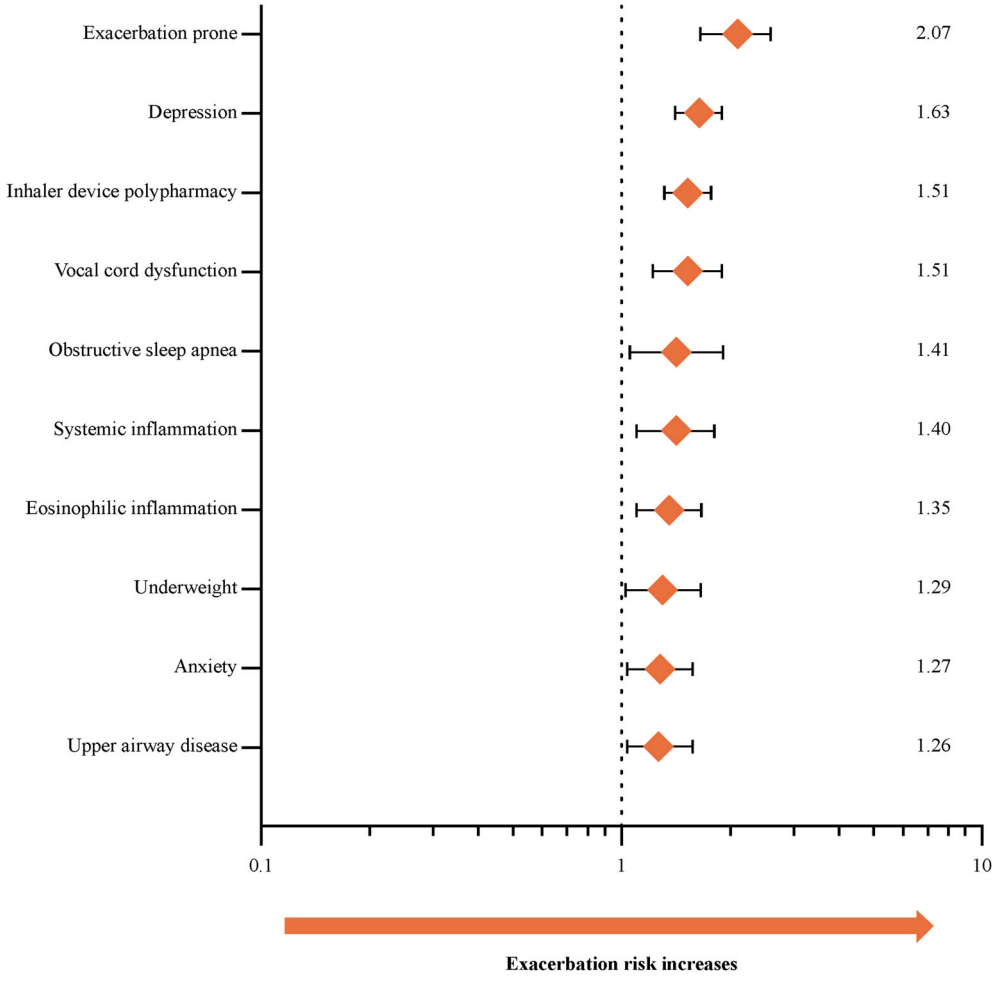

Fig. 2. Treatable Traits and risk of exacerbations in severe asthma [32].

exacerbations despite appropriate maintenance bronchodilator use with blood eosinophil counts >300 cells/μL are most likely to benefit from the addition of ICS to long-acting bronchodilators to prevent future exacerbations. On the other hand, the risk of pneumonia appears to be higher in those COPD patients with older age, lower body mass index, greater overall frailty, receiving higher ICS doses and those with blood eosinophil counts <100 cells/μL [44]. These observations have now been adopted by the GOLD recommendations and clearly support the need for a personalized and precise management of COPD [14]. This is further reinforced by other studies that found improved outcomes in COPD using a combination of multidimensional assessment and measurement of inflammation to tailor treatment to individual patients [45]. In this context, personalized pulmonary rehabilitation programs are particularly helpful to address lifestyle and behavioral TTs in COPD patients [9,14,46,47].

2.2.3. Towards a TT strategy in COPD

The most recent GOLD recommendations for the clinical management of patients with COPD emphasize the need for a TT approach based on symptoms and exacerbations, and the use of blood eosinophils as a biomarker to identify patients who may best respond to the addition of ICS to one or two long-acting bronchodilators [14,48–51]. They also recommend a TT approach for non-pharmacological management, such as use of supplemental oxygen for hypoxemia and pulmonary rehabilitation for reduced exercise tolerance [14,52,53].

3. Implementation of a TT-based care model: Challenges, opportunities and hurdles

A TT-based care model aims to build on existing successful approaches in personalized medicine. As discussed above, some of them are already being recommended in guidelines [12,14,54]. Although the TT approach is likely more complex than the traditional stepwise one, from the above discussion it is anticipated that a TTs model of care will provide both primary care physicians and specialists a better framework for the assessment and treatment of patients with chronic airways diseases [5,9]. Yet, as with any new initiative, there are challenges, opportunities and hurdles that need to be addressed.

3.1. The patient's perspective

Qualitative data from patients with asthma and COPD who were over the age of 55 indicated a desire for a more person-centered approach to their care [55]. Of particular importance was an approach that valued the participants' individuality [55]. They pointed to the need for timely diagnosis and better understanding and education about their condition, which included the need for ongoing assessment of their disease and relevant feedback on their progress [55]. More widespread implementation of TTs could improve this by providing clear guidance for clinicians on what to look for and treat as well as approaches that involve patients in clinician-patient decision making. Existing technology such as smart inhalers may become increasingly useful as a tool for implementation of a TT-based model of care [8,56,57]. Finally, a discussion with clinicians caring for patients with severe asthma indicated that a personalized model of care would be welcomed [58].

3.2. Supporting scientific evidence: The RCT dogma

Treatment recommendations in current asthma and COPD guidelines are supported by high quality research evidence for specific therapeutic interventions in the tightly controlled environment of an RCT [59], but the effectiveness of the stepwise approach/model of care itself has never been formally tested in a RCT. Likewise, due to the restrictive inclusion and exclusion criteria of any RCT, included participants do not represent the general population at large, where treatments will be applied in real life [5–9,59–61]. However, this inter-subject heterogeneity is not consistently addressed in current management recommendations and it is often not considered by clinicians when selecting treatments. So, while acknowledging that there is no formal RCT testing the TT strategy versus the currently recommended stepwise approach (itself never tested in an RCT either), several examples support the use of targeted treatment based on specific TTs and validated biomarkers. These include anti-immunoglobulin E, interleukin (IL)-5, and IL-4 antibodies, approved for uncontrolled allergic and eosinophilic (type 2) asthma [62]. A broad spectrum of other agents is currently being tested in clinical trials; the ongoing PreCISE (Precision Interventions for Severe and/or Exacerbation-Prone Asthma) Network Study, due to complete in 2023, is currently evaluating six therapies (imatinib mesylate [kinase receptor inhibitor], itacitinib [Janus kinase 1 inhibitor], clazakizumab [anti-IL-6 antibody], medium chain triglyceride [nutritional ketosis], broncho-vaxom [bacterial extract], and cavosonstat [S-nitrosoglutathione reductase inhibitor]) to identify novel therapies with utility in biomarker defined subgroups (NCT04129931). Notably, IL-6 is causally associated with significantly higher risks of asthma and is also considered an important target for precision therapy [63]. In regard to COPD, targeted treatment to reduce sputum eosinophilia in asthma and COPD reduced the frequency of severe exacerbations compared with standard management [33,64]. Likewise, a study comparing treatment of asthma in pregnancy found a significant reduction of exacerbations and short-acting β-2 agonist use in patients following a FeNO-guided protocol for escalation of ICS or LABA, versus a standard clinical algorithm based on guidelines [34]. Finally, mepolizumab (an anti-IL-5 biologic treatment) was ineffective in patients with asthma at large, but it was highly effective to prevent exacerbations in those with a specific TT (eosinophilic inflammation) [6,8,65]. A strategy based on TT may overcome the somewhat artificial debate created by the proposal of an asthma−COPD overlap because it goes beyond the diagnostic label and focuses on what TTs a given patient has and on how to best help her/him. These results exemplify that treatment targeted to a given TT is more effective, so the need for an RCT that tests the strategy as a whole may not be mandatory, provided implementation studies are performed in different settings.

3.3. Resource considerations

Logistical barriers such as geography, culture, finance, and healthcare resources may affect the provision of care in chronic airways diseases, especially for some targeted or multidisciplinary interventions [7,9,11,14,66]. Implementation strategies need to recognize these barriers and adapt to the resources available, including ensuring access to appropriate investigations and training in how to respond appropriately to findings [66]. However, although additional resources may be required to meet these needs in some situations, a TT-based strategy can help to not 'waste' drugs on the wrong patients [66]. Expected outcomes are the reduction of unnecessary costs and risk of overtreatment [66] as well as medication and hospitalization/healthcare use, which are the major direct costs of airways diseases [3,51,67], so the approach may prove cost effective for the system as a whole. Although secondary/specialist care is likely to have more time, expertise, and resources to identify and treat more complex TTs than primary care, it is possible to envisage a TT strategy appropriately scaled for primary care [5]. This requires focusing on certain key traits that can be easily identified and managed in this setting [66]. Finally, simplification of prescribed treatment and of information provided to patients and carers following a TT assessment has the potential to reduce the carer burden and facilitate focus on the most relevant specific TTs [68].

3.4. Hierarchy of TTs

Some TTs should be prioritized based on cost, clinical utility, impact, prevalence, and patient understanding [7,9]. Traits requiring pharmacological intervention, such as type 2 inflammation [9,66] and airflow limitation [9,66], and non-pharmacological interventions, such as poor inhaler technique [66,69,70], non-adherence (intentional and non-intentional)

[8,56,66], smoking [11,13,14,66], and nutritional status [66], have each been identified as key TTs [66] with a number of traits associated with an increased risk of exacerbations in asthma (Fig. 2) [71]. Identification and management of these traits may be particularly well suited to primary care and lower-resource settings [45]. It is also important to recognize that patients and physicians may place different priorities on which outcomes are more important and should be prioritized. For example, clinicians may be concerned about lung function and risk of exacerbations while patients will be more focused on their daily symptoms and impact on daily living, requiring very different choices of therapy to optimize such disparate outcomes [9,32].

4. Future considerations and directions

A number of RCTs have already assessed the TTs approach as a whole [31,32,61,72], as well as examining how specific TTs can be targeted [21,22,45] and, in fact, several current guidelines for airways diseases already acknowledge the existence and benefits of treating multiple TTs across domains [10,12–14]. Yet, further supportive evidence is needed. Here, real-world trials such as the innovative Salford Lung Study, a prospective, phase 3, pragmatic RCT in patients with COPD and asthma [73,74], could be used to evaluate the effectiveness and safety of treatments in a setting reflective of real clinical practice, while maintaining the scientific rigor of RCTs [74]. The next consideration should therefore be how evidence supporting a TTs model of care can be incorporated into current guidelines and future management strategies, following the example of the proposed joint guidelines on chronic asthma from the British Thoracic Society, Scottish Intercollegiate Guideline Network, and National Institute for Health and Care Excellence (https://www.brit-thoracic.org.uk/about-us/pressmedia/2019/bts-sign-and-nice-to-produce-joint-guideline-on-chronic-asthma).

5. Conclusions

The complexity and heterogeneity of asthma and COPD are increasingly recognized but not always appropriately addressed. A TTs approach recognizes and targets this complexity and heterogeneity, both between patients and over time, and acknowledges the variability of the underlying pathophysiology (endotypes) as well as clinical presentation (phenotypes) by addressing features of these diseases across multiple domains. Existing tactics using personalized medicine suggest that a TTs approach in chronic airways diseases is likely to be successful, and there is already a growing body of evidence to support its use. Further investigations will provide additional guidance towards implementing the TTs approach across a range of settings and resources.

Author contributions

All authors contributed to the conception/design, data analysis and interpretation, writing and approval of the manuscript and decision to submit for publication.

Disclosures/conflicts of interest

AA has received speaker's honoraria from AstraZeneca, Chiesi, GlaxoSmithKline, and Menarini. He has also received honoraria for attending advisory panels for AstraZeneca, Chiesi, and GlaxoSmithKline, and grant support for research projects from AstraZeneca and GlaxoSmithKline. AA is the Chair of the Board of Directors of GOLD (Global Initiative for Chronic Obstructive Lung Disease).

NB is an employee of GlaxoSmithKline and holds share options. DL and LY are also employees of GlaxoSmithKline with no further disclosures.

AAC reports non-financial support from GlaxoSmithKline during the conduct of the study. He has also received consultancy and speaker's honoraria from AstraZeneca, Chiesi, Eurofarma, Glenmark, Mylan, Novartis, and Sanofi. He has also received grant support from GlaxoSmithKline.

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HI has participated in Advisory boards and has received speaker's honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Chugai, GlaxoSmithKline, Kyorin, Merck Sharp & Dohme, Novartis, and Sanofi. He has also received research/educational grant support from Boehringer Ingelheim, Chugai, GlaxoSmithKline, Kyorin, Merck Sharp & Dohme, Novartis, Ono, Pfizer, Sanofi, Shionogi, Taiho, and Teijin-Pharma.

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SW has nothing to disclose.

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