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TREATABLE TRAITS IN AIRWAY DISEASE: FROM THEORY TO PRACTICE

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Abbreviations:

BMI: body mass index

COPD: chronic obstructive pulmonary diseases

CVD: cardiovascular disease

HCP: health care professionals

ICS: inhaled corticosteroid

IL: interleukin

LMIC: low- and middle-income country

MAbs: monoclonal antibodies

NNT: Number needed to treat

OCS: oral corticosteroids

TT: treatable trait

TIM: trait identification marker

ABSTRACT

Chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) are prevalent and complex conditions that often coexist in the same patient. To address this complexity in clinical practice, and to move forward towards personalized and precision medicine of airway diseases, a strategy based on the identification and treatment of so-called “Treatable Traits” (TTs) has been proposed. A TT is a recognizable phenotypic or endotypic characteristic that can be assessed and successfully targeted by therapy to improve a clinical outcome in a patient with airway disease. Importantly, TTs can co-exist in the same patient, so they are not mutually exclusive. The TTs strategy proposes to investigate in each individual patient with chronic airway disease the number and type of TTs present, and to treat each of them according to guideline recommendations. This strategy is agnostic (i.e., independent) to the traditional diagnostic labels (asthma, COPD), so it can be applied to any patient with airway disease. Currently, there is firm evidence supporting the adequacy and validity of the TT strategy. Here, we review the current state-of-the-art of this topic, first by presenting its theoretical background and then by discussing how to best implement it in clinical practice.

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INTRODUCTION

Chronic airway diseases, including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis, are prevalent and complex conditions that often coexist in the same patient [1-3]. In this setting, "complex" means that they have several elements with non-linear relationships between them (FEV1, exacerbations, symptom perception, and comorbidities, among others), so they cannot be predicted from the presence/absence of the others [4]. Further, not all these elements are present in all patients, and in a given patient they may change over time (due to disease progression and/or as a result of treatment) [4].

In 2016, a strategy based on the identification and treatment of so-called "Treatable Traits" (TTs) was proposed to address this complexity and to move forward towards personalized and precision medicine of airway diseases [5]. Since then, more than 70 papers related to TT have been published, including two systematic reviews [6, 7] and two proof-of-concept clinical trials: one in severe asthma [8] and another in COPD [9]. Collectively, this large body of evidence strongly supports the TT strategy for the management of patients with chronic airway diseases. Below, we review the current state-of-the-art on this topic. To do so, we first present the theoretical background of the TT strategy and then discuss how to best implement it in clinical practice.

FROM THEORY …

What is a treatable trait?

A TT is a recognizable phenotypic or endotypic characteristic that can be assessed and successfully targeted by therapy to improve a clinical outcome in a patient with airway disease [5]. Importantly, TTs can co-exist in the same patient, so they are not mutually exclusive. TTs must share three characteristics [10]: *(1) clinical relevance*, which means that they are linked to a relevant clinical outcome such as exacerbations, quality of life or lung function decline; *(2) detectable* either "phenotypically" (i.e., clinically; e.g. presence of emphysema on computed tomography) and/or based on deep understanding of critical causal pathways ("endotypes") through validated "trait identification markers (TIM)" (e.g. circulating eosinophils, see below); and, *(3) treatable*, meaning that effective treatment is available and accessible, and when implemented leads to a clinically important outcome for patients with airway diseases. Admittedly, there are currently untreatable traits, but they may also be important to consider in the clinical management of the patient and they clearly constitute targets for research. A well-recognized example of a TT is eosinophilic airway inflammation [11]. This is an endotype of airway disease mediated by specific cytokines such as interleukin (IL)-5 [11]. Increased levels of eosinophilic inflammation are associated with increased exacerbation risk in both asthma and COPD, indicating it is clinically relevant [11]. This trait can be detected via blood eosinophil count (a TIM) and can be treated via inhaled corticosteroids, oral corticosteroids, or T2 directed monoclonal antibody (mAbs) therapy. The endotype of eosinophilic airway inflammation meets each of the three criteria named above for designation as a treatable trait because it is relevant, detectable, and treatable.

What is the Treatable Traits strategy?

The TTs strategy proposes to investigate in each individual patient with chronic airway disease the number and type of TTs present, and to treat each of them according to guideline recommendations [5]. This strategy is agnostic (i.e., independent) to the traditional diagnostic labels (asthma, COPD, bronchiectasis), so it can be applied to any patient with airway disease [5]. In clinical practice, these traditional diagnostic labels may constitute a good starting point of the diagnostic process, not its end. This is, after having established a first diagnostic approximation (label), it is imperative to deconstruct the clinical and biologic complexity of each patient using a TTs strategy.

Prevalence of TTs

There are many potential TTs in chronic airway diseases which can be ordered into three domains, namely pulmonary traits, extrapulmonary traits, and risk factor/behavioural traits (Table 1) [5, 10]. Very recently, the NOVELTY study [12], a large (19 countries around the globe), real-life study of 11,226 patients with asthma, COPD and asthma-COPD recruited from primary care clinic and specialized referral hospitals, has shown that the prevalence of 30 TTs determined in this population vary widely (Figure 1A) and that, albeit there were no large global geographical variations, the prevalence of TTs was different (generally lower) in primary versus specialized clinics[12].

Patients typically have more than one TT present at any one time. For example, in severe COPD and severe asthma, patients express an average of 10 treatable traits [8, 13]. In the NOVELTY study, which included milder patients too, the mean TTs prevalence was lower but still considerable (Figure 1B): 4.6 (asthma), 5.4 (COPD) and 6.4 (asthma-COPD) TTs per person [12]. Figure 2 shows the network of TT co-occurrence (i.e., the proportion of patients presenting two given TTs) by disease label. In asthma, the most frequent TT pairs included rhinosinusitis, respiratory and non-respiratory allergies, T2-high markers, obesity, occupational exposures, indoor use of biomass/coal and frequent reliever use. In COPD, the most prevalent TT pairs included non-reversible airflow limitation, emphysema, frequent productive cough, environmental exposures (including smoking), exacerbation prone and frequent reliever use. Finally, the cooccurrence network was most complex in patients diagnosed with asthma-COPD [12].

Relationship with disease label and severity

Some TTs are relatively specific to the diagnosis and severity of disease, but many others are not. For example, the trait of airflow limitation occurs in 100% of patients with COPD [14], but only in up to 60% in patients with severe asthma [15]. In asthma, the pulmonary trait of eosinophilic inflammation has a similar prevalence in severe and mild-moderate asthma (40%), whereas fixed airflow limitation is more prevalent in

154 severe asthma than mild asthma (56% vs 20%, p<0.001) [15]. Some comorbidities are
155 more prevalent in severe disease, such as osteoporosis, systemic inflammation, and
156 physical inactivity which are more prevalent in severe than mild COPD [14].

157

158 In the recent analysis of the NOVELTY cohort, six pulmonary TTs, including nasal
159 sinus polyps and several allergies in asthma, and non-reversible airflow limitation, and
160 emphysema in COPD (plus smoking and comorbidities), were distinctly associated with
161 their respective diagnostic label [12]. By contrast, the prevalence of 18 pulmonary, extra-
162 pulmonary and/or behavioural/environmental TTs was independent of the diagnostic
163 label, including some TTs traditionally considered almost exclusive to asthma or
164 COPD, such as bronchodilator reversibility, T2 and frequent productive cough [12]. This
165 is clinically relevant because it indicates that these 18 TTs should be considered in any
166 patient with chronic airway disease, irrespective of the diagnostic label. This analysis in
167 NOVELTY also showed that the prevalence of some, but not all, TTs increased with
168 disease severity and that the number of TTs typically associated with a perception of a
169 more severe disease varied between disease labels, whereas the prevalence of other TTs
170 did not change at all [12].

171

172 Collectively, therefore, these results underscore the heterogeneity of traits that are
173 present in airway disease [16]. Actually, it is both the *presence* and *absence* of TTs what
174 forms a *pattern* that is recognized by clinicians to establish a diagnosis, grade its
175 severity and prescribe which they think is the best treatment option for that patient in
176 particular [12].

177

178 **Clinical relevance**
179 There is firm evidence that treating each individual TT (Table 1) is clinically relevant,
180 as summarized in guidelines [1, 2, 17] and detailed reviews [18, 19]. For instance, individual
181 traits have been associated with severe asthma exacerbations [20], impaired quality of life
182 [21], and lung function decline in COPD [14]. The evidence base supporting the treatable
183 traits approach is also apparent. Clinical trials in both severe asthma and COPD have
184 tested a model of care that used multidimensional assessment with trait identification
185 markers to detect the traits, and then applied targeted pharmacological and non-
186 pharmacological therapy to treat the evident traits, with implementation of the treatment
187 via a multidisciplinary team supported by a nursing case manager. These trials resulted
188 in significant improvements in health-related quality of life and biological outcomes in
189 both conditions [8, 9]. Furthermore, a recent systematic review and meta-analysis which
190 sought to determine the effectiveness of interventions targeting treatable traits
191 demonstrated that treatable trait interventions improve HRQOL (mean difference [MD]
192 -6.96,95% CI: -9.92 to -4.01), hospitalizations (odds ratio [OR] 0.52, 95% CI: 0.39 to
193 0.69), all-cause mortality (OR 0.65, 95% CI: 0.45 to 0.95) and symptoms including
194 dyspnoea, anxiety, and depression [7]. A treatable traits intervention was defined as an
195 individualized assessment and targeting of at least one trait within the pulmonary,
196 extrapulmonary or behavioral/risk factor domain. These studies have evaluated models

of treatable traits care that target multiple traits. Other studies have also demonstrated superiority when targeting one or two traits. Targeting the trait of eosinophilic inflammation measured by induced sputum [22, 23] or fractional exhaled nitric oxide [24] has demonstrated superiority in exacerbation reduction over symptom-based management in both asthma [24] and COPD [25] populations. In the double-blind, randomized, parallel-group, phase 3 study (Clinical Study in Asthma Patients Receiving Triple Therapy in a Single Inhaler [CAPTAIN]), higher dose ICS reduced exacerbations in patients with moderate asthma who had elevated markers of T2 inflammation [26]. Collectively, these studies support the TTs approach, by demonstrating a range of improved outcomes following identification of a trait and management with a targeted therapy.

Comorbid diseases are also important TTs, which are frequently amenable to treatment [18, 27]. Of note, a recent analysis of the Tasmanian Longitudinal Health Study showed that distinct longitudinal trajectories of asthma and allergic disease from 7 to 53 years of age are associated with different profiles of extrapulmonary comorbidities and varying risk of COPD [28]. Authors concluded that their observations could inform personalized management based on TTs, with comorbidity profiles emerging as a new target for early identification and intervention [28]. Likewise, a study in the Framingham Offspring Cohort showed that young adults (25 years of age) with reduced lung function were at higher risk of cardiovascular and metabolic comorbidities and premature death [29]. This highlights the potential role of spirometry as a global health marker [30-32].

Finally, social determinants of health, including income, education, employment security, working conditions, food security housing, early childhood development social inclusion, access to affordable healthcare and structural conflict (https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1) are clinically important and identifiable but as yet we can't establish if they are treatable. So, they actually represent *potential* TTs.

Trait Prioritization

The demands and resource limitations in clinical practice mean that it is necessary to prioritize certain TTs for assessment and management. This prioritization can be done based on several different parameters, including outcomes, prevalence, setting. In fact, so-called "super-traits" can be identified by a structured assessment of each trait against preset criteria of ability to predict future attacks, the size of the treatment effect, or whether treating the trait addresses more than one trait or outcome[33].

TTs can be prioritized into those that relate to specific outcomes, such as disease exacerbations or frequent oral corticosteroid use. This approach targets a high burden outcome and reduces the number of assessable traits to 11 (Figure 3). These traits are recognized by a specific TIM and are then targeted for treatment. These traits respond to a combination of specific pharmacotherapy and behavioral interventions.

Issues related to prevalence of TTs have been discussed above (Figure 1). To start by targeting the most prevalent TTs may be adequate in some health-care settings. For instance, a tertiary care setting offering a severe asthma service might choose to assess many traits and offer therapy, recognizing the high disease burden of their patient group [34]. In primary care, and in LMIC, a more focused approach is required, based on available resources, including time[35]. This allows a minimum number of traits to be identified. These include: T2 inflammation, airflow limitation, smoking, inhaler device technique/adherence, key comorbidities/risk-factors, such as high BMI and physical inactivity [35, 36].

An emerging concept is that of *super-traits*. These are traits that are essential to identify and treat in order to effectively manage other traits, or traits that have such a large positive treatment effect that management is crucial, that once identified and treated lead to improvement on other apparently unrelated traits. Examples of super-traits with each of these characteristics are:

- *Adherence/Inhaler device technique:* this trait is foundational for the pharmacological and behavioral treatment of many other traits. For example, adequate inhaler device technique is essential for successful therapy of the traits of T2 high eosinophilic inflammation (with ICS), and airflow limitation (with inhaled long-acting bronchodilators). Adherence underpins successful pharmacotherapy of all traits. Similarly, adherence is essential to the behavioral change required to improve traits such as obesity, physical inactivity or smoking.
- *T2 inflammation:* the effect size of treating T2 inflammation with ICS (in mild-moderate asthma) or targeted mAbs (in severe eosinophilic asthma) is large with NNTs of 2-3 for ICS [37] and an average 50% reduction in severe exacerbations with T2 mAbs in severe asthma. This means T2 inflammation may be a super-trait in airway disease.
- *High BMI/obesity*: targeting this trait with a 5-10% weight loss leads to improvement in other traits, such as dyspnea, cardiovascular risk factors, and comorbidities such as diabetes, hypertension, obstructive sleep apnea [38-40].
- *Smoking* may also be a super-trait to target with smoking cessation since it will influence lung function decline, exacerbation risk, ICS treatment responsiveness, mucus hypersecretion, and recurrent infective bronchitis.

… TO PRACTICE

The current approach to asthma and COPD management is stepped care, and risk reduction [1, 2]. While these approaches have led to major advances in asthma and COPD outcomes, and despite a movement toward more personalized guideline-based approaches, treatment recommendations continue to be single disease/diagnosis focused. This is problematic as real-life patients present with overlapping diagnoses and heterogeneous and complex clinical conditions [12, 13]. A diagnostic label–centered approach can lead to a failure to identify and address many problems experienced by people with airway disease. Attempting to apply a diagnostic label to people with overlapping disease can cause confusion for clinicians, and disregarding the multiple traits can limit treatment success [41]. However, it is necessary for both patients and clinicians to have a handy short-hand label to use in communication about their

condition(s). This label, or disease diagnosis, can be selected so that it aids communication and does not cause confusion, as in the case of diagnosis overlap. Examples include using a compound diagnostic label, such as 'eosinophilic COPD', or 'non-eosinophilic asthma'; or using an umbrella term, for example 'airways disease' or 'obstructive airways disease'. Treatable traits offer a solution to these clinical conundrums by identifying the traits that exist in each patient irrespective of diagnosis, and personalizing treatments accordingly [5]. Due to the ongoing symptom, exacerbation and mortality burden associated with these conditions, the priority now is to implement new approaches that address the complexity, heterogeneity, and the residual burden that patients continue to experience [42]. We propose that we are ready to implement the treatable traits model of care, and rather than conducting large scale efficacy randomized controlled trials we ought to focus on real world implementation. This does not differ from the implementation of guideline-based management that uses level one evidence to recommend treatments of stepped care. At no stage has the stepped care model of management been evaluated in a RCT, but there is nonetheless confidence for the implementation of this approach because the specific treatments are supported by evidence. Similarly, the treatable traits approach offers evidence-based treatment recommendations to be implemented via this model of care. Table 1 gives an example of the traits, their treatments, and the associated evidence level. Of course, as discussed above, there remains traits that are perhaps not yet treatable or modifiable, and further efficacy research is necessary to advance treatment. Examples of these traits include neutrophilic inflammation and systemic inflammation. Importantly, while the treatable traits approach has been proposed in children, we are not aware of any studies that have tested this approach as a model of care. Evaluating treatable traits in paediatric populations is an area for future research.

What is challenging about implementation?

Implementing evidence to practice is challenging. Studies conducted from the 1980s through to 2011 indicate that it takes 17–20 years to move clinical innovations from research into practice; and that less than 50% of clinical innovations ever translate [43]. This lag in implementation of research to practice halts progress in patient care and in improving patient outcomes. Patients with airway disease cannot afford this to happen and improving the lag in implementation must be a priority for policy makers and health care professionals. In relation to treatable traits, criticism of the approach has been that it is not feasible within the current health care system, especially primary care, that it has cost implications, and that it is too hard for patients. As proponents of the TT strategy, we refute these claims.

To demonstrate the feasibility of implementing a 'treatable traits' approach, an analogy may be drawn with other diseases, such as cardiovascular disease (CVD). In the mid-1990s risk stratification was successfully implemented in primary care to estimate the risk of heart attack and to prevent future events. This approach has had major positive impacts on cardiovascular outcomes [44]. Traits or risk factors (blood pressure, cholesterol, age, smoking) are assessed and a risk profile determined using nomograms.

Uptake of this approach in primary care has been highly successful. Drawing on this experience a similar approach has been proposed in asthma to prevent asthma attacks. Couillard *et al* have developed a theragnostic risk assessment prototype (ORACLE) that was derived using trial-based data [45]. The prototype is purposely similar to the CVD risk assessment in its presentation and color and instead of blood pressure and cholesterol, T2 biomarkers of FENO and blood eosinophils, and important clinical risk factors such as asthma control, smoking, FEV1, adherence, β2 overuse are used to determine the predicted annual asthma attack rates [45]. Using trial-based data the validation of this prototype suggests that the tool can quantify excess risk of asthma attacks in T2 high population and that the risk can be removed using anti-inflammatory treatment[45]. This does however require validation in clinic populations, but it is an example of how treatable traits could be implemented in primary care in a similar way that was so successful for CVD. Of note, FeNO reflects IL-13 driven T2 processes, which represents a different but complementary pathway to blood eosinophil counts which are driven by IL-5 mediated pathways. Because of this complementarity, FeNO and blood eosinophils have additive predictive and prognostic value[45].

In terms of cost, while to date and to our knowledge there has been no health economic analysis of treatable traits versus usual care, we anticipate that while there may be an initial increase that this will become cost neutral when considering the potential impact on exacerbations, health care utilization for acute events, and the impact on quality adjusted life years (QALYs). Economic modelling from Australia suggests that under highly conservative assumptions targeted therapy could result in savings in the direct cost of asthma of $130 million over ten years [46].

In addressing the assumption that it is too hard for patients, qualitative data indicate that patients with asthma (and their careers [47]) and COPD are seeking more personalized approaches to care, desire feedback on objective testing, and want to be involved in decision making [48]. The key is to engage patients in the approach. This is addressed in a later section.

What are the key elements for implementation?

Patients with airway diseases are managed across a continuum of health care settings, with patients with mild disease managed predominantly within primary care, and as disease severity and complexity increases patients are referred to secondary and tertiary care models. As severity and complexity escalates the needs of both the patient and the health care delivery services also increase. In fact, the NOVELTY study showed that the prevalence of TTs differed according to primary and specialist clinics [12]. Consequently it is important to tailor the multidimensional assessment according to the setting in which the patient is receiving care [49]. An example of such an approach is presented in Figure 4: the increasing number of TTs or refractoriness to the individualized trait treatments should prompt referral to specialist care for a more comprehensive assessment and management plan.

In any case, we propose that TTs should be implemented for all patients with chronic airway disease regardless of the disease severity or the setting in which the patient is receiving their care. We also recognize however that the model of TTs should be different according to the setting and the resources available. Approaches have been proposed to address this and include a focused versus a broad approach [10], that is focusing on dominant traits, for example identifying T2 high inflammation and airflow limitation, and treating these traits with ICS and bronchodilators in the first instance and then identifying the remaining traits should the patient not respond [50]. The broad approach would simultaneously or even sequentially assess the array of interacting traits within the pulmonary, extra pulmonary, and risk-factor/behaviour domains (Table 1). Others have proposed a phased approach to assessment and management [51].

Some studies have attempted to outline a hierarchy of traits. In analysis of 434 patients with severe asthma and 102 patients with uncontrolled asthma who underwent an assessment to characterize treatable traits and were followed prospectively for up to two years, the authors identified 10 traits that predicted future exacerbations. These were in the three domains of pulmonary, extra-pulmonary and behavioral and risk factors. In order of risk the traits included being exacerbation prone (incident rate ratio [IRR] and 95% confidence interval 2.07 (1.66,2.58)), depression (1.63 (1.41,1.88)), vocal cord dysfunction (1.51 (1.22,1.88)), inhaler device polypharmacy (1.51 (1.05,1.89)), obstructive sleep apnea (1.41 (1.05,1.89)), systemic inflammation (1.40 (1.10,1.79)), eosinophilic inflammation (1.35 (1.10,1.65)), being underweight (1.29 (1.00,1.64)), anxiety (1.27 (1.03,1.56)) and upper airway disease (1.26 (1.03,1.55)) [20]. In another study Hiles *et al* [21] performed Bayesian model averaging using data from two small treatable traits trials to first understand the traits that predict future decline in quality of life (measured by the St George's Respiratory Questionnaire (SGRQ)) and secondly to see which treatment of traits was associated with the greatest improvement in quality of life. In this analysis the TTs that were most substantially associated with worse HRQOL at baseline were frequent chest infections, breathing pattern disorder, inadequate inhaler technique, systemic inflammation (C-reactive protein >3 mg/L), and depression [21]. In another analysis that used data from the English Longitudinal Study of Ageing (ELSA) and evaluated the treatable traits that predict lung function and quality of life decline in a COPD cohort [14], chronic bronchitis (β −0.186, 95% CI −0.290 to −0.082), breathlessness (β −0.093, 95% CI −0.164 to −0.022), underweight (β −0.216, 95% CI−0.373 to −0.058), sarcopenia (β −0.162, 95% CI −0.262 to −0.061) and current smoking (β −0.228, 95% CI −0.304 to −0.153) were shown to predict decline in forced expiratory volume in 1 s (FEV1), and depression (β −7.19, 95% CI −8.81 to −5.57) and poor family and social support (β −5.12, 95% CI −6.65 to −3.59) were the strongest predictors of QoL decline. This analysis did not include inflammatory biomarkers in its evaluation [14].

While there is no evidenced based answer on the ideal approach within different settings, we propose a pragmatic one. One that considers the setting and capacity of

primary, secondary, and tertiary care, and that considers the needs of patients. This approach could prioritize TTs in terms of their severity, their prevalence, or their impact on specific outcomes (exacerbations, symptoms and health status, death), as well as those that have high importance from a patient and clinician perspective. Such an approach would commence in primary care with a confirmation of an airway disease diagnosis. Pulmonary traits that can be easily assessed in most settings and are excellent predictors of future risk include airflow limitation using spirometry, and T2 inflammation with blood eosinophil count from a full blood count. There are however other important risk- factor traits that impact clinical outcome, that can be assessed and addressed in primary care or in low and middle income countries. These include what we consider the 'super-traits' of inhaler device technique and inhaler device polypharmacy, adherence, and smoking [35]. Once these are assessed and appropriately managed in primary care there are red flags that should prompt referral to specialist centers for comprehensive multidimensional assessment and a personalized treatment program based on the results of that assessment (Figure 4).

So how do we engage clinicians, patients, and payers in this management paradigm? To change practice, we need to first understand the barriers and enablers to practice change in this area. Majellano *et al* [52] conducted a qualitative study to determine health care professionals' (HCP) perceived barriers and enablers that influence the implementation of personalized care in severe asthma. The authors reported that the barriers span multiple levels, including HCPs' perceived patient-, system-, and provider related factors. These data were mapped to the Theoretical Domains Framework (TDF) [53] to further understand these barriers and enablers in relation to practice change. From the TDF mapping six overarching domains were identified which included: (i) belief about consequences, (ii) environmental context and resources, (iii) belief about capabilities, (iv) social/professional role and identity, (v) goals and (vi) knowledge. Essentially clinicians require improved knowledge of new biological therapies and approaches to care. Access to information and open communication is key. Whilst attitudes play part, clinician's knowledge, effective communication strategies and effective transfer of information between clinicians in various settings have a key role to play in improving personalized airway disease management. Other practice tools to help clinicians in the implementation of treatable traits include smart phone applications, treatable traits action plans, desk top control panels, online toolkits, and massive open online courses, as well as system redesign to support personalized practice. These are important areas of implementation research that require focus in this space.

At the centre of this precision medicine model of care for airway disease is the patient. Implementation of the treatable traits approach must consider the needs of the individual requiring care. These needs are multifactional and should include an assessment of the traits and outcomes of greatest importance to the individual [54 55], their disease knowledge, and their understanding of the traits and how the individualized treatment targets the trait, (knowledge and health literacy), acceptance of the treatment (adherence), their own illness perception and their relationship or rapport with their

clinicians, and involvement in shared decision making. Tools (smart phone apps, infographics, information resources, decision tools) that support patients in the implementation of the treatable traits approach are also needed (Figure 5).

A way to facilitate implementation using these factors is with case-management. A key aspect of the trials reported by McDonald *et al.* [8, 9] was the inclusion of a nursing case manager to implement the treatable traits intervention. The nursing case manager had an integral role in providing education, delivering nonpharmacological interventions, and ensuring that patients understood the rationale for the treatment, and engaged in the treatment advice. In a primary care setting this role could be provided by a practice nurse and in specialist care by a member of the multidisciplinary team, usually a specialist nurse [34].

Finally, TT is a proven model of care that could be used to implement guideline recommendations. For instance, GOLD has already adopted it to guide pharmacologic management of COPD patients during follow-up by identifying two key TT: dyspnea and exacerbations [2].

CONCLUSIONS

A precision medicine strategy based on the identification and treatment of TTs was proposed six years ago as a way to improve the clinical management of patients with chronic airway diseases [5]. Since then, a large body of evidence now supports it [10, 21, 56, 57]. Thus, the question is no longer “what” but “how”. To address this, we reviewed above a number of logistic issues that need to be considered when deploying a TT strategy into clinical practice in different health-care settings. Now it is your turn; it is up to you to move forward in your institution and implement a TT perspective for the benefit of your patients.

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Table 1: List of potential Treatable Traits, their Trait identifications markers, their treatments and the associated evidence level. Super traits are highlighted in bold.

Pulmonary Traits	Trait identification marker/diagnostic criteria	Possible Treatments	I-IV[#]
Airflow limitation	**FEV1/FVC <0.7 and FEV1<80%**	**Bronchodilators - maintenance: LABA/LAMA; rescue: SABA/SAMA/rapid-acting LABA**	**I**
Systemic allergic inflammation	Elevated serum specific IgE	Anti-Immunoglobulin E monoclonal antibody therapy, allergen avoidance, immunotherapy	I
Dyspnoea	Dyspnoea score ⩾2, modified Medical Research Council scale	Pulmonary rehabilitation, breathing retraining	I
Emphysema (loss of elastic recoil)	Chest CT, plethysmography, lung compliance	Smoking cessation, lung volume reduction surgery, lung transplantation, α1-anti-trypsin replacement if deficient	I
Airway inflammation (eosinophilic)	**Sputum eosinophils ≥3% and/or FeNO ≥25 ppb and/or blood eosinophils ≥0.3 × 10^9/L**	**Corticosteroids, anti-interleukin-5, -13, -4 monoclonal antibody therapy**	**I-II**
Pulmonary hypertension	Doppler echocardiography, brain natriuretic peptide, right heart catheterisation	Oxygen therapy, pulmonary vasodilator therapy, lung transplant	I-II
Bronchiectasis	High Resolution Chest CT	Physiotherapy, mucociliary clearance techniques, macrolides, pulmonary rehabilitation, vaccination	I-II^
Bacterial colonisation	Presence of a recognised bacterial pathogen in sputum (sputum culture, quantitative PCR)	Antibiotics and tailored antibiotic written action plan for infections	II
Airway inflammation (neutrophilic)	Sputum neutrophils ≥61%	Macrolides, tetracyclines, roflumilast	II
Cough reflex hypersensitivity	Capsaicin challenge, cough counts, cough questionnaires	Speech pathology intervention, gabapentin	II
Mucus hypersecretion	Volume ⩾25 mL of mucus produced daily for the past week in the absence of an infection	Mucociliary clearance techniques with a physiotherapist, inhaled hypertonic saline, macrolides	II

Hypoxaemia	Pa02 ⩽ 55mmHg; pa02 56-59 mmHg and evidence of complications of hypoxaemia e.g., pulmonary hypertension, polycythaemia, right-sided heart failure	Domiciliary oxygen therapy	II

Extra Pulmonary Traits	**Trait identification marker/diagnostic criteria**	**Possible Treatments**	**I-IV[#]**
Depression	Questionnaires (e.g., HADS depression domain score ≥8, GADS score >5), psychologist/liaison psychiatrist assessment	CBT, pharmacotherapy	I
Anxiety	Questionnaires (e.g., HADS anxiety domain score ≥8), psychologist/liaison psychiatrist assessment	Pharmacotherapy (i.e., anxiolytics/antidepressants), breathing retraining, CBT	I
Dysfunctional breathing	Nijmegen Questionnaire Total score ⩾23, B-PAT (breathing pattern assessment tool) score >4, breath holding time, manual assessment of respiratory motion (MARM)	Breathing retraining	I
Decreased bone mineral density (osteoporosis)	T-score ⩽−2.5	Pharmacotherapy based on osteoporosis guidelines, Vitamin D supplementation, resistance training	I^, II
Overweight/obesity	**Overweight: BMI 25–29.9 kg·m−2, Obesity: BMI ≥30 kg·m−2**	**Caloric restriction, exercise, bariatric surgery, pharmacotherapy**	**I-II**
Sarcopenia	Appendicular skeletal muscle mass index. Males: <7.26 kg·m−2, females: <5.45 kg·m−2	Diet (high protein), resistance training	I^, II
Deconditioning	Cardio-pulmonary exercise testing, 6MWT	Structured exercise program, rehabilitation	I^, II
Rhinosinusitis	History and examination, imaging (sinus computed tomography), Sino-Nasal Outcome Test (SNOT- 22)	Topical corticosteroids, leukotriene receptor antagonists, antihistamines, biologics for chronic rhinosinusitis with polyps, surgery, intranasal saline lavage	II

Vocal cord dysfunction	Questionnaires (i.e., e.g., Pittsburgh ≥4), laryngoscopy, dynamic neck CT, inspiratory flow–volume curve	Speech pathology intervention, laryngeal botulinum toxin, gabapentin/pregabalin, psychology/psychiatry	II
Systemic inflammation	Leukocyte count >9 × 10^9/L or High-sensitivity CRP >3 mg·L−1	*Statins	II
Anaemia	Males: Hb < 140 g·L−1, females: Hb < 120 g·L−1	Haematinic (iron/B12) supplementation	I^, IV
Cardiovascular disease	**Doppler echocardiography, Electrocardiogram, brain natriuretic peptide**	**Pharmacotherapy (β-blockers, diuretics, angiotensin-converting enzyme inhibitors), surgery**	**II**
GERD	Questionnaires, gastrointestinal Endoscopy, pH monitoring	Anti-reflux lifestyle measures, antacids, proton pump inhibitors, fundoplication surgery	II
OSA	Questionnaires (i.e., STOP-Bang Questionnaire), polysomnography	Continuous positive airway pressure, mandibular advancement splint, positional therapy, weight loss	III-2

Behavioral/Risk Factors Traits	**Trait identification marker/diagnostic criteria**	**Possible Treatments**	**I-IV#**
Sub optimal inhaler technique	**Direct observation and standardised assessment checklists, assessment via chipped inhalers.**	**Education including demonstration and regular reassessment**	**I**
Sub optimal adherence	**Prescription refill rates, self-reported use of <80% of prescribed medication, chipped inhalers, FeNO suppression test, measurement of drug concentrations**	**Self-management support, education, simplification of medication regime (i.e., reduce number of medications, frequency of doses and number of devices)**	**I**
Smoking	**Self-reported current smoking, elevated exhaled carbon monoxide, urinary cotinine**	**Smoking cessation counselling +/- pharmacotherapy**	**I**
Side-effects of treatments	Patient report, Monitored withdrawal	Optimisation of treatment, alternative therapy, change device	I

Absence of a written action plan	Patient does not possess a written action plan, or reports not using the prescribed plan during exacerbations	Individualised self-management education with a written action plan	I
Exercise intolerance	<350 m on 6MWT	Pulmonary rehabilitation	I
Physical inactivity and sedentary behaviour	Actigraphy, International Physical Activity Questionnaire	Pulmonary rehabilitation, physical activity, breaking bouts of sedentary activity	I
Sarcopenia	Appendicular skeletal muscle mass index. Males: <7.26 kg·m−2, females: <5.45 kg·m−2	Diet (high protein), resistance training	I^, II
Exposures (Occupational/ Indoor coal/biomass)	History, Radio allergen absorbance test, skin-prick testing, Exhaled concentration of carbon monoxide	Avoidance where possible	I
Frequent β2 use	History	Self-management education	I

PC_{20}, provocative concentration causing a 20% fall in FEV_1; LABA, long-acting β2-agonists; LAMA, long-acting muscarinic antagonist; SABA, short-acting β2-agonists; SAMA, short-acting muscarinic antagonist; IgE, Immunoglobulin E; CT, computed tomography; FeNO, exhaled nitric oxide fraction; PCR, polymerase chain reaction; PaO2, partial pressure of oxygen.. HADS; hospital anxiety and depression scale; GADS, Goldberg Anxiety and Depression Scale; CBT, cognitive behavioural therapy; BMI, body mass index; 6MWT, 6-minute walking test; VCD, vocal cord dysfunction; CT; computed tomography; High-sensitivity CRP, High sensitivity c-reactive protein; Hb, haemoglobin; GERD, gastro-oesophageal reflux disease; OSA, obstructive sleep apnoea; CPAP, continuous positive airway pressure. FeNO; exhaled nitric oxide fraction; 6MWT, 6-minute walking test. [#] NHMRC level of evidence currently available for the management/treatment of each trait. ^evidence from the general population. *Currently research only. Content has been reproduced with permission from the Centre of Excellence in Treatable Traits, originally developed as part of the Centre of Excellence in Treatable Traits (https://treatabletraits.org.au)

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673 **FIGURE LEGENDS**

674 **Figure 1.** Results from the NOVELTY cohort. *Panel A*: prevalence of the 30 TTs
675 studied (pulmonary, extrapulmonary and behavioral/ environmental frequency); *Panel*
676 *B*: distribution of number of TTs per patient in those with asthma, COPD or
677 asthma+COPD. Reproduced with permission from reference [12]. For further information,
678 see text.

679

680 **Figure 2.** Network of TT co-occurrence (i.e., the proportion of patients presenting two
681 given TTs) by disease label in the NOVELTY cohort. Color node indicates their
682 pulmonary, extra-pulmonary or behavioral/environmental origin. Node size is
683 proportional to its prevalence, and the width of the edge (links) indicates the proportion
684 of patients in whom a given TT pair co-occur. COPD, chronic obstructive pulmonary
685 disease; PRISm, preserved ratio impaired spirometry; Th2, T2 airway inflammation.
686 Reproduced with permission from reference [12]. For further information, see text.

687

688 **Figure 3.** An example of prioritizing TTs into those that relate to specific outcomes,
689 such as disease exacerbations or frequent oral corticosteroid. Content has been
690 reproduced with permission from the Centre of Excellence in Treatable Traits,
691 originally developed as part of the Centre of Excellence in Treatable Traits
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694 **Figure 4.** A model for the implementation of the TT strategy across different health
695 care settings. Content has been reproduced with permission from the Centre of
696 Excellence in Treatable Traits, originally developed as part of the Centre of Excellence
697 in Treatable Traits (https://treatabletraits.org.au).

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699 **Figure 5.** Essential aspects of person-centered treatable traits implementation. Content
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