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Early View

REVIEW

Treatable Traits: a new paradigm for 21st century management of chronic airway diseases

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Treatable Traits: a new paradigm for 21st century management of chronic airway diseases

Treatable Traits Down Under International Workshop Report

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Take-home message: Treatable Traits is proposed as an approach for personalised medicine for people with airway diseases. We highlight the essential components of this approach and how we can progress research and implementation

ABSTRACT

Treatable Traits have been proposed as a new paradigm for the management of airway diseases, particularly complex disease, that aims to apply personalised medicine to each individual to improve outcomes. Moving new treatment approaches from concepts to practice is challenging, but necessary. In an effort to accelerate progress in research and practice relating to the Treatable Traits approach, an International Research Workshop – Treatable Traits Down Under, was convened in Melbourne, Australia in May 2018. In this article we report the key concepts and research questions that emerged in discussions during the meeting. We propose a programme of research that involves gaining international consensus on candidate traits, recognising the prevalence of traits and identifying a potential hierarchy of traits based on their clinical impact and responsiveness to treatment. We also reflect on research methods and designs that can generate new

knowledge related to efficacy of the Treatable Traits approach and consider multidisciplinary models of care that may aid its implementation into practice.

Key words: Treatable traits, Disease Management, Asthma, COPD

Introduction

In the early and mid-20th century, pharmacotherapy was driven by Paul Ehrlich's *zauberkugel* (magic bullet) theory and best characterised by the use of antibiotics for infectious diseases, where a single drug could precisely target the infectious agent causing the disease, resulting in cure. The latter half of the 20th century saw a dramatic rise in the burden of non-communicable diseases (NCD) such as cardiovascular disease, type-2 diabetes mellitus, cancer and chronic airway diseases, where the *zauberkugel* approach could not be usefully applied because a single etiological agent could not be identified. A step-therapy approach was then developed to treat these conditions where drugs were added (stepped-up) or withdrawn (stepped-down) based on the risk, severity and level of responsiveness to treatment. Step-therapy has become a dominant treatment paradigm for NCD, particularly in airway disease. This is characterised by the step-wise escalation of long-acting bronchodilators and/or inhaled corticosteroids. While this approach significantly improved asthma outcomes, in the early 21st century its limitations have become apparent, and improvements in airway disease outcomes have now stalled [1, 2]. Individual variability in both clinical presentation and treatment response is increasingly recognised, but whether this is systematically addressed is questionable. Furthermore, the pathway for development of impactful new treatment approaches has been haphazard, typically failing to recognise the advantage of targeting treatments [3].

In response to the limitations of step-therapy, the Treatable Traits approach has emerged. Treatable Traits is a new strategy where patients are individually assessed for a specified set of treatable problems, and an individualised treatment programme is developed and

implemented based on this multidimensional assessment. This new paradigm of disease management offers great promise in individualising care and improving outcomes for patients with airway diseases, particularly complex conditions like severe asthma, older people and those with multimorbidity COPD. As these conditions tend to have more severe disease and increased comorbidities[4, 5]. A case illustrating this approach is presented in table 1. Previous articles have described the key Treatable Traits and their recognition[1, 6], and have proposed research methodologies to test the concept[7], but many questions in relation to the practical implementation of the Treatable Traits approach remain, and new questions continue to emerge.

In considering our approach to this new treatment paradigm, it may be useful to examine lessons learnt in other disease areas, for example Cystic Fibrosis (CF). Like severe asthma and COPD, CF is both a complex and heterogeneous disease. Yet, in contrast to asthma and COPD, outcomes for CF patients have dramatically improved over the last three decades, mostly due to discoveries and innovations ranging from the identification of the CF gene to the implementation of disease modifying treatments[8]. Importantly, CF was one of the first pulmonary diseases where the importance of specialist multidisciplinary teams was recognised. Patients attending specialist centres achieved superior outcomes than those attending non-specialised centres[9, 10]. Hence, the provision of multidisciplinary care in CF is now the standard[9]. These major advances in outcomes for patients with CF illustrate nicely what it is possible to achieve when a complex airway disease is managed using multidimensional assessment and targeted therapy, even before treatments that modify the underlying genetic defect are available. We believe that this provides clear support for a similar model in other chronic airway diseases. Specifically, that by combining the

recognition of specific Treatable Traits in each individual and the additional complexities related to older people with multimorbidity, and implementing a multidisciplinary team approach, we may eventually achieve outcome improvements of a similar magnitude to those observed in CF patients. We also urge that this approach is generally applicable to chronic disease management and issue a challenge to other disciplines involved in treating of NCDs to consider evaluation of such an approach, for example in diabetes and heart failure.

In this article, we report the outcomes of an international workshop, *Treatable Traits Down Under - 2018*, that was held on the 7th and 8th of May in Melbourne, Australia, to critically review the Treatable Traits approach, identify the importance (hence, priority) of different traits, develop a research agenda to test and validate specific Treatable Traits approaches, and consider ways to implement this strategy into clinical practice.

Treatable Traits: theoretical underpinnings

What is the Treatable Traits approach and why is it necessary?

Biology, thus medicine, is complex [11, 12]. This means that health and disease are emergent properties that result from the interaction of different complex networks at different biological levels (genes, proteins, metabolites, cells, organs, environment) [11, 12]. Therefore, in order to improve medical diagnosis and treatment it is necessary to gain a better understanding of this biomedical complexity [13-15].

An early approach to address this complexity was based on the concept of “clinical phenotypes”, defined as “a single or combination of disease attributes that describe differences between individuals with the same disease as they relate to clinically meaningful outcomes” [16]. A strict interpretation of this definition may suggest that “clinical phenotypes” are mutually exclusive, whereas we know that diseases often present with several, non-mutually exclusive characteristics. Accordingly, the concept of “clinical phenotypes” evolved to that of “Treatable Traits”, defined as “therapeutic targets identified by “phenotype” or “endotype” through validated biomarker(s)” [6]. The term endotype refers to a “subtype of a disease defined functionally and pathologically by a molecular mechanism or by treatment response” [17]. In contrast, a “biomarker” is “a characteristic (not necessarily a molecule; lung function or chest imaging may work as biomarkers too) that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention” [18]. We refer to these indicators as trait identification markers.

Importantly, potential Treatable Traits are not restricted to the lungs. It has been recognised since its original proposal that there are pulmonary, extra-pulmonary and even behaviour/lifestyle risk-factors that deserve specific treatment if present [6]. In essence, it is hoped that the adoption of a strategy based on the recognition and treatment of validated Treatable Traits may improve the efficacy and safety of therapies of complex human diseases in general, and chronic airway diseases in particular [7, 19, 20]. Needless to say, this hypothesis requires formal, prospective, validation in appropriately designed clinical trials [7]. The first steps to test/validate this approach are to define how to recognise traits and how to assess their relative importance.

How should we identify candidate Treatable Traits?

First, it is important to recognise that a given patient may have more than one treatable trait (actually, this is often the case). In other words, Treatable Traits are not mutually exclusive. Having said this, candidate Treatable Traits should fulfil the following three characteristics.

1. *Clinical relevance:* A trait is required to be clinically important; this is, a trait should be associated with specific disease outcomes such as symptoms, health-status, risk of future events (e.g. exacerbations, cardiovascular events, cancer), lung function decline, prognosis and/or death. In essence, we need to identify Treatable Traits that matter[4] [7, 21].

2. *Identifiable and measurable:* A trait identification marker is used to objectively identify the presence of a trait, in preparation for targeted therapy. Typically, this would be a biomarker, such as blood eosinophil count to recognise Type-2 airway inflammation. However, it can also be a questionnaire result, such as the Nijmegen questionnaire score for dysfunctional breathing, or an anxiety and/or depression scale to recognise psychological dysfunction. The markers that are used as diagnostic criteria for the trait should have a high specificity, allowing a high degree of confidence in 'ruling in' or identifying the presence of the trait. In some situations, this gold-standard marker may be prohibitively resource-intensive to be measured in all patients with airways disease; for example, at present, the use of high-resolution computed tomography to identify bronchiectasis is not feasible in all patients with chronic airway disease because of cost and the cumulative risk from radiation

exposure, and incidental findings that may occur. In these situations, there may be a role for a high-sensitivity screening tool to 'rule out' the diagnosis in the majority of patients and select a sub-set for further investigation. In any case, there is a need to identify and validate new trait identification markers with better operating characteristics, improved feasibly and/or greater cost efficiency.

3. *Treatable*: A trait should be able to be effectively treated in order to be called a 'treatable' trait. Ideally, treatability is determined in a randomised controlled trials (RCT) but research opportunities exist in treatment implementation and optimisation in real life, so the effect size is increased and/or side effects are reduced [22]. Further, even for those traits that are not currently treatable, or are only partly treatable, there are discovery science opportunities to identify new treatments for these traits (Table 2).

How can we assess the importance of specific Treatable Traits?

Are some traits more important than others? Should they receive greater priority in patient assessment and management? How should traits be prioritised? The significant resource requirements for assessing all of the potential pulmonary, extra-pulmonary and risk-factor/behavioural traits, so targeted and individualised interventions can be implemented, highlights the need to prioritise certain traits above others [4, 7, 21]. An example of this prioritisation would be to target a few traits exclusively, such as symptoms and exacerbations in COPD (currently recommended by GOLD) and, adding eosinophilic inflammation, also now recommended by GOLD[23] (shown previously to be a valid identifying marker of the presence of eosinophilic airway inflammation, a higher

exacerbation risk and better treatment-response to inhaled corticosteroids)[24, 25] [26] [27].

But are there other traits that need to be addressed, and with what priority? Traits could be prioritised based on their *clinical-impact*, that is their severity, prevalence, or their impact on specific outcomes (exacerbations, symptoms and health-status, death, others). McDonald *etal.* assessed clinical-impact in an analysis of Treatable Traits in severe asthma using the Australasian Severe Asthma Web-based database (SAWD) registry[4]. The authors identified Treatable Traits that were predictive of future exacerbation risk. From 24 identified traits, 10 were associated with an increased risk of future asthma attacks. The strongest predictors were past-year exacerbation, depression, vocal-cord dysfunction, inhaler-device polypharmacy and obstructive sleep apnoea (Figure 1a)[4] . This list of traits could be a potential 'hit list' to begin prioritisation for implementation of the Treatable Traits approach in severe asthma, and also as a model to allow prioritisation in asthma and COPD (Figure 1a). Although we also recognise the need to identify the traits that impact other outcomes, in particular the long-term natural history of a diseased state, or the development of a new disease.

Other ways to prioritise traits include *connectivity* and *patient impact*. A trait that is a nodal point in a disease network may influence multiple other traits, and therefore would be important to target [11, 28, 29]. For example, in obese COPD patients, targeting treatment to the single trait of obesity led to significant improvements, not only in body-weight, but also in several other important traits such as skeletal-muscle strength, exercise-tolerance, depression and several cardiovascular and metabolic risk-markers (Figure 1b) [30].

Patient impact, that is a trait rated as a high priority by patients, is another way to prioritise the importance of traits. At present few data exist to inform this approach in airway diseases. In one study, patients with asthma and COPD older than 55 years, underwent a multidimensional assessment to characterise traits, and patients ranked the importance of their individual traits [31]. The most important from the patient's perspective included dyspnoea, activity limitation, airflow limitation, airway inflammation and obesity [31]. Importantly, these rankings were different from those provided by their physicians. However, after involving patients in shared-decision making, which involved an explanation of the trait, its impact, how it was treated, and sharing the rating of the physician, patients became more engaged in the adoption of a complex Treatable Trait intervention, which lead to improved outcomes [32]. These results highlight the importance of seeking patient preferences in prioritising traits and targeted treatments.

Current Data and Future Research Needs

There are limited data currently available on the prevalence of Treatable Traits in different populations, but data for some traits can be derived from existing observational studies and disease-registries. With this in mind, the prevalence of traits such as eosinophilic airway disease and airflow limitation have been well described in asthma and COPD settings, whereas the prevalence of other traits such as vocal-cord dysfunction have predominantly been reported in the setting of severe asthma [33, 34], and not in unselected airway diseases or patients with COPD. The reported prevalence of a trait is likely to vary according

to the threshold used, diagnostic-label, severity, and setting in which it is described. This variability is clearly illustrated by the trait of eosinophilic airway inflammation: estimates from the Severe Asthma Research Programme (SARP), TENOR II cohorts, and the UK primary-care database indicate that, depending on asthma severity, the prevalence of blood eosinophils (≥0.3x10^9/L) in asthma patients ranges between 26% and 43% [35-37]. By contrast, in the Australasian SAWD, eosinophilic airway inflammation (defined using a composite of sputum eosinophilia >3%, FeNO ≥30ppb, or blood eosinophils ≥0.3x10^9/L) was present in 53% of patients with severe asthma and 60% non-severe asthma[38] . A further complication arises when comparing asthma and COPD, as the majority of COPD studies used a blood eosinophil cut-off of ≥2% of total white cell count at baseline, rather than an absolute cut-off. For instance, in the ECLIPSE study, 84% of participants with COPD had blood eosinophils >2% on at least one measurement (equivalent to a ≥0.15x10^9/L cut-off for the majority of participants) [39]. However, trait stability over time must also be considered as only 37% of patients with COPD had blood eosinophils persistently ≥2% of total white cell count over a three-year period, but another 49% met this criterion intermittently [27].

The Treatable Traits approach allows for rapid management shifts in response to dynamic changes in trait identification markers, which diverges from traditional thinking of relatively fixed diagnoses. The normalisation or absence of a trait identification marker may indicate successful management, which may instigate clinical review of management strategies. Dimensional approaches that consider the severity, rather than simply presence, of traits may also assist in guiding management of traits that vary over time.

Table 3 illustrates, reviews of Treatable Traits and similar approaches show considerable variation in both traits and trait definitions proposed to date [1, 5, 7]. Consensus on trait identification markers can be agreed through a Delphi process and this will provide a bedrock on which an evidence-base can be established. A key consideration will be the composition of the expert panel contributing to the Delphi process, ensuring inclusion of a range of healthcare professionals and specialist interests.

Thus, given these limitations of existing evidence, to evolve the Treatable Trait strategy from a useful conceptual tool to an evidence-based approach to diagnosis and treatment, a specific research programme is required. Table 4 lays out some of the key questions that need to be answered and suggests appropriate methodologies to address them. The immediate priority must be to avoid replicating the challenges previously encountered with both COPD and asthma, particularly the overlap of these conditions, where differences in definition result in conflicting estimates of the prevalence of the conditions [40], and hampered interpretation of the evidence [41]. Once trait identification markers are agreed, existing datasets from large observational cohorts can be used to estimate the prevalence of individual Treatable Traits in different populations. Severe asthma registries, COPD observational cohorts, and cohorts derived from random population samples will provide complementary information on trait prevalence, variation in prevalence according to diagnosis of asthma or COPD, and association with current symptoms, disease control, and health-status. Longitudinal cohorts will be required to determine trait stability over time and associations with future risk, particularly relating to exacerbations and lung-function decline.

Candidate traits which are common and found to be strongly associated with the domains of symptom control, health-status, or risk of future events should represent priorities for investigation and treatment. Some traits may require considerable resources for their investigation, and others may be at present sub-optimally or ineffectively treated. Current inability to treat a trait should not be an absolute barrier to its recognition, as traits that are strongly associated with important outcomes but are not yet treatable may represent important avenues for development of new therapies. Consumer-involvement should also be used to inform the setting of research priorities. It is clear that patients and healthcare professionals differ over concepts such as what constitutes acceptable asthma control [42] and the priority for treatment of specific traits [31], and similar differences may exist over the relative importance of traits which affect current symptoms versus future risk.

When testing the utility of the Treatable Trait strategy through RCTs, key considerations include the disease population in which the strategy is tested, and which traits are targeted. The decision should be made whether to test a Treatable Trait intervention within a population of patients with the disease-label of either asthma or COPD, or to include participants with symptoms of airway diseases irrespective of the current label. If trait prevalence studies suggest that the label of asthma or COPD is associated with particular sets of traits, then study designs should reflect this and may differ; for example, a Treatable Traits study in the setting of asthma may prioritise different traits from one in the setting of pulmonary rehabilitation for COPD. The diagnosis of asthma or COPD should not be the end of the diagnostic procedure. It should be an intermediate step [20]. Linked to this is the question of whether to assess all traits at once, the ‘broad’ approach akin to systematic assessment in the severe asthma clinic [43], or to target the most prevalent or most

important traits, the ‘focused’ approach. An example of a focused approach which has been proposed would be to target the two traits of eosinophilic airway inflammation and airflow limitation, adjusting the use of ICS and bronchodilators accordingly [44]. Powell *et al*. used this approach in the antenatal clinic setting for managing asthma in pregnancy and established that it was superior to a step-based approach[24], and Green *et al* [26] reported similar findings in patients with severe asthma. The focused approach may lend itself more to implementation in primary-care, where targeting eosinophilic airway inflammation and airflow limitation can be achieved effectively in the majority [6]. A broad approach requires a more time-consuming systematic assessment but the relative simplicity of the focused approach may limit the potential benefit of the interventions. A resource efficient design may be a ‘phased’ approach, where patients are initially treated according to a focused algorithm but progress to an extended or ‘broad’ assessment if they do not achieve acceptable disease control.

Conventional parallel-group RCTs are the most appropriate model for testing the efficacy of a Treatable Traits based multi-component intervention. However, they are not the most efficient way to determine the best methods of assessment and treatment for individual traits. Given the many possible traits, and the heterogeneity of the populations, a programme of trials providing evidence for the investigation and management of each trait would take several decades to complete. A more feasible methodology may be to design master protocols [45], to simultaneously assess interventions across multiple traits. An adaptive platform RCT of Treatable Traits could also aid implementation of the research findings, as once a treatment is shown to be superior all new participants are allocated to this arm [46]. Implementation may be further assisted by a Treatable Traits dynamic control

panel [47] embedded within the electronic health-record. Such a system (Figure 2), could draw on existing data in the health-record, such as blood eosinophil levels and spirometry, and highlight priority traits to target in an individual. This sort of algorithmically-assisted medicine may facilitate a Treatable Traits approach in time and resource limited settings and should be a focus for implementation research.

Study Outcomes for Research

Concept of burden. Assessing the impact of a new strategy for managing airway diseases requires some consensus about the endpoints that are appropriate for assessing that impact. The concept of "burden of disease" has been used as a common currency for describing the impact of diseases and risk-factors. Burden of disease represents a measure of health loss and is estimated in two, mutually exclusive, components: years of life lost due to premature death and years of life lived with disability. The former is the sum of life expectancies, at the time of death, of all people whose death is attributed to the specified disease or risk-factor. The latter is sum of all periods of disability, weighted by the level of disability, attributed to the specified disease or risk-factor. These two components are then summed to give the burden of disease, attributed to the specified disease or risk-factor, in units of disability-adjusted life years (DALYs) [48]. This approach has been widely used to estimate and analyse the global burden of disease.

A strength of this approach is its generalisability across diseases and global contexts. The holistic approach to assessment of impact is a further strength. One potential limitation of this approach is that descriptors used to assign levels of disability to various stages of disease (mild, moderate and severe) are largely based on regular symptoms and limitations

[49]. This does not account for the impact of exacerbations, which are sporadic in nature and are a major component of the impact of the disease that the Treatable Traits strategy seeks to mitigate. These limitations, particularly the latter, can and should be addressed in future work on the burden of disease measures. Another limitation may be that these are population estimates and, in an era of precision, individualised, medicine there may be substantial interindividual variability [50].

How can we implement the Treatable Traits Approach into Practice?

Assuming that appropriate research shows that the Treatable Traits approach is more efficient, effective, and safer than the traditional approach, implementing it in clinical practice is a major challenge. Yet, there are a number of potential ways that could be considered here, such as using guidelines, pulmonary rehabilitation, and/or multidisciplinary team assessment and treatments.

Guidelines as a vehicle to implement a Treatable Traits strategy

Guidelines present a comprehensive approach to airway disease management, and in doing so they may be already dealing with many of the issues identified in the Treatable Traits approach. However, there are important differences between the Treatable Traits strategy discussed above and the current guidelines approach. So far, guidelines do not advocate the use of biomarkers to select therapy, although based on current evidence [27], this may change in the near future. In general guidelines tend to be based on 'lumping', with the level of treatment determined by the degree of symptoms and risk of future events. In contrast, the Treatable Traits approach personalises treatment based on 'splitting', with systematic

identification and treatment of the disease characteristics that are evident in each individual and that contribute to poor respiratory health. The consequence of the 'lumping' approach is that there may be, for example, untreated eosinophilic inflammation when symptoms alone are used to guide therapy. Eosinophilic inflammation often occurs in patients with COPD but can also occur in those with mild asthma, as well as poor symptom perceivers, where there is a weak association between eosinophilic inflammation and symptoms [51]. Several RCTs now show that biomarker guided-therapy directed at the treatable trait of airway T2 inflammation is superior to symptom-guided therapy [24, 26, 52]. Moreover, how to efficiently implement this approach in primary- or secondary-health care settings remains unclear [6]. Finally, even though some guidelines, for example the New Zealand asthma guidelines [53], already recommend the novel approach of assessing Treatable Traits in a systematic manner within four domains (overlapping disorders, comorbidities, environmental and lifestyle factors) at each consultation, and before using the stepwise-approach to asthma drug treatment, the successful implementation of existing guidelines remains a challenge [54, 55].

Pulmonary rehabilitation as a vehicle to implement a Treatable Trait strategy

Pulmonary rehabilitation, defined as the delivery of 'patient tailored therapies … designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours' is a highly effective intervention to improve wellbeing in people with chronic respiratory disease [56]. Although pulmonary Treatable Traits are infrequently addressed directly in pulmonary rehabilitation, many important extra-pulmonary and behavioural/lifestyle traits are addressed routinely. Examples include the extra-pulmonary treatable trait of

deconditioning, addressed through provision of an individualised exercise training programme, and behavioural Treatable Traits related to inhalation-technique, adherence to treatment, smoking cessation and family and social support.

Pulmonary rehabilitation is a complex, multi-component intervention that can be considered as a 'stacked' approach to management [7]. This provides the opportunity to address multiple Treatable Traits at once, which may be of particular advantage in people with more severe airway disease. Such an approach requires patients to make health-behaviour changes across multiple domains. Pulmonary rehabilitation programmes provide an environment where this can be supported by case-management and coordination of care. Another advantage of embedding the Treatable Traits approach in pulmonary rehabilitation is that measurement of patient-centred outcomes (e.g. health status) is strongly embedded in routine rehabilitation practice.

Whilst pulmonary rehabilitation offers opportunities for implementation of the Treatable Traits approach, there are some potential limitations that need to be considered. The 'stacked' nature of pulmonary rehabilitation could be one by limiting our understanding of the mechanisms of treatment-response. For example, there is strong evidence of improvement in the extrapulmonary Treatable Traits of anxiety and depression following pulmonary rehabilitation, but it is not clear which components of rehabilitation confer these benefits [57]. Another potential limitation is that the Treatable Traits approach should span the spectrum of airway diseases, but the benefits of pulmonary rehabilitation for those with mild disease have not been convincingly demonstrated [58, 59]. Finally access and uptake of

pulmonary rehabilitation remain suboptimal across the world [60], which may limit its utility as a vehicle to deliver the Treatable Traits approach.

Multidisciplinary teams as a vehicle to implement a Treatable Traits strategy

Evidence suggests that optimal management of patients with chronic airway diseases requires a multidimensional assessment and targeted treatments [32, 56, 61, 62]. Engaging a multidisciplinary team enables the management of the complexities that characterise this patient population and could be a useful platform to identify Treatable Traits, and to implement a targeted treatment programme based on these traits. A multidisciplinary team approach for management of severe asthma and COPD has been shown to reduce hospital admissions, improve health-status, reduce exacerbations and reduce the number of bed days [63-65].

The minimum recommended personnel for the multidisciplinary team within the severe asthma clinic include a respiratory physician/pulmonologist, a specialist-nurse and a pulmonary function scientist, but the speech pathologist, dietitian, psychologist, and physiotherapist are also necessary to address the complexities associated with the disease [61]. Referral pathways to other specialities for the treatment of common comorbidities or traits (such as gastroesophageal reflux disease, sinusitis, cardiovascular disease) should also form part of a multidisciplinary team protocol. In COPD the team is very similar. Using a multidisciplinary team meeting format, patients can be presented by the case-manager to discuss the individual's identified Treatable Traits using a multidimensional assessment approach, then treatment of the identified traits can be planned and treatment pathways actioned [5, 32, 66].

Whilst there is good evidence for the benefits of the multidisciplinary team approach in managing airway diseases, there are no published RCTs that have utilised the multidisciplinary team in the evaluation of the Treatable Traits approach. This identifies another important area for future research.

Knowledge Translation

A further important consideration for the implementation of the Treatable Traits strategy is knowledge translation. We must consider ways of bringing about behaviour change of multidisciplinary clinicians to successfully create a paradigm shift in disease management. In an era of social media, artificial intelligence and information technology these strategies need to be embraced to launch public health campaigns promoting the approach and to provide training for clinicians. These strategies could be supported by our international respiratory communities such as the European Respiratory Society and perhaps even the World Health Organisation.

Expansion and Future Development of Treatable Traits – Who, Where and What

Treatable Traits are proposed as a general framework to use when managing any patient with airway diseases. Yet, to date, much of the research focus has been on people with specific diagnoses of COPD or asthma. Specifying the population in whom to apply the Treatable Traits approach has implications for which traits are accepted into the framework [20]. For instance, bronchiectasis has been listed as a trait [6], yet can equally be considered

an airway disease defined by traits of mucus hyper-secretion, dyspnoea, chronic infection and cough [19]. Clear trait identification markers may resolve confusion and open the Treatable Traits approach to more patients.

How to implement Treatable Traits across settings also requires consideration. As discussed above, Guidelines, pulmonary rehabilitation, and multidisciplinary team management all show potential as vehicles to implement the Treatable Traits approach, but good evidence of effectiveness is required. A good test case for Treatable Traits may be patients hospitalised for an exacerbation of airway disease (asthma or COPD), who often have under-recognised extra-pulmonary traits [67]. Here patients can be intensively investigated and diagnostic equipment, multiple treatment options and multidisciplinary expertise are often available. Prevention of re-hospitalisation is a logical treatment endpoint. The corollary however is that this is a time where it is proven to be more difficult to engage patients in some interventions, such as pulmonary rehabilitation. Furthermore, while Treatable Traits may be feasible in well-resourced hospitals, how it may be adapted for settings with limited resources is an open question. Primary-care, low-to-middle income countries, rural and remote locations, and other under-resourced settings may require a leaner model and a structured approach to facilitate uptake. Research to establish whether traits have similar prevalence and impact across settings, and describe implementation barriers and facilitators, will help develop a translatable and equitable Treatable Traits approach.

Finally, an expanding evidence-base produces an expanding catalogue of potential Treatable Traits. The scope of the catalogue partly depends on two questions: 1. Do traits need to have a mechanism of effect on the airways, or can they include downstream effects of

airway diseases and its treatment, as in the case of osteoporosis? 2. Is current treatability necessary? Traits that are potentially, but not yet, treatable may also be considered if they have substantial impact on patient outcomes. For instance, although we have no established treatments specifically targeting neutrophilic airway inflammation, it is identifiable in sputum, prevalent across airway diseases and clinically relevant [68]. Although it is tempting to propose a laundry list of traits, we need first to revise traits to reduce redundancy and carefully consider new traits to ensure an economical and non-burdensome approach. Candidate new traits that may be important for clinical outcomes include skeletal-muscle dysfunction, fatigue, osteoporosis, chronic cough, poor diet quality, physical inactivity, frailty, poor disease mastery and poor health literacy.

In terms of potential limitations of the Treatable Traits strategy we recognise that at present there are no RCTs that report efficacy or effectiveness data. This is a major limitation and highlights the need for a framework to advance our knowledge in this field, which we offer. One criticism of the approach is the complexity involved in the assessment of many traits within three different domains. This requires additional resourcing and multidisciplinary teams working effectively together. Of course, in addition to efficacy data, health economic evaluation is also a priority, as the strategy is likely to be more resource intensive initially but become cost neutral or cost saving.

Conclusions

The *Treatable Traits Down-Under -2018* international workshop brought together international experts in COPD and asthma, who had an interest in progressing precision

medicine in these diseases, using the new paradigm of Treatable Traits. The meeting provided opportunities to identify and design a research programme that will generate new knowledge in relation to defining consensus of candidate traits, establishing efficacy of the approach, and identifying pathways to enable implementation of Treatable Traits into practice.

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Table 1: A case of a patient treated according to the Treatable Traits strategy.

<table>
<tr><th colspan="2">Case history</th></tr>
<tr><td colspan="2">Denise is 60 year old woman with COPD. She presents to the clinic with cough and exertional breathlessness.

Over the past 12 months she reports experiencing four acute lung attacks, each requiring antibiotics and oral corticosteroids. She is a current smoker with a 44 year pack history. She reports a history of sinusitis and a fracture of her left wrist six years earlier.

Spirometry shows severe airflow limitation with a Forced Expiratory Volume in one second (FEV_1 L (% predicted)) of 1.05 (45%), Forced Vital Capacity (FVC) of 1.90 (66%), giving a Forced Expiratory Ratio 0.55 with no bronchodilator response. Chest radiograph revealed hyperinflation. Her 6 -minute walk distance is reduced at 395 metres (66%). Her BMI is 22.3 kg/m^2, her BODE index 3 units and she reports a MMRC of 2. She expectorates ~50mls of whitish/yellow sputum every day.

She is prescribed optimal pharmacotherapy for COPD quadrant D, including, budesonide/formoterol 400/12 mcg two inhalation bd via dry-powder inhaler, tiotropium 18 mcg daily via a handihaler and salbutamol 100 mcg prn, via a pMDI.

When Denise was asked what her biggest problem was related to her chest condition she said, 'I have a horrible cough! It's embarrassing. There is lots of phlegm every morning and I have so many flare ups, these limit my activity'. Her quality of life score measured by the St. George's Respiratory Questionnaire (SRGQ) is impaired with a score of 63.3 units.</td></tr>
<tr><td colspan="2">As part of her management Denise underwent a multidimensional assessment guided by the Treatable Traits model. This revealed a number of treatable traits including:</td></tr>
<tr><td>TREATABLE TRAIT</td><td>INDIVIDUALISED TREATMENT DELIVERED VIA CASE MANAGEMENT</td></tr>
<tr><td colspan="2">PULMONARY DOMAIN</td></tr>
<tr><td>• Airway eosinophilic inflammation: sputum eosinophils 6.5%</td><td>▸ Oral corticosteroids (OCS) - 37.5mg/day and sputum monitoring to guide treatment reduction</td></tr>
<tr><td>• Airway hyperresponsiveness</td><td>▸ Continue inhaled corticosteroids</td></tr>
<tr><td>• Proneness to lung attacks</td><td>▸ Written action plan, self management education to identify early signs of an attack and action, and treatment of the underlying pathology (airway inflammation and mucus hypersecretions)</td></tr>
<tr><td>• Mucus hypersecretion</td><td>▸ Mucociliary clearance techniques with a physiotherapist and inhaled hypertonic saline</td></tr>
</table>

• Pathogen colonization: haemophilus influenzae	▸ Antibiotic based written action plan based on antibiotic sensitive to pathogen
EXTRA PULMONARY DOMAIN	
• Osteopenia= BMD -T scores = total body -1.8, hip -2.4	▸ Alendronate 70mg weekly
• Sarcopenia= ASMMI 5.4kg/m^2	▸ Nutritional counselling with a high protein diet and resistance exercise training
• Activity limitation	▸ Enroll in pulmonary rehabilitation
• Dysfunctional breathing	▸ Breath retraining
BEHAVIOURAL	
• Sub optimal self management skills: Inadequate inhaler, inhaler device polypharmacy and no written action plan for lung attacks	▸ Self management education with an antibiotic and OCS based written action plan, inhaler device training and a change of inhaled therapy to one inhaler platform.
• Current smoker, but ready for quit attempts	▸ Smoking cessation counselling and pharmacotherapy

The outcomes for this individualised Treatable Traits approach are outlined below:

Outcome	Baseline	3 months	6 months
SGRQ	63.3	56.3*	59.2*
FEV1% predicted	45	54*	50*
6 MWD, metres	395	450*	488*
Sputum eosinophils %	6.5	2*	3.5*
Mucus volume mL/day	50	25*	25*
Smoking status | eCO	20/day|14	0/day|5*	20/day|12
ASSMI kg/m^2	5.4	5.8	5.5
BMD T score	-1.8	-1.6	-1.4
BODE	3	2*	2*
Self management skills	Sub-optimal	optimal	optimal

The evaluation of treatable traits is feasible in practice with the use of a multidisciplinary team. When the identified traits are treated using a case management approach, improvements are achieved in the three treatable trait domains in addition to overall health status.

KEY: BMI, BODY MASS INDEX; BMD, BONE MINERAL DENSITY; ASSMI, APPENDICULAR SKELETAL MUSCLE MASS INDEX; SGRQ, ST. GEORGE'S RESPIRATORY QUESTIONNAIRE; ECO, EXHALED CARBON MONOXIDE; BODE, BODY MASS INDEX, OBSTRUCTION, DYSPNEA, EXERCISE TOLERANCE; MWD, MINUTE WALK DISTANCE. * CLINICALLY SIGNIFICANT RESPONSE

Table 2: Key components of Treatable Traits and research opportunities

Domain	Essential	Clinical application	Research Opportunity
Clinically relevant	Y	Trait predicts/associates with clinically important outcomes.	Identify and/or quantify clinical relevance.
Trait Identification Marker	Y	Identifies the presence of a trait. Appreciation of the measurement characteristics of the test (i.e. sensitivity, specificity) is required for optimum use. A test with high specificity is required to 'rule in' the presence of a trait. A highly sensitive test can be used to screen, or 'rule out' the presence of a trait.	New markers at lower cost or improved feasibility Novel diagnostics, e.g Artificial intelligence based probabilities derived from composite molecular signatures. Mechanism-oriented research to yield better molecular diagnostics for more precise identification of subsets.
Treatable	Y	Trait is responsive to a specific targeted therapy. Established via randomised controlled trials.	Discovery science to identify new treatment for 'untreatable' traits. Implementation science to define best way to treat the traits in clinical practice.

Table 3: Comparison of candidate Treatable Traits in the literature

PULMONARY TREATABLE TRAITS			
Trait	**Agusti et al., 2016[7]**	**Gibson McDonald & Marks, 2010[5]**	**Pavord et al., 2017[1]**
Airflow limitation/obstruction	FEV1/FVC <0.7 (or LLN)	FEV1/FVC ratio <70%, and FEV1<80% predicted, or use agreed standards	FEV_1/FVC < LLN bronchodilator reversibility and short-term PEF variability consistent with variable airflow obstruction and large component of ASM contraction, ICS/OCS response consistent with inflammation associated with airflow limitation (i.e., mucosal oedema, mucus plugging), loss of airway support probable if imaging or physiological evidence of emphysema. More work is needed to identify tests capable of discriminating these processes
Exercise intolerance	X	6MWD (distance <350m^2)	
Airway smooth muscle contraction	Bronchodilator reversibility, peak expiratory flow variability, positive PC20	X	
Loss of elastic recoil (emphysema)	Chest CT, DLCO, compliance	X	
Airway mucosal oedema	Chest CT, spirometry-induced bronchoconstriction	X	
Eosinophilic airway inflammation	Sputum eosinophils, blood eosinophils, FeNO, (periostin)	Eosinophils >3%	FeNO, serum periostin, blood eosinophils, sputum eosinophils
Mixed airway inflammation	X	Neutrophils >61%; paucigranulocytic if neutrophils <61% and eosinophils <3%, mixed if neutrophils >61% and eosinophils >3%	X
Chronic bronchitis	Cough and sputum 3 months for 2 years (no eosinophilic airway inflammation)	X	X
Infection	X	X	Sputum culture, sputum PCR

Frequent chest infection	X	≥2 antibiotic courses in 12 months	X
Airway bacterial colonisation	Sputum culture, quantitative PCR	X	X
Pathogen colonisation	X	Sputum culture, presence of a recognised bacterial pathogen	X
Bronchiectasis	Chest CT	X	X
Cough reflex hypersensitivity	Capsaicin challenge, cough counts, cough questionnaire	X	Increased cough reflex sensitivity (i.e., capsaicin), increased cough counts, cough symptom scores
Pre-capillary pulmonary hypertension	Doppler echocardiography, brain natriuretic peptide, right heart catheterisation	X	X
Mucus hypersecretion	X	Volume ≥25 mL of mucus produced daily for the past week in the absence of an infection	X
Chronic respiratory failure			
Oxygen desaturation	X	SpO_2 <90% either at rest or during 6MWD test	X
Arterial hypoxaemia	PaO^2 <55 mmHg	X	X
Arterial hypercapnia	$PaCO^2$ >45 mmHg	X	X
EXTRAPULMONARY TREATABLE TRAITS			
Deconditioning	Cardio-pulmonary exercise testing, 6MWD	X	X

Activity limitation	X	Self-report, defined as self-reported impairment because of an inability to achieve personal activity goals	X
Obesity	BMI	BMI >30 kg/m^2	X
Overweight	X	BMI between 25 and 30 kg/m^2	X
Obesity/deconditioning	X	X	BMI, cardiorespiratory exercise test.
Cachexia	BMI		X
Malnutrition	X	BMI <20 kg/m2	X
Obstructive sleep apnoea syndrome	Questionnaires, polysomnography	X	X
Cardiovascular disease	Electrocardiogram, Doppler echocardiography, brain natriuretic peptide	X	X
Cardiac dysfunction	X	Chest radiography, echocardiogram, NT-proBNP >1000 fmol/mL	X
Gastro-oesophageal reflux disease	Gastrointestinal endoscopy, pH monitoring	X	Oesophageal manometry
Upper airway diseases: rhino-sinusitis	History and examination, imaging	X	Suggestive symptoms, imaging
Upper airway diseases: inducible laryngeal obstruction (vocal cord dysfunction)	Fibre optic laryngoscopy, flow-volume curve, dynamic neck CT	X	X

Psychiatric disorders: depression	Questionnaires, psychologist/liaison psychiatrist assessment	HADS depression domain score ≥8 GADS score >5 suggests depression	HADS
Psychiatric disorders: anxiety/other behavioural aspects including breathing pattern disorders, or vocal cord dysfunction	Questionnaires, psychologist/liaison, psychiatrist assessment	HADS anxiety domain score ≥8	Disproportionate breathlessness, air hunger, frequent sighs, dizziness, light headed, tingling hands and face, chest tightness, increased Nijmegen questionnaire score, noisy inspiration
Persistent systemic inflammation	High-sensitivity CRP	High-sensitivity CRP >3 mg/L	X
Treatment associated morbidity	X	X	Angiotensin-converting enzyme inhibitor associated cough, breathlessness or tiredness secondary to β blocker
Other pulmonary or non-pulmonary condition	X	X	Focal chest signs, prominent crackles, clubbing, weight loss, haemoptysis, chest pain, cardiac history or risk factors, restrictive spirometry, abnormal chest x-ray or CT
Anaemia	X	Haemoglobin <120 g/L for women or <140 g/L for men	X
Dysfunctional breathing	X	Nijmegen questionnaire Total score ≥23	X
BEHAVIOURAL TREATABLE TRAITS			
Smoking and other environmental exposures	Cotinine, exhaled concentration of CO	Self-report and exhaled CO, admit to smoking and exhaled CO≥10 ppm or deny smoking and show exhaled CO	Smoking history, urinary cotinine, exhaled CO
Exacerbation management	X	Self-report, patient does not possess written action plan or does not use the prescribed plan during exacerbations	X

Non-adherence	Prescription refill rate, chipped inhalers	Self-report by a series of open-ended questions, reported use of <80% of prescribed treatment	Prescription refill rates
Inhaler device polypharmacy	≥3 different types of inhaler devices being used	Medication review. Prescription of ≥3 different inhaler devices	X
Inhaler device technique	Observation, training devices	Direct observation and standardised assessment, technique rated as inadequate	Drug concentrations, FeNO suppression test, chipped inhalers
Social and behavioural issues	X	X	Social history, home visit, school and workplace information
Exposure to sensitiser (allergen, occupational)	Radio allergen absorbance test, skin-prick testing	X	Atopic tendency (presence of disease, family history), history (i.e., latency), relevant exposures, skin prick tests and radioallergosorbent tests
Symptom perception	Mismatch between subjective and objective findings	X	X
Side-effects of other treatments	Monitored withdrawal	X	X
Family and social support	None given	X	X

FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, LLN= lower limit of normal, PEF= peak expiratory flow, ASM= airway smooth muscle, ICS= inhaled corticosteroids, OCS= oral corticosteroids, 6MWD= six minute walk distance, PC20= provocative concentration causing 20% fall in forced expiratory volume, DLCO= diffusing capacity of the lung for carbon monoxide, FeNO= exhaled nitric oxide fraction, PCR= polymerase chain reaction, SpO_2= oxygen saturation, PaO2= arterial oxygen tension, PaCO2= arterial carbon dioxide tension, BMI= body mass index, NTproBNP= N-terminal pro-brain natriuretic peptide, HADS= hospital anxiety and depression scale , GADS= Goldberg anxiety and depression scale, CRP=C reactive protein, CT= computed tomography, CO= carbon monoxide. X indicates that the trait was not included in the publication

Table 4: Key Treatable Traits Research questions

Question	Methodology
How should we define individual traits?	Delphi process / consensus statement
What is the prevalence of the different traits?	Existing datasets, supplemented by prospective data collection where necessary
Which Treatable Traits matter?	Existing cross-sectional & longitudinal datasets for quality of life, control & future risk
Is a broad or narrow/focused approach to managing Treatable Traits preferable?	Prospective randomised controlled trial 3 arms, stratification by baseline diagnosis asthma/COPD • Guideline based • Broad approach at baseline • Focused approach at baseline
What is the best treatment for specific traits?	Master protocol randomised controlled trials
How best to implement Treatable Traits?	Implementation studies - Dynamic control panel embedded in electronic record

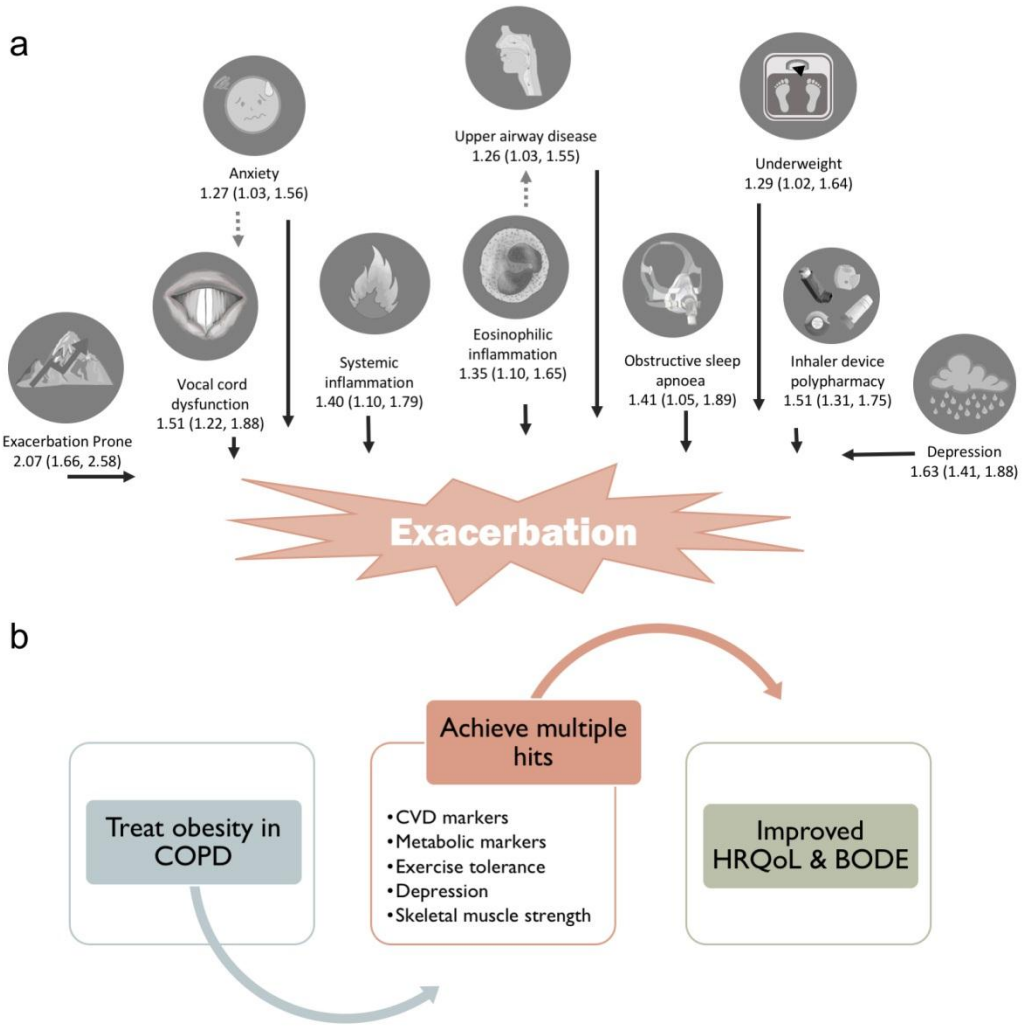

Figure 1: a) Treatable traits significantly ($p<0.05$) associated with increased risk of exacerbations over time. Numbers are the incident rate ratios (IRR) and 95% confidence intervals for the total effect of each trait on exacerbations over time. Adapted with permission from[19]. b) An example of an intervention targeting one trait but achieving multiple positive outcomes including health related quality of life (HRQoL) and Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE)[29]. Illustrations by Olivia J McDonald

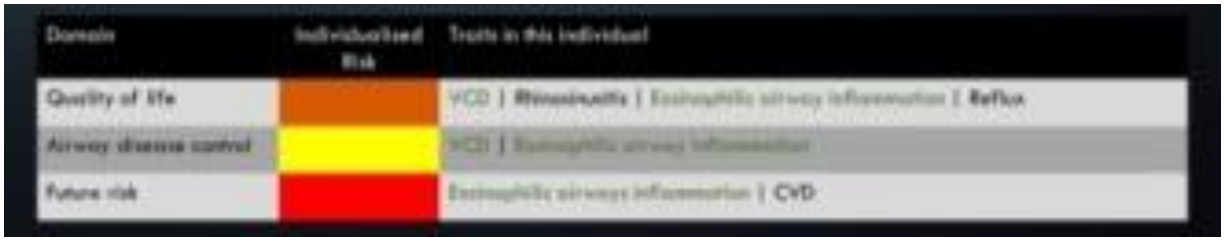

Figure 2: Example of a dynamic control panel, which could be embedded in an electronic patient record. Traits will appear based on the presence of relevant medication, diagnosis coding, or test results. Colours in the individualised risk column reflect the composite risk score for the individual based on identified traits. Priority traits for treatment are highlighted in green based on their association with risk and treatment responsiveness, VCD= vocal cord dysfunction, CVD= cardiovascular disease.