

Treatable traits in asthma: moving beyond diagnostic labels

A precision medicine approach to asthma places the patient at the centre of their care

Asthma is a common inflammatory disease, affecting over 300 million people worldwide,¹ including one in nine Australian adults.²

Asthma imposes a major burden on the health care system, on patients, and within society.³ In the late 20th century and the early 2000s, there were major improvements in asthma outcomes, largely because of the introduction of inhaled corticosteroids to treat eosinophilic airway inflammation, and asthma self-management education initiatives.⁴ These improvements in asthma outcomes are now being lost. Hospitalisations and mortality from asthma have begun to rise as adoption of new assessment techniques and biomarkers into practice stagnates, and we experience sluggish development of new drug discovery in comparison to other diseases.⁴ Asthma deaths have risen in Australia, the United Kingdom and the United States,⁴ with at least one person in Australia dying every day from asthma.²

The need to improve outcomes for people with asthma is therefore great. Despite advances in treatment, people continue to die, they experience an ongoing burden from acute attacks⁵ and symptoms,³ and those with severe disease suffer severe iatrogenic consequences of treatment, in particular from oral corticosteroids.⁶ This results in major deleterious impacts on patients' relationships, their ability to live the life they desire, and workplace absenteeism and loss of productivity.³

These issues mandate a new approach to asthma management, and indeed airway disease. We propose that this be addressed using a precision medicine approach. Precision medicine is delivering real and significant outcomes in many areas, including cancer and other respiratory diseases,⁷ and it is now time to progress precision medicine in asthma.

Treatable Traits is a precision medicine approach that has been developed and proposed for the management of obstructive airway diseases, including asthma.⁸⁻¹⁰

It is achieving global support in the international guidelines for chronic obstructive pulmonary disease (COPD)¹¹ and severe asthma,¹² as well as being the subject of major symposia at national and international respiratory meetings. A PubMed search (16 December 2020) using the term "treatable traits" identified 192 publications since 2016, the date of the first publication proposing the term for the approach.⁸

Treatable Traits should be considered as a model of care,¹⁰ where a patient undergoes a multidimensional assessment to identify clinically important and treatable problems (traits). A specific treatable trait is defined as a "therapeutic target identified by phenotypes or endotypes through a validated biomarker".⁹ Importantly, and as an extension to holistic care, individual treatable traits have



three attributes; they are (i) clinically important (eg, associated with adverse health outcomes like asthma attacks); (ii) recognisable and measurable; and (iii) responsive to treatment (treatable). Traits are recognised using objective trait identification markers, which could be biomarkers, genetic tests, or phenotypic characteristics, and a treatment plan that addresses these traits is developed and implemented.^{9,13} We assign traits within the domains of pulmonary and extra-pulmonary traits and behavioural or risk factors.⁹ A case study illustrating the Treatable Traits approach is available at <https://treatabletraits.org.au/wp-content/uploads/2022/02/MJA-TT-Case-Final.pdf>.

In this framework, the Treatable Traits approach fulfils the definition of precision medicine proposed by Jameson and Longbo:¹⁴ "precision medicine is treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations". Improving clinical outcomes for individuals and minimising unnecessary side effects for those less likely to respond are inherent goals of precision medicine. Treatable Traits looks beyond the airways and encapsulates the many comorbidities and phenotypic, psychological and behavioural traits that are often present in individuals with asthma and applies treatments to these individual traits. The goal is to improve outcomes and ensure that targeted treatments are delivered to those most likely to respond, with improved efficacy and minimised adverse effects.

There are similarities to other disease areas such as diabetes mellitus, where in addition to the diagnosis, there is a multidimensional assessment to identify disease complications, and biomarker guided treatment of blood glucose levels to achieve diabetic control. There are also opportunities to adapt Treatable Traits to other complex chronic diseases such as

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cardiac failure, cancer, chronic cough, sleep apnoea, and acute lung injury.

Why do we consider this new approach to be a paradigm shift in management and an improvement on the current approach to asthma management? The answer is multifactorial. Treatable Traits recognises the complexity and heterogeneity that is characteristic in asthma and other airway diseases such as COPD. It recognises that not all types of asthma (or, indeed, individuals) are the same, and provides an approach that addresses this, in contrast to the one-size-fits-all approach promoted by treatment guidelines based on stepped therapy. Furthermore, Treatable Traits addresses the issues that arise when, commonly, patients present with features of more than one airway disease (asthma–COPD overlap).^{9,15}

The current approach to airway disease management is based on the Oslerian paradigm, which has been used in practice, with great merit, for more than 100 years. Within the Oslerian paradigm, the classification of human disease using diagnostic labels is based on the principal organ system where signs and symptoms manifest with some physiological, anatomical and histopathology correlates.⁸ This approach, however, is becoming somewhat outdated with advances in technology, such as genomics, proteomics, metabolomics, metagenomics and transcriptomics, allowing recognition of disease endotypes and phenotypes that can be treated with targeted interventions.

So far, we have discussed the Treatable Traits approach in the context of asthma. However, the paradigm has been developed and proposed as an approach for the management of airway diseases in general. Moreover, it is an approach that is free from diagnostic labels.⁸ The proposal is not new but has resurfaced. In 1959, the use of defining criteria was promoted over traditional diagnostic labels for airway disease,¹⁶ although it did not gain widespread traction. Treatable Traits is now moving the field of airway disease beyond the Oslerian paradigm to a label-free approach, extending the defining criteria concept and introducing new and improved trait identification markers and novel targeted treatments.⁸

The first step of a Treatable Traits approach is to confirm that airway disease is present. This is achieved through a thorough medical history and assessment of airway disease risk factors, and measurement of lung function by spirometry and biomarkers including blood eosinophils and fractional exhaled nitric oxide, a surrogate marker of type 2 airway inflammation. This allows for the conclusion of a high or low probability of airway disease, as well as identifying the two dominant airway traits of airflow limitation and eosinophilic inflammation. Patients with a high probability of airway disease will then undergo a multidimensional assessment of treatable traits to establish the clinical phenotypes and biological endotypes present in that individual. Individualised treatments are then directed according to the traits present.⁸ This is not to say that the Treatable Traits approach should not be used when a diagnosis of asthma or COPD is confirmed. Discarding the diagnosis is not mandatory for the approach; however,

it can be useful. An advantage of Treatable Traits is that it is tolerant of diagnostic imprecision. This is a common problem in medicine, especially in complex airway diseases where precise diagnosis of asthma or COPD is often not possible.¹⁵

The Treatable Traits approach has been tested in individual airway diagnostic groups. In people with COPD¹⁷ and asthma¹³ who were treated within tertiary care, the mean number of treatable traits identified using a multidimensional assessment was 11 and 10 traits, respectively. This attests to the complexity and heterogeneity of airway disease, neither of which are captured with the simple label of asthma. In both asthma and COPD, each additional trait identified was associated with a clinically significant decrement in health status, many of which are associated with an increased risk of future asthma attacks.⁶ These results demonstrate the clinical importance of identifying the many treatable traits that are present in people with obstructive airway disease, and provides a mechanism to do this via multidimensional assessment of trait prevalence.

The Treatable Traits approach has been tested in clinical trials of both asthma and COPD, in comparison to usual care, and significant improvements in health-related quality of life were observed in the intervention groups.^{13,17} Improvements in biological outcomes^{13,17} and reductions in primary care visits were also observed.¹³

Treatable Traits is now a well developed and described management approach for asthma and other airway diseases. The challenge now is to progress this new way of thinking into clinical practice. Randomised controlled trials have ensured strict inclusion and exclusion criteria based on diagnostic labels, resulting in a large proportion of the population being excluded from the clinical trials that guide our practice. For example, it is estimated that less than 5% of a clinic population would be eligible for entry into the large asthma clinical trials that inform guidelines.¹⁸ Traditional clinical practice guidelines are disease specific, recommending treatments based on a disease label, and essentially treating all patients with that diagnosis in a similar way. The limitations of this are starting to be recognised. There have been recent steps toward more personalised approaches to care within guidelines, and the emergence of pragmatic real world trials in airway disease to increase generalisability of results. Strategies that focus on knowledge exchange and translation to practice are needed, in addition to implementation studies. Examples of these initiatives include training resources for clinicians, webinars, and postgraduate training programs targeted at both tertiary and primary care.

We also need to consider how we communicate this approach to patients. Qualitative data from people with asthma and COPD indicate that patients desire more objective testing for the diagnosis and monitoring of their disease, and that they want to receive feedback from their clinicians about their results and what it means.¹⁹ Furthermore, a study that compared the physician and patient ranking of traits in terms of importance identified discordance

in terms of what was most important.²⁰ This cannot be ignored; improving health literacy from a patient's perspective relating to new treatment approaches is a priority for uptake, adherence and treatment success.

Airway diseases, including asthma and COPD, are heterogeneous, complex and frequently overlap. It is no longer enough to apply a diagnostic label of asthma and expect that to adequately address the patient's issues. Treatable Traits overcomes these practice conundrums and provides clinicians with a vehicle to apply personalised and precision medicine for asthma that places the patient at the centre of their care.

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